

ORAL PRESENTATION

S1 - Immunotherapy in bladder cancer

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Immunotherapy presents a completely new approach in systemic treatment in oncology, recognized also in genitourinary tumors and bladder cancer as well. In contrast to renal cancer, where we have some therapeutic options of systemic treatment for some time and thus more or less known sequence of treatment lines, for metastatic bladder cancer we had very few treatment options. For several decades they are based on chemotherapy-protocols (so called MVAC-protocol or cisplatin and gemcitabine-combination), but with no further standard lines of treatment. Except much less toxicity, immunotherapy showed surprisingly high activity, which we haven't seen for last 30 years. The basic concept of this kind of systemic treatment is founded on interaction between PD-molecule (PD=programmed death) expressed on host (immune) cells and PD-L1 (ligand for PD), produced by tumor and immune cells, as well. Antibodies which we examined as therapy, bind on the PD-molecule or PD-L1 molecule thus disturbing their interaction. Among new antibodies, there is *atezolizumab* (IgG1 anti-PD-L1 monoclonal antibody), tested in clinical study phase II, known as *Imvigor*, which included 429 patients, previously treated (N=310) or untreated (N=129) by chemotherapy based on chemotherapy. Objective response was 15%, and 26% in those with tumors infiltrating 5% of PD-L1 expressing cells (N=100). US FDA (Food and Drug Administration) has granted *atezolizumab* accelerated approval in May 2016 for first line treatment of metastatic urothelial cancer, as a first anti-PD-L1 immunotherapy. Phase III study is on going. The drug is applied in dose of 1200 mg intravenously, q3w during 60 min infusion until progression of disease or unacceptable toxicity. There are also very encouraging results with other agents, like *pembrolizumab*, showing similar response of 25% (7/28). In phase III clinical study (KEYNOTE-045), *pembrolizumab* was compared to chemotherapy, given up to 24 months, and overall survival was superior in immunotherapy arm (10.3 vs 7.4 months, $p=0.0022$). *Avelumab* is next agent (IgG1 anti-PD-L1 antibody, completely by mechanism of antibody-dependent cell cytotoxicity), with overall response of about 18% (8/44). These results led to further clinical trials with PD-1/PD-L1-targeted agents, either in combination or as monotherapy. *Nivolumab* was granted approval by US FDA in February 2017, as additional PD-L1 inhibitor in treatment of urothelial cancer. *Nivolumab* is given 240 mg intravenously in 60 minutes-infusion, every 2 weeks, until disease progression or unacceptable toxicity. In phase II single-arm clinical trial (Checkmate-275), there were 270 patients

Nivolumab was studied in phase II study (Checkmate-275), with 270 patients, with overall response of 19.6%, 23% of patients had stable disease. In conclusion, we still do not have clear criteria for patients expecting to have benefit from immunotherapy. Nevertheless, a portion of patients showing good response in urological malignancies is mostly comparable to results obtained from other primary tumors treated with immunotherapy (about 20%). Thus, this promising treatment is recommendable for only part of our patients.

S2 - Therapeutic options in treatment of hormonal resistant breast cancer

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Approximately 70% of breast cancers (BC) may be considered hormone responsive due to expression of estrogen and/or progesterone receptors (ER and PR). Hormonal therapy (HT) is a standard treatment option for hormonal receptor positive (HR+) BC in all disease stages. HT include nonsteroidal and steroidal aromatase inhibitors (AI), selective ER modulators (tamoxifen), ER down regulators (fulvestrant), progesterin as well as androgens, and high-dose estrogen.

Despite standard adjuvant hormonal therapy, approximately 20–30% of patients with HR+ BC will suffer recurrences and the development of metastatic disease. It is estimated that ~30% of patients with metastatic BC regress with initial HT and another 20% have prolonged stable disease. Response duration to subsequent therapies correspondingly decreases, and all patients with metastatic disease ultimately become resistant to HT.

De novo or acquired resistance to HT remains an important therapeutic challenge. Resistance to HT in HR+ breast cancer is associated with diverse molecular mechanisms, including acquired mutations in ER- α , cross talk between ER and growth factor receptor signalling such as PI3K/Akt/mTOR pathway, HER family members and fibroblast growth factor receptor (FGFR) pathways, constitutive activation of cyclin-dependent kinases (CDK) 4 and 6 as well as epigenetic modifications by histone deacetylase (HDAC) and interactions with tumor microenvironment and host immune response.

Increased understanding of hormonal resistance mechanisms has led to the development of targeted agents that overcome resistance and enhance the efficacy of HT. The several clinical trials showed that addition of a targeted therapy to HT *versus* HT alone allows prolongation of progression-free survival (PFS) in HR+, HER2 negative BC. Based on such clinical trials two agents are currently approved by European Medicines Agency (EMA), including the mTOR inhibitor everolimus and the CDK 4/6 inhibitor palbociclib.

PI3K/AKT/mTOR is the most commonly altered pathway in HR+ BC, and there are a number of agents targeting this specific pathway. In clinical trial BOLERO 2 combination of mTOR inhibitor everolimus and a steroidal AI exemestane was compared with exemestane alone and showed the doubling of the PFS, however prolongation of survival was not statistically significant.

CDK 4 and 6 interacts with cyclin D1 in an active protein complex, that promotes cell proliferation. There is a strong link between the actions of estrogen and CDK4/6 activity. Therefore, CDK 4/6 represent potential therapeutic targets for HR+ breast cancer. Inhibition of the CDK 4/6 pathways is possible by small molecule inhibitor drugs such as palbociclib, ribociclib, and abemaciclib. Palbociclib was the first and at that time only anti-CDK 4/6 drug approved by EMA based on the PALOMA 2 and 3 clinical trials, which showed that addition of palbociclib either to letrozole in first line or fulvestrant in second line doubled PFS compared to HT alone.

Other targeted therapies next to mTOR inhibitors and CDK4/6 inhibitors that are being actively investigated in the clinic include, PI3K inhibitors (buparlisib, alpelisib, and taselisib), HDAC inhibitors (entinostat), FGFR inhibitors (dovitinib and lucitinib), and others.

S3 - Future treatment of triple-negative breast cancer

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Breast cancer is the most commonly diagnosed cancer in female population worldwide. Advances in understanding tumor biology, particularly signaling pathways, have led to the development and approval of novel therapeutic agents, especially in HER2 positive and hormone receptor positive subtypes. Triple-negative breast cancer (TNBC) is defined by lack of expression of estrogen receptor, progesterone receptor and HER-2 amplification and accounts for approximately 15-20% of breast cancers. It is also a heterogeneous group of tumors which tend to have an aggressive phenotype with higher recurrence rates and lower survival rates. This subtype lacks unifying molecular alterations that can guide therapy decisions.

To date, there are no approved targeted therapies specifically for this subtype; however, many are in development. The most important future strategies will be those for targeting triple-negative breast cancers through novel receptors, harnessing the immune system, and new ways of targeting angiogenesis.

Ongoing research is investigating targetable novel cell surface receptors, the use checkpoint inhibitors, and identifying subgroups likely to benefit from platinum-based therapies and poly(adenosine diphosphate-ribose) polymerase inhibitors. The androgen receptor (AR) has been identified as a possible predictive biomarker for antiandrogen therapy in ER- breast cancer. AR positivity has been associated with more favorable prognoses in TNBC. There are several studies that show AR is associated with lower Ki-67 proliferative marker, lower mitotic score, lower histologic grade and lower clinical stage.

Since the presence of residual disease after completion of neoadjuvant therapy predicts poor prognosis, numerous clinical trials are designed to test the value of further adjuvant therapy in TNBC patients with residual disease. Preliminary results of the CREATE-X (JBCRG-04) trial by the Japan Breast Cancer Research Group were presented at the 2015 San Antonio Breast Cancer Symposium. Two ongoing US studies examine the value of more chemotherapy or immunotherapy as adjuvant treatment for patients with residual TNBC after neoadjuvant chemotherapy.

While numerous studies investigating anti-vascular endothelial growth factor (VEGF) therapy in the neoadjuvant setting suggest improved pathologic complete response rates, especially in TNBC, studies to date have not demonstrated a survival benefit in the adjuvant setting or metastatic setting.

A promising field of clinical research in breast cancer is the use of immune checkpoint inhibitors. By blocking inhibitory molecules or, alternatively, activating stimulatory molecules, these treatments are designed to enhance pre-existing anti-cancer immune responses. Several studies investigating checkpoint inhibitors are currently enrolling breast cancer patients. Approximately 20% of TNBCs express PD-L1, and expression of PD-L1 is associated with poor prognosis, thus making this aggressive phenotype attractive subtype in which to investigate PD-L1 blockade.

S4 – Genomics and epigenomics in cancer research and their potential use in diagnostics, prognostics and therapy

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Genomic, epigenomic and proteomic (-omic) analyses of 50 different types of most frequently occurring malignant tumors (and over 10 rare ones) are in the focus of current research involving top Institutions and Universities around the globe led by the National Cancer Institute (NCI) at the National Institutes of Health (NIH) and Human Genome Sciences in the USA.

Why is it important to look for changes not only in the genome but also in the epigenome of cancer, and primarily in cancer stem cells? Studying cancer has revealed defects in genes that drive the development and growth of a large number of different tumors and their subsequent transformation into a malignant state. The cancer stem cell, through numerous mutations progressively evolves into a more aggressive phenotype, which ultimately ends with metastatic spreading. Epigenetic changes seem to contribute to a significant level in these events, and studies should reveal their frequency, pattern and role in various types of cancer. All this information will further improve our understanding of the biology of cancer and, in turn, would lead to new methods of diagnosing, classifying, predicting the outcome and treating the disease. For example, novel cancer-specific mutations and/or epigenetic changes are reasonable targets for therapeutic intervention. However, not all of them could turn out to be useful, as a large part of mutations of most solid cancers are random and have almost no influence to the course of the disease. They are predominantly a consequence of a failure in the genetic repair machinery. This usually occurs at a stage when cancer stem cell becomes genetically unstable and accelerates its mutation rate. Pathophysiologic factors that are involved in the development of cancer would only be found if we exclude the contribution of “false-positive” ones due to haphazardness of mutations at terminal stages of the disease. There are numerous methods aimed at studying cancer -omics in the search for novel therapeutic targets, and some of them will be presented and explained during the presentation.

Recent introduction of cancer immunotherapies signals hope to development of more successful standards in medical oncology. Majority of clinical research and trials is currently oriented towards finding new immune-checkpoint inhibitors or a combination of already existing ones (anti-PD1, anti-CTLA4) with chemotherapies. In addition, new -omics' research information will definitely have the highest potential to develop better prevention and treatment strategies.

S5 - Aggressive variant of castration resistant prostate cancer: Case report

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A subset of patients with castration-resistant prostate cancer (CRPC) may present with distinct clinical features, different from the classic prostate adenocarcinoma, including rapidly progressive disease with bulky symptomatic tumor masses, exclusive visceral metastases, a predominance of lytic bone metastases, relative low prostatic-specific antigen (PSA) concentration and resistance to androgen ablation. Biopsies performed in such patients may show poorly differentiated carcinomas, neuroendocrine, small-cell or mixed carcinomas. These aggressive tumors often demonstrate low or absent androgen receptor (AR) expression and sometimes express markers of neuroendocrine differentiation. Patients meeting clinical criteria of aggressive prostate cancer have been shown to have poor prognosis and should be considered for platinum-based chemotherapy.

Toward development of a precision medicine, many next-generation sequencing studies have led to significant advances in understanding of genomic alterations in prostate cancer. Except the most common genomic aberrations like fusion of TMPRSS2-ETS and mutations in TP53, AR, RB1 and PTEN/PIK3CA, there is a lot of interest in somatic and germline aberrations in DNA repair genes, such as BRCA2 and ATM that can be targeted by platinum and PARP inhibitors.

This is the case of 62-year-old patient with initially metastatic prostate adenocarcinoma, who, after a period of one year of disease control with androgen ablation, was diagnosed with CRPC with relative low PSA, bulky cholin PET - positron emission tomography negative liver metastases. Treatment with docetaxel chemotherapy failed. Biopsy of liver metastases showed small-cell carcinoma with neuroendocrine differentiation. Subsequently he was treated with combination chemotherapy with cabazitaxel/carboplatin without response. The combination chemotherapy with cisplatin/etoposide achieved excellent clinical and a good radiological and biochemical response. The response was short-lived and patient died.

The aim of this presentation is to stress the importance of recognition of the aggressive variant of prostate cancer to improve patients outcomes. It should serve as a reminder that not all prostate cancer share the same biology and that androgen receptor is not the sole driver of this disease.

S6 - Primary mediastinal germ cell tumors: Case reports

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Germ cell tumors are called extragonadal if there is no evidence of a primary tumor in the testis. They are rare, 1-5% of all germ cell tumors, with the mediastinum and the retroperitoneum being the most common primary sites in adults. Pathogenesis and histology are identical to gonadal (testicular) germ cell tumors, both are divided into seminomas and non-seminomas, but with different biology and prognosis. According to one hypothesis they are derived from primordial germ cell that fail to complete the normal migration to the testis during embryonal development. Like their testicular counterparts primary mediastinal germ cell tumors occur typically in young men, but their prognosis is worse.

Treatment of extragonadal tumors is similar to treatment of testicular germ cell tumors. Standard treatment approach of mediastinal germ cell tumors consists of four courses of cisplatin-based chemotherapy followed by surgical resection of the residual tumor in non-seminomas. Primary mediastinal non-seminomas carry a poor prognosis with 40-50% overall survival after cisplatin-based chemotherapy and surgery. In contrast, mediastinal seminomas have a good prognosis with 88-90% overall survival.

I presented two young men with primary mediastinal non-seminomas but with different tumor biology and clinical outcome. One tumor was inoperable and treated with cisplatin-based chemotherapy, tandem high-dose chemotherapy supported by hematopoietic stem-cell transplantation and salvage chemotherapy, but the patient died of disease progression. The other was operable and was treated with cisplatin-based chemotherapy followed by surgery with complete resection.

Primary mediastinal non-seminomas have very poor prognosis. The most important is that the standard treatment is cisplatin-based chemotherapy followed by surgery.

S7 - Biological therapy of malignant melanoma

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BRAF mutations are present in 40-60% of melanomas. BRAF inhibitors vemurafenib, dabrafenib and encorafenib are used only when a BRAF mutations is present. In comparison with chemotherapy-dacarbazine, BRAF inhibitors used in monotherapy show similar improvements of the overall survival (OS), progression free survival (PFS) and response rate (RR). Resistance to BRAF inhibitors monotherapy develops after 5-7 months of median PFS. The resistance to BRAF inhibitors is associated with a rapid recovery of the MAPK pathway corresponding to a rapid clinical progression. A complete inhibition of the MAPK pathway is obtained by the combination of BRAF and MEK inhibitors which may delay or prevent MAPK-dependent resistance. Another advantage of this combination is that the paradoxical activation resulting in BRAF wild-type melanomas may be reduced, what diminishes adverse events (AEs).

Combination of BRAF and MEK inhibitors are analyzed in three randomized phase 3 clinical trials. In all clinical studies the valuable and consistent results are shown. After three years, in the arm of BRAF+MEK combination therapy 44% of patients are alive, in comparison with anti-BRAF monotherapy (32% are alive). Similar results are obtained with vemurafenib + cobimetinib combination (37% patients survived three years).

In combination studies of BRAF and MEK inhibitors, LDH value, ECOG performance status and the number of metastatic sites have impact on OS and RR.

The more frequently reported AEs with the combination therapy are: pyrexia in 53% of patients, paraesthesia in 31% of patients. AEs which are less evident with anti-BRAF monotherapy than in combination, such as decrease of cardiac EF and chorioretinopathy, which are more frequent in combination; 8% and 1% respectively, but all skin manifestations, including squamous carcinoma are less common.

The quality of life is improved in combination therapy with BRAF and MEK inhibitors in comparison with anti-BRAF monotherapy.

S8 - What is optimal treatment for majority of NSCLC patients: Treatment of patients with NSCLC without activating mutations

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Lung cancer is the most common cause of death among malignant diseases in the World and it is responsible for almost 1.5 million deaths worldwide each year. According to histology, lung cancer is divided in two major subgroups: small cell lung cancer, which accounts for around 15% of all cases, and non-small cell lung cancer (NSCLC). Non-small cell lung cancer is further divided according to histology subtypes to adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Around 20% of patients with non-squamous NSCLC harbour activating mutations in EGFR or ALK gene and therefore can be treated with targeted therapies like EGFR tyrosine-kinase inhibitors (gefitinib, erlotinib, afatinib) or ALK inhibitors (crizotinib, ceritinib, alectinib). Still, vast majority of patients with advanced NSCLC are candidates for systemic treatments. In patients with advanced squamous cell lung cancer, initial systemic treatment is platinum – based doublet (either cisplatin or carboplatin) with cytotoxic agents of third generation like gemcitabine, vinorelbine, paclitaxel or nab-paclitaxel. In patients with non-squamous histology, initial cytotoxic treatment is also platinum based doublet, but preferred combination is pemetrexed with cisplatin or carboplatin. Above mentioned platinum –based doublets are also option in upfront treatment of non-squamous NSCLC. In patients who are initially treated with pemetrexed and cisplatin, after four to six cycles re-evaluation is required and in patients with stable disease, partial or complete response monotherapy with pemetrexed is indicated until progression of the disease. Maintenance treatment with pemetrexed significantly prolongs survival compared to standard 4-6 cycles of platinum-based doublet chemotherapy. Other initial option in patients with non-squamous NSCLC is addition of anti-VEGF drug bevacizumab to paclitaxel-carboplatin combination. Mentioned triplet extended survival for more than two months compared to paclitaxel-carboplatin alone. Choice between two options is left to the physicians and availability of the drugs in each country. In recent years, immunotherapy has emerged as new treatment option in patients with lung cancer. Recent phase III trial in highly positive PD-L1 patients showed superiority of pembrolizumab over platinum-based chemotherapy doublet prolonging both progression-free and overall survival. Unfortunately, nivolumab didn't show the same efficacy in phase III trial as pembrolizumab.

In conclusion, vast majority of patients with non-small cell lung cancer don't harbour activating mutations and are candidates for chemotherapy treatments. Small fraction of patients, approximately 1/3 of them, who express high positivity of PD-L1, can be candidates for pembrolizumab treatment.

S9 - Access to innovative medicines for metastatic melanoma in South-East Europe

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A tremendous breakthrough in oncology has been made with the recent developments, with targeted therapy and immunotherapy for different cancers, including metastatic melanoma. These developments are accompanied by significant rise in unit price of medicines and also their number, leading to the rise in share of expenditure for oncology drugs, and in many countries, including countries of South-East Europe, to the restricted access to these medicines.

In a recent survey of the European Association of dermatologic oncology, a great discrepancy exists in metastatic melanoma treatment across Europe, with restricted access in countries to first-line recommended treatments per current guidelines: combination BRAFi and MEKi, and anti-PD1 immunotherapy. These restrictions were in correlation with health expenditure per capita and human development index, as well as with a health policy performance scores for each country, and will prove to significantly affect the overall survival of this group of patients. While in Greece, Slovenia and Bulgaria innovative medicines are reimbursed after a relatively short delay, in majority of other countries of SE Europe there is a significant delay in reimbursement. In Croatia, first-line targeted therapy and anti-PD1 immunotherapy are fully reimbursed from 2017. In Serbia BRAFi monotherapy (not the combination) and immunotherapy only for BRAF negative patients are reimbursed from 2017. In Romania, Albania and Montenegro, only BRAFi monotherapy is reimbursed, while in Bosnia and Herzegovina innovative medicines for metastatic melanoma are still not reimbursed. Similar results were obtained for other cancer types in a recent ESMO study that showed a large difference in the availability of innovative agents for cancer treatment, particularly for metastatic melanoma, renal cell cancer and non-small cell lung cancer where access to innovative drugs defines therapeutic outcome, classical oncological treatment being mostly ineffective. Several efforts of the European Commission, oncological organizations and patient organizations are underway to improve the access to innovative medicines. Also, pharmaceutical industry is developing several affordability strategies and risk/sharing agreements with the national insurance funds. However, further development of new access models will be mandatory, as well as harmonization of health technology assessment strategies and reimbursement process throughout Europe. Also, a constant adaptation to the latest development in medicine in national healthcare systems is crucial to substantially improve the current situation of cancer care disparities.

The access to innovative treatment for metastatic melanoma (but also for other cancer types) is a major public health problem in the majority of countries of South-East Europe. Therefore, it is crucial to continuously increase the awareness of national and European policymakers, oncological societies, melanoma patients' associations and pharma industry regarding this issue.

S10 - Immunotherapy of metastatic melanoma

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The incidence of melanoma in both males and females continues to rise during the past 40 years despite the stable or declining trends for most cancer types. This aggressive disease accounts for approximately 75% of skin cancer related deaths. Historically, treatment options for patients with advanced stage melanoma have been limited by modest response rates and failure to improve overall survival. The treatment landscape for advanced stage melanoma has changed since 2011 with the approval of ipilimumab (anti CTLA-4) antibody) and BRAF inhibitor vemurafenib, both of which improved overall survival in phase III clinical trials. Since then programmed cell death 1 (PD-1) inhibitors, such as pembrolizumab and nivolumab, second BRAF inhibitor dabrafenib and MEK inhibitors trametinib and cobimetinib, have greatly extended the potential for the treatment success for advanced melanoma. Overall survival rate and long-term benefits had been significantly increased with pembrolizumab and nivolumab in multiple large clinical trials. Combination of nivolumab and ipilimumab is even more effective than nivolumab or ipilimumab alone, however it is more toxic, too. The adverse events associated with these new treatments are generally tolerable and mild to moderate in severity; however, care should be taken when selecting a therapy, since the specific adverse events associated with these treatments are unique, and serious events have been reported.

Therapeutic decisions are complicated by the need to consider patient and disease characteristics, individual treatment goals as well as the different efficacy and safety profiles of agents with varying mechanisms of action and depending on the line of treatment. Long-term survival of patients with advanced melanoma is now a realistic goal, creating the additional need to re-establish how clinical benefit is evaluated. Future will bring also different combinations and sequencing approaches of current treatments which is expected to increase the number of patients who experience clinical benefit.

S11 - Hepatocellular carcinoma

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Evidence-based management of patients with hepatocellular carcinoma (HCC) is key to their optimal care. The Barcelona Clinic Liver Cancer algorithm is the most widely used staging system. Patients with single liver tumors or as many as 3 nodules <3 cm are classified as having very early or early-stage cancer and benefit from resection, transplantation, or ablation. Those with a greater tumor burden, confined to the liver, and who are free of symptoms are considered to have intermediate stage cancer and can benefit from chemoembolization if they still have preserved liver function. Those with symptoms of HCC and/or vascular invasion and/or extrahepatic cancer are considered to have advanced-stage cancer and could benefit from treatment with the kinase inhibitor sorafenib. Patients with end-stage HCC have advanced liver disease that is not suitable for transplantation and/or have intense symptoms. Studies now aim to identify molecular markers and imaging techniques that can detect patients with HCC at earlier stages and better predict their survival time and response to treatment.

Sorafenib is now the standard systemic therapy for HCC. In a phase 3 SHARP trial performed in the West, sorafenib reduced patients' risk of death by 30% (median survival time of 10.7 months with sorafenib vs 7.9 months without). In a trial performed in the East, patients had shorter survival times because they entered the study with more advanced-stage HCC; median survival times were 6.5 months with sorafenib versus 4.2 months without. The magnitude of improvement was the same in each study, indicating that the drug is active in different populations. The most frequent adverse events are hand/food/skin reactions, asthenia, diarrhea, and arterial hypertension, the incidence of which is higher in Asian patients. Up to 30% of the patients have to discontinue treatment because of adverse events, but adverse events (all dermatological AE in first 60 days) correlate with a better outcome. Careful management of patients and appropriate dose adjustments are therefore needed.

Sorafenib is the first treatment option for patients with HCC of BCLC stage C and for patients with HCC of BCLC stages A or B who are not candidates for curative or locoregional treatments due to treatment stage migration and/or untreatable progression because of tumor burden. Sorafenib improves overall survival of patients with HCC with the absence of objective response. Thus, time to tumor progression (TTP) is used to capture benefits of novel molecular agents, but proof of its surrogacy with survival is lacking. This was the reason that treatment was continued beyond progression in the sorafenib trials with refinement of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Thus, PPS (postprogression survival) is influenced by progression pattern and not solely by simultaneous impairment of liver function and performance status.

S12 - Role of angiogenesis inhibitors in treatment of ovarian carcinoma

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Ovarian cancer is the most lethal gynecologic cancer. A significant unmet clinical need exists in ovarian cancer, with no treatment innovation over the past 15 years and minimal improvement in outcomes. Angiogenesis seems to play a major role in the natural history of ovarian cancer, promoting tumor growth and progression in the form of ascites formation and metastatic spread creating a strong rationale to use angiogenesis inhibitors to improve patient outcomes. Bevacizumab, recombinant humanized monoclonal IgG1 antibody that targets vascular endothelial growth factor (VEGF)-A is the angiogenesis inhibitor that has been most extensively studied in ovarian cancer.

Two phase II trials indicate that bevacizumab has single-agent activity in ovarian cancer, both in terms of response rates and progression free survival.

Four phase III randomized trials have been published evaluating the addition of bevacizumab to standard chemotherapy as front-line treatment of advanced ovarian cancer (GOG-0218, ICON 7) and evaluating the combination with chemotherapy in recurrent ovarian cancer (OCEAN trial for platinum-sensitive and AURELIA trial for platinum-resistant disease).

All these trials showed a statistically significant improvement in progression-free survival with no improvement in overall survival has been reported. Although, in ICON 7 trial, an exploratory analysis of 502 patients who had disease with poor prognosis showed a significant difference in overall survival of over 4 months in women who received bevacizumab plus chemotherapy compared to those who received chemotherapy alone.

Many questions remain to be answered regarding the optimal use of bevacizumab in patients with ovarian cancer. These include the optimal dose and duration of treatment. It remains unclear whether bevacizumab maintenance needs to be extended until disease progression, as it was done in trials for recurrent ovarian cancer. These studies showed a larger hazard ratio for PFS favoring the use of bevacizumab suggesting that administration until progression may represent the optimal schedule. Another question is can biomarkers identify the groups more likely to benefit from bevacizumab? Efforts to identify biomarkers with potential prognostic and predictive value in ovarian cancer patients treated with bevacizumab are critical in selecting patients for therapy and are the subject of ongoing research.

There are several ongoing trials evaluating the optimal timing of bevacizumab, duration of treatment, benefit in continuing beyond progression and re-challenging bevacizumab in ovarian cancers.

In conclusion, we can say that amongst new biologic drugs, bevacizumab is the first agent to show clear therapeutic activity in recurrent disease and first-line therapy along with an acceptable toxicity profile.

S13 - Metastatic non-small cell lung cancer treatment algorithm in Croatia

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Lung cancer is the most common malignant disease in men and third is the occurrence of women in the Republic of Croatia, and rates of incidence and mortality are continuously increasing. According to the Pulmonary Department of University Hospital Centre Zagreb data, 60% of the patients suffer from lung adenocarcinoma while about 30% have squamous cell carcinoma and 10% non-small cell lung cancer (NOS).

The standard first-line treatment for advanced non-small cell lung cancer patients is platinum-based chemotherapy doublet with the addition of a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes), which has been approved for Croatian patients as well. According to ESMO Guidelines, the use of nab-paclitaxel is indicated in selected patients, which has not been approved for the treatment of lung cancer patients in our country, as well as the addition of necitumumab to gemcitabine and cisplatin in the first-line treatment for patients with squamous cell carcinoma expressing EGFR by IHC. In the first line treatment according to CHIF guidelines, patients with non-squamous lung cancer can not be treated with pemetrexed nor with bevacizumab, although this therapy is a standard of treatment for many years in Europe and all over the world.

The standard second line treatment is monotherapy with pemetrexed or docetaxel both in Europe and in Croatia. The addition of ramucirumab (all) or nintedanib (NSCC) to docetaxel is not a standard of treatment nor the use of erlotinib in patients with wild type EGFR or afatinib for the treatment of SCC in Croatia. Immunotherapy with nivolumab or pembrolizumab is not an treatment option according to CHIF guidelines.

EGFR mutated patients may receive EGFR tyrosine kinase inhibitors in the second line treatment after chemotherapy only, without the use of bevacizumab, and in the case of disease progression and positive mutation T790M, the use of osimertinib has not yet been approved. ALK + patients may receive crizotinib in the first line, which is the standard of treatment according to all valid guidelines, while in later treatment lines after the progression of the disease it is not possible to get second generation ALK TKI at the expense of CHIF and the therapeutic option is chemotherapy treatment.

Although the need to amend the insurers guidelines for the treatment of patients with non-small cell lung carcinoma has been recognized in Croatia, the CHIF's modification process is considerably slower than the progress of medical knowledge, resulting in the inability to apply optimal patient treatment and contributing to a worse outcome and higher mortality.

S14 - Breast cancer immunotherapy

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In the era of the large number of innovative drugs metastatic breast cancer has become a chronic disease, due to the prolonged survival of patients over many years. However, the innovative drugs are mainly placed in the HER2 positive subtype, as well as with hormone therapy contribute to better treatment of the disease. Due to absence of target therapies, patients with triple negative breast cancer (TNBC) have a much poorer survival than other subtypes. On the other hand large number of somatic mutations in TNBC, and frequently the presence of tumor-infiltrating lymphocytes is an ideal ground for application of immunotherapy. Checkpoint inhibitors (anti-PD 1 / PD-L1 antibody), showed remarkable results in the treatment of TNBC. In the phase I atezolizumab, anti-PD-L1 antibody, had a response rate (ORR) of 33% in PD-L1 + TNBC. Also pembrolizumab, anti-PD-1 antibody is produced a remarkable results in same subset of patients. Shortly afterwards in phase Ib a combination of nab-paclitaxel and atezolizumab demonstrated the disease control (CR + PR + SD) in 89% of patients, which led to the design of the phase III trials. In addition, checkpoint inhibitors are tested in neoadjuvant and adjuvant phase of TNBC treatment. In non-TNBC subtypes checkpoint inhibitors have a lower response rate, and those subtypes required different strategies of immunotherapy. The monovalent vaccines against HER2 antigen, although not prolonged time to progression (PFS) compared to placebo, gave some hope and intrigued researchers for further reasearc, since in patients in whom achieved response survival was extremely long. PANVAC, polyvalent vaccine, showed prolonged PFS combination with docetaxel in patients HER2 negative breast cancer. Immunotherapy has its place in the management of breast cancer, and we are looking forward to the final results of phase III study checkpoint inhibitors.

S15 - From personalized to precise medicine – current status of molecularly targeted therapy in advanced non-small cell lung cancer (NSCLC)

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Personalized medicine was a phrase used to explain a therapeutic approach in oncology that was aimed at optimising therapy for each individual patient. It is a humanized approach, but applicable only in a minority of patients, helped with the principles of pharmacogenomics. US National Institutes of Health proposed a more appropriate phrase, precision medicine, defined as *an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person*.

In the last two decades a great number of molecular targets, as a tumor's growth *driver* were identified in the tumor cell of NSCLC. Unfortunately, a small number of efficient drugs against those targets were successfully developed, most of them being small molecules, tyrosine-kinase inhibitors (TKI).

Epidermal growth factor and its receptor (EGFR) was the first, in 2004, to demonstrate therapeutic importance of the mutation of this receptor in lung cancer, and clinical benefit from inhibition of one or more receptors in this receptor family. TKIs erlotinib and gefitinib were developed first, then it was noticed that Asian patients, women, non-smokers and those with adenocarcinoma have better response to therapy and longer progression-free-survival (PFS), and lastly it was revealed that gene mutations of the EGFR gene are predictors of response to EGFR TKI. Those mutations are of different mechanisms, develop early in the tumor growth, located on exons 18-21 on chromosome 7. The frequency of these mutations is 10-15% in Caucasian patients, compared with more than 40% in Asian patients. After a median of 8-12 months of therapy with first or second generation TKIs, most patients progress. In about half of them, the existence of a secondary mutation, T790M, has been discovered, and we are able to offer these patients osimertinib, a third generation TKI that may prolong PFS for another 10-12 months.

Anaplastic lymphoma kinase (ALK), a member of the insulin receptor tyrosine-kinase family, is encoded by the *ALK* gene on chromosome 2p23. In NSCLC it appears as a fusion gene, with *ELK4* gene, as a result of a translocation between chromosomes 2 and 5. Its frequency in NSCLC is 3-7%, more common among patients with a never/light smoking history, adenocarcinoma histology, younger age, female gender and in tumours wild type for *EGFR* and *KRAS*. Crizotinib as a TKI is an efficient drug not only against ALK translocated tumors, but also against ROS1 mutated tumors, with a median PFS of up to 12 months. Today, we have a palette of drugs with proven activity in second-line treatment (ceritinib, alectinib, brigatinib etc).

Precise medicine is today a reality in NSCLC treatment but only for about 20% of patients. The importance of even this small success lies in the enormous number of NSCLC patients worldwide. New therapeutic challenges are targeted therapy for squamous NSCLC patients, and the initial success of immunotherapy, that has different biomarkers and safety profile. The start of precise medicine in NSCLC was successful, and this type of treatment will continue to rise in oncology of solid tumors.

S16 - Survival strategies of cancer cells

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With respect to tumor cell metabolism many of us still have the classical picture in mind: Tumor cells are energetically surviving by aerobic glycolysis, called *Warburg Effect*, i.e. uptake of glucose and metabolizing via glycolysis to lactate, winning just 2 ATP. Recently cellular and molecular oncologists investigated the intermediary metabolism of glucose (and other molecules) in different tumor cell lines and discovered:

- Tu-cells are able slipping artfully through the vascular endothelium, then migrating into the tissue behind.
- Tu-cells stimulate surrounding tissue to proteolysis in order to deliver essential amino acids for their own protein synthesis.
- Tu-cells *steal* mitochondria from surrounding tissue, integrating them in their own tissue in order significantly to increase cellular ATP supply.
- Tu-cells, when located in oxygen deprived tissue, suppress the gene expression of their tumor suppressor genes, gaining malignancy.
- Tu-cells trigger in vivo the surrounding tissue to produce inflammatory signals, with the consequence that the hepatic circadian rhythm of the host is broken, and liver metabolism is switched to permanent glucose production for uninterrupted glucose supply of the Tu-cells.

These and other findings hopefully will enable oncologists to develop new strategies of tumor therapy by disrupting tumor cell metabolism in a tumor specific way. Certainly the application of 3-Bromopyruvate, used in single cases in Germany with fatal consequences, should be avoided.

S17 - PARP inhibitors in ovarian cancer treatment

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PARP inhibitors represent targeted therapy in ovarian cancer treatment. They are specifically active in cells that have impaired repair of DNA by the homologous recombination (HR) pathway. Cells with mutated BRCA have HR deficiency which is also present in a significant proportion of non-BRCA-mutated ovarian cancer.

BRCA mutations can be inherited (germ-line mutations) or acquired (somatic mutations).

Olaparib is the first oral PARP inhibitor investigated in addition to chemotherapy and as maintenance therapy following chemotherapy.

In maintenance, olaparib showed statistically improved progression free survival (PFS) (19,1 vrs 5,5 months, $p > 0,0001$) in patients with platinum-sensitive, relapsed BRCA-mutant ovarian cancer.

Clinical trials were also conducted with other PARP inhibitors (rucaparib, niraparib, veliparib) and those trials included also non-BRCA-mutated ovarian cancer.

Rucaparib is approved for the treatment of BRCA-mutated advanced ovarian cancer in patents who have received at least two prior lines of chemotherapy.

Niraparib has been recently approved for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer regardless of BRCA mutation status.

High-grade ovarian cancers are more often platinum sensitive and moreover have the most underlying defects in DNA repair. Furthermore, patients with high-grade, platinum sensitive ovarian cancers may also benefit from PARP inhibitors irrespective of BRCA status.

Second-generation studies are investigating the combination of PARP inhibitors with anti-angiogenic, immuno-oncology and DNA-repair inhibiting agents.

S18 - Liposomal irinotecan in the treatment of pancreatic cancer

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Currently there is no consensus about the most beneficial treatment as first line for metastatic adenocarcinoma of pancreas, but there are two options that are preferred protocols according to NCCN guidelines (FOLFIRINOX vs nab-paclitaxel + gemcitabine- MPACT). Recently old drug but in new formulation had proven its efficacy in a three-arm, randomized, open-label study (known as the NAPOLI-1 trial), which was conducted in 417 patients with metastatic pancreatic adenocarcinoma whose cancer had progressed after treatment with gemcitabine alone or in combination with other agents. Based on that trial, liposomal irinotecan was granted approval by regulatory agencies (FDA and EMA) for indication of a second line treatment after progression or failure due to toxicity from gemcitabine base therapy. Liposomal irinotecan should be used in combination with fluorouracil and leucovorin as this combination has proven to be superior compared to liposomal irinotecan monotherapy considering overall survival. Patients treated with this combination of liposomal irinotecan plus fluorouracil+leucovorin lived for an average of 6.1 months, compared with 4.2 months for those treated with only fluorouracil+leucovorin in the control group, and 4.2 months for patients in another group who were treated with liposomal irinotecan alone. Liposomal preparations of drugs can have different toxicity profiles compared to their regular formulations together with different pharmacokinetic profiles. The aim of this lecture would be to present efficacy and safety profiles of protocols consisting of new formulations of irinotecan used in the treatment of pancreatic cancer.

S19 - Treatment algorithm of non-small cell lung cancer (NSCLC) in 2017 in Serbia

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Lung cancer is still one of the leading causes of death from malignant disease throughout the world. Each year, about 5200 new cases of lung cancer are diagnosed in Serbia. About 80-85% of these are NSCLC, while small-cell lung cancer (SCLC) represents about 15-20%. According to data from Serbian Institute for Public Health, lung cancer is the third most common cancer in women, and the second leading cause of death from malignant disease, while in men it is the most common cancer, and the leading cause of death.

When symptoms first appear, a patient is seen by their primary care physician, who conducts initial diagnostics (usually chest x-ray). In case of findings indicative of lung cancer, the patient is referred to a general hospital or a specialised tertiary cancer center or pulmonology clinic. Further diagnostic procedures, CT scan and histopathologic diagnosis, most frequently by bronchoscopy, are conducted there. After a diagnosis of lung cancer is confirmed, the patient is referred to a specialised cancer center, where a decision on the treatment course is made by a multidisciplinary team.

In Serbia, the availability of drugs used in the treatment of cancer is directed by the Drug List of the National Health Insurance Fund, and all state institutions must abide by it. The treatment of lung cancer patients is conducted in tertiary cancer and pulmonology centers, as well as oncologic and pulmonologic centers in general hospitals, according to territorial accessibility.

Regardless of histologic type of lung cancer, most third generation drugs are reimbursed for first and second line therapy: gemcitabine, paclitaxel, vinorelbine, as well as second generation drugs etoposide, cisplatin and carboplatin. Pemetrexed and bevacizumab are not reimbursed for the treatment of lung cancer in Serbia. Docetaxel is reimbursed in second-line treatment only for stage IIIb. Maintenance therapy as such is not recognised, but individual patients may be treated with gemcitabine maintenance.

Testing for EGFR activating mutations has been done in Serbia since 2011. In patients with adenocarcinoma, stage IIIb and IV. Gefitinib, erlotinib and afatinib are reimbursed for first line therapy of EGFR mutation positive adenocarcinoma patients. Erlotinib is also reimbursed for second line therapy of advanced lung adenocarcinoma patients who experienced high-grade toxicity of first line therapy.

ALK testing is not routinely done in Serbia, since no ALK inhibitors are reimbursed. Crizotinib is registered for treatment of lung adenocarcinoma patients. Testing for other gene abnormalities is also not routinely done.

Immunotherapy is not available in Serbia at this time.

Tertiary cancer centers usually have palliative and supportive care teams or units that are responsible for early integration of palliative care in the treatment of lung cancer patients. When a patient is at home, home care teams from primary health care are responsible for administering palliative/supportive care.

Over the last few years, we have seen an important improvement in the availability and accessibility of drugs for the treatment of lung cancer in Serbia, but there are still important restrictions which make treatment of these patients challenging.

S20 - HER2-positive breast cancer: Challenges and progress in the treatment

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Advances that have been made over the past two decades in the treatment of patients with HER2-positive breast cancer, both in the metastatic and in the neo/adjuvant setting, have dramatically improved the prognosis of HER2-driven BC. Since the introduction of trastuzumab, the first anti-HER2 directed therapy, several other HER2-targeted agents have been successfully designed and approved for the treatment of HER2-positive BC.

Numerous trials have studied a role of trastuzumab, a recombinant humanized monoclonal antibody that inhibits ligand-independent HER2 signaling, in all settings. The addition of trastuzumab to chemotherapy in patients with previously untreated MBC led to a significantly higher objective response rate, prolonged time to progression and improved overall survival compared with chemotherapy alone. Furthermore, the addition of trastuzumab to chemotherapy significantly improved long-term disease-free survival and overall survival among patients with early-stage BC, while combining trastuzumab with chemotherapy in the neoadjuvant setting enabled higher pCR rates and longer event-free survival.

The introduction of lapatinib, a dual tyrosine kinase inhibitor of HER2 and EGFR, offered new choices for patients with advanced HER2-positive BC, although the drug has failed to show efficacy in the adjuvant setting. Patients with ABC/MBC who have already progressed on regimens that included trastuzumab, an anthracycline, and a taxane had a better TTP when they received lapatinib in combination with capecitabine compared with those who received capecitabine alone. These were the first results to show that continuing HER2-targeted therapy after progression on a HER2-targeted regimen improves outcomes.

Pertuzumab is a novel humanized monoclonal antibody directed at the dimerization domain of HER2. Specifically, it inhibits ligand-dependent signaling between HER2 and HER3, which is known to activate a potent cell-survival signal. Because of the different binding sites, trastuzumab and pertuzumab have different but similar and complementary mechanisms of action. The combination of pertuzumab with trastuzumab and a taxane significantly prolonged both PFS and OS compared with trastuzumab and docetaxel alone in MBC patients (CLEOPATRA). The benefit of dual HER2 blockade with pertuzumab and trastuzumab was also confirmed in neoadjuvant setting (NeoSphere, THRYPHENA), while the use of pertuzumab in the adjuvant setting is still being evaluated (APHINITY).

Trastuzumab emtansine (T-DM1), another novel anti-HER2 therapy, is an antibody-drug conjugate in which trastuzumab is stably linked to a potent microtubule inhibitor, a derivative of maytansine. This first-in-class drug was developed in an attempt to overcome trastuzumab resistance. T-DM1 was compared with lapatinib and capecitabine in the second-line, advanced-disease setting in the EMILIA study. Patients with HER2-positive MBC whose disease progressed on trastuzumab and taxane-based therapy had a significantly longer OS in the T-DM1 arm compared with the control group. In the TH3RESA trial, a heavily pretreated patient population with advanced HER2-positive BC had significantly improved PFS compared with physician's choice therapy, providing further evidence of the activity and tolerability of T-DM1 against the current standard therapy.

Altogether, owing to the introduction of effective anti-HER therapies, including trastuzumab, pertuzumab, lapatinib, and T-DM1, the outcome of patients with HER2-positive MBC has significantly improved. The median survival time using these modern combination therapies is now approximately 5 years compared with approximately 1.5 years in the pretrastuzumab era.

Although the currently available anti-HER2 therapies have changed the natural history of HER2-positive BC, new therapeutic options are necessary because the disease is essentially incurable in the metastatic setting and a relevant proportion of patients with early-stage disease still relapse in spite of the use of currently available neo/adjuvant therapies. Neratinib, a pan-HER tyrosine kinase inhibitor, is one of the most promising new drugs for HER2-positive BC. Other drugs, such as ONT-380 (an oral, small-molecule, HER2-selective inhibitor) and MM-302 (an anti-HER2 antibody-drug conjugate carrying pegylated liposomal doxorubicin) have shown initial promising activity and good tolerance among patients with HER2-positive BC. Interest in the inhibition of downstream signaling of the HER2 pathway with mTOR/PI3K/Akt and CDK4/6 inhibitors is currently under clinical evaluation. Some immunologic approaches (vaccines, alone or in combination with trastuzumab, inhibitors of immune checkpoints) are also being tested in HER2-positive BC.

Deeper understanding of the biology of HER2-positive BC (mechanisms of resistance to HER2 directed therapies, cross-talk between HER2 and ER, biomarkers, different mechanisms of action of monoclonal antibodies and signal transduction inhibitors) is necessary to further improve outcome of patients with HER2-positive BC.

S21 - What is new in the treatment of recurrent, persistent or metastatic cervical cancer

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Cervical cancer accounts for 9% of all new cancer cases per year, with the biggest incidence rate in developing countries. In Croatia in 2014, 307 women were diagnosed with this disease, and 130 of them died. Patients are mostly diagnosed at the age of 50-54 years. The underlying cause of the disease is most often HPV infection and hypoxia. The basis of treatment for recurrent, persistent or metastatic cervical cancer is a systemic antineoplastic therapy. Polychemotherapy was the usual framework of treatment until the angiogenesis and its importance in the process of development of cervical cancer was recognized. By the addition of bevacizumab (study GOG 240), the overall survival and time to progression of the disease were significantly improved, and this treatment is now standard in developed world. Today, there is much talk about immunotherapy and a whole series of clinical studies are performed in the treatment of cervical cancer. The results are relatively modest. One study that should be emphasized is the one using *Hinrich's* adaptive immunotherapy model, with which an excellent objective response was achieved, although it included a small number of patients. The use of the checkpoint inhibitor ipilimumab showed a modest partial response in 6% of the patients. In the *Keynote 028* study, use of pembrolizumab has led to a response rate of 17%. The concept of the use of the *Monocytogenes* Monolithic bacterium as HPV antigen vector (*Axalimogen filoliscac* - HPV) is also very interesting and the results of this study (*NRG 0265*) are very promising (38% of patients survived for one year). To conclude, anti-angiogenic therapy is the first targeted therapy that has shown benefit in overall survival combined with polychemotherapy, compared to the current standard of polychemotherapy alone. Immunotherapy studies are ongoing and represent new approach in treatment of recurrent, persistent or metastatic cervical cancer.

S22 - Nutrition of oncology patients – new guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN)

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Tumor cachexia is a multifactorial syndrome characterized by loss of muscle mass (with or without fat loss) that can not be fully recovered by the standard nutritional support, resulting in progressive weakening of the body functions. In 2011, a panel of international experts has developed a framework for the definition and classification of tumor cachexia. Tumor cachexia should be understood as a continuity that begins with diagnosis of malignant disease. Our task is to recognize the right stage of tumor cachexia so that the patient could be provided with adequate nutritional support. We should not fully rely on our clinical assessment and it is necessary to standardize the assessment using different screening tools. The most commonly used NRS 2002 (Nutritional Risk Screening) is a validated tool. However, this tool is not specific for cancer patients, so today the Good Nutrition Practice (GNP) tool is also being implemented. The necessity of compulsory nutritive screening from the time of diagnosis of cancer is recognized by ESPEN in its new guidelines issued in 2016. In accordance with their recommendations, it is necessary to evaluate the intake of nutrients and symptoms affecting the nutrition status after screening. Nutritional support is mandatory in all patients with nutritional risk for which curative or palliative surgery is planned; in patients planned for radiation therapy, especially of head and neck, chest and gastrointestinal tract; and during systemic antineoplastic therapy. If oral ingestion of nutrients is insufficient, if necessary, enteral and parenteral nutrition should be initiated. Access to nutritional status must be regular and multiprofessional and should last for the entire duration of the disease. Treatment of cachectic patients must be multimodal, and it includes nutrition, exercise and pharmacological preparations. It is recommended to take omega-3 fatty acids (at least 2 grams per day) as it consequently reduces the formation of inflammatory mediators, improves appetite and affects body mass increase. It is necessary to increase the share of energy obtained by fat degradation rather than the share obtained by decomposition of carbohydrates.

A timely staging of tumor cachexia, the initiation of a multimodal approach within the multiprofessional team and following the ESPEN guidelines is necessary to influence the quality of life of cancer patients and all other patients in nutritional risk.

S23 - Options and sequencing of systemic treatment of metastatic renal cell carcinoma(mRCC) – clinical practise and clinical guidelines

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The last 10 years bear witness to a dramatic change in the treatment portfolio of mRCC. This is primarily due to our better understanding of RCC molekular biology and the consequent evolution of targeted treatment. After a long period of very limmited efficiency of cytokne treatment of mRCC, tyrosine kinase inhibitors, sorafenib and sunitinib, were the first new treatment modalities registered in the years 2005 / 2006. Based on the results of a phase III clinical trial which confirmed a significant PFS and OS benefit of sunitinib compared to interferon- α (IF α) in first line mRCC treatment, sunitinib became the new standard first line treatment option for mRCC patients. A significant PFS as well an OS benefit of the combination of bevacizumab (monoclonal VEGFR antibody) with IF α compared to IF α monotherapy was confirmed in two other clinical trials. However, due to the sc application of IF α and iv application of bevacizumab as oposed to the oral use of TKI, this drug combination remained sutable only for a limited group of patients with mRCC. based on the results of two studies, a pivotal study comparing the efficiency and toxicity of another TKI, pazopanib, to placebo in the mRCC group of treatment naive patients and in the patients who had progressed on cytokine treatment and a noninferiority study which proved the noninferiority of pazopanib in comparison to sunitinib, pazopanib became another standard option for first line treatment of mRCC patients. Based on numerous clinical studies, there are currently 9 targeted agents registred for the treatment of mRCC patients: sunitinib, sorafenib, pazopanib, axitinib, cabozantinib and lenvatinib from the TKI family, mTOR inhibitors: temsirolimus and everolimus, and finally, the VEGFR monoclonal antibody bevacizumab. In first line treatment, the use of sunitinib or pazopanib is recommended, based on the patient's individual profile, most importantly their comorbidities and the expected toxicity profile. In some cases sorafenib and bevacizumab with IF α are used as a first line option as well. Everolimus, axitinib, sorafenib, cabozantinib and the combination of lenvatinib and everolimus are targeted therapies used in 2nd and further lines of mRCC treatment. In 2015 the renesance of immune treatment emerged with the results of the CHECKMATE 025 study, which confirmed a survival benefit of patients treated with nivolumab (a PD-1 inhibitor) over the group of patients treated with everolimus in the 2nd line mRCC treatment following the progression on the anti-VEGFR therapy. Despite the improvement of treatment due to targeted therapy, a cure for mRCC patients is still far out of sight. The challenges of the mRCC treatment in the near future remain the prognostic and predictive factors of mRCC, efficient new drugs as well as new methods of sequencing and combination schemes.

S24 - Anticoagulant therapy in patients with cancer

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Venous thromboembolism or VTE represents a major health problem that is not uncommon among patients with cancer and is one of the major causes of mortality and morbidity. Patients with malignant disease have a greater tendency to develop hypercoagulable state, and therefore a greater propensity to venous thromboembolism compared with patients without diagnosed cancer. VTE represents the second leading cause of death in patients with malignant disease, immediately after the mortality resulting from complications of cancer. Thromboembolism encompasses two interrelated conditions that are part of the same spectrum, pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT). Association between idiopathic venous thromboembolism and occult malignancy has been observed in the 19th century by Prof. Trousseau. However, emerging data indicated that venous thromboembolism is multifactorial condition and absolute risk depends on the presence of several factors, such as age of the patient, prolonged immobilisation, surgery, type of tumor, stage of disease, use of hormone- and/or chemotherapy, the presence of a central venous catheter, duration of anesthesia, as well as the previously confirmed diagnosis. The risk of DVT in patients with malignancy could be reduced by prophylactic methods, with their restriction in all risk clinical cases that have a tendency of recurrent thrombosis, serious bleeding and the emergence of other comorbidities. Therefore, the use of the prophylactic method is directed to the patient as non-pharmacological and pharmacological treatment. The goal of the non-pharmacological method is to achieve an augmentation of venous blood flow especially in lower limbs with passive exercise, walking and use of external mechanical medical devices. From the point of pharmacological approach to treatment, we have a treatment for our patients that is directly oriented to the use of different anticoagulant drugs, such as unfractionated heparin, low molecular weight heparins, inhibitors of activated factor X and/or the use of oral anticoagulants.

S25 - Tumor infiltrating lymphocytes (TIL) and androgene receptors (AR) in triple – negative breast cancer (TNBC) – new biomarkers on horizon?

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Triple Negative Breast Cancer (TNBC) makes a clinically heterogeneous group of tumors, with the common feature of the most aggressive and deadliest breast cancer subtype. TNBC patients have higher rates of tumor disease return and worse overall survival than other breast cancer subtypes. The molecular feature of TNBC is the lack of immunohistochemical expression of estrogen receptors (ER), progesterone receptors (PR), as well as HER2 receptors. Approximately 12-17% of breast cancer patients have TNBC and they fall into the group of patients with poor prognosis, with no effective endocrine therapy or HER2-mediated drugs. Due to the frequency of mutations (resulting in immune response inducing neo-antigens), the increase in the number of infiltrating lymphocytes (TILs) (evidence of immune detection) and the increased expression of PD-L1 protein (inhibits T-cell anti-tumor response), TNBC represents a potential target for immunotherapy (especially PD-L1 targeted therapy). The TILs have prognostic value in TNBC, predictive of the effect of preoperative chemotherapy, and may be associated with the effectiveness of the use of immunotherapy with checkpoint inhibitors. There are currently controversies over the estimation of TILs role in breast cancer, both localization and quantification. Namely, it appears that the stromal TILs have a higher prognostic value than the intratumor TILs, and the cut-off value is also unclear (high versus low expression). The role of lymphocyte count in the blood is also unclear as a prognostic factor in TNBC. The predicted value of TILs in TNBC was investigated, depending on the type of chemotherapy applied and the greater expression of TILs was shown to be associated with a better outcome. More pronounced TILs are associated with a higher rate of complete pathological response to preoperative chemotherapy in TNBC. The basic expression of TILs may be associated with a better response to the use of a checkpoint inhibitor atezolizumab.

Androgen Receptors (AR) belong to a group of nuclear receptors, as well as ER and PR. AR is structurally similar to progesterone receptor and progestins at higher concentrations block AR. AR are expressed in over 70% of breast cancer. Also, part of the TNBC has an expressed AR, although there is no expressed ER or PR. In literature, the presence of AR in TNBC ranges from 10-54%. Negative AR expression is significantly associated with higher clinical stage, higher mitotic index, higher grade and high Ki-67 proliferation index, and significantly more AR negative tumors are seen in the group of tumors with positive basaloid immunophenotype and basaloid morphology. At present, there are good results of clinical studies with the application of immunotherapy, PD-1 and PD-L1 inhibitors, pembrolizumab and atezolizumab, in TNBC. Also, early clinical studies have shown promising results in the use of antiandrogens in the advanced TNBC.

S26 - Recurrent ovarian cancer (ROC): treatment recommendations and every day clinical practice

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Approximately 70% of ovarian cancer patients are diagnosed in FIGO III/IV stages when the chances for cure are limited even after optimal cytoreduction and platinum based first line chemotherapy.

Relapses occurred in approximately 70-80 % of patients usually within first 3 years (median 18 months) after initial diagnosis. Relapsed ovarian cancer (ROC) is generally incurable disease; however time to progression and subsequent treatment as well as survival might be prolonged dependant on effectiveness of systemic treatment and less often also on relatively indolent biology of some cancers.

Gold standard of ROC treatment is re- challenge with platinum based chemotherapy, dependant of platinum free interval (PFI).

PFI represents sensitivity to platinum and is defined as the interval between last platinum dose and date of relapse. In every day clinical practice, this is the most widely accepted simple clinical surrogate for chemotherapy response/resistance prediction, also representing important criteria for prognosis predictions. PFI stratify patients in 4 cohorts: (1) platinum refractory - progression during platinum treatment or within <1 month after last planned dose; (2) platinum resistant - progression within 1-6 months; (3) partially platinum sensitive - progression after 6-12 months; and (4) platinum sensitive - progression after >12 months.

Although this is widely used method for platinum sensitivity prediction, it has some limitation. Relapses can be diagnosed in a various ways dependant on follow-up practice that could directly influence PFI definition.

For instance, ROC might be diagnosed only upon CA125 increase while patient is completely free of detectable metastases and symptoms. Marker increase might proceed to symptomatic/imaging detectable relapse for months.

ROC might be diagnosed with more sophisticated imaging methods PETCT that might detect very small, asymptomatic lesions, or can be ultimately diagnosed clinically upon symptoms development, and then confirmed by other tests.

All that issues have been discussed during several Ovarian Cancer Consensus Conferences (OCCC), and it was suggested that method used to diagnose ROC should be mandatory recorded especially if treatment is planned in clinical trials. However, clinical trials with new drugs for ROC are rare, focused on first or second line treatment and majority of patients are treated according to (local) guidelines. Some effective drugs are unavailable in lower income countries.

Patients with platinum sensitive ROC are usually re-challenged with platinum based (carboplatin/paclitaxel) chemotherapy, and dependant on response and duration of response, the same regimen might be repeated in further relapses. Major problem in repeating platinum is development of hypersensitive reactions (HSR). Risk increases with platinum lines and might develop in ~ 40% of patients treated with carboplatin in third line. Short PFI predicts lower responses and worse outcome also with non platinum drugs that includes single agents: paclitaxel (preferably weekly regimen), doxorubicin, gemcitabin (+ carboplatin if combined with bevacizumab). Maintenance with bevacizumab and PARP inhibitors (limited to patients with BRCA1/2 mutations) are effective but are discussed elsewhere.

However, resistance to any treatment is just a matter of time; and resistant relapses are a primary cause of death.

S27 - Cooperation and experience of clinical pharmacist and oncologist through the case of a patient with colon cancer

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When we look at the multidisciplinary team working with cancer patients, we focus on the front line health care professionals - oncologist, pathologists, radiologists, nurses and other vital to providing the best care. But there is another major group of professionals that has had to fight hard for recognition of their contribution. Pharmacist play a key role in the health care team through the provision of high quality medication, appropriate information on treatment schedules and effects of medication, as well as advice on the management of adverse events and use of complementary treatment. Degree of implementation of clinical pharmacy practice in the health care system is different. The highest is in highly developed countries such as Canada, USA, UK.. in Europe, although there was some progress, it can not be said that pharmaceutical services are fully implemented.

In Macedonia, there is a lack of clinical pharmacist, national guidelines and standard operative procedures for the responsibilities of clinical pharmacist. It is very important for clinical pharmacist to know, what are the expectations of health workers from them and why do they need pharmacist.

Through the case report about 72 – year old patient with adenocarcinoma of ascending colon, after surgical procedure of right hemicolectomy and with liver metastases, with comorbidities such as arterial hypertension, diabetes mellitus, receiving chemotherapy protocol XELOX + antiangiogenic agent bevacizumab, oncology physician will explain the need of pharmacist and why they must participate in ward rounds with physicians and provide their suggestions or recommendations wherever needed. Multiprofessional teams are key to a good outcome. As clinical pharmacist have the precise knowledge about antineoplastic drugs and regular interaction with prescribers, they are ideally placed to bridge the gap between patients and oncology physicians. Both pharmacist and oncology physicians are learning to form multiprofessional teams.

S28 – Workshop: Biological therapy – from production and administration to side effects monitoring

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Biological drugs belong to new set of drugs developed for various diseases. Biological drugs are produced in living cells by recombinant technology and are effective in stimulating or inhibiting the action of natural compounds. Biological drugs differ from those of chemically synthesized molecules due to their origin and their complex structure. An assessment of immunogenicity is important for biological drugs, in line with current guidelines in preclinical and clinical studies and is included in the Pharmacovigilance Risk Management Plan. Therapeutic proteins are produced using genetically modified cell lines or transgenic animals. Residual process contamination can be the cause of immunogenicity. Glycosylation or pegylation of molecules can mask immunogenic epitopes. Substances which migrate from primary package can stimulate creation clusters of higher immunogenic potential. The goal of the workshop is to point out basics and simple characteristics of biological medicines, a traceability of the applied biological therapy through serialization and writing of protected names of the drug as well as indicating the follow up and reporting of side effects. Presentation of cases associated with a particular biological therapy will point to the critical points of the biological drug tracking chain from receiving drugs in hospital pharmacy, to the application of drug and reporting of observed side effects.

S29 – Workshop: Love and sexuality in oncology patients

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Oncology patients are facing numerous psychological consequences (hard disease, mourning for lost functions, anxiety, depression, fear of the future) among which are very often neglected changes in the field of love and sexuality. Because of disease and the treatment (chemotherapy and radiotherapy) there are multiple physical changes which may result by damaging the secondary health (e.g. iatrogenic menopause, hormonal imbalance, atrophy of the vaginal mucosa). Some frequent sexual problems are low sexual desire, problems with libido and dyspareunia. However, beside of the physical changes, there are psychological changes which can effect the sexuality (low self-esteem, changed body image, fear of losing attraction in partner, and depression) which may have as consequences the avoidance of sex, reduced sexual desire and reduced intimacy. Apart from sexuality, there is often loss of intimacy between partners and due to reducing communication their love and closeness can be affected. Considering patients which will never first speak about their sexual and love problems, every expert (doctor, pharmacist) who participate in the treatment of oncology patient should learn skills how to communicate with the patient about love, sex and methods how to keep their sexual health. This consultation should involve education about physiology and psychology of sexuality, using of sexual toys, imagination, stimulation, improving communication between partners, stimulating their conversations, exploring and experimenting in changed conditions and tighten their relationships, love and closeness.

S30 - Counseling center for palliative care

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Palliative care is comprehensive (health, psychological, social and spiritual) care with the aim of providing the necessary care to patients with unbearable disease that significantly shortens life expectancy. The main goal of the palliative care is to reduce pain and unpleasant symptoms of disease so that a patient who is at the last stages of the incurable illness or has a chronic severe illness, lived better. According to definition IASP (International Association for the Study of Pain), the pain is unpleasant sensory and emotional experience associated with acute and possible damage. The most commonly used pain measure is that one which is defined by duration. According to it, pain could be acute, chronic non-malignant and chronic malignant. Acute pain is a consequence of tissue injury either by mechanical, thermal or chemical means and it lasts relatively short to calm the inflammation and healing of the injury. Chronic non-malignant pain occurs due to the illness of the musculo-skeletal system, the internal organs or the nervous system. Chronic malignant pain is a consequences of tumor tissue injury or diagnostic or therapeutic procedure. Research indicates that every fifth person suffers from chronic pain that significantly affects the quality of life, sleep, work activity and overall health care costs. In order to improve cooperation between patients and prevent side effects when they use medications, a consulting centres are organised, for patients and their family, where they can consult with the expert about analgetics drugs or other drugs they use. In pharmacy, through elaborated forms, a pharmacist with patients who suffer from chronic pain or a family member, cares for each area related to pain pharmacotherapy (medicines, drug use, disposing of medicines, side effects, diaries....). Work of pharmacist is introduced to the physician or anesthesiologist from a clinic. Showing a few examples of pharmacist's work in counseling center we will show how to communicate with patient or a family member and discover the difficulties associated with the use of pain medicines. Pharmacist with individual approach to the patient, which includes education of the patient or family member, can improve treatment and moderate the pain or side effects.

S31 - Immunotherapy in oncology - interdisciplinary cooperation among immunologist, oncologist and pharmacist

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Immune status and immune response becomes an important factor for decision about patient treatment, particularly in time of growing immunotherapy in oncology. Results from Immunoscore programme in our department show that patients with stage II colorectal cancer have predominantly a depression in cellular immunity. Plasma levels of immunoglobulins were also reduced. Most patients showed some clinical symptoms of immunodeficiency, such as frequent respiratory tract infections and/or herpetic infections. The correlation of neoangiogenic and immunosuppressive factors, as well as the state of anti-cancer immunity, could help in the future as a prognostic marker and contribute to the selection of targeted immune therapy in patients with colorectal cancer. For this reason 'Ambulance' of Immunooncology was established in our department, where medical oncologist, immunologist and oncology pharmacist cooperate. The aim is to select immunocompromised patients, not only with colorectal cancer, and help to stratify them for the most suitable therapy.

S32 - Novelties in antiemetic supportive therapy

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Nausea and vomiting caused by antitumor drugs and procedures are the most commonly undesirable consequences of oncological treatment for the patients. Uncontrolled nausea and vomiting, undoubtedly are reducing the quality of life of a patient, also they could lead to the appearance of various complications such as dehydration, electrolyte imbalance, aspiration pneumonia, esophageal rupture, anorexia, malnutrition and worsening of the general condition. Clearly, all of these also significantly affects the patient's compliance with the planned oncology therapy, leading to a possible, probable reduction in its effectiveness. It is estimated that 60-80% of patients treated with chemotherapy are suffering from nausea and vomiting to a certain extent, whereas in patients treated with high doses of cisplatin this percentage is as high as 90%. Therefore, the patient's individual risk and emetogenic potential therapy should be determined before the therapy begins and on the basis of these two facts, the strategy for the prevention of acute and delayed nausea and vomiting. The use of prophylaxis according to the recommendations in the guidelines so far allows for the majority of (> 90%) patients receiving high emetogenic chemotherapy to successfully prevent nausea and vomiting and thus provide a civilized, quality oncological therapy in the planned form, which results in optimal treatment results. Despite the fact that guidelines for the prevention and treatment of nausea and vomiting induced by chemotherapy are widely available and based on evidence that well-conducted prophylaxis effectively improves control of nausea and vomiting in patients, the clinical use of the guidelines remains unacceptably low. Today's gold standard for the prevention of high and medium emetogenic oncological therapies rests on a combination of selective inhibitors of P / neurokinin 1 (NK1) and 5-HT3 receptor inhibitors. The oral composition of the combination of said drugs, neupitant and palonosetron is an optimal formulation from the point of view of the medicine (single oral dosage), efficacy (potentially more effective than a combination of separate medications), and pharmacoeconomic aspects (the price is significantly lower than the price of drugs currently on the HZZO Medicines List in said indication). The results of the clinical trials gave a clear confirmation that the oral administration of the netupitant / palonosetron in combination with dexamethasone effectively prevents acute and delayed nausea and vomiting associated with high and moderate emetogenic chemotherapy. The safety profile of the fixed combination of the netupitant / palonosetron drug is favorable and is no different than expected for this drug group, and the frequency of side effects is rare and they are mostly of a mild nature.

S33 - Value-based medicine and pharmacy

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The health system of our time is characterized by Evidence-Based Medicine (EBM), patient-centered care and cost-effectiveness of treatment. EBM involves the conscientious and rational clinical decision making on individual patient care based on the best available data from research, clinical experience and taking into account patient preferences. This avoids medical errors during treatment and increases the quality of patient care. Value-Based Medicine (VBM) is a medicine based on objective value (eg, prolongation of life and / or quality of life) that is assigned to health interventions using standardized parameters that are most commonly used to estimate values and cost-effectiveness.

VBM starts with the best evidence-based data and translates them into comprehensible data for value-based patients and allows clinicians to achieve higher quality of patient care than EBM alone.

VBM is not only cutting costs but also improving efficacy and cost-effectiveness of therapy. Value-based practice is increasingly important in oncology. Physicians, patients and health-insurances are open to innovative oncology treatments, but are all underpressure to choose the treatment that offers not only the best clinical outcome and the risk and benefits ratio, but also the best cost-effectiveness for investing in the treatment. VBM and EBM are both responses to an increase in the complexity of the healthcare decision-making process. VBM relies on values in clinical decision making, as EBM relies on facts. The ultimate goals of VBM are to raise the quality of the health system and to efficiently use the resources within the health system. The critical component of understanding the value is measurement, so the parameters for estimating the value and the methodology for quantifying these parameters needs to be specified. Oncology pharmacists, because of their unique knowledge, qualifications, practice, skills and responsibilities play an important role in providing oncology patients care. As cancer treatments become more complex, more targeted and personalized, the oncological drug market is growing, and with it also the need for educated healthcare professionals. Thus, the role of a pharmacist, as a member of the multiprofessional team for the care of oncology patients, extends to cover all aspects of that care. Oncology pharmacists cooperate with doctors, other healthcare professionals and patients to ensure that prescribed medicines contribute to the best possible treatment outcomes for patients.

Pharmaceutical skills certainly affect the patient value of treatment through the education of patients, their caregivers and other health professionals, assessment of care (including taking medical history and therapy adjustment), counseling of patients on proper therapy administration, emphasis on adherence, prevention and treatment of side effects as well as toxicity of treatment, providing supportive care, monitoring of therapy, all with the ultimate goal - improving the quality of life of the patient.

S34 - Evaluation of pharmacist counseling on oncology patients

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More than half of oncology patients occasionally or continuously take different non-prescription medications and / or dietary supplements. Apart from the fact that the latter burdens budget of the patients and their families, administration of drug combinations and various dietary supplements without supervision by healthcare professionals can lead to unwanted reactions and side effects that may delay oncology therapy. This brings into question the outcome and success of the oncology treatment and impairs quality of patient life. The role of Oncology Pharmacist at Oncology Clinics has not yet been sufficiently recognized in the region. In the Sestre milosrdnice University Hospital Center, in the University Hospital for Tumors, the Pharmacist is implemented as an indispensable member of the multiprofessional team, where the first infirmary in Croatia of The Pharmacist counseling on oncology patients was established. In order to evaluate the work of an oncological pharmacist, it is necessary to find patterns on the basis of evaluation of such work in countries that already have an established system. The Pharmacist counseling of oncology patients is being performed at the University Hospital for Tumors since November 2015. Counseling is intended for all oncology patients, their family members, or caregivers who want to be educated on oncology therapy, non-prescription drugs and dietary supplements. Counseling is carried out with the aim of: preventing medication errors and drug interactions, adjustment of therapy, patients counseling how to properly take their prescribed therapy, patients counseling about potential side effects of oncological therapy, education on the necessity of strict control of taking dietary supplements. There are many papers that have proven that the pharmacist counseling is cost-effective. By researching scientific and professional literature on the evaluation of counseling by oncology pharmacists, we have come up with a form that would serve as a pattern for developing a national model for evaluation of work. The experience of the infirmary of The Pharmacist counseling on oncology patients of the University Hospital for Tumors, Zagreb, and the form of a model for evaluating the work of Oncology Pharmacist in the Republic of Croatia will be presented.

S35 – Workshop: Melanoma – new systemic therapy and its side-effects

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Melanoma belongs to the group of the most aggressive malignant tumors in humans. It is caused by the malignant transformation of melanocytes, melanin-producing cells which is important for the protection of skin from UV-mediated damage. Its characteristic is very early metastasis by lymph and hematogenic pathway, leading to a death. Its incidence, as well as the mortality, has been increasing in the last decades. Unlike other tumors, it affects a relatively younger population. According to the official data of the Republic of Croatia's Cancer Registry in 2013, the incidence of melanoma was 12.3 per 100,000 inhabitants. In recent few years there has been an evolution, or revolution, in the treatment of patients with advanced stage melanoma. The use of new targeted drugs and oncology immunotherapy leads to longer survival of the patients, and studies with a combination of these drugs suggest further improvement in the treatment outcomes even at this stage of the disease, which had been recently associated with poor prognosis.

At early stage, the best treatment mode represents the surgical removal of the tumor entirely. In the treatment of patients with metastatic melanoma, we have several procedures available: surgical treatment of metastatic disease is especially recommended if there are solitary (individual) metastases located at the site available for surgery; non-surgical treatment of locoregional metastases involves methods such as intratumor interleukin 2 administration; local administration of immunomodulators, imiquimod, and substances known to be contact allergens such as dinitrochlorobenzene (DNCB). Electrochemotherapy is a combination of intralesional application of cytotoxics (cisplatin or bleomycin), with the use of electrical pulses.

T-VEC is a genetically engineered oncolytic HSV-1 virus. Applies directly to the tumor. It has systemic and local effects. It can be combined with immunotherapy.

Systemic treatment of metastatic melanoma: a. targeted therapy includes the application of: 1) BRAF inhibitors (vemurafenib, dabrafenib) in patients with BRAF-positive tumor. Prior to the use of this drugs patients must be confirmed to have a BRAF mutation V600 positive tumor; 2) MEK inhibitors (kobymetinib, trametinib) inhibit the action of mitogen-activating protein kinases; 3) Combination of BRAF and MEK inhibitors in clinical studies delay the development of BRAF therapeutic resistance and improve overall survival. Today it is considered as a *golden standard* in the treatment of BRAF positive patients. b. oncological immunotherapy includes the application of: 1) Ipilimumab (a monoclonal antibody that binds to the CTLA-4 receptor or for one of the control immunological points); 2) anti-PD-1 inhibitors (also acting on control immunological points): pembrolizumab and nivolumab; 3) Combination therapy is indicated in patients who can tolerate toxicity, whereas monotherapy is indicated in patients with a poorer general condition. The advantage of immunotherapy is that they act on the disease and in BRAF-negative tumors, and can also be used after development of resistance to BRAF inhibitors.

Side effects of systemic melanoma therapy are: a) side effects of combination target therapy are mostly mild to moderate. The most severe side effects (pyrexia, decreased ejaculation fraction) occur during the first weeks of treatment and decrease with time on therapy, and by decrease in dosage of one drug; b) side effects of oncological immunotherapy are caused by the activation of the immune system. They can affect any organic system. They appear most commonly in the induction phase but may occur even months after the end of the therapy, so it is recommended to monitor the patient up to 5 months after the end of the therapy.

S36 - Left-right colon cancer and the effectiveness of targeted antibodies

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Colon carcinoma is one of the most common malignant diseases. Therapeutic protocols used in its treatment are based on 5-fluorouracil in combination with oxaliplatin (adjuvant and metastatic treatment) and irinotecan (metastatic treatment). Apart from chemotherapy, for the treatment of metastatic carcinoma of the colon are used targeted antibodies that can be divided by their basic mechanism of action on the inhibitors of the epidermal growth factor receptor (EGFR) and the inhibitors of the vascular endothelial growth factor (anti-VEGF). EGFR inhibitors that are used in the Republic of Croatia are cetuximab and panitumumab. These two drugs showed no significant difference in their activity when tested in a *head to head* study, and therefore it's considered that there is no significant difference between these two antibodies. Also it is important to highlight that the EGFR inhibitors are in use for the treatment of a wild-type RAS colorectal tumor while for the RAS mutated tumors is used anti-VEGF therapy, in particular bevacizumab. Difference in effectiveness regarding RAS mutation is obtained from randomized controlled studies (FIRE-3), which showed superiority of cetuximab compared to bevacizumab in a direct comparison. The superiority of cetuximab was based on the increase of overall survival compared to bevacizumab. However, recently published subanalysis of the two large studies including the FIRE-3, showed that the effectiveness of targeted antibodies depends of the primary location of the tumor. Tumors of the right side of colon have poorer survival compared to the tumors of the left side of colon and also had an unexpected difference in the efficacy of targeted antibodies. Bevacizumab showed a similar efficacy regardless the side of the colon, while cetuximab surprisingly showed the lack of efficacy compared to bevacizumab in a wild-type RAS tumor of the right side of the colon. The aim of this lecture will be to present the latest findings on the effectiveness of targeted antibodies in patients with metastatic carcinoma of the colon, depending on the primary location of the tumor.

S37 - Central Preparation of Antineoplastic Drugs: Practice and Experiences

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Medical errors related to antineoplastic drugs are subject to multiple researches, whereas in the Republic of Croatia, that is still a subject of discussion. Insufficient information which would serve as a basis for a conclusion about the extent medical error is present in Croatian hospital system.

By supervising prescribed drugs, dosages, solutions, and correct preparation and instructions for accurate application, oncology pharmacists can to a great extent contribute to a safe application of drugs in hospitals, reducing, by doing so, the margin of medication error.

Drugs that make part of the chemotherapy protocol of a patient, accompanied or not by biological therapy, get prepared in accordance with instructions from the Summaries of Product Characteristics (SPC). Due to individual differences between patients and the need to adjust these protocols, other referential data from literature are also used. Antineoplastic drugs are prepared in microbiologically validated space by manipulation in aseptic conditions. Sterile state of the prepared drug is of outstanding importance, because the immune system of oncology patients is often compromised due to side effects which are the consequence of the therapy itself.

By organizing the entire procedure, from receiving and control of the request for chemotherapy, the pre-preparation procedure, the preparation, visual control of ready preparations, the packaging of chemotherapy and its application at wards, an entire system of multiple controls prior to application is established. In this way, we attempt to reduce the occurrence of undesired events which could threaten the health of the patient and increase treatment costs.

In everyday work the most used are the world and the national guidelines as well as QUAPOS - Quality Standard for the Oncology Pharmacy Service edited by ESOP (European Society of Oncology Pharmacy).

S38 - Oncology pharmacy and oncology pharmacy education

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Oncology Pharmacy is a specialized branch of pharmacy, which includes a pharmacist's activity and service, which complete the personalized treatment of the patient. That presupposes a rational and optimized use of drugs, and activities complementary to those of other medical professionals.

A pharmacist will take part in the work of a multiprofessional health care team focusing on oncology pharmacy and oncology pharmacy practice. Oncology pharmacy practice includes activities such as handling antineoplastic drugs and counselling of oncology patients.

In order for an oncology pharmacist to take part in professional counselling in everyday work, a special education and training are required. That is why the graduate course at the Centre for Applied Pharmacy performs education and professional training as a part of the subject entitled 'Pharmaceutical Care'. Students acquire knowledge relative to pharmaceutical care for an oncology patient. A total of 13 periods of education in Oncology Pharmacy take place as a part of a Specialized Course in Clinical Pharmacy. The lecturer is Damir Vrbanec, MD PhD, with support of Robert Šeparović, MD PhD, and Vesna Pavlica, MPharm PhD, Borislav Belev, MD PhD, and Natalija Dedic Plavetic, MD PhD. As a part of subject 'Pharmacotherapy in Clinical Oncology', specializing interns spend a month in the Medical Oncology Ward, Department of Medical Oncology and Radiotherapy of the University Hospital for Tumors, Sestre milosrdnice University Hospital Center, mentored by Robert Šeparović, MD PhD. Practical work in Oncology Pharmacy takes place in the pharmacy of the same clinic, for two months, supervised by Vesna Pavlica, MPharm PhD, and Martina Kranjec Šakić, MPharm.

Likewise, a subject of Pharmacotherapy of Malignant Diseases (15 periods) has been introduced at the fifth year of the Pharmacy Course of the Pharmaceutical - Biochemical Faculty of the University of Zagreb.

The heads in this subject are Vesna Bačić Vrca, MPharm PhD, and Damir Vrbanec, MD PhD, whereas Robert Šeparović, MD PhD, and Vesna Pavlica, MPharm PhD, are the collaborators.

The book authored by Semir Bešlija, MD PhD, and Damir Vrbanec, MD PhD, entitled 'Medical Oncology' is the most useful tool in our everyday work.

The Center for Applied Pharmacy of the Pharmaceutical Biochemical Faculty of the University of Zagreb organizes the student internship and Professional Training for Pharmacists, a total of 720 hours. The programme is based on the Croatian Pharmaceutical Competency Framework and contains a list of activities to be undertaken for achieving the expected competencies for student interns. There is a special programme within it for the students who want to spend this part at the University Hospital for Tumors, with heads being Vesna Pavlica MPharm PhD and Robert Šeparović MD PhD. These are the issues a special emphasis is placed on: safe handling of antineoplastic drugs, optimization of therapy by providing pharmacists' care to the oncology patient and side effects.

Everyday work at the University Hospital for Tumours takes place at the Medical Oncology Ward, at the outpatients clinic, day hospital and at the pharmacy. Education also takes place as a part of pharmaceutical counselling of oncology patients concerning the application and coordination of drugs and nutrition supplements.

Patient counselling is intended for all oncology patients and their family members who wish to get educated on the over the counter drugs, herbal drugs and nutrition supplements. Such counselling is performed in order to prevent medical errors and drug interaction, to have therapy harmonization, perform patient counselling on therapy adherence and educate on the need for strict control of nutrition supplements. Combining can lead to undesired side effects, which can result in postponing official therapy, thus jeopardizing the outcome and success of patient treatment and interfering with the patients' quality of life. The expert team for quality counselling needs to have insight into the officially prescribed therapy (medical documentation) and other drugs prescribed by a GP. By talking to the patient the team members will learn about all over the counter drugs and nutrition supplement their patients take. Based on the information thus obtained, personal patient training will take place. Counselling is performed by a team of top-notch professionals: Vesna Pavlica, MPharm PhD, Robert Šeparović, MD PhD, Eugen Javor, MPharm, Martina Kranjec Šakić, MPharm, Dahna Arbanas MPharm, and Marko Skelin, MPharm. This kind of education, along with the direct contact with the patient, is the best for helping train the best future experts in oncology pharmacy, with objective of improving treatment outcome, quality of life of the patient, adherence and pharmacoeconomical saving.