

ORAL PRESENTATIONS

GENERAL

S1 - NEUROPATHIC PAIN - THERAPEUTIC APPROACH

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Evidence suggests that there are both nociceptive and neuropathic components of cancer-induced pain. We have observed that changes in intrinsic membrane properties and excitability of normally non-nociceptive A β sensory neurons are consistent in rat models of peripheral neuropathic pain and cancer-induced pain. This has prompted a comparative investigation of the intracellular electrophysiological characteristics of sensory neurons and of the ultrastructural morphology of the dorsal horn in rat models of neuropathic pain and cancer-induced pain. Neuropathic pain is defined as *pain caused by a lesion or disease affecting the somatosensory system* and may lead to both loss of function and also increased pain sensitivity and spontaneous pain. Neuropathic cancer pain (NCP) is caused by nerve damage attributable to the cancer *per se*, and/or treatments including chemotherapy, radiotherapy, and surgery; the prevalence is reported to be as high as 40%. NCP is subdivided into plexopathy, radiculopathy, and peripheral neuropathies, among several other categories. Pharmacological treatment options include opioids, non-opioids and *adjuvant analgesics*, either alone or in combination. In all clinical studies with cancer pain patients, tapentadol PR was well tolerated and provided adequate analgesia, which was at least non-inferior to the standard opioids morphine CR or oxycodone CR. Based on the high level of evidence derived from two independent randomized, double-blind, active-controlled phase III trials (one of which was larger than any trial on opioids in this setting), together with the admittedly weaker evidence from various open-label or observational clinical studies, tapentadol PR can be considered a universal, strong, centrally acting analgesic drug for the management of moderate-to-severe cancer pain, both in opioid-naive and already opioid-pretreated patients. Its good analgesic efficacy seems to be due, at least in part, to the inherent synergistic mechanisms of tapentadol acting also on neuropathic components of cancer pain. Adjuvant drugs are those traditionally used for a primary indication other than pain, but with analgesic properties under some circumstances. These agents are often used first-line for neuropathic pain, so the term is something of a misnomer but is still often used. Adjuvant agents used in neuropathic pain include tricyclic antidepressants (TCAs) and anticonvulsants. Pregabalin bind to the calcium channel $\alpha 2\text{-}\delta$ subunit resulting in decreased central sensitization and nociceptive transmission. Serotonin norepinephrine reuptake inhibitors (SNRIs) work to block the presynaptic serotonin and norepinephrine transporter proteins, which inhibits the reuptake of these neurotransmitters. Duloxetine inhibits the neurotransmitters equally. Steroids are another adjuvant drug which can be used in cases of nerve compression causing neuropathic pain. Cancer-related neuropathic pain can also be treated using opioids or non-opioids, in combination with TCAs or anticonvulsants where required. Other treatment options discussed in the ESMO guidance include ketamine and interventional treatments. Non-pharmacological interventions are also important in multimodal management of neuropathic cancer pain, as in all forms of cancer pain. It is well-recognised that inadequate patient education can provide a barrier to effective pain management in cancer. There is also increasing evidence of the importance and effectiveness of patient education in reducing

pain intensity and pain interference in cancer patients. Self-management interventions for people with cancer pain are one such example. These aim to increase patients' knowledge, skills and confidence to manage their condition, and importantly, to become active in their own management.

Keywords: neurophatic cancer pain, duloxetine, pregabalin

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BREAST CANCER

S2 - THE ROLE OF NEOADJUVANT THERAPY OF BREAST CANCER TODAY

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Neoadjuvant therapy (NAT) in breast cancer (BC), refers to presurgical systemic therapy (PST) administered prior to definitive surgery. In this review we'll discuss recent advances in NST according to breast carcinoma surrogate subtypes. Historically, it was developed for patients with locally advanced, inoperable BC with the intention of downstaging unresectable tumors, or decreasing the extent of surgical intervention to replace radical mastectomy. These indications were mainly referred to neoadjuvant chemotherapy (NACT). For patients with inflammatory BC, NACT is considered a standard of care.

Nowadays, with advances in the molecular characterization of BC, NACT is being widely used for operable tumours also, particularly in aggressive subtypes like triple negative BC (TNBC) and HER2-positive (HER2+) BC. Neoadjuvant evaluation of new drugs was significantly improved by the introduction of pathologic complete response (pCR) rate as a quantitative surrogate endpoint for distant disease-free survival (DDFS) and event free survival (EFS).

Combination of anthracycline and taxane-based chemotherapy with pertuzumab and trastuzumab has become a standard NAT regimen for HER2+ disease. Clinical data for non-anthracycline based regimens and dual anti-Her2 blockade are recently presented on ASCO 2020 meeting. Postneoadjuvant treatment for those with residual disease after NACT was also a matter of research with positive KATHERINE trial with trastuzumab emtanzine given postneoadjuvant.

In contrast, role of NACT in hormone receptor positive (HR+) HER2- BC is still matter of the debate, mainly due to low rates of pathological complete response (pCR) and lower accuracy of pCR as a surrogate predictor of long-term outcome. Neoadjuvant endocrine therapy (NET) still remains an unused potential in the management of HR+HER2- subtype, with key issues concerning the optimal treatment length, appropriate comparisons with NACT and its use in premenopausal patients. It has gained a central role as a platform to test new drug combinations in treatment naive patients or in *window of opportunity* trials. The activity of neoadjuvant endocrine therapy in combination with cyclin-dependent kinase inhibitors (CDKis) (palbociclib, ribociclib, and abemaciclib) is an area of active investigation. During the COVID-19 pandemic, the new role of NET was established in delaying surgery for some patients with the ER-positive/HER2-negative subtype. Further progress will likely come from the use of functional biomarkers such as the mPEPI and PEPI score, and genomic assays, in NET.

Currently, the standard NACT for early-stage TNBC is anthracycline and taxane-based chemotherapy. Several new strategies have been investigated in the NAT of TNBC in order to individualize treatment and achieve higher rates of pCR. According to the recent trials with checkpoint inhibitors, KEYNOTE-522 and IMpassion 031, the proportion of patients with pCR was significantly higher among those who received pembrolizumab or atezolizumab plus NACT.

Further rationale for starting treatment of TNBC with NAC is provided by the recent discovery of effective adjuvant chemotherapy for patients with HER2-negative breast cancer who fail to achieve pCR. Postneoadjuvant therapy with capecitabine was evaluated in early TNBC in several trials: CREATE-X, GEICAM/2003-11_CIBOMA/2004-01 and SYSUCC-001 trial presented at ASCO 2020. In the SYSUCC-001 trial 1 year of metronomic capecitabine versus observation showed 5-year DFS of 83% versus 73% (HR 0.63, 95% CI 0.42–0.96, $P = 0.027$). In contrast to CREATE-X, this trial was not based on pCR status after neoadjuvant therapy.

Strategies without chemo with single agent PARP inhibitors like talazoparib are also under the spotlight for BRCA1/2 mutated tumors.

Despite being initially adopted as downstaging therapy before surgery, neoadjuvant trials for early breast cancer have accelerated the investigation of novel anticancer agents allowing registration trials with shorter duration and fewer participants. The neoadjuvant phase 2 platform trial I-SPY 2 simultaneously tests multiple drugs across different breast cancer subtypes using adaptive randomization for assessment of drug efficacy. There are lot of efforts put into the development of effective biomarkers for predicting the early responses to NAT with intention to de-escalate NAT particularly through novel MRI biomarkers.

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S3 - OPTIMAL SEQUENCING IN LUMINAL METASTATIC BREAST CANCER TREATMENT

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Hormone receptor (HR) positive breast cancer (BC), early and metastatic, is the most common subtype (up to 70% of the cases). Between 5 and 6% of breast cancer patients have metastatic disease at the time of diagnosis, and approximately 30% of patients diagnosed in the early stages will experience a relapse with the appearance of distant metastases. At present, metastatic breast cancer (MBC) is still incurable with median overall survival (OS) of 42 months, and the main treatment goal is to improve OS and quality of life. Endocrine therapy (ET) is the mainstay of treatment of this type of BC in adjuvant and metastatic settings. ET alone is an effective option even in the presence of visceral metastases unless there is visceral crisis or proof of endocrine resistance. ET consists of either: selective estrogen receptor modulator (SERM) (tamoxifen), selective estrogen receptor down regulator (SERD) (fulvestrant), aromatase inhibitors (AIs) (anastrozole, letrozole and exemestane) and progestin (megestrol acetate). Luteinizing hormone-releasing hormone (LHRH) agonists administration or surgical castration in combination with one of the above mentioned ET drugs is recommended for premenopausal women. Despite the fact that ET is the most effective treatment for HR+ mBC, vast majority of these patients will develop disease progression due to *de novo* or acquired ET resistance. Until recently, the only systemic treatment option for ET refractory disease was chemotherapy with its limitations regarding efficacy (less effectiveness than in ER-tumors) and toxicity. In order to overcome or delay the ET resistance, plenty of preclinical and clinical researches have been done. As a result, there are two main treatment directions in the current clinical practice: inhibition of the mammalian target of rapamycin/PIK3CA (mTOR/PIK3CA) pathway by specific inhibitors (everolimus and alpelisib) and intervening in the cell cycle progression by targeting cyclin-dependent kinase 4/6 (CDK4/6). Three CDK4/6 inhibitors have been approved in metastatic HR +/HER2 - BC: palbociclib, ribociclib, and abemaciclib as first-line treatments in association with AIs (PALOMA-2, MONALEESA-2, and MONARCH-3) or as 2nd line therapies associated with fulvestrant (PALOMA-3, MONALEESA-3, and MONARCH-2). One trial addressed only pre-menopausal patients who received goserelin, and AI or tamoxifen combined with ribociclib obtained the same magnitude of benefit (MONALEESA-7). Introduction of CDK4/6 inhibitors with AIs in the 1st line treatment resulted in a progression-free survival (PFS) gain of about 10 months, a consistent significant hazard ratio (HR) ranging between 0.55 and 0.57, and an improvement in overall response rate (ORR). Quality of life is maintained over all of the 1st -line trials and the side effects consisting mainly of hematological toxicity which are easily manageable. CDK4/6 inhibitors showed positive results beyond 1st -line settings when associated with fulvestrant: there was a consistent PFS gain of about 5 to 7 months and a consistent significant HR ranging from 0.50 to 0.55. Moreover, data concerning the overall survival (OS) were reported in the PALOMA-3 and MONALEESA trial. Due to the results of the OS, CDK4/6 inhibitors gain high appraisal in ESMO magnitude of clinical benefit scales. Nevertheless, there are some differences in the safety profile among the three CDK4/6 inhibitors. Abemaciclib showed promising single-agent activity, and possibly an activity against brain metastases knowing its ability to cross the blood-brain barrier.

Constitutional hyperactivation of the PI3K-AKT-mTOR pathway in luminal MBC leads to tumor cell survival. Everolimus and alpelisib target pathway at different points of downstream signaling in combina-

tion with ET in order to arrest tumor cell progression. In the pivotal BOLERO-2 phase III trial, it was demonstrated that everolimus (mTOR inhibitor) with exemestane prolonged the PFS and increased the ORR as compared with exemestane alone after progression on AIs: gain in PFS of about 4 months (HR:0.43, 95% CI(0.35-0.54); $p<0.001$). Another drug, alpelisib, an alpha-selective PI3K pathway inhibitor, in combination with fulvestrant in PI3K-mutated luminal mBC tested in SOLAR 1 trial shown significant PFS gain (mPFS 5.7 vs 11 months, HR:0.65, $p<0.00065$). SANDPIPER trial shown that combination of fulvestrant and taselelisib prolongs mPFS from 5.7 to 7.4 months (HR:0.70, $p=0.0037$).

Introduction of CDK4/6 inhibitors, everolimus and alpelisib in combination with ET gave us an opportunity to improve treatment results, still there is room for improvement. The answer is probably in identifying more predictive biomarkers, better knowledge about tumor biology leading to more precise patient selection for each treatment option. Most of the trials did not include pre-menopausal women, but most of the consensus recommend the same treatment as for post-menopausal women with ovarian suppression or ablation. Another issue is treatment of very young women (chemotherapy vs ET+CDK4/6) and older or fragile patient (ET alone or combination with CDK4/6 or PI3KCA inhibitor), or what about bone only disease?

The optimal sequencing of ET and targeted treatment association is still unresolved. For instance, the mTOR inhibitor trials mainly did not include patients pre-treated with CDK4/6 inhibitors and vice versa. Would the response to mTOR inhibitors be the same as it was before the era of CDK4/6 inhibitors? We still don't know is there any benefit on potential continuation of CDK4/6 inhibition beyond progression in advanced ER +HER2 – BC. What about fulvestrant reintroduction in combination with alpelisib in later treatment lines. Another hypothesis is testing in several ongoing trials: the combination of CDK4/6 inhibitors with different PI3K/mTOR inhibitors.

Keywords: metastatic breast cancer, estrogen receptor positive, HER2 negative

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S4 - OPTIMAL TREATMENT OF METASTATIC HER2 POSITIVE BREAST CANCER PATIENTS

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The treatment of HER2 positive metastatic breast cancer is has been associated with great improvement in PFS and OS of patients. Depending on the stage of diagnosis, pretreatment in the neoadjuvant and adjuvant setting and event free survival prognosis and treatment in metastatic stage is determined. First line therapy has been established with the combination of pertuzumab, trastuzumab and taxanes (based on Cleopatra Phase III study), and in the second line so far T-DM1 (mainly based on the EMILIA study) is the therapy of choice. After progression o T-DM1 there the greatest changes can be expected in the new treatment guidelines, since in the beginning of this year there have been two important EMA approvals, tucatinib in the combination with capecitabine and trastuzumab, based on the data generated in the Her-2climb study, and trastuzumab deruxtecan, with efficacy demonstrated in the Destiny 01 trial, single arm Phase II study. In the coming months further data are awaited. Additional data are generated with immune checkpoint inhibitors, CDK4/6 and PIK3CA inhibitors and further TKIs as well as dual antibody blockade with pertuzumab and trastuzumab beyond further lines of treatment as suggested by the Precious study with an impact on OS of patients. All these data together have led to a significant improvement of treatment possibilities and associated outcome data of metastatic HER2 positive breast cancer patients and will increasingl influence treatment algorithms in coming months.

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S5 - TRIPLE NEGATIVE BREAST CANCER TREATMENT: CURRENT STANDARDS AND FUTURE PERSPECTIVE

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Triple-negative breast cancers account for ~15% of all breast cancer and are related with generally poorer prognosis with median 5-year survival of 65% in early disease. Chemotherapy is the standard of care (antracyclins, taxanes, platinum salts and 5-FU, antimetabolites, vinca-alcaloids). In early breast cancer standard is neoadjuvant chemotherapy, followed by surgery, radiotherapy when indicated, and adjuvant capecitabine in patients that did not achieved pCR. Results of phase 3 trial SYSUCC-001, showed that treatment with low dose capecitabine for one year resulted in significant improvement of 5-year DFS (85.5 vs 75.8%), but not in OS.

Although TNBC shows chemosensitivity, chemotherapy is of limited benefit, especially in relapsed TNBC. Novel agents are developed for patients with PD-L1 positivity and gBRCA mutations, but they represent only fraction of all TNBC patients, and not all of them are responders. Recently, various agents and combinations are investigated to understand TNBC behavior and find effective therapy targets and strategies.

TNBCs are more immunogenic than other breast cancers, more tumor-infiltrating lymphocytes and higher level of PD-L1 expression. In metastatic disease nab-paclitaxel and atezolizumab (anti PD-L1 antibody) showed efficacy as a first-line therapy in Impassion 130 trial, though only in PD-L1 positive TNBC patients. Median PFS was 7.5 vs 5.0 months, median OS 25 vs 18 months. Atezolizumab efficacy was also evaluated in early breast cancer, in Impassion031 trial, with chemotherapy vs placebo. The pCR rate was 57.6% vs 41.1% in placebo arm, benefit in PD-L1+ population of 19.5% and in PD-L1- of 13.3%. Trial showed PD-L1 as predictive biomarker for chemotherapy response. In neoadjuvant NeoTRIPaPDL1 trial, atezolizumab or placebo was added to carboplatin and nab-paclitaxel. Although small difference in pCR was seen (52.3 vs 47.7%), improved pCR rates in patients with TILs infiltrating tumors $\geq 40\%$ (71 vs 63%) were observed. Pembrolizumab showed efficacy in tumors with high microsatellite instability (MSI-H) or mismatch repair deficient (dMMR). Less than 2% of breast cancers belong to this group. Its efficacy was investigated in combination with chemotherapy by physician's choice vs placebo in KEYNOTE-355 trial. Pembrolizumab showed PFS benefit in PD-L1+ tumors: 9.7 vs 5.6 months. KEYNOTE-522 trial compared efficacy of chemotherapy +/- pembrolizumab in early BC. With pembrolizumab, pCR was 64.8% vs 51.2%, and EFS at 18 months 91.3% vs 85.3% in placebo arm. The benefit was more profound in PD-L1+, but seen in PD-L1- patients. Higher pCR rates were found in connection with PD-L1 and level of TILs. Tonic trial was based on hypothesis that short-term therapy (chemo- or radiotherapy) can enhance sensitivity to immune checkpoint inhibition. The best response was seen with doxorubicin, followed by combination of nivolumab/doxorubicin after two weeks, with ORR of 35%. Studies confirmed that chemotherapy is backbone, that immunotherapy adds benefit in subset of patients, and PD-L1 status (KEYNOTE-119 trial confirmed it as predictive biomarker), TIL status and TIL/PD-L1 ratio influence the response.

PARP inhibitors have shown efficacy in patients with gBRCA 1/2 mutations. Approximately 10-30% of TNBCs have BRCA mutation. Olaparib is approved after showing its efficacy in Olympiad trial, in HER2-metastatic disease in patients with BRCA1/2 mutations. Olaparib was compared to chemotherapy of phy-

sician's choice, and showed PFS of 7 vs 4 months in gBRCAm, with no improvement in OS (19.3vs 17.1months), except potentially, in patients that had no prior chemotherapy for metastatic disease. EMBRACA phase III trial compared talazoparib to chemotherapy in gBRCAm HER2- metastatic breast cancer. Talazoparib increased median PFS: from 5.6 to 8.6 months.

Sacituzumab-govetican (SG) is antibody-drug conjugate: it consists of an anti-TROP-2 antibody (expressed in > 90% of TNBCs), an irinotecan metabolite SN-38, and cleveable linker. ASCENT trial compared efficacy of SG to therapy of physician's choice, in patients that received at least two prior therapies for metastatic disease. SG demonstrated significantly better median PFS compared to chemotherapy: 5.6 vs 1.7 months. Ladiratumzumab vedotin (LV) targets LIV-1, a TM protein expressed in > 90% breast tumors. LV with auristatin showed ORR of 25% in heavily pretreated patients. In neoadjuvant setting with pemrolizumab, showed ORR of 35%, due to LV induction of immunogenic cell death, more favorable environment for pembrolizumab action.

Many strategies are in development: conversion of TNBC to endocrine sensitive, immune stimulants, CDK 4/6 and PI3K/AKT inhibitors, antiandrogen/AR antagonists, adenosine antagonists and PD-1inhibitors, combinations of PARP and PD-L1/PD-1 inhibitors, pan-CDK inhibition, transcription factors blockade.

Treating triple negative breast cancer is not satisfactory, with chemotherapy being still the standard of care for most patients. Though progress has been made, finding true predictive and prognostic biomarker is crucial. Hopefully, many of recent trials with various agents based on specificities of triple-negative breast cancer, will result in more efficient therapies and improved survival of these patients.

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S6 - METASTATIC BREAST CANCER AS AN INITIAL DIAGNOSIS: A CASE REPORT

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The mortality rate of breast cancer has decreased in developed Western countries as a result of the widespread use of mammographic screening. Despite the fact that some patients with breast cancer are aware of their breast mass, they do not seek medical help for a long time.

A 52-year-old woman with a history of peptic ulcer disease was admitted to the Clinic of Internal medicine because of epigastric pain in June 2014. On the physical examination her left breast was enlarged, with marked edema, erythema and induration. Left infraclavicular and axillary lymph nodes were palpable. The diagnostic workup [the multi-slice computed tomography (MSCT) of the thorax, abdomen and pelvis, bone scintigraphy and a brain magnetic resonance imaging (MRI) scan] showed suspected primary tumor of the left breast with metastases in the left infraclavicular and left axillary lymph nodes, lungs and bones.

Patient underwent a palliative left radical mastectomy in July 2014. The histopathological examination revealed a mucinous breast cancer. Estrogen receptors (ER) were positive in 90% of the tumor cells, progesterone receptors (PR) were positive in 70% of the tumor cells and human epidermal growth factor receptor 2 (HER-2) status was negative. Ki-67 proliferation index was 10%.

The patient was then referred to our hospital. Six cycles of chemotherapy, the doxorubicin-paclitaxel regimen (doxorubicin 60 mg/m² IV every 3 weeks + paclitaxel 80 mg/m² IV every week), were administered and stable disease was achieved (with decreasing value of the blood-based biomarker CA15-3). She also began therapy with zoledronic acid (4 mg IV every 4 weeks). Then, in December 2014, patient was switched to the endocrine therapy with letrozole given orally in a 2,5 mg daily dose with vitamin D3 and calcium supplementation. The restaging in May 2017 showed a progression of an osteolytic lesion in right frontal bone. Patient underwent a cranioplasty. The histopathological examination revealed a metastatic breast cancer. ERs were positive in 95% of the tumor cells, PRs were positive in 10% of the tumor cells and HER-2 status was negative. She continued endocrine therapy with letrozole. Diagnostic work-up in December 2017 showed progression (metastatic skull lesion in the right parietal bone measuring 22x12 mm, with infiltration of tabula externa and interna, and osteolytic skull lesion in the right parietal region measuring 14x10 mm). Endocrine therapy with Tamoxifen given orally in 20 mg daily dose was then prescribed to the patient (from December 2017 to May 2018).

In May 2018 patient started treatment with a combination therapy of the cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor ribociclib and aromatase inhibitor exemestane (days 1-21: ribociclib 600 mg orally once daily, days 1-28: exemestane 25 mg orally once daily) as part of the Compassionate Use Programme. She continued treatment with zoledronic acid (4 mg IV every 3 months). Partial regression of bone metastases, stable disease on the lungs, continuously decreasing value of CA15-3 and clinical improvement have been achieved, with a good toxicity profile. At present, partial clinical response remains after 34 months of ongoing treatment. Up to now, no serious adverse event was reported during this treatment.

Keywords: breast neoplasms; neoplasm metastasis; cyclin-dependent kinases; treatment outcome

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S7 - CASE REPORT OF METASTATIC BREAST CANCER DURING PREGNANCY

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Breast cancer is the most common cancer in women worldwide and it is one of the most common cancers diagnosed during pregnancy. When diagnose is made during pregnancy, there is an increased risk of detecting the disease at an advanced stage. The review of the scientific literature on this topic is very poor because of the rarity of the disease. Diagnostic and therapeutic procedures should be guided by a multidisciplinary team for breast tumors and associated with obstetrician and neonatologist.

We report a case of an advanced breast cancer initially diagnosed in pregnant woman. A 37-year old pregnant woman, at 30 weeks of gestation, came to the emergency gynecological clinic in a poor general condition with symptoms of weakness, nausea and vomiting. Because of the back pain in past three months, she had been taking analgesics and was treated by an orthopedist and a physiatrist. In physical examination an enlarged, palpably painful right breast, the appearance highly susceptible to cancer had dominated. Axillary and supraclavicular lymph nodes were also enlarged. As there had been signs of fetal distress and mother's condition had been rapidly deteriorating, one day after hospitalization, the pregnancy had been terminated by caesarean section in the best interest of the child. A male child had been born with an Apgar score 5/7 and body weight of 1790g. Newborn had been given to the neonatologist for further care. During the section, ascites had been observed and a sample of it had been sent for cytological analysis. A liver had been riddled with nodules suspected of metastasis. Cytological analysis of the ascites had proved breast cancer. Soon after, CT scan of brain, thorax and abdomen has been performed. In CT scan report, disseminated breast cancer with metastases to lymph nodes, lung, liver and bone had been described. Patient condition had been discussed on multi-disciplinary tumor board for breast cancer. Due to the very bad condition of the patient, any active form of oncological treatment had not been feasible. A patient had been in the terminal phase of the disease and had passed away 6 days after hospitalization. An autopsy had been performed which confirmed breast cancer, not specific type, according to the TNM classification pT4bN3cM1 and molecular subtype Luminal B (HER-2 positive).

Keywords: breast cancer, pregnancy, metastatic

S8 - CASE REPORT: PATIENT WITH VISCERAL CRISIS

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Visceral crisis is a condition of severe organic dysfunction that involves severe symptoms, most often as a reflection of rapid disease progression, and can be confirmed by laboratory findings. In metastatic breast cancer, the entity visceral crisis implies a condition that requires rapid recognition and therapeutic treatment, with the intention of managing symptoms and vital clinical and laboratory parameters. Our case report is about a patient who initially presented to a medical oncologist as a young woman in the early stage of the disease, treated successfully at the time being, and stopped the adjuvant antihormonal treatment due to achieving pregnancy. The notable aspects of this case include the patient's unusual presentation of metastatic disease, a short clinical history of symptom onset, rapid neurological deterioration and a final diagnosis of paraneoplastic bulbar syndrome, accompanied by impending liver failure, or liver manifestation of visceral crisis.

After initial surgical treatment of early luminal, HER2-negative breast cancer, adjuvant chemotherapy (AC x4 + paclitaxel x12) and radiotherapy were performed, and additional antihormonal therapy with tamoxifen was introduced. Adjuvant antihormonal treatment was discontinued due to the patient's desire to achieve motherhood. Five years after the initial diagnosis, metastatic disease was verified, which was presented by paraneoplastic bulbar syndrome. The patient had progressive swallowing and speech disorders, a generalized lesion of the lower motoneuron and a disseminated disease in liver and bones by imaging findings, accompanied by significant liver lesion, recognised through localised pain and bilirubin, prothrombin time and liver enzyme progressive rising in consecutive measurement. She was at extreme visceral risk, which is why the multidisciplinary team decided to start the treatment of impending visceral crisis with doxorubicin monochemotherapy. During the interventional treatment with doxorubicin, stabilization of the clinical picture, neurological symptoms and laboratory findings was achieved, with accompanying control of visceral risk. Unfortunately, after three months of treatment, objective radiological findings showed disease progression, predominantly in liver and bones. Since, at that stage, there were no more signs of acute visceral risk, there was a chance to perform further diagnostic procedure, in order to characterise the metastatic disease biology better. Liver metastasis biology revealed maintained luminal HER2 negative biology of disease and so, after performing surgical castration to this premenopausal patient, antihormonal therapy in combination with CDK4 / 6 inhibitor was introduced. The named combination brought the disease under control, and is currently still ongoing.

Through this example, we recall the importance of timely intervention with chemotherapy and achieving a rapid response, when it comes to acute disease threat, in terms of visceral crisis, or "break-down" of organs or organ systems under the burden of disease. Even when objectively progressive disease dynamics follow, the benefit of disease stabilization in an acute situation is reflected in the stabilization of organ function, gradual normalization of alarming laboratory parameters, and clear clinical recovery.

LUNG CANCER

S9 - NATIONWIDE LUNG CANCER SCREENING PROGRAM – CROATIAN MODEL

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Lung cancer is one of the leading causes of death from malignant diseases, both worldwide and in Croatia. With more than 3000 new diagnoses of lung cancer and more than 2900 lung cancer deaths each year, lung cancer is one of the main public health problems in Croatia. Despite recent advances in the treatment of lung cancer, five year survival rates for lung cancer patients is very poor. One of the main reasons is that approximately two-thirds of patients are being diagnosed at advanced stages when surgical treatment is not possible, leaving only systemic treatments available. Taking this into consideration along with a high smoking prevalence, we decided to implement the National Lung Cancer Screening Program. The first national lung cancer-screening program in Europe to cover high-risk populations, completely integrated into an existing healthcare system and covered by the National Health Insurance Fund in full. The Croatian model places general practitioners (GPs) in the central role of the integrated approach checking for eligible candidates (based on inclusion and exclusion criteria) during dedicated or non-dedicated visits as well as searching their digital archive for stored data on smoking history. Screening candidates are then enrolled in a smoking cessation program and referred to one of 16 low dose CT (LDCT) centers nationwide for baseline screening. Specially trained radiologists, along with the aid of Artificial Intelligence (AI) will then assess the baseline LDCTs to identify large or advanced cancers that require immediate diagnosis and treatment, with subsequent LDCTs to identify smaller non cancer nodules (NCNs) that require follow up. Lung nodules will be measured by using volumetric analysis and I-ELCAP guidelines. The aim of the Croatian program is to establish pulmonology nodule clinics across the country to offer quick and comprehensive management of suspected lung cancers. The purpose of these clinics is to diagnose and treat patients with suspected lung cancer earlier to try to increase the cure rate in this group of patients.

The final goal of the program is to decrease the mortality of lung cancer by at least 20% in the next 10 years.

Keywords: Lung cancer, screening, smoking cessation, national program, LDCT

S10 - NOVELTIES IN ADJUVANT AND NEOADJUVANT TREATMENT OF NSCLC

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Lung cancer is the most common killer among all malignant diseases with five-year survival below 20%. Unfortunately, despite all progresses that have been done with the treatment of metastatic disease there were little progress in improving survival in the last decade. One of the reasons for that is that only one third of patients are diagnosed in early stage or locally advanced disease where curative treatments, like surgery or chemo-radiotherapy are possible. Surgery is treatment of choice in patients with early stage non-small cell lung cancer (NSCLC). Nevertheless, 5-year survival rates in stage IA are 80 to 90%, in stage IB 70%, in stage II 50 to 60%, and in stage III below 50%. The current common perioperative treatment strategy is chemotherapy, either as neoadjuvant or in adjuvant setting. The idea of adding chemotherapy to radical surgical treatment is to improve survival by killing potential micro-metastases present at the time of surgery which are not possible to detect by current diagnostic procedures. LACE meta-analysis has proven that adding platinum-based chemotherapy after radical surgery is improving survival in early stages of non-small cell lung cancer patients. A meta-analysis of preoperative treatment showed that there is prolonged overall survival (OS) compared with surgery alone. Preoperative chemotherapy and postoperative chemotherapy are similarly effective according to clinical trials. However, some studies suggested that the effect of preoperative chemotherapy is poorly efficacious for the N0 and N1 stage, and vast majority of positive results were driven by effect in N2 disease.

Perioperative treatment with molecular targeted agents

Epidermal growth factor receptors (EGFR) tyrosine kinase inhibitors (TKIs) were most heavily tested in perioperative setting in early stage NSCLC. Studies RADIANT and CTSUBR19 performed in adjuvant setting included unselected patients failed to show improvement in overall population of included patients. However, in subgroup of patient with present EGFR driver mutations improvement in overall survival was noticed. The CTONG1104 trial comparing gefitinib with chemotherapy only in EGFR positive patients showed an increase in disease free-survival (DFS) but there was no improvement in overall survival. Recently published ADAURA trial compared osimertinib with chemotherapy in EGFR positive radically resected early stage NSCLC showed statistically and clinically significant improvement in DFS. OS data are still awaited but this really significant difference in DFS put osimertinib as standard of care in EGFR positive patients who are radically operated.

Perioperative treatment with an immune checkpoint inhibitor

Perioperative therapies using immune checkpoint inhibitors (ICI) are likely to develop in the future, but unfortunately, they are only early phases of clinical trials published. ICI are tested as neoadjuvant approach like monotherapy or in combination with chemotherapy or in adjuvant setting, mostly as monotherapy. Forde and colleagues reported preoperative immunotherapy with nivolumab, an anti-PD-1 anti-

body, in a pilot study. There were no significant safety issues, and 45% achieved a major pathological response (MPR). Several other studies with nivolumab together with ipilimumab, monotherapies with pembrolizumab or atezolizumab, have reported improvements in MPRs in neoadjuvant settings. Large phase III trials are investigating different ICIs in adjuvant settings, but we should still wait for the results of these studies because OS is major end-point in adjuvant setting.

Conclusion

In patients with early stage lung cancer treatment with curative intent is indicated. There are several strategies hot to improve survival. The mostly used one at the moment is perioperative use of cisplatin-based chemotherapy, either in neoadjuvant or in adjuvant setting. Molecular based adjuvant treatment (especially in EGFR positive patients) is coming into everyday clinical practice. Immune-check point inhibitors are widely used in advanced stages of NSCLC and at the moment they are largely tested as a part of perioperative treatment in early stages of NSCLC.

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S11 - THE POSSIBILITIES OF NON-SMALL CELL LUNG CANCER TREATMENT WITH TARGETED THERAPY IN CROATIA

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It is unquestionable that targeted therapies in patients with metastatic non-small cell lung cancer (NSCLC) have superior outcomes and far less toxicity compared to chemotherapy. Despite the new possibilities they offer, the targeted therapies however bring in challenges and complexity in diagnostic and therapeutic approach. Additional challenge lies in the fact that the targeted therapies greatly increase the costs of NSCLC patients treatment. From the health system perspective, the lack of pharmacoeconomic analyses makes it even more difficult to take smart decisions in managing limited resources we have available.

Currently in Croatia we have approved targeted therapies for patients with EGFR, ALK and ROS 1 gene alterations.

The patients with EGFR mutations in first-line can be treated with first generation tyrosine kinase inhibitors (TKIs) (erlotinib, gefitinib) or slightly more efficient, but also more expensive second generation TKI afatinib. The best results in the first-line treatment are obtained with third generation TKI osimertinib, which is significantly more expensive. Osimertinib is so far not approved in the first-line treatment in Croatia, it is approved only in the second-line treatment for patients who progressed on first or second generation TKIs due to secondary T790M mutation.

The patients with ALK rearrangement in Croatia also have available three generations of TKIs. Second generation of TKI (alectinib, ceritinib, brigatinib) are significantly more efficient than first generation TKI crizotinib. Following the Croatian Health Insurance Fund indications (limitations), in the first-line treatment we almost always use alectinib, and after the progression of the disease we use lorlatinib or brigatinib.

At the present moment our patients with ROS 1 rearrangement can benefit only from one target drug – crizotinib, which has in a great extent improved the outcomes of the treatment of this patients compared to the chemotherapy. We hope that soon other ROS1 TKIs, with better efficiency in central nervous system (primarily entrectinib), will be approved.

We can reasonably expect that in near future we will have approved in Croatia the FDA-approved targeted therapies for NSCLC with positive BRAF V600E mutation, NTRK gene fusion, MET exon 14 mutation and RET rearrangement.

To fully exploit all the capacities that the targeted therapy for NSCLC patients offers, we have to make further steps in several fields.

Efficient and quick identification of genetic alterations that can be treated with existing therapies is a precondition for the treatment improvement. Therefore we need to implement next generation sequencing (NGS) or similar techniques in our everyday clinical practice. In the treatment of patients with targeted drugs resistance mutations represent a serious problem. So, to fully implement individualised, precise medicine we need such diagnostic improvements not only for the initial diagnosis, but also in each progression of the disease.

In the individualised, precise medicine that we aspire to, the indications given by the Croatian Health Insurance Fund make the optimal use of the drugs the Fund has approved more difficult. When we add to

it the dynamics and complexity of the targeted therapy, a big challenge is posed in front of every doctor who treats such patients.

Taking in account gross domestic product (GDP) and in comparison to other EU countries, Croatia is in a favourable position in terms of targeted drugs approved by the Croatian Health Insurance Fund. So, by solving the above mentioned issues and with personal engagement and dedication of each doctor in this field, we can further improve the outcomes of the NSCLC patients with driver genetic alterations.

Keywords: non-small cell lung cancer, targeted therapy, Croatia

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S12 - TOXICITY OF IMMUNOTHERAPY - INDIVIDUAL APPROACH

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Immune checkpoint inhibitors, such as CTLA-4 inhibitors (ipilimumab), PD-1 (nivolumab, pembrolizumab), and PD-L1 inhibitors (atezolizumab, durvalumab) have become standard in the treatment of numerous malignant tumours.

Immunotherapy blocks the body's natural protective measures with immune checkpoint inhibitors. It prevents immune over-activation, but it can also affect normal tissue, and cause autoimmune side effects. They cover a diverse spectrum of events and require different treatment approaches. Immune-related side effects can affect any organ or tissue, but most commonly affect the skin, colon, lungs, liver, and endocrine organs (such as the pituitary or thyroid).

They can be divided into infusion reactions, immune-induced side effects, and adverse events of particular interest. Most of these side effects are mild to moderate and reversible if detected early and treated appropriately. Side effects of treatment with immune checkpoint inhibitors usually occur within a few weeks or months of starting the treatment but can occur at any time during the treatment - as early as a few days after the first infusion, but sometimes 1 year after the end of treatment. The most common side effects with CTLA-4 inhibitor and PD-1 / PD-L1 inhibitor are skin symptoms (such as rash and itching). Gastrointestinal symptoms (such as diarrhoea) are more common with CTLA-4 inhibitors while lung symptoms and thyroid dysfunction occur more frequently with the use of PD-1 / PD-L1 inhibitors. Fatigue is one of the common side effects with anti-PD 1 (16% - 37%) and anti-PDL 1 (12% -24%) inhibitors while its pathogenesis stays unclear and only a small number of cases can be attributed to hypothyroidism. Treatment with combinations of CTLA-4 inhibitors and PD-1 is more likely to cause side effects.

The treatment of immunological side effects can be divided into the general principle of treatment and special recommendations considering the affected organ. It is important to determine the side effect, and the degree of the same to be able to treat it adequately. First-degree side effects are mild, second grade moderate, third grade severe, and fourth grade very severe. The principles for the management of side effects associated with immune checkpoint inhibitors generally include treatment of first and second grade symptoms, without interruption or permanent cessation of immunotherapy treatment. Patients with persistent second grade symptoms may need to skip one or more doses of treatment. They also need to be treated until their symptoms are alleviated or resolved with corticosteroids (prednisone 0.5 mg/kg/day or equivalent). Exceptions are second grade thyroid dysfunction side effects, which can be treated with replacement therapy without interruption of immunotherapy. With third or fourth grade symptoms, treatment is in most cases discontinued and the patient is treated with high doses of intravenous corticosteroids (1-2 mg/kg/day or equivalent) in a hospital setting. Also, the patient is referred to a specialist depending on the affected organ. Patients that benefit from corticosteroid therapy usually improve their condition within 3 days. In those patients who do not improve on steroid therapy, infliximab 5 mg/kg is introduced rather than continuing corticosteroid therapy. Infliximab is not used in patients with increased liver function tests because it causes hepatotoxicity.

The association between the incidence of irAE and the antitumor efficacy of immunotherapy is somewhat controversial. Some studies suggest that irAE correlates with improved response and survival rate,

while others have failed to show such association. Further studies are needed to confirm if the experience of irAE is also a prediction of treatment outcomes. The use of corticosteroids or other immunosuppressants, according to the available data, does not significantly affect the efficacy of immune checkpoint inhibitors. However, for patients who plan to re-administer immunotherapy after experiencing irAE, concomitant administration of immunosuppressive therapies is associated with reduced efficacy of immunotherapy.

PCP prophylaxis is recommended to patients receiving glucocorticoids for an irAE in the setting of combined chemotherapy plus immunotherapy; to those with underlying pulmonary conditions receiving glucocorticoids for an uncomplicated irAE; or to those with a complicated irAE (eg, those requiring longer than six weeks of glucocorticoids or additional immunosuppressive therapy).

Re-administration of immunotherapy after immunotherapy in patients with significant irAE during initial treatment with either a CTLA-4 inhibitor and/or a PD-1 / PD-L1 checkpoint inhibitor can be safely repeated after discussing the benefits and risks. The choice to repeat immunotherapy depends on several factors: the severity and nature of the initial irAE, the response to systemic immunosuppression, the clinical response to the initial immunotherapy regimen, and the availability of alternative treatment options. Data on the effectiveness of this approach are limited and clinical studies are needed to confirm it.

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S13 - RADIOTHERAPY OF NSCLC BRAIN METASTASES IN THE AGE OF TARGETED THERAPY AND IMMUNOTHERAPY

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Primary lung cancers account for 40% to 50% of brain metastases (BM), with 16% to 20% of patients with lung cancer developing BM over their treatment course. When discussing BM, it is important to keep in mind that they are not a single clinical entity, but a heterogenous group of tumours with differing molecular profiles. The focus of this lecture is to review the various classes of targeted therapy and immunotherapy that are often prescribed in combination with brain radiation therapy for BM.

Radiotherapy (RT) is considered administered *concurrently* with targeted therapy and immunotherapy when administered in a period shorter than five half-lives of the drug. Nowadays, oncologists are faced with insufficient information on the safety and toxicity of these new drugs that are increasingly being used in combination with brain RT. The efficacy and safety of these agents in combination with brain RT may be a function of the radiation volume, radiation dose schedule, drug mechanism of action, normal brain versus brain tumour penetrance, drug half-life, and timing of radiation versus drug exposure.

As one considers whether targeted therapy or immunotherapy may increase the risk of adverse effects of brain RT, we also have to take into account traditional risk factors for radiation toxicity to the

brain, which should not be overlooked. Randomized clinical trials published since 2010 suggest that whole-brain RT has a higher risk of neurocognitive dysfunction beginning as early as 3 to 4 months after treatment. As systemic treatments for many malignancies advance, every effort should be made to avoid whole-brain radiation in order to preserve cognition in patients who will survive for many years.

Over the past decade, major advances have been made in the understanding of non-small cell lung cancer (NSCLC) molecular biology. Systemic treatment options for patients with NSCLC BM include immunotherapy agents and targeted therapies for ALK rearrangement-positive, EGFR mutation-positive, ROS1 rearrangement-positive, etc. Molecularly targeted agents include small molecule tyrosine kinase inhibitors (TKI) and macromolecule monoclonal antibodies (mAb).

EGFR targeted agents are particularly relevant in the treatment of selected patients with NSCLC. Erlotinib and gefitinib were the early agents approved in this class and are the most studied in combination with brain RT. Newer generation agents, including osimertinib and afatinib have an overall response rate in the central nervous system (CNS) of over 80% to 90%. The optimal combination and timing of anti EGFR agents and brain RT remain controversial in the absence of prospective clinical trials that include these newer agents in combination with radiotherapy. NSCLC with the ALK fusion occurs in about 3% to 5% of patients. An additional 1% to 2% will have a ROS mutation. Similar to EGFR-positive patients, ALK- or ROS-positive patients respond well to targeted agents. There are no prospective studies to define the safety of brain radiation with ALK-targeted agents. Due to that fact, a short break during cranial radiation may be indicated.

Patients receiving immunotherapy (anti-PD-L1 and anti-PD-1 agents) and brain RT, have been reported to have improved response rates, CNS control and overall survival, especially when administered concurrent with radiosurgery. Be that as it may, multiple institutions are prospectively investigating the safety and optimal timing of these agents in the treatment of BM. For patients receiving intracranial RT for BM and immunotherapy for extracranial disease, most oncologist continue immunotherapy concurrently with radiation.

In an era of declining use of whole brain RT, focal radiation, including radiosurgery, offers additional advantages of minimizing the delay in administering systemic therapy. Since the clinical evidence to define the optimal integration of targeted therapy and immunotherapy and brain RT is lacking for most drugs, treating physicians are left to make pragmatic clinic decisions based upon extrapolations, preclinical study data and pharmacology. One practical strategy is to limit breaks for most agents to a few days or a week for whole brain RT and radiosurgery, and no breaks for some classes of drugs, such as immunotherapy checkpoint inhibitors.

Keywords: brain metastases radiotherapy, targeted therapy, immunotherapy, NSCLC

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S14 - WHY ARE WE NOT SUCCESSFUL IN TREATMENT OF SMALL CELL LUNG CANCER?

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Small cell lung cancer (SCLC) accounts for approximately 15-20% of all cases of lung cancer. It is characterized by aggressive biology due to the rapid growth, early chemo- and radiosensitivity, early occurrence of distant metastases, and 5- year survival rate of patients with extensive stage (ES) SCLC of less than 5%. Platinum- based chemotherapy, hyperfractionated thoracic radiotherapy, prophylactic cranial irradiation (PCI) and second- line topotecan have been the standard of care for more than 30 years. Numerous treatment strategies and systemic agents (over 60 agents including inhibitors of VEGF, IGFR, mTOR, EGFR, HGF and p53 vaccine) investigated in first- and second- line treatment of ES showed lack of efficacy, so SCLC has been referred to as „a graveyard for drug development“. Understanding the complex biology and mechanisms of resistance is crucial in the efforts to improve poor treatment outcomes of patients with SCLC.

Mechanisms of chemotherapy resistance

Intrinsic and acquired drug resistance has long been recognized as the main reason for chemotherapy failure. Drug resistance mechanisms in SCLC are: overexpression of multidrug resistance related proteins, abnormal expression of intracellular enzyme systems, apoptosis escape, abnormality of cell repair systems, cancer stem cells, etc. Data support the complex network of multiple factors contributing to drug resistance at the same time. Efforts have been made to improve the efficacy of chemotherapy but so far have not improved clinical outcomes. It is widely accepted that chemotherapy for SCLC has probably reached its plateau and further evaluation of chemotherapy variations is probably not warranted.

Lack of molecular alterations in SCLC as potential therapeutic targets

In contrast to non- small cell lung cancer (NSCLC), identifying therapeutic targets in SCLC has been challenging. These tumors typically carry a high mutation burden, largely attributable to heavy tobacco

exposure, with only 2% of cases occurring in never- smokers. Almost all SCLC tumors show genomic instability, with functional activation of both TP53 and RB1 being the most frequent ones, however, attempts to target these alterations have failed. Some alterations are currently untargetable (e.g. amplification of MYC family members which is observed in approximately 20% of SCLC), and some (PTEN loss, activating PI3K mutations, FGFR1 amplifications) are currently investigated. A cell surface ligand DLL-3 is upregulated in neuroendocrine cells; in SCLC it inhibits the Notch pathway, allowing for growth of aberrant neuroendocrine cells. Rovalpituzumab- tesirine (Rova-T) is an antibody- drug conjugate that inhibits DLL-3 expression. The results of the TRINITY phase 2 trial with Rova-T showed overall response rate (ORR) up to 30% in some patient subsets, but subsequent phase III trials MERU and TAHOE failed to meet their primary endpoints and were stopped after a futility analysis.

Lurbinectedin, a selective inhibitor of oncogenic transcription has been evaluated in the second- line setting in a phase II basket trial and showed the ORR of 35.2% and acceptable safety profile, so FDA granted priority review of this agent in February 2020. Despite early promising results, the combination of lurbinectedin with doxorubicin did not show OS benefit.

Targeting DNA damage- response pathway mediators, such as poly- ADP- ribose polymerase (PARP) and others, have demonstrated promising therapeutic opportunities, given the high expression of PARP1 in SCLC. Early- phase trials with PARP inhibitor veliparib in combination with chemotherapy showed conflicting results. It seems that combination of PARP inhibitors with immunotherapy could yield some benefit, as shown in the phase II trial of olaparib plus durvalumab.

Recent gene expression profiling of SCLC have led to a proposed categorization of four major subtypes of SCLC distinguished by differential expression of four key transcriptional regulators (ASCL1, NEUROD1, POU2F3 and YAP1). It remains to be seen whether this categorization would have predictive and prognostic impact for SCLC patients.

Modest immunotherapy efficacy in SCLC

Despite the high somatic tumor mutational rate, SCLC has a highly immunosuppressive phenotype. These tumors are likely to have low expression of the class I major histocompatibility antigens, low levels of tumor infiltrating lymphocytes (TILs) and low expression of PD-L1. In March 2019, an anti- PD-L1 antibody atezolizumab added to first- line platinum/etoposide (PE) chemotherapy was approved, given the 2- months OS benefit over chemotherapy alone, as shown in IMpower133 trial. Durvalumab, the PD-1 antibody was recently approved for the same indication given the results of the CASPIAN trial, which also showed 2 months OS benefit when added to PE. Two PD-L1 antibodies (pembrolizumab and nivolumab) were approved for the third- line setting, based on the durable response rates observed in CheckMate 032 trial and KEYNOTE-158 and 028 trial, respectively. The utility of PD-L1 expression as the useful biomarker in SCLC is currently unknown. It is compromised by its low prevalence, heterogeneous expression on SCLC tumor cells and the lack of clear correlation between PD-L1 expression and the efficacy of immunotherapy. It seems that high tumor mutational burden is more useful in predicting outcomes of patients treated with nivolumab alone or in combination with ipilimumab, as shown in biomarker analysis of the CheckMate 032 trial. Overall, the challenge with immunotherapy in advanced SCLC is two-fold. First, due to the high disease burden and rapid progression the time needed for response (typically 3-6 months) may exceed the OS of the patient. Second, checkpoint- inhibitor- treated patients are at higher risk of developing life- threatening immune- related toxicities since a variety of paraneoplastic immune- mediated syndromes are already associated with SCLC.

Brain as a *sanctuary site* for SCLC metastases

In SCLC CNS failure rates are approximated to be 50–60% at 2 years following diagnosis and are associated with poor prognosis. There is a clear role for PCI in LD-SCLC who demonstrate a complete response to chemotherapy with both local control and OS benefit. The routine use of PCI in ED-SCLC is less clear; it seems reasonable to consider PCI in patients with ED-SCLC upon response to initial chemotherapy. Whole brain radiotherapy (WBRT) is the most common treatment modality for SCLC brain metastases and there has been persistent interest in combining chemotherapy with radiation. However, a meta-analysis of 3 randomized control trials (n = 192) showed that chemotherapy is able to prolong PFS in patients with intracranial metastases from SCLC, but this does not translate to improve OS.

Conclusion

Recent insights into the biology of SCLC have promoted the development of molecular targeted and immunotherapy strategies. Continued focus on an integrated platform of basic discoveries and clinical translational research is needed for this particularly refractory disease.

Keywords: small cell lung cancer, treatment resistance, targeted therapy, immunotherapy, brain metastases

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S15 - CASE REPORT: TREATMENT OF ALK-POSITIVE LUNG CANCER

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Introduction: Anaplastic lymphoma kinase (ALK) mutation is a rare mutation in non-small-cell lung cancer (NSCLC), occurring in about 4 % of adenocarcinomas. The mutation is even more rare in squamous-cell carcinoma. But nevertheless, it provides an opportunity for targeted therapy with tyrosin kinase inhibitors (TKI).

ALK positive tumors are more common in younger patients, non-smokers and women than any other lung cancer.

According to the studies, targeted therapy gives our patients with advanced stage ALK positive tumors up to 7 years of overall survival.

Squamous cell ALK positive tumors have somewhat worse response rates to TKI targeted therapy, but additional research is required.

Case report: In autumn of 2017 a 64-year old female patient, a non-smoker, with no previous medical history, displaying persistent cough and shortness of breath, underwent a pulmonary exam. Performed thorax MSCT-scan revealed left sided upper lobe tumorous formation, with conglomerates of lymph nodes paratracheal left. Bronchoscopy found no malignant cells, therefore EBUS was performed with cytological confirmation of squamous-cell lung cancer.

Before the initial therapy, PET/CT scan was performed, and revealed positive retroclavicular lymph nodes on the left, mediastinal lymph nodes on both sides, and a suspected metastasis in pubic bone. The clinical stage of the tumor was IVA.

Initial therapy was a combination chemotherapy, that consisted of cisplatin and gemcitabine. After 4 cycles, reevaluation MSCT -scan revealed new metastasis in the right adrenal gland.

Since our patient was female and non-smoker, we requested mutation analysis, and found a rare ALK mutation in squamous-cell lung carcinoma.

As the ALK mutation was found, we started treatment with TKI, crizotinib, in the dose of 250 mg twice a day. After only 4 months of therapy the disease progressed. The size of the primary tumor was reduced, along with the lymph node status, but the metastasis in adrenal gland progressed. We decided to switch therapy to second line TKI, alectinib.

Our patient started therapy with alectinib in the dose of 600 mg twice a day, applied for a year until progression. After only one cycle of alectinib, the metastasis of the adrenal gland was almost not visible on the MSCT-scan, along with a significant regression of mediastinal lymph nodes. The disease was stable for 12 months. On the last reevaluation, the MSCT-scan showed progression in both mediastinal and abdominal paraaortal lymph nodes, and the metastasis in the adrenal gland progressed. The primary tumor remained unchanged.

During the therapy with TKI our patient had grade 1 neutropenia and fatigue. None of the side effects required dose reduction.

After progression we decided to continue the treatment with chemotherapy docetaxel, and 6 cycles were applied. After chemotherapy, the MSCT-scan revealed progression in mediastinal lymph nodes, and regression of abdominal lymphadenopathy and adrenal metastasis.

Radiotherapy of mediastinum in the total dose of 3000 cGy was performed subsequently. Our patient wanted a break from therapy afterwards. We respected her wishes, as the disease was stable.

After three months, the MSCT-scan revealed postirradiation changes along with progression in the adrenal gland.

We started treating with weekly vinorelbine in January of 2021, and are currently continuing the said therapy.

There is still a great deal of unknown, but according to previous case reports, squamous-cell ALK positive lung cancer has worse response rates to targeted therapy than adenocarcinoma.

Similar results were shown in our case report.

Keywords: non-small cell lung carcinoma, ALK mutation, targeted therapy (TKI)

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S16 - THE REINITIATION OF IMMUNOTHERAPY AFTER IMMUNOLOGICALLY CAUSED PNEUMONITIS - A CASE REPORT OF LUNG CANCER

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Lung cancer is the leading cause of cancer death with only 19% of cases alive 5 years after diagnosis. Patients with metastatic lung cancer who are eligible for immunotherapies survive significantly longer. Immunotherapies target immune checkpoints which cancers use to decrease immune activity. Anti-PD-1/PD-L1 immunotherapies are associated with specific toxicity profiles with relatively delayed onset and autoimmune nature. Generally, rates of any-grade pneumonitis for PD-1/PD-L1 monotherapy have been reported at or below 5%, and around 1% for high-grade pneumonitis. Median time to irAE onset from start of treatment has been reported at 2.5 months. Corticosteroids are the mainstay of treatment of most high-grade irAEs. Short-term use of corticosteroids to treat irAEs has not been shown to reduce antitumor efficacy. Patients should be tapered off corticosteroid slowly with resolution of symptoms before considering immunotherapy resumption. In this report we present a case of a 60 year old male patient diagnosed with stage IV metastatic lung adenocarcinoma in December 2019. The diagnosis was made on one of the ultrasound examinations of the neck after extirpation of the left ear squamous cell carcinoma. The diagnosis was metastatic lung adenocarcinoma of a lymph node which was PD-L1 positive in 80% of tumor cells and ALK, ROS1 and EGFR negative. The patient stopped smoking 5 years earlier (35 pack-years), did not complain of any difficulties, had a good appetite and did not lose weight. According to ECOG classification his performance status was 0. On physical examination he was breathing normally, with auscultatory normal breathing sounds. Chest X-rays showed bilaterally smaller inhomogeneous shadows and larger right hilus. Brain MSCT revealed no focal changes and thoracic and upper abdomen MSCT showed numerous nodular bilateral pulmonary metastases up to 18 mm in diameter. Thickened centrilobular septa were

also visible, mainly in the right upper lobe suspicious of lymphangiosis. There were enlarged lymph nodes in all stations of the mediastinum bilaterally up to 30 mm in diameter. The primary tumor could not be reliably separated from enlarged and fused lymph nodes and was most likely located in the upper pole of the right hilus: a polycyclic formation measuring 37x37 mm. There was no dissemination in the upper abdomen and skeletal scintigraphy was normal. According to all relevant guidelines' recommendations for the treatment of disseminated lung adenocarcinoma whose more than 50% of cells express PD-L1 without positive driver mutations, the patient was offered treatment with pembrolizumab - a monoclonal antibody to PD-1. Treatment was started in January 2020 and the first CT control was done after 3 cycles of pembrolizumab. The CT showed a steady state of the neoplasm, intrapulmonary disseminates and enlarged lymph nodes, but progression of parenchymal consolidations and reticulations corresponding to concomitant pneumonitis. The patient did not complain of any difficulties, there were no signs of respiratory failure, so pneumonitis was assessed to be of grade ½. The patient was prescribed methylprednisolone 32 mg/day for 7 days and then tapered by 8 mg/week over 2 weeks, then by 4 mg/week over 4 weeks. During that time his vital capacity was stable (75%), carbon monoxide diffusing capacity improved from 65% to 73%, and chest X-ray was stationary. After discussion on multidisciplinary tumor board the fourth cycle of pembrolizumab was administered in April 2020. In the meantime he stopped taking methylprednisolone and immediately afterwards began to feel shortness of breath. Thoracic MSCT revealed interstitial changes in progression and were predominantly attributed to lymphangiosis, but component of grade 3 pneumonitis could not be ruled out. The rest of the neoplasm was without detectable difference. Pembrolizumab was then discontinued and methylprednisolone reintroduced at a dose of 16 mg/day leading to a significant reduction in symptoms, improvement in pulmonary function tests and chest X-ray. The entire time the patient was afebrile, with no increase in laboratory markers of inflammation, and the PCR of nasopharyngeal swab for SARS-CoV2 was negative. In May 2020. specific oncologic treatment was continued in the form of platinum based chemotherapy. In conclusion, pneumonitis as a side effect of immunotherapy was difficult to distinguish from tumor lymphangiosis in our patient. The chronology of the occurrence of symptoms, pathological signs, and the response to treatment were instructive. Unfortunately, the reoccurrence of high-grade pneumonitis after reintroduction of pembrolizumab led to treatment discontinuation and prevented the desired therapy effect.

Keywords: lung adenocarcinoma, immunotherapy, pembrolizumab, pneumonitis.

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GASTROINTESTINAL TUMORS

S17 - PERIOPERATIVE TREATMENT OF GASTRIC CANCER AND ITS IMPLEMENTATION IN CROATIA

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Adenocarcinoma of the gastroesophageal junction (GEJ) and the gastric cancer is a disease associated with poor outcome in most patients.

Perioperative chemotherapy became a standard of care for resectable adenocarcinoma of the upper GI tract in most Western European countries based on the results of the MAGIC-trial, and it was approved in several Asian trials. Including patients with Stage II or III resectable adenocarcinoma of the stomach, GEJ and lower esophagus, this study demonstrated the benefit from chemotherapy with three cycles of the ECF-regimen (epirubicin, cisplatin, 5-fluorouracil) applied before and after surgery as compared to surgery alone. The results of the MAGIC-study were essentially supported by the French ACCORD-trial. In the ACCORD-trial there was a significant higher R0-resection rate and a non-significant decrease in lymph node metastasis in the chemotherapy arm.

Summarizing, both studies showed that preoperative chemotherapy can induce downstaging and enhanced the possibility of potentially curative R0-resection, thus increasing the probability of disease-free survival and overall survival.

The next step was perioperative chemotherapy. The combination of docetaxel, cisplatin, and fluorouracil improved efficacy in gastric cancer, but was associated with substantial toxicity. This study was designed to incorporate docetaxel into a tolerable biweekly (once every 2 weeks) oxaliplatin-based chemotherapy regimen

Between Aug 8, 2010, and Feb 10, 2015, 716 patients were randomly assigned to treatment in 38 German hospitals or with practice-based oncologists. 360 patients were assigned to ECF/ECX and 356 patients to FLOT. In FLOT arm, patients received 4 cycles of chemotherapy before, and 4 cycles after surgery.

Overall survival was increased in the FLOT group compared with the ECF/ECX group (hazard ratio [HR] 0.77; 95% confidence interval [CI; 0.63 to 0.94]; median overall survival, 50 months [38.33 to not reached] vs 35 months [27.35 to 46.26]).

At the same time it became evident that adjuvant chemotherapy could only be applied in about half of the patients, which may lead to the hypothesis that the undisputable benefit from perioperative chemotherapy can be induced by the preoperative part of treatment.

The NeoFLOT-study therefore investigates the application of prolonged neoadjuvant chemotherapy (NACT). Patients with T3, T4, and/or node-positive adenocarcinoma were eligible for this multicenter phase II trial. NACT consisted of 6 cycles of oxaliplatin 85 mg/m², leucovorin 200 mg/m², 5-fluorouracil 2600 mg/m² and docetaxel 50 mg/m² (FLOT) every 2 weeks without adjuvant chemotherapy. The primary endpoint was R0-resection rate. This study indicates that intensified NACT with 6 cycles of FLOT is highly effective and tolerable in resectable GEC especially in intestinal type of tumor.

The CRITICS trial aimed to compare perioperative chemotherapy with preoperative chemotherapy and postoperative chemoradiotherapy in patients with resectable gastric adenocarcinoma. Postoperative chemoradiotherapy did not improve overall survival compared with postoperative chemotherapy in patients with resectable gastric cancer treated with adequate preoperative chemotherapy and surgery. It is explained with poor postoperative compliance in both group, so we need further trials.

According to this, perioperative chemotherapy is incorporated in all guidelines for treatment of gastric cancer. All patients should be treated in centers with good multidisciplinary approach and experience in treatment of these patients.

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S18 - METASTATIC COLON CANCER - IS THERE ROOM FOR PERSONALIZED TREATMENT?

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Today's basis for the treatment of metastatic colorectal cancer (mCRC) continues to be cytotoxic therapy based on 5-fluorouracil, irinotecan and oxaliplatin. The main objection to this type of therapy is the non-selective use and unacceptable toxic profile, and it was clear that an attempt was being made to seek a different therapeutic approach aimed at the individual patient and the characteristics of the tumor. The importance of gene alterations in colon cancer has been recognized through numerous preclinical and translational studies, and recent advances in the next-generation sequencing methods have enabled accessible, rapid, and comprehensive molecular profiling. In doing so, we have improved our understanding of molecular diversity with a consequent direct impact on various new treatment options for advanced colon

cancer. In this regard, testing of biomarkers, such as RAS, BRAF, HER2, MSI and NTRK fusions is of particular importance.

Prognostic and predictive significance obtained by identifying the RAS mutation in approximately 40% of mCRC affected different types of treatment outcomes (response rate, progression free survival, and overall survival). Namely, RASwt tumors are sensitive to the use of anti EGFR monoclonal antibodies such as chimeric cetuximab or fully humanized panitumumab. Efficacy is independent of use in monotherapy or in combination with cytotoxic therapy, and this therapy has become the standard in everyday clinical practice for the last 20 years, especially in clinical situations with the need to achieve a rapid and pronounced therapeutic response.

The BRAF V600E mutation is present in 8–10% of mCRC patients and is associated with more aggressive clinical course, poorer response to cytotoxic therapy, and resistance to anti-EGFR therapy (due to constitutional activation of the MAPK signaling pathway downstream of RAS). Consequently, in clinical practice, the use of intensified chemotherapy protocols (5-FU / LV, oxaliplatin and irinotecan) with anti-VEGF therapy with bevacizumab was positioned for this group of patients. Testing for the BRAF V600E mutation is widely available in everyday work, and it is interesting to note that carriers of the non-V600 BRAF mutation (2-5% of them) represent a different clinical subtype, have a better prognosis, and may respond to anti-EGFR therapy. An attempt to administer monotherapy with BRAF inhibitors such as vemurafenib, in mCRC as opposed to, for example, melanoma, did not lead to a clinically significant outcome. The reason is found in the activation of additional signaling pathways on the EGFR signaling pathway, which is of great importance in mCRC. This finding was the basis for the combined use of cetuximab and irinotecan with vemurafenib (ORR 35%, PFS 7.7 months) in patients previously treated with different chemotherapy protocols (*Hong et al. 2016*). Following this research, an attempt was made to apply the so-called triplet therapy (encorafenib, binimetinib and cetuximab) which, in addition to EGFR and BRAF, also targets MEK in a population of patients previously treated with at least one line of therapy. An ORR of 41% was achieved, and it was concluded that binimetinib supplementation did not contribute to the efficacy of encorafenib and cetuximab (BEACON study). There are also studies with dabrafenib, trametinib, and panitumumab, with a best response of 21% and a PFS of 4.2 months (*Corcoran et al. 2018*). The above information represents a strong clinical rationale in the population of patients with BRAF V600E mutant tumors that have progressed to a single treatment line.

HER2 amplification is found in 3 - 5% of patients with RAS wt mCRC. By combining trastuzumab and lapatinib in patients with mCRC refractory to previous standard therapy, an ORR of 30% was achieved (HERACLES study). By combining pertuzumab and trastuzumab in patients with mCRC refractory to previous standard therapy, an ORR of 32% and a PFS of 2.9 months were achieved with a mean response time of 5.9 months (MyPathway study). Numerous studies are underway to block the HER2 signaling pathway (such as the combination of tucatinib and trastuzumab (MOUNTAINEER study) or the administration of TDM-1 after progression to trastuzumab and lapatinib (HERACLES-RESCUE)).

In about 5% of patients with mCRC, we can find tumors with high microsatellite instability or with a lack of repair mechanism of misaligned bases. With the use of pembrolizumab in patients with mCRC refractory to previous standard therapy, an ORR of 57% was achieved (*Le et al. 2016*). This was followed by a series of studies with nivolumab or in combination with ipilimumab with excellent responses (eg 60% ORR in first-line combination use - Checkmate -142). However, a 16.5-month PFS score compared to an 8.2-month comparison of first-line pembrolizumab vs. standard polychemotherapy with a 40% reduction in disease risk of recurrence in mCRC patients (KEYNOTE - 177) is to be singled out. This year, we expect the results of overall survival, although these results are a strong basis for changing clinical practice.

NTRK fusions are rare (<1% of mCRC patients), slightly more common in RAS wt, right-sided MSI-H tumors, and elderly patients. They represent a poor prognostic parameter with an overall survival of 15 months. Larotrectinib and entrectinib are interesting tumor agnostic therapeutic partners in this situation.

It is obvious that we have achieved a certain maximum in the treatment outcomes of patients with mCRC by combining the therapeutic possibilities so far. Additional information on the biology of the disease that we obtained through gene profiling opened new therapeutic possibilities, but also a better insight into the prognosis of the disease. This will further influence the personalized approach to each individual patient, the development of a treatment plan, better outcomes, and better tolerance of therapy.

S19 - CONTROVERSIES IN TREATMENT OF RECTAL CANCER

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The most common newly diagnosed cancer in Croatia in 2020 was colorectal cancer with 3706 new cases. In the same year, rectal cancer alone was the 7th most common cancer in the world and the 10th leading cause of cancer death in the world.

Over the last three decades, in most countries, a standard of treatment has been neoadjuvant chemoradiotherapy (nCRT) (50.4 Gy in 28 fractions with 5-fluorouracil (5-FU) or capecitabine) followed by total mesorectal excision (TME) 6-8 weeks after nCRT and then postoperative adjuvant chemotherapy (aCT). In Sweden short-course neoadjuvant radiation (25 Gy in 5 fractions) followed by TME one week after the end of neoadjuvant radiotherapy (nRT) resulted in better overall survival (OS). The standard approach reduced the frequency of local recurrence to 5-10%. However, the 5-year cumulative incidence of distant metastases remained high (30-35%) and is the leading cause of death from rectal cancer.

Magnetic resonance imaging (MRI) should be performed prior to treatment to precisely detect patients requiring nRT/nCRT, and again after neoadjuvant treatment to assess treatment efficacy. The circumferential resection margin (CRM), extramural vascular invasion, multiple nodal involvement and T4 are poor prognostic factors for local recurrence and OS.

Data from clinical trials does not support the addition of oxaliplatin, irinotecan and targeted therapy to fluoropyrimidine concurrently with RT. The results of Stockholm III trial revealed that short-course RT with surgery delayed for 4-8 weeks is a safe option with similar oncological outcomes to short-course RT with immediate surgery and long-course RT.

It has been recognized that patients with pathological complete response (pCR) have better outcome. As about 15-20% of patients have pCR after standard treatment, the concept of “watch and wait (WW)” has been arisen in patients with a clinically complete response (cCR). Digitorectal, endoscopic and radiological examinations are necessary for cCR assessment. Local relapse after cCR occurs in about 20-30% of cases, most often during the first 2 years of follow-up (> 80%), located in the rectal wall and therefore, in a high percentage can be cured by “salvage surgery”. In studies, the first assessment is usually done 6-8 weeks after nCRT and then further every 3-4 months. This is certainly a good option for individual patients although we do not yet have the results of a prospective, randomized study that has shown the same efficacy as radical surgery after nCRT in cCR. However, a completely different approach has been investi-

gated in radiotherapy-free trials (PROSPECT). Recently, in FORWARC trial, mFOLFOX6, with and without RT, did not significantly improved 3-year disease-free survival (DFS) versus 5-FU with RT in patients with locally advanced rectal cancer.

Although heterogeneous older studies showed improved survival with aCT, based on the results of recent clinical studies (I-CNR-RT, PROCTOR-SCRIPT, EORTC 22921, CHRONICLE, ADORE) this benefit has not been strongly demonstrated in patients treated with nRT/nCRT before surgery. In addition, only 50% of patients received planned aCT. Therefore, with the aim of improving OS and DFS as well as compliance, the concept of total neoadjuvant therapy (TNT) has been developed. There are two main modes of TNT: application of CT after nCRT (consolidation) or before nCRT (induction). Recently, in patients with high-risk locally advanced rectal cancer, randomized phase III trial RAPIDO showed that short-course RT followed by 18 weeks of chemotherapy (CAPEOX or FOLFOX) before surgery decreased the disease-related treatment failure by 6.7% compared with nCRT with or without aCT. The probability of distant metastases was reduced by 6.8%. In the experimental arm group 28.4% of patients had pCR compared to 14.3% in the control arm. The PRODIGE 23 phase III trial investigated six courses of mFOLFIRINOX followed by nCRT, surgery and aCT 12 weeks versus standard approach in patients with stage II and III. Three-year DFS was improved in the experimental arm (75.7% vs. 68.5%, HR 0.69) as well as 3-year metastasis-free survival (MFS) (78.8% vs. 71.7%, HR 0.64). The pCR was more than doubled in the experimental arm (27.5% vs. 11.7%). The OPRA trial (phase II) compared induction and consolidation mode. Besides, according to the protocol, patients with response to therapy had the option of WW. There were no difference in DFS and distant metastases-free survival (DMFS). However, patients who received CRT and consolidation CT were more likely to preserve rectum ($p = 0.007$).

In phase II and III trials treatment compliance was 80-90% with nCT, and pCR rate was increased in comparison to standard treatment.

It seems that we have entered a period of personalized medicine in treatment of rectal cancer. The goal of improvement of treatment outcomes persists and is accompanied by the goal of avoiding overtreatment and unnecessary toxicity in each individual patient. How to distinguish a patient in whom therapy should be intensified from one in whom therapy should be desintensified? How to early identify patients who do not respond to treatment? We hope that studies will answer this questions during the next years. Certainly, it is important to continue evaluating surrogate and clinical endpoints of clinical studies.

Keywords: neoadjuvant chemoradiotherapy, neoadjuvant short-course radiotherapy, watch and wait, total neoadjuvant therapy

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S20 - THE MOST RECENT ADVANCES IN IMMUNOTHERAPY WITH CHECKPOINT INHIBITORS IN GASTROINTESTINAL CANCERS

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Immune checkpoint inhibitors targeting programmed death-1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) has revolutionized anti-tumor treatment in various tumor types in recent years.

In metastatic colorectal cancer (mCRC), the clinical benefit is limited in patients with deficient mismatch repair (dMMR)/high levels of microsatellite instability (MSI-H), comprising approximately 5% of cases. Current studies with immune checkpoint inhibitors are moving forward to the first-line treatment. The clinical benefits of pembrolizumab versus standard chemotherapy as a first-line treatment in 307 patients with dMMR/MSI-H mCRC were demonstrated in the randomized phase III KEYNOTE-177 trial. Treatment with pembrolizumab resulted in doubling progression free survival (PFS), compared with chemotherapy (median = 16.5 vs. 8.2 months; HR 0.60; $P = .0002$). Overall response rates (ORRs) were significantly higher with pembrolizumab (44% vs. 33%), a complete response was observed in 11% of patients receiving pembrolizumab, compared with 3.9% of those receiving chemotherapy. 83% of pembrolizumab responders were still responding after 2 years or longer, compared to the 35% of the chemotherapy responders. The rates of grade 3-5 treatment-related adverse events (AEs) were 22% for pembrolizumab and 66% for chemotherapy. The overall survival (OS) data are not yet mature. In the phase II CheckMate-142 trial which was conducted to evaluate the treatment efficacy of nivolumab in 74 chemorefractory patients with dMMR/MSI-H mCRC (cohort 1) the estimated rates at 12 months were 50% for PFS and 73% for OS. This trial included a cohort of 119 pretreated patients with dMMR/MSI-H mCRC who received nivolumab and ipilimumab. Indirect comparisons of nivolumab plus ipilimumab cohort with the nivolumab monotherapy cohort revealed promising results for nivolumab plus ipilimumab: ORR, 55% vs. 31%; 12-month PFS rate, 71% vs. 50%; 12-month OS rate, 85% vs. 73%. Combined treatment with nivolumab and ipilimumab versus nivolumab monotherapy resulted in an increased rate of treatment-related AEs (grade 3 to 4 = 32% vs. 20%). Promising preliminary results were obtained when nivolumab and ipilimumab were combined in the first-line treatment of 45 patients with MSI-H/dMMR mCRC in the cohort 3 of this trial. ORR of 69% and a CR of 13% were observed. The 24-month PFS and OS rates were 74% and 79%.

Immunotherapy has also demonstrated promising efficacy and good tolerance in gastroesophageal cancer. The most recent advances were noted in the first-line and adjuvant treatment. In the phase III CheckMate-649 trial, nivolumab in combination with chemotherapy demonstrate superior OS and PFS as first-line treatment for previously untreated HER-2 negative unresectable or metastatic gastric cancer (70% of the population), gastroesophageal junction cancer and esophageal adenocarcinoma. 1581 patients were randomly assigned to: nivolumab plus chemotherapy (XELOX/FOLFOX), chemotherapy alone or nivolumab plus ipilimumab. Of these patients 60% had tumors with a PD-L1 Combined Positive Score (CPS) ≥ 5 expression. The dual primary endpoints were OS and PFS in patients with a PD-L1 CPS ≥ 5 . A statistically significant OS benefit was seen in patients whose tumors expressed a PD-L1 CPS ≥ 5 and in all randomly assigned patients. Median OS was 14.4 months with nivolumab plus chemotherapy vs 11.1 months for chemotherapy in the PD-L1 CPS ≥ 5 population (HR 0.71; $P < .0001$). The differences were also statistically significant for the PD-L1 CPS ≥ 1 population (HR = 0.77; $P = .0001$) and for all randomly assigned patients (HR = 0.80; $P = .0002$). Median PFS was 7.7 and 6.1 months (HR = 0.68; $P < .0001$) in the PD-L1 CPS ≥ 5 population. Results for the nivolumab and ipilimumab were not yet presented. The ATTRACTION-4 phase II/III trial randomly

assigned 724 Asian patients with gastric or gastroesophageal junction cancer to first-line treatment to nivolumab plus chemotherapy (oxaliplatin plus S-1 or capecitabine) vs. chemotherapy alone. Median PFS was significantly improved with the combination, from 8.3 months with chemotherapy to 10.5 months with nivolumab plus chemotherapy (HR = 0.68; P = .0007). At the final analysis, with a median follow-up of 27 months, OS was similar, 17.2 and 17.5 months. The incidence of grades 3 to 5 treatment-related AEs was 57.9% with nivolumab plus chemotherapy and 49.2% with chemotherapy alone. KEYNOTE-590 is a randomized, international, double-blind study of first-line pembrolizumab + chemotherapy vs. chemotherapy alone in 749 patients with unresectable or metastatic adenocarcinoma or esophageal squamous cell carcinoma (ESCC) or Siewert type 1 esophagogastric junction adenocarcinoma (GEJC). Pembrolizumab + chemotherapy vs chemotherapy was superior for OS in patients with ESCC CPS ≥ 10 (median 13.9 vs 8.8 months; HR 0.57; P < 0.0001), ESCC (median 12.6 vs 9.8 months; HR 0.72; P = 0.0006), CPS ≥ 10 (median 13.5 vs 9.4 months; HR 0.62; P < 0.0001), and all patients (median 12.4 vs 9.8 months; HR, 0.73, P < 0.0001). PFS was superior with pembro + chemotherapy vs chemotherapy in ESCC (median 6.3 vs 5.8 months; HR 0.65; P < 0.0001), CPS ≥ 10 (median 7.5 vs 5.5 months; HR 0.51; P < 0.0001), and all patients (median 6.3 vs 5.8 months; HR 0.65; P < 0.0001). Confirmed ORR was 45.0% vs 29.3% (P < 0.0001) in all patients. Grade 3-5 drug-related AE rates were 72% vs 68%. CheckMate-577 is the first randomized, double-blind, phase III study to report the efficacy and safety of a checkpoint inhibitor in the adjuvant setting after trimodality therapy for adenocarcinoma or esophageal squamous cell carcinoma or GEJC. 794 patients with resected (R0) stage II/III EC/GEJC who received neoadjuvant chemoradiotherapy and had residual pathologic disease were randomized 2:1 to nivolumab or placebo. Maximum treatment duration was 1 year. Approximately 70% of patients had adenocarcinoma and almost 60% had a pathologic lymph node status $\geq ypN1$ in both groups. At a pre-specified interim analysis, adjuvant nivolumab showed a statistically significant improvement in disease free survival (DFS) vs placebo (HR 0.69, P = 0.0003); median DFS was doubled (22.4 vs 11.0 months). The majority of treatment-related AEs were grade 1 or 2.

Keywords: immune checkpoint inhibitors, gastrointestinal cancers, microsatellite instability-high metastatic colorectal cancer, pembrolizumab, nivolumab

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S21 - THE ROLE OF TARGETED AND RADIONUCLIDE THERAPY IN THE CONTEMPORARY TREATMENT OF NEUROENDOCRINE NEOPLASMS

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Introduction: Neuroendocrine tumors (NETs) are neoplasms that arise from neuroendocrine cells. Their peculiarity is that they are classified collectively because they share similar behavior and have common microscopic features (such as the presence of secretory granules in cells, production of biogenic amines and polypeptide hormones). Since some of them produce hormones, they can lead to symptoms associated with increased secretion of the same. However, 90% of cases are so-called non-functional tumors in which symptoms of hormone hypersecretion are not present. Neuroendocrine cells are present not only in the endocrine glands, but also in all other tissues of the body. NETs most commonly occur in the small intestine (55%), lungs (20–25%), pancreas (17–20%), and colorectum (<5%), while other sites are less common (e.g., thyroid, adrenal gland, cervix, ovaries, skin...). Metastases most commonly occur in the liver, lungs, and bones. Historically, small bowel NETs were first distinguished from other tumors in 1907, and were termed carcinoids (*cancer-like*) because of the specificity of the microscopic appearance of the malignant tumor, while biological behavior is benign (given their slow growth). However, in 1938, it became known that there are also very malignant forms of NETs. Therefore, the name carcinoid is no longer recommended for use. Today, the most commonly used classification of NETs is according to the World Health Organization, which divides NETs by grade into tumors of grade 1 (Ki-67 <3% and <2 mitosis / mm²), 2 (Ki-67 3-20% and 2-20 mitosis / mm²) and 3 (Ki-67 >20% and >20 mitosis / mm²). Grade 3 tumors have traditionally been considered neuroendocrine carcinomas, but today it is known that this is a diverse population of patients and within this group attempts are made to distinguish patients with neuroendocrine tumors of grade 3 and those with neuroendocrine cancers, in order to treat them differently.

Diagnosis: In the diagnosis of NETs, standard imaging and other diagnostic methods are used, depending on the location of the primary tumor: computed tomography, magnetic resonance imaging, ultrasound and endoscopy (including endoscopic ultrasound). In addition to these standard methods, there are those that are used specifically in this disease. Namely, many NETs (especially those of grades 1 and 2) show the expression of somatostatin receptors, thus giving a specific target for diagnosis (and therapy). Octreotide is a synthetic modification of somatostatin, and can be used for this purpose in the OctreoScan method (somatostatin receptor scintigraphy). OctreoScan uses an intravenously administered radioactive substance (In-111) bound to octreotide, in order to detect tumors that accumulate octreotide. It can also be used to monitor the effect of treatment. Nowadays, Tc-99m-tectrotide (tectrotide scan) is more commonly used, due to its lower cost. It is also possible to do a SPECT / CT tectrotide scan. Furthermore, scintigraphy with PET offers even better resolution with the possibility of obtaining 3D images (so-called Ga-68 receptor PET / CT), and today is the method of choice in large NET centers. Standard PET / CT with FDG is used in high-grade NETs (neuroendocrine cancers), which in most cases do not have somatostatin receptor expression. Tumor markers are also in use, such as chromogranin A (CgA), 5-hydroxyindoleacetic acid (5-HIAA) in 24-hour urine, neuron-specific enolase (NSE), pancreatic polypeptide (PP), and others (the choice of tumor marker depends on the primary tumor location). It should also be noted that most NETs occur spontaneously, but can also occur as part of genetic syndromes such as MEN1 and MEN2, von-Hippel Lindau syndrome, and neurofibromatosis.

Treatment: In the case of functional tumors with symptoms of increased hormone secretion, relief of symptoms can be achieved with somatostatin analogues (octreotide, lanreotide). For their use, expression of somatostatin receptors on the tumor cells is necessary, proven by somatostatin receptor scintigraphy or other adequate method, otherwise the therapy will have no effect. These drugs can also anatomically stabilize or shrink the tumor, as shown by the earlier PROMID clinical study - the average tumor stabilization was 14.3 versus 6 months for placebo. Therefore, somatostatin analogues are also a good choice in the first line therapy of non-functional NETs, especially in patients with grades 1 and 2. In the second line therapy or in patients who have a negative somatostatin receptor scintigraphy test, we usually have a choice between chemotherapy and targeted therapy. Regarding chemotherapy, a combination of capecitabine and temozolomide is most commonly prescribed, while streptozocin is less commonly used in combination with 5-fluorouracil. Everolimus and sunitinib are available targeted therapy drugs, according to previous clinical trials SUN1111 and RADIANT-3. The choice of therapy depends, among other parameters, on the location of the primary tumor (for example, highest level of evidence for sunitinib is in pancreatic NETs), general condition of the patient and his/her preferences. In neuroendocrine cancers, cisplatin and etoposide chemotherapy (protocol for NETs) remain the standard. In the second or subsequent lines of treatment, the use of peptide receptor radionuclide therapy (PRRT) is also an option. This method uses a radionuclide (Lu-177, Y-90 or In-111) bound to a peptide / hormone administered intravenously. It is a type of precision radiation in which a radionuclide binds to somatostatin receptors, enters a tumor cell and damages it with radiation. PRRT is a highly effective and accurate therapy for tumors with high somatostatin receptor expression, and has minimal side effects because radiation is absorbed in the tumor area while by-products are excreted in the urine. The effect is gradual, and it has been shown that cell death can last up to 2 years after administration. It is mainly used in low and medium grade tumors.

Keywords: neuroendocrine tumor, neuroendocrine cancer, peptide receptor radionuclide therapy, targeted therapy, everolimus, sunitinib.

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S22 - ANAL CANCER – CASE PRESENTATION

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Anal cancer is considered a rare cancer, representing approximately 1-2% of malignancies occurring in the gastrointestinal tract. According to the Croatian National Cancer Registry there were 48 newly diagnosed patients (25 males and 23 females) in 2018. We report the case of a 40-year-old female with anal cancer related to infection with Human Papilloma Virus (HPV).

She presented to a general hospital in her hometown, with history of bloody stools and abdominal discomfort. Her symptoms started six months prior, and her family doctor treated her with hemorrhoid ointment. Digital rectal examination detected an anal tumor; biopsy specimen indicated it was a squamous cell carcinoma. At least five years prior to current diagnosis she was in annual gynecologist checkups due to HPV+ p16+ cervical intraepithelial neoplasia grade II/III. Pelvic magnetic resonance (MRI) described tumor, with infiltration of the anterior part of the circumference of the anal wall, possibly infiltrating surrounding adipose tissue and vagina, with one enlarged lymph node on both sides in the mesorectal adipose tissue. Computed tomography of thorax, abdomen and pelvis showed no distant metastases, so the patient was staged as T4N1M0, stage IIIc (AJCC-TNM 8th). She was offered immediate surgery - abdominoperineal resection (APR). Not wanting colostomy, she came to our Institution for a second opinion and after presentation on Multidisciplinary tumor board (MDT) for digestive tumors, it was decided to perform definitive concurrent chemoradiotherapy. She received tumor dose of 4500 cGy to pelvis and inguinal lymph nodes and 900 cGy boost to primary tumor, concurrently with mitomycin-C on day 1 and 29 and continuous infusion of 5- fluorouracil 1000 mg/m² /day on days 1-4 and 29-32.

Two months after completing the planned treatment, MRI showed complete regression. In the second year of follow-up a pelvic MRI described local recurrence above the anal sphincter and two enlarged lymph nodes in the right inguinal area. Biopsy confirmed the diagnosis of squamous cell carcinoma, HPV+, p16+. She had no signs of distant metastases. After discussion on the MDT, she was presented with surgical options - APR and dissection of inguinal lymph nodes. Respecting the patient's wish not to receive a colostomy, she was treated with local ablative radiotherapy (SBRT, 30 Gy in 5 fractions on the tumor recurrence) and dissection of inguinal lymph nodes.

In conclusion, even though it is a rare type of cancer, anal cancer should not be overlooked in everyday practice, especially in cases of pre-existing HPV infection. Decision on further treatment should be made on MDT and discussed with the patient. Since local recurrence develops in 10-30% of the cases, SBRT may be an alternative to surgery in highly selected cases with low volume disease, in order to maintain the patient's quality of life.

Keywords: anal cancer, HPV, SBRT, multidisciplinary tumor board.

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S23 - MULTIMODAL AND MULTIDISCIPLINARY APPROACH TO PATIENT WITH HEPATOCELLULAR CARCINOMA: A CASE REPORT

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Background: In the past two decades incidence of hepatocellular carcinoma (HCC) has been increasing worldwide. Although, lately many improvements were made in different treatment modalities, relative 5-year survival rate remains less than 20% and in advanced stages even less than 15%. Here we present a patient treated with different modalities depending on stage and possibilities at the time.

Case report: In 2012, a 70-year-old male, diabetic with arterial hypertension, without known liver disease, was diagnosed with HCC - BCLC stage A. Following biopsy, surgical resection of two focal lesions in liver segments V and VI was made. Histology report confirmed well-differentiated HCC with microvascular invasion and steatohepatitis with mild fibrosis. Surveillance imaging in February 2016 described new multiple hypervascular lesions and alpha fetoprotein (AFP) rise, indicating HCC recurrence. At first, treatment with radiofrequency ablation was considered, which was not possible due to proximity of the diaphragm. Liver transplantation as an alternative therapeutic option was also dismissed due to microvascular invasion on initial biopsy report and suspicion of dissemination in one lymph node in the right phrenicocardial region on PET-CT scan. Further treatment was continued in December 2016 with transarterial chemoembolization with doxorubicin-eluting beads (TACE-DEBDOX). This procedure was performed three times successfully until progression was noticed. In June 2017 liver and lung metastases were detected on CT scan with further AFP increase, so first line treatment for metastatic disease with sorafenib was started. After twenty days, treatment was complicated with leukocytoclastic vasculitis and paused until full resolution. Afterwards the patient continued sorafenib treatment until progression nine months later. Second line treatment with regorafenib was started in September 2018. It was well tolerated with mild side effects (flatulence and rash). Four months later, further progression was seen on CT scans. Systemic treatment was discontinued and best supportive care was recommended as all treatment methods, available to us at the time, were exhausted.

Conclusion: Most treatment options are most effective in early stages of HCC. Therefore, more effort should be put into prevention of liver diseases and early detection and treatment of HCC. The BCLC classification system still represents a basis for decision guidance facilitating timely surgical, interventional radiological and non-interventional procedures. On the other hand, new and better systemic therapies for advanced disease are becoming available to clinicians which will undoubtedly result in a change in the therapeutic algorithm as well.

Keywords: HCC, multidisciplinary approach, multimodal approach, locoregional therapy, systemic therapy

S24 - HOW TO BEAR AND ENDURE ILLNESS?

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In this presentation we are discussing difficulties experienced by oncological patients, from their inner perspective, beside the struggle with the severe illness itself. Hereby are also being discussed subjects such as thoughts and feelings which connect patients with their surroundings – their significant others, that is family – a professional medical team and medicine as a system of principles. It is important to see how psychological states of patients influence the medical staff and transfer to them. And finally, we ask ourselves the question: what are we going to communicate to our patients, both verbally and non-verbally, as professionals and as persons?

Keywords: cancer; verbal - nonverbal communication; endure illness; professional team

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S25 - BURNOUT AMONG HEALTH CARE PROFESSIONALS IN COVID19 PANDEMIC

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Burnout is a longstanding problem for years, and the Covid-19 pandemic has exacerbated the problem.

In a survey of NEJM Catalyst Insights Council members in October 2020, 70% of respondents say that they anticipate health care provider burnout at their organization will get worse in the next two to three years, a period in which Covid-19's impact is likely to be greatly reduced (Weiner 2021). Only 9% say they expect things will get better, the data suggests that burnout will continue unless comprehensive organizational and systemic changes are made.

According to responses from Insights Council members (Weiner 2021) who are clinicians, clinical leaders, and executives at organizations around the world that are directly involved in care delivery, phy-

sicians (according to 90% of respondents), nurses (89%), and advanced practice providers (79%) have more serious or moderate problems with burnout than do clinical leaders (58%) or executives (43%).

The psychological traumatic impact of COVID-19 in frontline and non-frontline health care provider is a great issue, as emerged by almost all world studies (Kang et al., 2020; Tan et al., 2020).

Particularly, being female, younger, a frontline worker, a nurse, having less work experience, exposure to infected people, poor social support, difficult access to psychological material, insomnia and physical symptoms are all risk factors for traumatic symptoms.(Chew et al., 2020; Kang et al., 2020).

According to Insights Council members, the top two factors driving burnout are administrative burden and infrastructure, which includes information technology such as electronic medical records. These are well-known contributors to burnout, and they continue to be resistant

The top three manifestations in the survey that increased due to Covid-19 are anxiety and sadness, isolation, and difficulty concentrating (Romeo et al. 2020; Shah et. al. 2020.).

A clinical leader writes, *I think the biggest factor that drives burnout in physicians is the lack of autonomy/control over our lives. The second biggest factor is the way the administrative tasks of medicine have fallen to clinicians. In what other field does IT decrease productivity?*

Only 5% of respondents say there is no way to mitigate Covid-19 burnout other than to wait for a vaccine, showing that 95% think that burnout can be remedied to some degree. A higher incidence of executives (69%) and clinical leaders (64%) than clinicians (54%) indicate teamwork and coordinated care as top ways to mitigate burnout.

Burnout is a syndrome resulting from chronic work-related stress, which consists of three sequential components: emotional exhaustion, depersonalisation, and low personal accomplishment.

Burnout is negatively correlated to professional quality of life (QoL) and has been linked to reduced quality of care, more errors, job withdrawal, and absenteeism (Shanafelt et al. 2020), so, the organization should focus on fixing the system that is causing the burnout.

This includes reducing administrative overhead, creating a team structure to help distribute the tasks, so the physician is not the one burdened and to reduce the overall burden.

The literature suggests that people exposed to trauma can experiment with positive responses, reconsidering their values and appreciating their lives more as well as their work in emergency situations. These aspects can be fostered by psychological interventions (Brooks et al., 2020).

Personal characteristics may play a key role in determining how individuals react and deal with stressful situations, as it may be the case for oncologists in radiation oncology. Among these factors, there is growing evidence that difficulties in adequately recognizing one's own emotions (i.e. alexithymia) are associated with a variety of interpersonal issues, including social isolation and maladaptive behaviours. Alexithymic individuals typically show limited capacity to process emotional information, with resulting difficulties in identifying, understanding, and expressing their own feelings. In the working environment, these characteristics may lead to difficulties in coping with highly stressful and challenging situations, which in turn may increase the risk of occupational burnout for the individuals themselves.

Similarly, empathy, defined as *the ability to experience and understand what others feel without confusing oneself with others* (Franco et.al., 2020), is a core dimension of social functioning, enabling individuals to understand, share, and respond to the emotions, gestures, thoughts, and experiences of others. Growing evidence suggests a potential direct link between empathy and burnout. For instance, it has been shown that empathy was positively associated with personal accomplishment, but inversely related to burnout in a group of medical students.

Based on these observations, the PROject on Burn-Out in Radiation Oncology (PRO BONO) was carried out to assess the professional QoL, including burnout, amongst radiation oncology professionals and to explore the potential relationships with alexithymia and empathy (Franco et.al.,2020). The current findings highlight the importance of enhancing emotional competencies, in order to promote the positive dimensions of professional QoL and reduce the levels of distress and burnout experienced in the clinical practice. Dyadic (one-to-one) peer or group (Balint group) support could be a useful option in this context, to enhance emotional, informational and practical functioning of the professional, with assistance provided by a peer trained supporter.

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GYNECOLOGICAL TUMORS

S26 - PLACE OF IMMUNOTHERAPY IN TREATMENT OF CERVICAL CANCER

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Cervical cancer is common cancer type, with global high incidence which ranks it on fourth place in women worldwide. Its' mortality is especially high in underdeveloped regions in the world, such as east Africa, eastern Asia and South America. Nevertheless, because cervical cancer affects generally younger women, many in reproductive years, in comparison to other solid tumor types, it represents big socioeconomic burden to societies globally.

Therapy options in different stages of this cancer have not changed significantly for decades now, reflecting low investment in research and development of new drugs and treatment strategies for this disease. So, cervical cancer patients truly represent underserved population in terms of cancer care.

Cancer immunotherapy has made major impact on treatment of many patients with solid tumors. Immunotherapy offered a new hope especially for melanoma, kidney cancer, non-small cell lung cancer patients, but for many others also. Fortunately, cervical cancer represents a field of rapid and extensive immunotherapy research due to its' genuine ability to produce immunogenic response.

It is well known that almost all of the cervical cancers are caused by infection with oncogenic types of human papiloma virus (HPV), and the virus particles themselves, especially E6 and E7 component represent potent targets for immune reaction. So far, research in this area branches in several directions: use of checkpoint inhibitors, cancer vaccines, immune modulators, T-cell therapy, and therapy with dendritic cells.

Pembrolizumab, an anti PD-1 antibody, is first immunotherapy drug approved for treatment of recurrent/metastatic cervical cancer with positive expression of PD-L1 based on the results of KEYNOTE-158 study. In pretreated patients pembrolizumab elicited a response rate (RR) of 14.6% and a median overall survival (OS) of 11 months. This drug is still not approved in Europe for this indication.

Results of treatment of cervical cancer with other checkpoint inhibitors, such as nivolumab, ipilimumab, and combinations of anti PD-1 and anti CTLA-4 antibodies have been reported also. The combination of ipilimumab and nivolumab in women with squamous cell cancer of the cervix showed great response that was better than with existing chemotherapy regimens. The response rate in second-line metastatic disease was 36% with an OS that was not reached (>13.9 months).

While prophylactic vaccines have made a major change in prevention of cervical precancerous lesions, therapeutic vaccines active in developed disease are still in research.

Two phase II studies on *Listeria monocytogenes* based treatments in cervical cancer have been reported. This gram-positive bacteria serves as a vector for T fusion protein that includes a truncated fragment of listeriolysin O (tLLO) which is fused to human HPV-16 E7 and elicits potent cell immunity. The therapeutic compound made this way via bioengineering is called Axalimogene filolisbac or ADXS11-001.

In these studies, in pretreated cervical cancer patients, investigators observed a median survival ranging from 6.2 to 8.3 months, and 12-months OS in range of 35-38%.

Currently, there are numerous ongoing studies with combination regimens, such as chemotherapy-immunotherapy combinations, similarly to proven protocols used in other tumor types. Of special interest are ongoing studies in locally advanced cervical cancer that test concomitant whole pelvic radiotherapy with cisplatin and checkpoint inhibitors.

Besides PD-1 and CTLA-4 inhibition, immunotherapy against other targets, such as TIM-3, LAG-3, VISTA, and TIGIT, is in progress also.

A novel approach using tumor infiltrating lymphocytes (TILs) is being tested in HPV induced cancers, including cervical cancer. In cervical cancer TILs are connected with better clinical outcomes, and in limited number of patients infusion of specially engineered and expanded TILs induced promising treatment response.

Altogether, immunotherapy has shown promising activity in cervical cancer. So far, we still lack results of big randomized phase III studies that are currently recruiting patients. If they show positive results, treatment paradigm in cervical cancer could be changed across broad spectrum of the disease, from locoregional to advanced stages. Proper patient selection for every modality is of paramount interest and novel biomarkers beyond PD-L1 have been explored.

Keywords: cervical cancer, immunotherapy, checkpoint inhibitors, vaccines, tumor infiltrating lymphocytes

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S27 - OPTIMAL SEQUENCING TREATMENT OF OVARIAN CANCER

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Ovarian cancer (OC) is the most common cause of gynecological cancer death. In Croatia, it is the 7th most common cancer and 7th cause of cancer death among women. Most patients with ovarian cancer present with advanced disease at diagnosis because of the lack of characteristic symptoms and effective screening tests for early detection. The standard of care for front-line therapy is a combination of cytoreductive surgery and platinum-based chemotherapy. In patients with a disseminated disease, one option is neoadjuvant chemotherapy with interval debulking surgery after three to four cycles of chemotherapy. Despite initial therapy, the majority of women with advanced-stage develop progression of the disease within 3 years. Various attempts had been made to improve systemic treatments for ovarian cancer. The two most promising molecular targeting agents are anti-angiogenic agents and poly-ADP ribose polymerase (PARP) inhibitors.

Bevacizumab is the first targeted therapy approved by the European Medicines Agency (EMA) for the treatment of the advanced and metastatic ovarian cancer in the first line therapy. It is approved due to the results of two randomized controlled phase III trials: GOG-0218 and ICON-7 study. These both studies demonstrated an improvement of progression-free survival (PFS), especially in the high-risk ovarian cancer population. In the ICON7 trial, a survival benefit was observed in an exploratory analysis of a high-risk subgroup and in the GOG-0218 trial a survival benefit was observed only in patients with FIGO stage IV. According to the these two trials, bevacizumab should be consider to be added to the chemotherapy in high risk OC patients.

Bevacizumab has been also investigated in neoadjuvant setting. The complete resection rate (CRR) was higher in the group with bevacizumab, but further studies are necessary to draw definitive conclusions.

Since 2018, there has been a shift in the treatment of newly diagnosed OC as a result of four randomized phase III trials (SOLO-1, PAOLA-1/ENGOT-OV25, PRIMA/ENGOT-OV26, VELIA/GOG-3005). All four trials demonstrated remarkable improvements in PFS with PARP inhibitor therapy (olaparib, niraparib or veliparib) and overall survival data are expected. Despite the clear positive outcome of these four trials and the consistent message supporting use of PARP inhibitors in the first-line setting, the numerous differences in the designs and the results of the trials are challenging when trying to develop an updated algorithm for the first-line treatment of ovarian cancer. The SOLO-1 trial led to EMA approval of olaparib as first-line maintenance therapy in patients with BRCA1/2 mutation who have partial or complete response to prior platinum based chemotherapy, establishing a new standard of care. In BRCA-mutated tumors, there is no doubt that all patients should receive a PARP inhibitor. The PAOLA-1/ENGOT-OV25 trial led to EMA approval of olaparib in combination with bevacizumab in patients with homologous recombination deficiency positive associated advanced ovarian cancer and result of PRIMA/ENGOT-OV26 trial is EMA approval of niraparib in advanced ovarian cancer irrespective of biomarker status.

Immunotherapy has also been investigated in first-line setting. Last year, the first results from the phase III IMagyn050/GOG3015/ENGOT-OV39 showed that addition of atezolizumab to bevacizumab and chemotherapy did not meet the primary end point of PFS. There is a strong rationale in combining immune checkpoint inhibitors (ICIs) with PARP inhibitors and several ongoing trials are addressing this issue com-

binning basically all the available PARP inhibitors with all the available ICIs in the first line setting. The results from these trials are expected.

Treatment of initial recurrent disease depends on many factors, including duration of initial treatment response, residual toxic effects from previous therapy, performance status, histology, location and burden of disease, tumor genomics and the preferences of the patient herself. The AGO DESKTOP III/ENGOT ov20 trial is the first prospective randomized study showing an overall survival benefit for debulking surgery in patients with recurrent ovarian cancer, especially in those patients in whose complete resection is expected. Platinum is the most active cytotoxic chemotherapy for ovarian cancer. We do not have molecular markers for resistance, so platinum-based chemotherapy should be used until clear evidence of platinum resistance.

Bevacizumab is approved for first relapse of the disease regardless of the time elapsed since previous platinum based chemotherapy. Two trials phase III: OCEANS and GOG-0213 showed that bevacizumab during chemotherapy (with gemcitabine/carboplatin or paclitaxel/carboplatin) and as maintenance therapy improved of PFI in patients with platinum-sensitive ovarian cancer. In clinical trial phase III ENGOT-OV18/ AGO-OVAR 2.21, replacing gemcitabine with liposomal doxorubicin in a standard platinum based regimen in combination with bevacizumab improved survival. Bevacizumab is also approved in patients with platinum resistant ovarian cancer according AURELIA phase III trial.

PARP inhibitors were initially developed as maintenance therapy in patients with objective response after platinum based chemotherapy for recurrent disease. The remarkable improvement in PFS in three randomized phase III trials, SOLO-2/ENGOT-OV21, NOVA/ENGOT-OV16 and ARIEL3 led to regulatory approval of olaparib, niraparib and rucaparib, respectively, as maintenance therapy for platinum-sensitive recurrent ovarian cancer, irrespective of biomarker status. In the final SOLO-2/ENGOT-OV21 analysis, maintenance olaparib provided a clinically meaningful improvement in median overall survival. Olaparib, rucaparib and niraparib monotherapy are also approved in various types of the treatment (rather than maintenance) setting for pretreated recurrent ovarian cancer. A recent MITO trial demonstrated that among patients treated with maintenance olaparib for platinum sensitive ovarian cancer, only 22% patients responded to subsequent therapy, suggesting that resistance to platinum is a real clinical challenge after PARP inhibition. While retreatment with bevacizumab is supported by results from MITO16B-MaNGO OV2B-ENGOT OV 17 clinical trial phase III, we await results from the OReO/ENGOT-OV38 clinical trial phase III which is evaluating retreatment with olaparib.

Response to PD-1/PD-L1 inhibitor monotherapy has been modest in recurrent ovarian cancer. Many ongoing clinical trials investigate combination of checkpoint inhibitors with PARP inhibitors and/or with antiangiogenic agents to elucidate possible synergistic antitumor effects of these combinations.

There is little doubt that the landscape of ovarian cancer management has changed dramatically with the introduction of new drugs into standard-of-care therapy. Ovarian cancer has been transformed into a chronic disease and there is a place for optimism that some patients may be cured.

Keywords: ovarian cancer, PARP inhibitors, anti-angiogenic therapy, immunotherapy

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S28 - PERSONALIZED TREATMENT OF ENDOMETRIAL CANCER

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Endometrial cancer is the most common gynecological cancer in Europe, and the incidence has been rising with aging and increased obesity of the population.

The prognosis of endometrial cancer depends on the stage, histology, grade and ethnicity of the woman.

For low-grade endometrioid endometrial cancer, the standard treatment is surgery, and when surgery confirms an early stage, surgical treatment is also the only treatment.

Indications for adjuvant treatment have been primarily based on clinical and pathological factors, such as age, grade, histological type, depth of myometrial invasion, and presence of lymphovascular space invasion. Substantial lymphovascular space invasion is a strong prognostic factor for pelvic recurrence, distant metastasis, and decreased overall survival. Based on these prognostic factors, low, intermediate, high-intermediate, and high risk groups have been identified, each having a distinct prognosis and indications for adjuvant treatment

So it would be desirable to identify the risk factors associated with an advanced stage and/or a higher recurrence rate by analyzing the histology and grade of the tissue obtained from tumor biopsy at the time of the first diagnosis

Current treatment options for patients with recurrent or metastatic endometrial cancer remain limited.

The backbone of first line treatment is platinum-doublet chemotherapy, usually carboplatin and paclitaxel. There is no standard-of-care option established for patients who experience progression with first line therapy.

Endometrial cancer has been classified into 2 Bokhman types based on histologic and molecular characteristics—type I (endometrioid) and type II (nonendometrioid)

In 2013, The Cancer Genome Atlas proposed a new classification system. This system divided endometrial cancers into 4 categories: POLE ultramutated, MSI hypermutated, copy-number low (endometrioid), and copy-number high (serous like)

PFS was most prolonged in patients with POLE-ultramutated disease and shortest in those with copy-number high disease, whereas those with MSI hypermutated or copy-number low disease fell between these extremes.

POLE ultramutated and MSI high tumors—also called *hot* tumors—are more likely to respond to immunotherapy. Conversely, the copy number low and the copy number high serous like tumors—also called *cold* tumors—are less likely to respond to immunotherapy

Results of molecular analysis of the PORTEC-3 showed that even in these high-risk endometrial cancers, all four molecular sub-groups are found, with clear prognostic differences. Strong and significant benefit of added adjuvant chemotherapy in patients with p53 mutational expression, whereas those with POLE mutation had almost 100% recurrence-free survival in both arms. Mismatch repair deficiency cancers do not seem to benefit from added chemotherapy, whereas those with no specific molecular profile had slightly higher relapse-free survival with chemoradiation, comparable to the overall PORTEC-3 trial outcomes.

In 2017, the FDA approved the first anti-PD-1 inhibitor, pembrolizumab, for adult and pediatric patients with unresectable or metastatic, MSI-high or mismatch repair deficient (dMMR) solid tumors that have progressed following previous treatment and who have no satisfactory alternative treatment options.

Patients with endometrial cancers characterized by significant genomic instability, namely MSI high/dMMR tumors, have experienced tremendous benefit from checkpoint inhibitor therapy. In patients with MSI-low or pMMR status, the combination of pembrolizumab and lenvatinib is highly effective and has been shown to achieve responses in non endometrioid tumors, serous type, and clear cell tumors, which are highly aggressive and typically have low responses to chemotherapy. Moreover, DNA damage induced by chemotherapy may be synergistic and enhance the response to immunotherapy of endometrial cancer, which is being explored in ongoing trials combining immunotherapy and chemotherapy in advanced disease. Finally, in the coming years, we hope to see results from randomized phase III trials combining immunotherapy with an antiangiogenic agent (KEYNOTE-775) or a PARP inhibitor (DUO-E/ENGOT-EN10).

The molecular classification will become the basis of molecular sub-group directed adjuvant treatment approaches and of new trial designs that explore novel, more individualized targeted treatments.

It was only a few years ago that endometrial cancer was considered an orphan disease because we lacked active therapies. As we have just seen, we are living in an amazing and promising time now that we can use immune checkpoint inhibitor-based therapies to better manage this disease.

Keywords: endometrial cancer, molecular classification, targeted therapy

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S29 - DIAGNOSTIC AND TREATMENT APPROACH TO THE NEWLY DIAGNOSED METASTATIC UTERINE CANCER IN THE ERA OF PRECISION ONCOLOGY: A CASE REPORT

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Case report: Uterine cancer is the most common cancer of the female reproductive system in the developed countries. While generally with good prognosis almost one fifth of patients presents with metastatic disease, where chemotherapy or hormonal therapy remain the main treatment strategies with rather low, disappointing, less than 12 months median time of overall survival. Precision oncology throughout the comprehensive genomic profiling and its findings is providing possibility of administrating the *right* therapy to the *right* patient. According to the The Cancer Genome Atlas (TCGA) uterine cancer expresses a high level of mutations and is, consequently, suitable candidate for potential application of targeted therapy. In this report we present a case of a 56 year old female patient diagnosed with, according to the Federation of Gynecology and Obstetrics (FIGO) classification, stage IV metastatic uterine cancer in June 2017. Firstly, she underwent the surgical procedure of hysterectomy, bilateral adnexectomy, omentectomy, appendectomy and peritoneal biopsy where she was diagnosed grade 2 endometrioid adenocarcinoma with estrogen and progesterone receptor positivity of 60% and 50% and Ki-67 index 3% with Ki-67 focal activity of up to 70%. Afterwards, by the multidisciplinary teams` (MDT) decision, patient has received 6 cycles of the TC (carboplatin with paclitaxel) chemotherapy ending in the December of 2017, without morphological signs of the disease. At the end of the first year of follow-up, she was diagnosed with recurrence of the disease on the vaginal cuff. Estrogen and progesterone receptors were expressed in 100% and 80% of the cancer cells and Ki-67 was 50%. However, diagnostic work-up from January 2019 (multi-slice computed tomography, MSCT) showed, beside the vaginal recurrence, peritoneal, hepatic and intrapulmonary dissemination. On January 22, 2019, hormonal therapy with megestrol-acetate (Megace a 160 mg daily) was administered according to the multidisciplinary team decision. The best hormonal treatment response observed was partial regression in June, 2019 and duration of the treatment was until the June 24, 2020 when diagnostic work-up has shown morphological progression of the disease. In the meantime, during megestrol acetate, she has received palliative radiotherapy to the vaginal cuff in Janu-

ary, 2020 due to the vaginal bleeding. Considering that our patient was in excellent general health, without any clinical signs of progression, and that we were provided with the comprehensive genomic profiling (CGP) as a hallmark of the development of the precision oncology in 2020, the MDT has decided to perform the CGP analyses on our patients' tumor specimen and that, in the meantime, our patient starts with the second line of hormonal therapy with aromatase inhibitors. CGP analyses has shown that our patients tumor had stable microsatellite status, however it had 11 mutations per megabase with immune checkpoint inhibitors (pembrolizumab, atezolizumab, avelumab, cemiplimab, durvalumab, nivolumab) opted as a targeted therapy, approved in the EU but in other tumor types. Also, genetic alterations found were mutations of NF2, PIK3CA, PTEN, FGFR2 and PALB2 with everolimus, temsirolimus, alpelisib, pazopanib, niraparib, olaparib, rucaparib and talazoparib opted as a targeted therapy, approved in the EU but in other tumor types. The best response to aromatase inhibitor (letrozole) observed was stable disease and after 4 months of the treatment, diagnostic work-up on October 27, 2020, has shown morphological progression of the disease. Consequently, we presented our patients' case to the MDT, pointing the results of the CGP analyses and that our patient was in excellent general health without any clinical signs of the disease. Thoroughly taking into account the above mentioned, MDT at our Clinic has decided for treatment with immune checkpoint inhibitors in accordance to the CGP analyses. We, then, started the standardized procedure of the drug procurement via compassionate program and our patient has started the treatment with atezolizumab on December 8, 2020. She has received 2 cycles of the treatment and while waiting for the approval of the regulatory authorities, she had clinical signs of the disease in terms of developing acute abdominal condition such as ileus and was operated in emergency on January 11, 2021 with placement of the transversal bipolar stoma. After her recovery and considering current unavailability of the targeted therapy options, we have reintroduced chemotherapy combination of paclitaxel and carboplatin and our patient have received two cycles so far. In conclusion, our patient is still in excellent general health and our main treatment strategy is to obtain maximal control of the disease with chemotherapy and continue to explore different ways of providing her with the *right* therapy.

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S30 - GRANULOSA CELL TUMOR - CASE REPORT

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Introduction: Ovarian sex cord-stromal tumors (SCSTs) are a group of benign and malignant neoplasms that develop from the sex cord or stromal cells of the ovary. They account for 7% of all ovarian neoplasms. Histologically, SCST are divided into pure sex cord tumors, mixed sex cord stromal tumors and pure stromal tumors. Granulosa cell tumors are pure sex cord tumors. Most patients with granulosa cell tumors present at an early stage and the disease is typically indolent. There are two types of granulosa cell tumors, adult type and juvenile type. For adult granulosa cell tumor, prognostic factors are: FIGO stage, age at diagnosis, intraperitoneal tumor rupture. For juvenile granulosa cell stage is the major prognostic factor. First line of treatment for granulosa cell tumors is surgery: fertility sparing surgery for early stage and radical surgery for advanced disease. For patients with high-risk stage I disease, postoperative recommendations are observation or platinum based chemotherapy. For patients with stage II-IV disease, recommended treatment options are radiotherapy for limited disease or platinum based chemotherapy. For treatment of relapse after initial treatment, repeated cytoreductive surgery should be performed whenever possible. Cytotoxic recurrence therapies include docetaxel, paclitaxel, paclitaxel/carboplatin. Another option is hormone therapy: aromatase inhibitors, tamoxifen or leuprolide. In certain cases, palliative radiotherapy may also be useful.

Patient: Our patient was first diagnosed with granulosa cell tumor when she was 26 years old. A fertility sparing surgery (bilateral ovarian resection) was performed. First local relapse occurred 16 years later and radical surgery was then performed (hysterectomy with bilateral adnexectomy). Six years later, another relapse occurred, but this time disease was more advanced with omental and peritoneal infiltrations. After surgical resection, patient has received 6 cycles of Oncovin/Actinomycin D/Endoxan chemotherapy. After 6 years, another relapse occurred. After that, relapses occurred in shorter time periods. In a time period of 9 years, 8 cytoreductive surgeries were performed. Additionally, in that time period 4 different lines of chemotherapy and 3 different hormonal therapies were conducted: 6 cycles of paclitaxel/carboplatin, BEP chemotherapy protocol which was aborted due to severe allergic reaction, 2 years of hormonal therapy with tamoxifen, 3 months of letrozole therapy, LHRH agonist, 4 cycles of docetaxel and 4 cycles of etoposide chemotherapy. Because of limited treatment options and deterioration of general condition of our patient, specific oncologic treatment was not continued.

Our patient lived 37 years following initial diagnosis and has lived with metastatic disease for 15 years.

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MELANOMA AND SARCOMA

S31 - THE CURRENT STATE OF ADJUVANT THERAPIES OF MELANOMA - NEW STANDARDS - NEW HOPE FOR MELANOMA PATIENTS

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During decades ago, adjuvant treatment for high risk melanoma patients was based on interferon alpha. Although many clinical trials and meta analysis were performed (Mocellin and co.) presenting modest benefit in PFS and controversially in OS, the usage of interferon alpha as adjuvant therapy did not become a standard of care worldwide. Multiple dosing schemes, toxicity and financing were additional problems with interferon usage.

New era in melanoma treatment started with approval of BRAF and MEK inhibitors and immune checkpoint inhibitors (anti CTLA-4 and anti PD-1). Revolutionary results in metastatic melanoma, regarding PFS and OS, were the milestone for adjuvant clinical trials.

EORTC 18071 phase III study showed benefit of adjuvant ipilimumab (anti CTLA-4 inh.) in completely resected stage III melanoma (IIIA, IIIB and IIIC). Patients (951) with completely resected stage III melanoma were stratified in 2 cohorts, one with ipilimumab 10mg/kg i.v. every 3 weeks/ 4 applications then every 12 weeks up to 3 years. Second cohort was placebo matched. After 6.9 years of follow up analysis showed benefit in PFS (HR 0,75), OS (HR 0,73) and distant metastasis free survival (DMFS, HR 0,76) for all subgroups. Toxicity, especially autoimmune adverse events (irAE) and 5 deaths related to treatment were a limiting factor for a worldwide acceptance. Further adjuvant studies with new immune check point inhibitors (ICI), anti programmed cell death protein-1 (anti PD-1), with a low incidence of irAE, have made ipilimumab in adjuvant setting almost obsolete.

Nivolumab, an anti PD-1 inhibitor showed favourable results over ipilimumab in phase III adjuvant trial Checkmate 238. More than 900 pts. with completely resected stage III (IIIB, IIIC) and stage IV melanoma were allocated in 2 cohorts. First one with nivolumab applied every 2 weeks, 3mg/kg up to one year, and second one with ipilimumab 10mg/kg i.v. every 3 weeks /1 year. After 18 months of follow up 63 % of patients in nivolumab arm and 53% of patients in ipilimumab arm were disease free. Nivolumab showed favourable results over ipilimumab in all subgroups and all primary and secondary endpoints with a low incidence of irAE.

Pembrolizumab, another anti PD-1 inhibitor showed similar results in adjuvant trial Keynote 054. Pembrolizumab 200 mg iv. every 3 weeks up to one year was superior in OS, PFS and DMFS over placebo in completely resected stage III melanoma (IIIA, IIIB and IIIC). After 18 months of follow up 71.4 % patients in pembrolizumab arm and 53.2% in placebo arm were disease free; HR 0,57.

Similar results were seen in clinical trials with adjuvant BRAF and MEK inhibitors in BRAF mutated stage III melanoma.

COMBI AD, a phase III adjuvant trial with more than 900 stage III melanoma patients (IIIA, IIIB, IIIC, with a diameter of metastasis > 1mm) showed benefit of 1 year adjuvant dabrafenib and trametinib over

placebo in all subgroups regardless of endpoint (OS, PFS, DMFS). Patients received dabrafenib 2x150mg daily and trametinib 2 mg daily p.o. over one year. After 4 years of follow up 54% pts. in dabra/trame arm and 38% pts. in placebo arm were disease free (HR 0,49). Around 86 % of pts. in dabra/ trame and 77% in placebo arm were alive at 3 years cut off (HR 0,57). Toxicity profile was similar as seen in metastatic clinical trials (COMBI-v, COMBI-d) with no deaths related to therapy reported.

Neo/adjuvant clinical trials in melanoma treatment are ongoing. Opacin NEO trial, a phase II study with neoadjuvant combined immunotherapy in stage III melanoma patients showed high level of pathological complete response (pCR) as a surrogate of prolonged PFS and OS. Continuously, next study, PRADO trial, showed that patients with pCR after neoadjuvant combined immunotherapy can be safely spared a TCLND without affecting RFS and probably OS.

Adjuvant therapy in stage III melanoma patients with ICI or BRAF and MEK inhibitors is revolutionary and promising (curative intervention?). For BRAF mutated melanoma patients both options are equally available. Further clinical trials are needed (oriented) for adjuvant treatment of stage II high risk melanoma patients, like stage II C.

Keywords: adjuvant, melanoma, immunotherapy, BRAF and MEK inhibitors

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S32 - THE INDIVIDUALIZATION OF IMMUNOTHERAPY IN MELANOMA PATIENTS

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Immunotherapy with Immune-Checkpoint Inhibitors (ICI) led to the revolution in oncology due to high rates of durable responses in patients with metastatic melanoma, and later on, with other types of malignancies. Consequently, after a while, a question of cessation of therapy in patients (pts) with substantial therapeutic response emerged in the hope of long-term remission or even cure.

Suggestions about the possibilities of a relatively safe cessation of immunotherapy with ICI are based on the experience obtained from several clinical trials. However, stopping effective therapy in potentially lethal disease is mixed with the fear of the disease relapse.

The cessation of immunotherapy can substantially contribute to patients' quality of life due to less time spent in a hospital and the reduced risk of toxicities, but it also has significant economic implications on society in general. This unexpected question of elective discontinuation of beneficial therapy in patients with excellent response to ICI-treatment without toxicity issues was, up to now, unimaginable. It emerged after the data from the KeyNote-001 clinical study was published, where 67 pts with complete response (CR) to pembrolizumab stopped treatment if the CR was confirmed on two consecutive CT-evaluations, i.e. if pts received therapy for at least six months, including at least two cycles of therapy after the confirmation of CR. After five years of follow-up, almost 90% of pts were alive and still in CR.

Afterwards, the growing number of clinicians accepted the same criteria for the discontinuation of ICI-immunotherapy. Recently, data from two retrospective analyses outside clinical trials of pts with metastatic melanoma on anti-PD1-therapy have been published, providing real-world data. In the first analysis, 185 pts (117 of them with CR) stopped anti-PD1 therapy without disease progression or unacceptable toxicity after 12 months of median therapy duration. After a median of follow-up of 18 months after therapy discontinuation, 86% of pts were without disease recurrence or progression. In the second study, 102 pts with CR electively stopped anti-PD1-therapy after 9.4 months of median therapy duration. After a median of follow-up of 21.1 months from the time of CR, the probability of being alive and not requiring additional treatment for melanoma was 72.1%, and the estimated 3-year overall survival (OS) from the time of CR was 82.7%.

The next important question concerns the need for long-term anti-PD1 therapy in patients with partial response (PR) or stable disease (SD). In the KeyNote-006 clinical trial, patients receiving pembrolizumab for two years (maximum therapy duration per study protocol) had the largest therapeutic benefit. Out of 103 pts that received pembrolizumab for two years, 21 patient had CR, 69 had PR, and 13 had SD, respectively. After a median follow-up of 34.2 months from completion of pembrolizumab therapy, the estimated 24-month progression-free survival (PFS) was 85.4% in patients with CR, 82.3% in patients with PR, and 39.9% in pts with SD, respectively.

In a previously mentioned real-world analysis of Jansen et al., among 185 pts that had discontinued therapy, the recurrence rates after a median follow-up of 18 months differed according to the maximal achieved therapeutic response, and were 14% in pts with CR, 32% in pts with PR, and 50% in pts with

stable disease, respectively. In the same analysis, patients with CR who received therapy for <6 months were more likely to relapse than those who received a longer course of treatment during >6 months (median PFS duration was 18.9 months for pts <6 months on treatment vs not reached for pts >6 months on treatment, $P < 0.05$). This would suggest that the minimal treatment duration should be six months. However, another retrospective analysis (Betof Warner et al.) showed no apparent association between treatment duration and treatment failure.

In CheckMate-67 clinical trial of combination immunotherapy with nivolumab and ipilimumab compared with nivolumab or ipilimumab as monotherapy in patients with metastatic melanoma, 36.4% of patients discontinued therapy due to toxicity in the induction phase of therapy. However, in these patients, the duration of response and survival were not significantly different (5-year OS 51%) than the outcome in patients who continued treatment (5-year OS 52%). Therefore, it is rational to suggest that, after the discontinuation of immunotherapy due to serious adverse events, it should be considered to withhold the treatment until disease progression because of the possibility of an ongoing clinical response to immunotherapy regardless of the treatment cessation. In patients with disease progression, treatment resumption should be considered if the benefit to risk ratio is deemed acceptable.

Classical radiologic evaluation of tumor response to immunotherapy can underestimate the magnitude of the response to immunotherapy, especially in some situations (residual sclerous bone lesions, pulmonary or liver fibrotic or nodular scars in the site of previous metastatic lesions). The distinction between CR and PR becomes a new challenge in patients on immunotherapy with near-total CR. In the assessment of the response in these cases, PET/CT or biopsy of the remnant disease with pathologic evaluation can be helpful.

There is no specific management approach for patients with mixed therapeutic responses in different metastatic lesions or patients with the initial response to immunotherapy and stable disease afterwards. In such patients, especially those with oligometastatic disease, additional local therapy (i.e. radiotherapy, ablation techniques or surgery) of the remnant or non-responding lesions can lead to the complete therapeutic response. Whether those patients with *assisted* CR have the same favourable outcome as the ones with complete response achieved solely with the application of immunotherapy is yet to be determined.

The lack of major dose-dependent effect in anti-PD1 therapy, as well as the possibility to administer immunotherapy cycles with doubled doses in doubled time intervals, with the maintained efficacy, which was granted by the recent approvals from the regulatory agencies, supports the hypothesis that the antagonistic effect of immunotherapy itself is sufficient to generate therapeutic benefit.

The critical question arising is the probability of the secondary response to immunotherapy if the disease relapses in patients who had a previous durable clinical response to ICI and had chosen to stop treatment. So far, there are some data available on a small number of patients in whom the immunotherapy was reintroduced upon disease progression (subgroup analysis from KeyNote-006, retrospective analysis /Gauci et al./), showing the efficacy of the second course of the same immunotherapy in at least some patients. Due to the lack of robust evidence, patients considering cessation of therapy should be informed that the therapeutic efficacy of the immunotherapy after the discontinuation cannot be guaranteed if the melanoma recurs.

Adjuvant immunotherapy with pembrolizumab or nivolumab is approved for the duration of 1 year in patients with completely resected high-risk melanoma. The 1-year duration of the adjuvant treatment is arbitrarily chosen. No data are available on the efficacy of shorter or longer adjuvant treatment duration. The potential implications of the administration of adjuvant therapy on response to subsequent therapy for metastatic disease, in the case of disease relapse, remain unknown at the time.

Additional prospective randomized clinical trials are needed to explore further the optimal timing of discontinuation of immunotherapy and potential biomarkers that would guide clinicians in that regard, such as ctDNA. Nowadays, the best predictive parameter for long-term survival and minimal risk of disease relapse after cessation of immunotherapy is the achievement of complete response, which should, therefore, become a new crucial endpoint in clinical trials.

Immunotherapy has, in recent years, achieved results that were unimaginable until immunotherapy-era in the treatment of metastatic melanoma patients. The full range of the individualization of immunotherapy will be achieved when more robust data on a much larger number of patients will be available, as well as reliable predictive and prognostic biomarkers.

Keywords: melanoma, anti-PD-1 therapy, duration of treatment, immunotherapy, therapy discontinuation

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S33 - ROLE OF RADIOTHERAPY IN SARCOMA TREATMENT

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Sarcomas are heterogeneous group of *solid* tumors arising from mesenchymal tissue. Because of wide variety of sarcoma originating tissues there can be recognized more than 50 different subtypes. Regarding the pathohistological differentiation sarcomas can be divided in two large basic groups: Soft tissue sarcomas (STS) and Bone sarcomas (OS).

Radiotherapy has a role in all stages of treatment. From intraoperative radiotherapy, neoadjuvant, adjuvant radiotherapy, concomitant with chemotherapy and in palliative setting. It is always combined with other treatment modalities.

Neoadjuvant radiotherapy aims to tumor volume decrease, and lowering the risk of disease spread in surgical procedures. Even if there is no visible effect on tumor shrinkage, preoperative radiotherapy can give an advantage by making thicker tumor pseudo capsule thus making surgical procedure easier. Surgery usually follows radiotherapy in the period of 3-6 weeks.

Adjuvant postoperative radiotherapy is indicated as a measure of improvement of local control of disease when there was a narrow surgical margin (less than 1cm) or R1 or R2 resection. Adjuvant radiotherapy must be considered when the status of surgical margins is not known. All STS with nuclear grade greater than G1 and any T greater than pT1 should be considered for adjuvant radiotherapy.

Intraoperative radiotherapy is used in institutions having this possibility as a measure of improvement of surgical procedure, *sterilizing* the tumor bed.

Definitive radical radiotherapy is used usually in conjunction with chemotherapy in surgically non-respectable tumors.

Palliative radiotherapy is used in relieving symptoms of metastatic or progressive disease with quality of life as a primary target. Nowadays a stereotactic radiosurgery (SBRT) is often used in treatment of lung or liver metastasis.

A key issue in successful and high quality radiotherapy is patient positioning and immobilization. Different immobilization systems can be used in order to get the maximal radiotherapy effect with minimal involvement of organs at risk (OAR).

The radiotherapy technique used in treatment of sarcomas is usually referred to as *cone down* or *shrinking fields* technique. Meaning of this approach is that in an initial phase a larger portion of tumor surrounding tissue is treated, followed by treatment with smaller fields targeting primarily the tumor itself at the end of the treatment.

The doses that are given are quite high ranging from 50 Gy in 25 fractions in neoadjuvant setting, to at least 64 Gy in 32 fractions as adjuvant radiotherapy. It has to be said that margins surrounding primary tumor bed are large resulting in large treatment fields. This means higher possibility of adverse events in organs at risk.

Bone sarcomas are even more radioresistant and the dose given in case of osteosarcoma is usually 70Gy and more. On the other hand for example there is a Ewing sarcoma, much more radio and chemo responsive, usually treated with radiotherapy doses of approximately 55 Gy.

In soft tissue sarcomas treated initially, with local control of disease, almost in 50% of patients there is local relapse or metastatic spread within 8-12 months from the beginning of treatment.

In osteosarcoma with multimodal approach (invasive surgical monitoring, SBRT, chemoth) five years overall survival can reach 50-70%.

All above mentioned confirms heterogeneity of sarcomas with variations in response according to therapeutic approach. This means that sarcoma treatment should be done in high volume centers with multidisciplinary teams dedicated to sarcoma treatment. Such an approach gives the maximal benefit to patient and allows appropriate treatment selection in adequate timing.

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S34 - CASE REPORT: A PATIENT WITH A MUCOSAL MELANOMA

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Introduction: A mucosal melanoma is a rare type of melanoma. It originates from mucosal epithelial cells of respiratory tract, genitourinary tract and gastrointestinal tract. It is mostly localized in the vulvar area and vagina in women, anorectal area, oronasal cavity and sinuses. Due to the fact that this is a rare type of melanoma, followed by limited possibilities of treatment and diagnostics, in the moment of diagnosis 25% of patients will already develop distant metastases. Genetic profiles of mucosal melanoma: KIT gene mutations (subtypes K642 E c-KIT, L 576P c-KIT, PDGFR exon 18 or PDGFR 42V) (7-17%), NRAS (15-20%), BRAF mutations (3-15 %), and PDL1 is less frequent than in cutaneous MM. New therapeutic

options are based on FMI: c-KIT inhibitors, BRAF / MEK inhibitors, and immunotherapy with a poorer response than to cutaneous MM.

Case report: During September 2018, a patient (male, 62 years old) was admitted in a regional health-care institution due to nausea, vomiting and abdominal pain spreading to the chest. During the diagnostics, an abdominal ultrasound was done on which a cystic pancreatic lesion was found.

An MSCT of the abdomen described an existing formation in the area where the pancreatic neck turns into the body of the pancreas, with lymphadenopathy, an expansive formation in the area of transversal colon, as well as an expansive formation in the mesentery of a small intestine.

Considering the abdominal ultrasound results and the MSCT of the abdomen, a biopsy of the tumor in the pancreas was done, but did not show any malignant cells. A colonoscopy was also done; pathological results were not found. After the examination, an abdominal surgeon indicated and performed a surgery - a medial laparotomy with the transverse colon resection and partial jejunum resection together with the extirpation of the mesenteric tumor.

During the operation, the tissue samples were taken (transverse colon, mesentery and jejunum) and sent to PH verification. PHD results showed that it was a melanoma, whereas the operation identified a solitary tumor in the projection of gastrocolic ligament which was pressing the transverse colon. Subsequently, an immunohistochemical profile of the tumor tissue was done; the test showed that tumor tissue is positive to vimentin and CD10 and that Ki67 was 70%.

At the end of December 2018, a patient was examined by an oncologist who recommended a PET CT for the staging and to determine the BRAF mutation. PET CT results showed a disseminated malignant disease with a various malignant deposits in the hypodermic and muscular lesions. A small changes in the liver were also found, however, too small for an accurate interpretation. Also, secondary changes in the lymph nodes of the right armpit and the right inguinal area were described. The cytological puncture of the lymph node of the right armpit was done and the results showed that it was a metastatic malignant melanoma. The tumor was positive to BRAF mutation.

At the beginning of 2019, the patient was presented at our oncology consilium, as well as to the multidisciplinary team for skin cancer. It was decided that BRAF and MEK inhibitors would be introduced into the therapy because they are the chosen medication in mucosal metastatic melanoma with the positive BRAF V600E mutation. According to the consilium's decision, the patient received a therapy with dabrafenib and trametinib (Tafinlar and Mekinist), continuously, from February to October, and was also evaluated by CT and PET CT.

In November 2019., PET CT showed an enlarged lymph node in the area of the right armpit, and the rest of the results spoke in favor of the regressive disease dynamics. At the end of 2019., the patient was once again presented at the oncology consilium. The consilium concluded that the disease was progressing, so the second-line therapy with pembrolizumab (immune therapy) was introduced during 3 months in 5 cycles. The patient, however, developed a side effect of the immune therapy: autoimmune colitis. Due to it, the patient received 4 out of 5 cycles of pembrolizumab. He was treated with corticosteroids.

In May, 2020, due to patient's bad general health status, an immediate PET CT was done and a considerable progression of the disease was described, along with many secondary tumors. At the oncology consilium together with the MDT held in May of the same year, it was decided that the patient's therapy would be continued with taxanes, along with the bisphosphonates. The patient was, from June to September, treated with paclitaxel (12 cycles were administered altogether); he endured the therapy well. Due to the big tumor mass in the area of his right armpit, a radiotherapy in TD 30 Gy in 10 fractions was con-

ducted as an anti-pain treatment. Another PET CT was done and it determined the progression of secondary tumors (in the armpit, pancreatic body, gallbladder, a convolution of the small intestine). Also, subcutaneous lesions of gluteal area, newly enlarged lymph nodes in the right inguinal area and a few minor intrapulmonary nodules were identified, as well. There was a pleural effusion visible on both sides. Considering the last PET CT results, the patient was presented at the oncology consilium once again and to the MTD in October, 2020. It was concluded that temozolomide should be introduced into the therapy plan. He has been receiving the treatment continuously since November, 2020. After 6 cycles of the therapy mentioned, a new evaluation with the PET CT is planned.

Conclusion: The treatment of metastatic mucosal melanoma is very demanding and it asks for a necessary diagnostic precision, an adequate pathohistological diagnostics and examination, clinical experience, as well as the possibility to use the newest and the most appropriate therapy. When discussing the therapy, today there are more options and more therapeutic modalities (based on FMI, for example) compared to earlier periods. To conclude, an opportune and precise diagnostics, as well as the adequate treatment are still a key in a successful recovery and a longer survival rates of oncology patients.

Keyword: immunotherapy, melanoma, oncology, radiation oncology, targeted therapy

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UROGENITAL TUMORS

S35 - HYPOFRACTIONATED RADIOTHERAPY FOR PROSTATE CANCER - PRECONDITIONS, BENEFITS AND LIMITATIONS

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The biology of prostate adenocarcinoma differs from the biology of most other malignant tumors. The doubling time of the number of tumor cells and the doubling time of the volume of prostate cancer is few times longer than in lung cancers, head and neck cancers, breast cancers or glioblastomas. Prostate cancer responds differently to radiation than other tumors. The alpha / beta value describing its radiobiological properties is 1.4 Gy, which is significantly less than other tumors in which these values are about 10 Gy. Different tumor responses to radiation are manifested by different responses to individual radiation dose regimens. In patients with prostate cancer, radiotherapy divided into a series of small fractions of radiation is less effective than when radiation is divided into larger daily fractions. The usual (conventional) fractionation scheme is radiation divided into daily radiation doses of 1.8 - 2 Gy. Hypofractionated radiotherapy is performed with daily radiation fractions at a dose greater than 2.5 Gy. Moderate hypofractionated radiation involves radiation at daily doses of 2.5 to 3.4 Gy. Extreme hypofractionation is radiation with daily doses greater than 5 Gy. Hypofractionation radiation shortens the total treatment time not only due to larger daily fractions, but also with a lower total dose that should achieve the same radiobiological effect as with conventional fractionation treatment.

Over the past decade, 10 prospective randomized studies have investigated moderate hypofractionated radiotherapy as part of radical treatment of prostate cancer patients. The largest 4 studies (CHHiP, HYPRO, RTOG 0415, PROFIT) tested whether hypofractionated radiotherapy was less effective than conventional radiotherapy (noninferiority trials). In all of these studies, hypofractionated radiotherapy has been shown to be at least as effective as radiation at daily doses of 2 Gy. Patients from all prognostic groups were included in the studies. Although treatment in some patients was performed by three-dimensional conformal radiation therapy (3D-CRT), more complex techniques involving intensity modulation (Intensity-modulated radiation therapy IMRT, Volumetric modulated arc therapy, VMAT) were more common. The target volume did not include pelvic lymph nodes. Different dosing regimens were tested, but most patients in the hypofractionation group received 60 Gy in 20 fractions or 70 Gy in 28 fractions. The Cochrane meta-analysis of all studies confirms the equal efficacy and toxicity of moderately hypofractionated radiotherapy and radiation with a conventional dosing regimen. The exception is the tendency towards a higher incidence of transient early, acute side effects from the gastrointestinal system in patients treated with hypofractionation. Published postoperative hypofractionated radiotherapy studies have not been randomized. To evaluate the value of this technique in postoperative treatment, one should wait for the results of the prospective studies RADICALS and NGR CU003. A significant advantage of hypofractionated radiotherapy is the better usability of radiotherapy equipment, and thus a significantly more favorable cost of the procedure itself. Hypofractionated radiotherapy contributes to the patient's quality of life and ensures a more rational disposal of health resources. The lower number of patients visits for radiation is more favorable in a COVID-19 pandemic environment.

According to the guidelines of all American professional societies (American Society for Radiation Oncology, ASTRO, American Society of Clinical Oncology, ASCO, American Urological Association, AUA), and the National Comprehensive Cancer Network (NCCN), hypofractionated radical radiotherapy is equivalent to radiation with a conventional dosing schedule. The same is recommended by the European Association of Urology (EAU). Hypofractionated radiotherapy has also been proposed in the guidelines of the Croatian Oncological Society (Hrvatsko onkološko društvo, HOD) as a therapeutic option in the radical treatment of prostate cancer. According to the guidelines, there are no clear contraindications for hypofractionated radiation with regard to the prognostic group, patient characteristics and disease. The exception is pelvic lymph node radiation, which is not recommended with this technique. For such a clinical situation, a possible therapeutic approach is simultaneous, irradiation of the lymph nodes with a conventional scheme and hypofractionated radiation of the prostate. Although some patients in clinical studies were irradiated with simpler techniques, in all guidelines there is a consensus that intensity-modulated radiotherapy (IMRT, VMAT) techniques with daily image-guided radiation therapy (IGRT) are necessary for hypofractionated radiation regimens. There is a growing acceptance of hypofractionated radical prostate radiotherapy worldwide. This is especially true for more developed countries. In North America, hypofractionated radiotherapy is a more common choice than conventional radiation in all patient groups. The British NICE (National Institute for Health and Care Excellence) proposes hypofractionated radiotherapy of the prostate as the first therapeutic choice in radical radiation of patients with prostate cancer.

Hypofractionated radical radiotherapy of prostate cancer is an equivalent therapeutic procedure as radiation with a conventional radiation scheme in the radical treatment. Because of organizational and financial advantages, and with the certain technical preconditions, we should regard it as a therapy of choice.

Keywords: hypofractionated radiotherapy, moderate hypofractionation, radiobiology

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S36 - NON-HORMONAL SYSTEMIC TREATMENT OF PROSTATE CANCER

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Modern non-hormonal systemic treatment for prostate cancer (PC) includes chemotherapy, immunotherapy and targeted therapy.

Docetaxel with prednisone or estramustine was the first agent to improve the median overall survival (OS) of symptomatic patients with metastatic castration-resistant prostate cancer (mCRPC) by 3 months in TAX 327 and SWOG 9916 trials compared to mitoxantrone with prednisone and has become a standard therapy since 2004. If administered before or after novel hormonal therapy (ARTA). Ten years later, docetaxel became the first treatment option in combination with androgen deprivation therapy (ADT) in patients with de novo metastatic hormone-sensitive prostate cancer, based on CHAARTED and STAMPEDE trials. If docetaxel is co-administered with ADT in high-volume patients, OS gain relative to ADT alone according to the CHAARTED trial was 1.1 years with HR 0.63, while in the STAMPEDE trial the gain in OS, regardless of disease volume, was an impressive 1.8 years. Meta-analysis of randomized clinical trials has shown significant survival gain in this setting regardless of disease volume.

Another taxane, cabazitaxel with prednisone, also showed a significant benefit in OS of patients with symptomatic mCRPC (slightly more than 2 months with HR 0.72) in TROPIC trial, compared to mitoxantrone with prednisone, but in second line after progression with first line docetaxel. Cabazitaxel has also been shown to be the treatment of choice in patients with mCRPC and progression to docetaxel and ARTA. In CARD trial, compared to ARTA sequencing, it significantly improved radiological progression-free survival (rPFS) by almost 4 months with HR 0.54 as well as OS by 2 months with HR 0.64.

In 2010, sipuleucel-T became the first new immunotherapy approved by the FDA in the treatment of patients with asymptomatic mCRPC, based on IMPACT trial in which it showed a 4-month survival gain over placebo with HR 0.78. Pembrolizumab has shown efficacy in the treatment of 2-5% of patients with mCRPC and MSI-H or dMMR tumors who have progressed to at least one systemic treatment line. The recommendation for pembrolizumab in the treatment of this group of patients is based on two so-called *umbrella* trials as well as nonrandomized Keynote-028 and Keynote-199 phase II trial. Achieved objective response rates (ORR) in those trials were up to 17% with duration of response up to 20 months.

Germlines and somatic mutations in homologous recombination repair genes (BRCA1, BRCA2, ATM,...) may be predictive of the clinical benefit of PARP inhibitors. At present, two PARP inhibitors are approved by the FDA for use in prostate cancer: olaparib and rucaparib, based on PROfound and TRITON2 trials. In PROfound trial olaparib was significantly better than sequencing of two ARTA in patients with the mentioned mutations in mCRPC, who could have previously received docetaxel, in rPFS with HR 0.34 and OS with HR 0.69. In TRITON2 trial with patients with the same mutations, who progressed to ARTA and at least one taxane, achieved an ORR of 43% and median rPFS of 9 months.

Key words: prostate cancer, chemotherapy, immunotherapy, targeted therapy

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S37 - COMPARISON OF SURGICAL TREATMENT AND CHEMORADIOTHERAPY FOR BLADDER PRESERVATION FOR LOCALIZED MUSCLE INVASIVE BLADDER CANCER - UROLOGIST VIEW

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Radical cystectomy remains the gold standard of local definitive therapy for muscle invasive bladder cancer. 5-year survival after RC is directly related to the pathologic stage and nodal status ranging from 50 to 81% depending on many factors such as neoadjuvant chemotherapy, stage, grade, number of lymph nodes removed, etc. Addition of neoadjuvant chemotherapy to radical cystectomy significantly improves survival. Drawbacks of this treatment approach include high rates of postoperative morbidity and mortality (as high as 64% and 2.7%, respectively) even in experienced referral centers and a decrease in the postoperative quality of life.

Trimodality therapy (TMT) consists of maximal TURBT followed by chemoradiotherapy with long-term surveillance. In the past, trimodality therapy (TMT) was usual option for patients unfit for RC. In the contemporary era, younger and fitter patients are opting for TMT. There is a growing body of evidence that suggests similar overall survival (OS) rates and potentially improved quality of life (QOL) in patients treated

with TMT versus RC. Still, in the absence of high quality data careful patient selection is critical. Unfortunately, most of the data come from retrospective studies as there are no randomized comparisons between radical cystectomy and TMT. A single randomised controlled study is available only in comparison of trimodal therapy (TMT) over bimodal treatment (TURBT followed by RT) for patients with MIBC and it clearly showed superiority of TMT. In the TMT vs. RC treatment comparison there are only few comparative observational studies. In a propensity-matched comparative analysis from the National Cancer Dana Base comparing patients undergoing radical cystectomy vs. chemoradiation, Ritch et al. found that chemoradiation therapy was associated with decreased mortality at year 1 (HR 0.84, 95% CI 0.74-0.96), but at 2 years (HR 1.4, 95% CI 1.2-1.6) and 3 years onward (HR 1.5, 95% CI 1.2-1.8) chemoradiation therapy was associated with increased mortality. Furthermore, the 5-year OS was greater for radical cystectomy than for chemoradiation (38% vs 30%, $p = 0.004$). This was subsequently reiterated in a follow-up NCDB study.

Some systematic reviews and meta-analyses that are recently published suffer from lack of methodological rigor and bias risk assessment. That is why AUA/ASCO/ASTRO/SUO guidelines strongly advocates radical cystectomy with bilateral pelvic lymph node dissection for surgical eligible patients with resectable non-metastatic (M0) muscle-invasive bladder cancer (Grade B). The European Association of Urology guidelines are in line with these recommendations. Not negligible are the differences in the total costs. These were significantly higher with TMT than with radical cystectomy at 90 days (\$80,174 vs \$69,181; median difference, \$8964) and at 180 days (\$179,891 vs \$107,017; median difference).

Therefore, current Guidelines still consider cystectomy with neoadjuvant chemotherapy to be the gold standard for the treatment of MIBC. European Association of Urology Guidelines on MIBC state that TMT can be considered for selected T2N0 tumors with the note that it is not a standard treatment while NCCN guidelines state that bladder preservation should optimally be offered to selected patients (without hydronephrosis, no concurrent extensive or multifocal carcinoma in situ, tumor < 6cm and with possibility of maximal debulking by transurethral resection).

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S38 - CONTEMPORARY BLADDER-SPARING MANAGEMENT OF MUSCLE-INVASIVE BLADDER CANCER - ONCOLOGIST STANDPOINT

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Modern oncology has witnessed adoption of organ-preservation strategies in many tumor sites where combination of debulking surgery, radiotherapy and systemic treatment has become a standard of care. Such paradigm-shift examples are head and neck cancer, anal cancer, breast cancer, prostate cancer etc.

According to relevant guidelines for management of muscle-invasive bladder cancer (MIBC), i.e. European Association of Urology, American Urology Association, radical cystectomy is considered standard of care for muscle-invasive disease and in majority of cases is treatment of choice for many patients. However, in certain jurisdictions bladder sparing has gained momentum, like in UK where up to 60% of MIBCs are managed by organ sparing approach. In this setting, cystectomy is kept for salvage.

Prospective studies of bladder preservation

There is plenty of data supporting the use of bladder preservation in management of patients with MIBC. The evidence has been cumulating over last three decades. Several key element of successful bladder preservation have been clearly established:

1. Appropriate patient selection
2. Maximal initial transurethral resection of bladder tumor (TURBT)
3. Precision radiotherapy with concurrent systemic treatment as radiosensitizer
4. Cystoscopic assessment of treatment response
5. Prompt cystectomy for non-responders
6. Strict cystoscopic surveillance protocol
7. Cystectomy for salvage of invasive recurrence

Ideal candidates for bladder preservation are MIBC patients with unifocal cT2 or cT3a tumor <5 cm and certain level of bladder functioning. These tumors are amendable for high quality debulking surgery. Many studies confirmed that patients with large tumors, with multifocal disease, with tumor-related hydronephrosis are not good candidates as these factors are associated with higher likelihood of invasive recurrence and preservation failure. In these patients the best option is radical cystectomy. Importantly, patients with carcinoma-in-situ component are at high risk of failure of chemoradiation therefore in these patients this option should not be offered.

Emphasis on debulking surgery

High-quality and maximal TURBT is the key for successful bladder preservation. Therefore, the urologist are important players in bladder sparing approach. Surgeon should resect all visible bladder disease. Also taking multiple biopsies from suspicious bladder areas are necessary to exclude CIS component.

Chemoradiotherapy

Radiation dose needed to control urothelial cancer is between 55 and 66 Gy. Urothelial cancer is radiosensitive disease. Local control with radiotherapy alone is 30-40%. RTOG trials established clinical

practice of bladder preservation and tested different approaches such as conventional radiotherapy vs hyperfractionated radiotherapy, giving neoadjuvant chemotherapy before bladder sparing, giving concomitant chemotherapy. Neoadjuvant chemotherapy has been shown not to improve outcomes of chemoradiation therefore is discouraged in this setting. On contrary, neoadjuvant chemotherapy before cystectomy for MIBC cisplatin-fit patients is still standard of care. Concurrent chemotherapy improves outcomes of bladder preservation (both local control and survival) by 20%. Most common radiosensitizing regimen is weekly cisplatin or gemcitabine. RTOG 0712 showed gemcitabine to be less toxic compared to cisplatin but equally effective. British trial BC2001 established mitomycin-C and 5-fluorouracil chemotherapy as standard concurrent chemotherapy option for patients not fit to receive cisplatin. Downsize of this regimen is needed for continuous intravenous infusion and is more resource intense. In appropriately chosen MIBC patients, with modern chemoradiotherapy, 5-year local control in range >80% can be regularly achieved.

How to manage bladder sparing failures?

In RTOG trials, assessment cystoscopy was performed in the middle of radiotherapy course (around 40 Gy) and if incomplete response observed, salvage cystectomy would be recommended. After completion full dose chemoradiotherapy (i.e. conventionally fractionated regimen 64 Gy in 32 fractions), surveillance cystoscopy is needed every 3-6 months.

Importantly, 20% of patients who did achieve a complete response of chemoradiation, will have superficial relapse (Ta, T1, CIS), and 15% will have muscle-invasive recurrence which should be managed with prompt cystectomy.

Biomarkers for bladder preservation

Optimally, we should aim to develop biomarkers to be able to identify optimal candidates for bladder sparing. This issue is under active research. RTOG studies showed that mutations in p53, CDKN2A and RB had no impact, however HER2 amplification led to higher treatment failure. In UK, MRE11 (DNA damage response gene) was investigated but showed not to be reliably assessed by routine immunohistochemistry. Other markers are investigated (like PD-L1 and molecular subtypes, especially immune-infiltrated), however there is no prospective validation.

To conclude, bladder sparing is an attractive organ-preserving option for significant portion of patients with MIBC and should be discussed at multidisciplinary meeting and offered to patients. NCCN guidelines endorsed bladder sparing as alternative management option in patients with MIBC comparable to cystectomy.

Keywords: chemoradiotherapy, muscle-invasive bladder cancer, organ preservation, radical cystectomy, radiotherapy

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S39 - UPCOMING POSSIBILITIES FOR SYSTEMIC TREATMENT OF ADVANCED BLADDER CANCER

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One in ten cancer patient worldwide suffers from bladder cancer. Most frequently, histopathological type is urothelial cancer, caused among other, by smoking.[i] Urothelial cancers most commonly arise in the bladder, followed by renal pelvis and ureter. Luckily, ¾ of cases are non-muscle-invasive disease, papillary noninvasive tumor (Ta), lamina propria invasive tumors (T1) or flat high-grade lesions (CIS), and in rest of the patients as a muscle-invasive disease and metastatic cancer.

Combination of chemotherapy and immune therapy was widely investigated, through trials such as BLASST -1, ABACUS or PURE-01. In BLASST-1 patients received cisplatin on day 1; gemcitabine on days 1 and 8; and nivolumab on day 8 every 21 days for 4 cycles followed by radical cystectomy within 8 weeks. The addition of nivolumab offered patients 49% complete response rate, comparable toxicity and further more, 66% of patients achieving non-invasive disease at surgery.

ABACUS and PURE-01 investigated the neoadjuvant use of monotherapy atezolizumab and pembrolizumab, respectively. Comparing the trials, PURE-01 included higher rate of T3 disease (63% vs 23% in ABACUS), and, interestingly, achieved higher rate of PRC, 42% vs 29%. pCR was more frequent in patients with higher PD-L1 positivity.

In the adjuvant setting, the updated analysis of POUT trial, a phase 3 trial, after 49 months of follow-up showed no significant overall survival benefit, but significantly increased DFS (disease free survival; HR 0.45, 95% CI 0.30–0.68; p=0.0001) and MFS (metastasis free survival, (HR 0.48, 95% CI 0.31–0.74; log-rank p=0.0007) with adjuvant chemotherapy given to high-risk upper urinary tract versus surveillance. Hence, adjuvant platinum based chemotherapy should be considered a new standard.

As clinical trials enroll in the direction of adjuvant immune therapy, the results of two clinical trials were conflicting: imVigor 010 and Checkmate 274. Atezolizumab showed no impact in terms of DFS (0.89 (95% CI 0.74, 1.08); $P = 0.2446$) nor OS (HR 0.85 (95% CI 0.66, 1.09), in high-risk, muscle-invasive urothelial cancer after radical cystectomy. The latter trial, Checkmate 274, showed very convincing results in similar patient population. Disease free survival in both ITT (HR 0.70) and, even more, in PD-L1 positive population was significantly prolonged (HR 0.53). In the subgroup analysis, the impact of nivolumab was consistent throughout the groups. There is no obvious answer to why the results of two similar trials differ - there was a difference in PD-L1 testing, in the comparator arm, in number of patients with $\leq T3$ tumors. The striking difference was in toxicity, which was three-fold higher in Checkmate 274 population, than in imVigor 010. However, although it has not met the primary endpoint, imVigor010 gave us a useful insight in exploratory bio-marker analysis as it showed that ctDNA positivity identified patients with high-risk MIUC likely to derive DFS and OS improvement from adjuvant atezolizumab.

In the first-line setting, the paper presented by Galsky, offered the possibility of first line immunotherapy with atezolizumab for platinum-ineligible patients, that are PD-L1 positive. The novelty in the treatment strategy is avelumab maintenance therapy. In the JAVELIN Bladder 100 study, avelumab plus best supportive care (BSC) significantly extended OS compared with BSC alone in the two primary populations of all randomized patients and patients whose tumors were PD-L1+, and significantly more patients who received avelumab as first-line maintenance were alive at one year. The clinical benefits of avelumab were seen across a range of patient populations. Median OS was 21.4 months (95% CI, 18.9 to 26.1) vs 14.3 months (95% CI, 12.9 to 17.9), respectively (HR 0.69; 95% CI, 0.56 to 0.86; $P < 0.001$). There was no difference in chemotherapy prior to avelumab treatment as HRs were 0.69 and 0.66 for cisplatin/gemcitabine and carboplatin/gemcitabine, respectively.

However, the biggest outbreak lately is the use of antibody-drug-conjugates or ADC's: enfortumab vedotin and sacituzumab govitecan. The results of EV-301 trial position enfortumab vedotin as a new standard of care for patients on +2L of treatment as its OS is impressive 12.9 months vs 8.9 months for chemotherapy (HR: 0.70 (95% CI: 0.56, 0.89), with its effect consistent in all subgroups. However, prescribing physicians should be aware of its toxicity profile as 51% of patients can develop higher grade toxicity.

In conclusion, muscle-invasive bladder cancer is very aggressive disease, with extremely poor prognosis. There are new agents and modalities on horizon, primarily immunotherapy that has, after proven benefit in metastatic setting, shown good results in early stages of the disease and is being tested in number of randomised clinical trials.

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S40 - OPTIMAL SEQUENCING OF SYSTEMIC THERAPY IN METASTATIC RENAL CELL CARCINOMA

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The landscape of systemic treatment regimens for metastatic renal cell carcinoma (mRCC) has expanded dramatically over the past 15 years. Although vascular growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) continue to have an important role, immunotherapy with antiprogrammed-death (anti-PD-1)/programmed death–ligand (anti-PD-L1) immune checkpoint antibodies in combination with either a second immune modulating antibody or a VEGFR-TKI have emerged to be the optimal choice for most treatment-naive patients.

Systemic frontline therapy options now include immune checkpoint inhibitor–based combination therapies such as nivolumab/ipilimumab, avelumab/axitinib, pembrolizumab/axitinib, nivolumab/cabozantinib, and the results from CLEAR study support the potential use of pembrolizumab/lenvatinib for the first-line treatment.

The first trial that demonstrated superiority for the combination of nivolumab (anti-PD-1 antibody)/ipilimumab (anti-CTLA-4 antibody) over sunitinib in patients with IMDC intermediate and poor risk mRCC was **CheckMate-214**. Updated results of this trial (48 months median follow-up) continued to show a persistent overall survival (OS) and progression free survival (PFS) benefit in favor of the nivolumab/ipilimumab arm in both the intermediate and poor risk group. Interestingly, the favorable-risk subgroup in CheckMate-214 seemed to fair better with sunitinib, with combination therapy providing an overall response rate (ORR) of 29% versus 52% ($p=.0002$) and PFS of 15.3 months versus 25.1 months ($p=.0001$) when compared with sunitinib monotherapy; survival appeared to be similar in this subgroup.

The other area of progress and interest in terms of recent studies are VEGFR-TKI and immunotherapy combinations as first-line therapy. The **Javelin-101 trial** evaluated patients with mRCC from all IMDC

risk subgroups and demonstrated the superiority of avelumab (anti-PD-L1 antibody)/axitinib (VEGFR-TKI) over sunitinib alone for patients regardless of PD-L1 status, with a median PFS of 13.8 months versus 8.4 months ($p=.0001$) for avelumab/axitinib versus sunitinib in the intention to treat arm.

Combination of pembrolizumab/axitinib was tested in the **KEYNOTE-426 trial**, in which this combination was compared with sunitinib, showing an 82.3% OS versus 72.1% OS at 18 months ($p=.0001$). This study also included all risk subgroups and showed a median PFS of 15.1 months versus 11.1 months ($p=.001$) in favor of the combination versus sunitinib alone.

Results of the phase III **CheckMate 9ER trial**, presented at ESMO Virtual Congress 2020, have provided a new first-line treatment option for patients with mRCC. After median follow-up of two years, cabozantinib in combination with nivolumab demonstrated superiority over sunitinib by doubling the PFS time (16.6 months versus 8.3 months, $p=.0001$), doubling ORR (55.7% versus 27.1%, $p=.0001$), and significantly improving OS.

Recent-breaking results of the randomized, open-label, phase III **CLEAR study**, presented at the 2021 Genitourinary Cancers Symposium, have demonstrated a significant PFS gain (23.9 months versus 9.2 months) with use of lenvatinib plus pembrolizumab versus sunitinib for the first-line treatment of clear cell mRCC. The PFS improvement of 14.7 months with pembrolizumab-levatinib is the largest versus sunitinib in a first-line mRCC trial, and the benefit was consistent across IMDC risk groups. A third arm of the CLEAR study showed a median PFS of 14.7 months with lenvatinib plus everolimus, which was superior to sunitinib (HR 0.65, 95% CI 0.53-0.80, $p<.0001$).

Combination of anti-PD-1/PD-L1 plus anti-CTLA-4 has not yet been compared head-to-head with immune checkpoint inhibitor plus VEGFR-TKI. Existing clinical decision making in daily practice currently relies on assumptions based on cross-trial comparisons; but, there is a growing body of evidence regarding clinical and genomic features that potentially might guide treatment selection. The ongoing **COSMIC-313 trial** (NCT03937219) is randomizing to triplet ipilimumab-nivolumab-cabozantinib versus ipilimumab-nivolumab and enrolled its first patient in June 2019. This trial aims for a primary outcome of improving PFS per RECIST 1.1.

The disease management after first-line therapy, and particularly after receipt of combination therapy, requires consideration of many patient- and disease related factors. For each of these aforementioned treatment modalities, only a certain proportion of the patients have demonstrated benefit across various measurable outcomes, including PFS, OS, and ORR. As such, all forms of treatment currently serve crucial roles in the current paradigm for the treatment of mRCC. If disease progression is confirmed, switching to an alternative class of agent is recommended. If immunotherapy is used in first line, a VEGFR-TKI is preferred. The only available prospective data in this setting are for axitinib from a phase II single-arm trial, though subgroup analysis of the phase III **METEOR trial** showed activity for cabozantinib in the post immunotherapy setting. If single-agent TKI is used in first-line therapy, data from **CheckMate-025** support the use of nivolumab as second line, but the combination of ipilimumab/nivolumab is also used in practice. There are limited data on optimal management after progression on first-line combination therapy. Some clinicians choose to switch patients to cabozantinib or the combination of lenvatinib and everolimus in this setting (if no prior exposure to these agents) or enroll patients in a clinical trial.

There is an urgent need for additional classes of therapy in RCC beyond VEGF-TKI and immunotherapy. Clear cell mRCC, often characterized by alterations in the Von Hippel-Lindau (VHL) gene, is the most common subtype, accounting for about 75% to 85% of cases. One promising target is HIF-2 α , which is linked to the VHL pathway and oxygen sensing. Phase I and II studies with HIF-2 α inhibitors are under way, with initial results showing evidence of single-agent activity in heavily pretreated patients. There are

efforts underway to combine this agent with other TKIs or immunotherapy in an attempt to boost response and circumvent resistance.

In conclusion, as the list of therapeutic options has grown, the selection of treatment among individual patients has become more challenging. Most patients ultimately require additional lines of therapy, and we must think carefully when switching to another therapy, particularly in situations of drug intolerance or apparent disease progression. The disease management after first-line therapy, and particularly after receipt of combination therapy, requires consideration of many patient- and disease related factors. Biomarker models are needed to help predict responses. Nevertheless, despite many recent drug approvals for mRCC, there remains a pressing need to identify new therapeutic targets in this disease.

Keywords: renal cell carcinoma, systemic therapy, sequencing

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S41 - ROLE OF RADIOTHERAPY IN THE TREATMENT OF LOCALLY ADVANCED PENILE CANCER

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Penile cancer is a rare but aggressive tumor that most commonly occurs between the ages of 50-70 years. The most common is squamous cell carcinoma that develops on the epithelium of the inner foreskin and glans. Early diagnosis is of great importance because 5-year survival is about 50 % (> 85% in patients with negative lymph nodes and 29% - 40 % in patients with positive lymph nodes and 0 % in patients with affected pelvic lymph nodes). Treatment modalities depend on the stage of the disease, but the backbone

of treatment is surgical resection of the primary tumor and regional lymph nodes with the use of neoadjuvant/adjuvant chemotherapy and radiotherapy.

A 59-year-old patient was examined in May 2020 by a urologist for bilateral inguinal lymphadenitis, scrotal and penile edema. Clinical examination in the right groin showed a tumor mass with the size of 5x10 cm. A biopsy of the change in the penis confirmed squamous cell carcinoma and cytological puncture of the lymph nodes reveals elements of granulomatous inflammation. In July 2020, a partial amputation of the penis and an excisional biopsy of the inguinal lymph nodes was performed, which confirmed the metastasis to the lymph nodes.

Diagnostic imaging revealed bilateral enlarged inguinal lymph nodes. The right diameter of the lymph node conglomerate was 64 mm and on the left diameter was 38 mm. A bilateral inguinal lymphadenectomy was performed. Pathohistological findings confirmed metastatically altered lymph node conglomerates up to 5 cm in size on both sides.

Follow up postoperative CT scan of the thorax, abdomen, and pelvis showed three suspected lung metastases up to 10 mm in size and multiplied and enlarged para aortocaval lymph nodes up to 20 mm in size. The patient is in good general condition but complains about swelling of both lower extremities. In August 2020, treatment with polychemotherapy according to the TIP protocol (paclitaxel, ifosfamide, cisplatin) was started. We opted for PKT according to the TIP protocol based on the results of a phase II study which showed that 50% of patients had a response to therapy and a longer time to disease progression and longer overall survival than the control group. In October 2020, the last (IV) cycle of systemic chemotherapy was applied, which was well tolerated by the patient. Follow up CT scan of the thorax, abdomen, and pelvis showed complete regression of metastatic changes in the lungs as well as para aortocaval lymph nodes but showed local recurrence in the area of the root of the penis and enlarged inguinal lymph nodes bilaterally. Cytologically confirmed squamous cell carcinoma. In December 2020, radiotherapy was started with concomitant administration of cisplatin. The patient received a total TD of 50 Gy in 25 fractions on the pelvic lymph nodes with a boost of 16 Gy in 8 fractions on the primary tumor and inguinal lymph nodes on both sides. A retrospective analysis from the National cancer database showed a benefit in terms of longer overall survival in patients in stage III of the disease receiving chemoradiotherapy after bilateral inguinal lymphadenectomy. The patient was referred for a control CT of the thorax, abdomen, and pelvis.

Penile cancer is an aggressive disease that can be cured at an early stage if adequate treatment is applied, but its prognosis largely depends on the involvement of the inguinal lymph nodes. Treatment requires a multimodal and multidisciplinary approach consisting of polychemotherapy, surgical treatment, and radiotherapy.

Keywords: penile cancer, neoadjuvant/adjuvant chemotherapy, radiochemotherapy, inguinal lymphadenopathy

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S42 - TESTICULAR CANCER – AN UNEXPECTED COURSE OF THE DISEASE

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Although testicular cancer is a rare tumor with an overall incidence of less than 1% annually, its incidence among men aged 20 to 34 is constantly increasing. There are two major histologic types: pure seminoma and nonseminomatous germ cell tumors. The latter ones are rarer but also more aggressive and include embryonic carcinoma, choriocarcinoma, yolk sac tumors and teratomas. Rarely, in 2% of cases, teratomas may contain elements of somatic cancer, such as sarcoma or adenocarcinoma and it is then referred to as a *teratoma with somatic type malignancy*. In this summary we present a case of a 25-year old man with no previous medical history who noticed painless swelling of his right testis in 4./2018. Clinical examination revealed a testicular cancer with biomarker levels β HCG 12.9 IU/L, AFP 63.8 IJ/mL, LDH 190 U/L. Patient underwent a right-sided orchiectomy and according to pathologic report tumor was seminoma, pT2, stage IB. We requested revision of pathologic report which confirmed the original finding. Postoperatively, tumor biomarkers were β HCG 0 IU/L, AFP 5.5 IJ/mL, LDH 180 U/L. According to all diagnostic findings it was clear that we diagnosed seminoma with increased levels of AFP which is treated as nonseminomatous tumor. Accordingly, we continued patient active surveillance until 12./2018. when PET-CT showed malignant activity in retroperitoneal lymph nodes measuring 5.3 x 3.6 cm. Due to the above, we decided to start a chemotherapy. Before starting chemotherapy we encouraged patient to do a semen cryopreservation. Also From January to April of 2019. patient received a total of 3 cycles of PEB chemotherapy and radiologic surveillance reported regression of the disease. In 12./2019. PET-CT finding showed progression of retroperitoneal lymph nodes conglomerate. After MDT discussion, in 2./2020. an open biopsy and partial resection of the conglomerate was done. Pathologic report verified teratoma with somatic neuroendocrine differentiation reaching the resection margin. Soon after the biopsy, disease progressed, so therefore in 6./2020. resection of tumor conglomerate, paraaortal lymph nodes and right ureter was done. Pathologic report confirms teratoma with somatic neuroendocrine differentiation. Two months after the surgery, PET-CT showed disease progression with retroperitoneal nodules up to 2.4 cm in size and new pathologic neck lymph node. Patient presented with severe pain of the anal region, tenesmus and fever. Clinical examination showed the remaining testicle was tumor-free. Due to rapid disease progression in 9./2020. we started second-line PEI chemotherapy. Patient received a total of 6 cycles of chemotherapy so far with a delay of last cycle for a few days due to overcoming COVID 19 infection. After six cycles of therapy patient is pain-free and PET-CT reports constantly show regression of the disease. Since

two independent pathologic analysis reported seminoma after orchiectomy, the question is wheather it is teratoma with somatic type malignancy. Due to rarity of these tumors, data supporting the tretament are obtained from several case reports and we need more reliable data from controled clinical trials in order to increase treatment success.

Keywords: testicular cancer, seminoma, extragonadal teratoma

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HEAD AND NECK TUMORS

S43 - NEWS IN THE TREATMENT OF HEAD AND NECK CANCERS

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At the beginning of 2021, a second updated meta-analysis of chemotherapy in non-metastatic head and neck cancers (MACH-NC) was published. It included 107 randomized trials completed before 2017, on 19805 patients with a median follow-up of 6.6 years. A significant association ($p < 0.0001$) was found between the effect of treatment on overall survival (OS) and the timing of chemotherapy (induction, concomitant or adjuvant). The effect was limited to concomitant chemotherapy, ($p < 0.0001$, HR 0.83) and an absolute benefit on 5 (10) year survival was 6.5 (3.6)%. Efficacy decreased as the patient's age increased ($p_{\text{trend}} = 0.03$). OS was not increased by the addition of induction (HR = 0.96) or adjuvant chemotherapy (HR 1.02). The efficacy of induction chemotherapy decreases with poorer performance status ($p_{\text{trend}} = 0.03$) This updated meta-analysis confirms the efficacy of adding chemotherapy to loco-regional treatment and the superiority of concomitant over induction or adjuvant chemotherapy. Taxane-based induction chemotherapy may play a role in the selected patients.

There are high expectations from the combination of immunotherapy and stereotactic body radiation therapy (SBRT) in the treatment of metastatic head and neck tumors. However, so far the only randomized phase II study on 62 patients with metastatic head and neck cancers found no difference in efficacy in nivolumab and SBRT-treated patients compared to nivolumab-alone patients. Based on the results of the study, the authors concluded that the addition of nivolumab to SBTR did not affect the safety profile, nor did it improve overall response rate (ORR), progression free survival (PFS), and OS. No abscopal effect was observed in nivolumab and SBRT-treated patients.

A phase III KEYNOTE-048 study was performed on 882 patients with three arms of therapy: pembrolizumab, pembrolizumab + carboplatin (or cisplatin) + 5-fluorouracil and carboplatin (or cisplatin) + 5-fluorouracil + cetuximab (EXTREME protocol). Patients with R/M head and neck cancers were included. In patients with PD-L1 CPS expression (combined positive score) ≥ 20 , the median survival was significantly better in the pembrolizumab monotherapy group compared to the EXTREME protocol, 14.9 : 10.7 months (HR 0.61; $p = 0.0007$), while ORR (overall response rate) and PFS were without statistically significant differences. Furthermore, pembrolizumab + chemotherapy with platinum salts and 5-fluorouracil had a better median survival than the combination according to the EXTREME protocol, 13.0: 10.7 months (HR 0.77; $p = 0.0034$). Based on these results, pembrolizumab monotherapy is the treatment of choice in the relevant clinical guidelines for first-line treatment of R/M head and neck cancers in patients with high PD-L1 expression, and the combination of pembrolizumab and chemotherapy with platinum compounds for the same indication regardless of PD- L1 expression.

In multicenter randomized phase 2 study (GORTEC 2014-01 TPExtreme) performed on 541 patients, randomization 1:1, the TPEX protocol (docetaxel, platinum, cetuximab) showed a comparable efficacy and safety profile compared to the EXTREME protocol (platinum, 5-fluorouracil, cetuximab) OS did not differ significantly between groups (median 14.5 months in the TPEX group and 13.4 months in the EXTREME

group) (HR 0.89), 214 (81%) of the 263 patients in the TPEX group receiving TPEX versus 246 (93%) of 265 patients in the EXTREME group had grade 3 or greater adverse events during chemotherapy ($p < 0.0001$). Protocol TPEX could have a favorable safety profile. Although the study did not reach a primary endpoint (without a significant improvement in OS with TPEX compared to EXTREME), TPEX could provide an alternative to standard therapy with the EXTREME regimen in the treatment of first-line patients with recurrent and metastatic head and neck tumors, especially in those who are not good candidates for immunotherapy with PD-1 inhibitors.

The results of the JAVELIN Head & Neck 100 study, which was the first randomized phase 3 study to combine checkpoint inhibitors and chemoradiotherapy in any tumor site, were presented at the ESMO 2020 virtual congress. The primary endpoint of study was PFS according to modified RECIST 1.1 criteria. It was performed on 697 patients with high-risk locally advanced head and neck cancers. Standard therapy (IMRT 70 Gy/35x + 3 cycles of cisplatin 100 mg/m²) was compared with the same therapy to which the PD-L1 inhibitor avelumab was added one week before of the start of chemoradiotherapy, during chemoradiotherapy and as maintenance therapy after the end of chemotherapy. The study was discontinued after the first preliminary analysis due to surprising results for PFS which was not significantly statistically better in the study arm with the addition of avelumab compared to standard therapy. Moreover, grade 3/4 side effects were higher in the group of patients receiving avelumab (80%:74%). Subsequent analysis found that HR for PFS was numerically more favorable for avelumab + CRT in patients with high PD-L1 expression.

Keywords: head and neck cancers, immunotherapy, stereotactic body radiation therapy

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S44 - CHALLENGES OF CNS TUMOR TREATMENT IN THE REPUBLIC OF CROATIA

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Treatment of central nervous system tumors is associated with major challenges that are common to the entire neuro-oncology community in the world, but there are still challenges that are somewhat more common in Croatia.

In general, we encounter unknown etiological factors, lack of early detection methods, the impossibility of radical surgical resection, complex pathohistological diagnosis, radiosensitivity and specific structure of the brain, blood-brain barrier, *immune desert*, poor treatment results, and late treatment sequelae.

Immunotherapy has not been shown to be effective and glioblastomas today, unfortunately, represent a model of resistance amid the success of immunotherapy in other cancers, thus focusing current efforts to alleviating the immunotolerance and evading the escape mechanisms of tumor cells to therapy, caused by inter- and intra-tumoral heterogeneity. Immunotherapy is likely to fail because of several reasons such as missing antigens, impaired T cell priming, systemic inflammation, and local inhibition. Ongoing clinical trials are investigating the efficacy of combinations of immunotherapy and chemotherapy, VEGF targeting therapy, oncolytic virus, double immune checkpoint inhibition, or vaccination.

Targeted therapy is becoming part of the modern treatment of patients with primary and secondary tumors of the central nervous system. Since the last WHO classification of CNS tumors in 2016, molecular markers have an increasing diagnostic, predictive, and prognostic value. New ones are recognized every day and are periodically published in the subclassifications of cIMPACT-NOW versions 1-7. Thus, for example, EGFR amplification, TERT p methylation, and +7 / -10 are important in the diagnosis of diffuse astrocytomas with molecular characteristics (and biological behavior) of glioblastoma or C11orf95, YAP1 fusion, and MYCN amplification in medulloblastoma.

Two-thirds of CNS tumors are benign tumors, and meningiomas are the most common. Although benign in the histological picture, 5-yrs. survival ranges from 83% for grade I to 32% for grade III. There is no standard systemic therapy. AKT1 and SMO mutations are of particular importance because they are found in cranial base meningiomas where radical surgical resection is limited. These findings led to the first clinical study to provide targeted therapy depending on molecular status (Alliance A071401). Patients divided into four groups receive SMO, AKT, CDK, or FAK inhibitor. To date, the analyzed group of patients receiving the FAK inhibitor has achieved the primary goal of the study and 50% of patients have stable disease after 6 months. Craniopharyngiomas are benign tumors of children and adults that, with their expansive growth, sample significant damage to surrounding structures. Two subtypes of craniopharyngioma are characterized by the existence of driver mutation; adamantinomatous with CTNNB1 mutation and papillary with BRAF V600E mutation. The Alliance / NCI A071601 clinical study included patients with the BRAF mutation receiving vemurafenib and cobimetinib.

Glioma tumors show an interesting molecular profile. In a series of 404 patients, 10% of patients had fusion with possible therapeutic significance, 11% glioblastoma, and up to 43% pilocytic astrocytomas. The most common are NTRK, MET, EGFR, FGFR3, BRAF, and PDGFRA fusions. First-generation NTRK inhibitors larotrectinib and entrectinib show a very high, long-lasting intracranial clinical and radiological response of 80% in primary and secondary central nervous system tumors. Despite the rarity of NTRK

fusion, the potential clinical benefit in patients with this change is immeasurable (6). Clinical trials involving patients based on molecular testing, such as NCI-MATCH and inSIGHT, are ongoing. Due to limited therapeutic options, NCCN guidelines recommend molecular testing, especially in rare tumors where there are no established treatment guidelines nor is it possible to conduct a randomized prospective clinical study.

Approximately 80% of low-grade glioma harbor mutant isocitrate dehydrogenase 1/2 (IDH1/2) driver mutations. Thus, inhibition of mutant IDH is considered a potential therapeutic target. Several mutant IDH inhibitors are currently in clinical trials, including AG-881 and BAY-1436032.

Treatment options are even more limited in the time of tumor recurrence. Thanks to the continuous improvement in radiation science and technology, reirradiation has emerged as a feasible approach for patients with brain tumors. Using stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT), either hypofractionated or conventionally fractionated schedules. However, there are still questions to be answered about the efficacy and toxicity associated with the second course of radiation.

In Croatia, we encounter some specifics and challenges in the treatment of CNS tumors. The number of people suffering from brain tumors is still unknown because the cancer registry records malignant diseases, and the line between malignant and benign is not as clear as in other tumor sites. Benign tumors may have malignant potential or because of their position lead to the same morbidity as malignant tumors and even death. It is for this reason that over time, in many countries (USA, Canada, Denmark, Austria, Japan) special registries are established for brain tumors that record benign, intermediate, and malignant tumors.

As rare tumors usually do not have treatment guidelines based on randomized clinical studies, the question arises as to the importance of molecular profiling, by which test, at what stage of the disease. In interpreting the findings, we encounter problems with the non-existence of a mutational tumor board that would include a pathologist and a molecular biologist, a geneticist, and possibly another profession. Sometimes the implementation of molecular profiling, and especially treatment according to the finding, is based on individual enthusiasm and not on the usual and well-known procedure. No matter how important multidisciplinary in oncology is due to the small number of oncologists dealing with tumors of the central nervous system, multidisciplinary teams often have one or two oncologists who then make the decision about oncology treatment. Therefore, it is extremely important to develop and strengthen the cooperation of neuro-oncologists at the level of the whole of Croatia. Pediatric neuro-oncology faces even greater challenges. Children with a history of brain tumors, and very often expressed sequelae of treatment, at the age of majority or a few years later continue treatment and follow-up with an oncologist. Maintaining MDT with pediatricians can facilitate this transitional process.

In the treatment of CNS tumors, especially in younger patients and rare diagnoses, it is necessary to differentiate the approach from tumors of high incidence where there are prospective randomized studies. This requires greater flexibility in approach, greater improvisation if there are no guidelines for treatment, and all this requires professional, organizational and financial support.

Keywords: brain tumors, molecular profiling, reirradiation, treatment

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