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ISHODI LIJEČENJA I ORGANIZACIJA ONKOLOŠKE SKRBI, KOMPARACIJA HRVATSKE I ZEMALJA U OKRUŽENJU

In extenso rad u prilogu

ANUŠKA BUDISAVLJEVIĆ[1], Renata Kelemenić-Dražin[2]

abudisavljevic@obpula.hr

[1] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*
[2] Opća bolnica Varaždin
• *Odjel za hematologiju, onkologiju i kliničku imunologiju*

Uvod: Tijekom posljednja tri desetljeća smrtnost od raka u Europi pokazuje povoljne obrasce, koji su bili manje povoljni za većinu istočnih zemalja, uključujući i Hrvatsku. Ovim pregledom htjeli smo analizirati koji su čimbenici odgovorni za loše ishode liječenja raka u Hrvatskoj u odnosu na zemlje u okruženju.

Metode: Analizirani su statistički podaci o raku u zemljama EU. Pri tome su korišteni podaci Državnog zavoda za statistiku, Hrvatskog zavoda za javno zdravstvo, Međunarodne agencije za istraživanje raka i Europske komisije.

Rezultati: Faktori rizika značajno su zastupljeni u hrvatskoj populaciji, najveći je postotak pretilih ljudi u Europi, 64.8%, dok se po prevalenciji pušača u odrasloj populaciji nalazi na 5. mjestu, a parametri zagađenja zraka za 50% su viši u odnosu na europski prosjek. Stopa odgovora na *screening* mamografije u Hrvatskoj iznosi 63% (EU 66%). Preventivni pregledi za rano otkrivanje raka debelog crijeva u ruralnim sredinama imaju odaziv svega 17% (EU 30%). Hrvatska je po broju onkologa ispod prosjeka EU; tijekom 2020. godine bilo je 3,1 onkologa na 10000 stanovnika, što je 10% niže od prosjeka EU za 2015. godinu, dostupnih je linearnih akceleratora 0,4/100000 stanovnika, EU prosjek je 0,8/100000. Izdaci za zdravstvo u HR niži su od prosjeka EU (HR 7,0 % BDP; EU 9,9 %) dok su ukupni troškovi za liječenja raka veći su od prosjeka EU (HR 7 %; EU 6 %). Smanjena produktivnost zbog obolijevanja činila je 44 % troškova liječenja raka u Hrvatskoj, za EU-u je to iznosilo 13 %. S druge strane, 26 % ukupnih izdataka za rak u Hrvatskoj odnosi se na izdatke za zdravstvenu skrb (uključujući lijekove), dok je prosjek EU-a 49 %.

Zaključak: Želimo li poboljšati ishode liječenja malignih bolesti u HR nužno je uložiti dodatne napore u poboljšanje svih segmenata onkološke skrbi.

Ključne riječi: rak, ishodi liječenja raka, onkološka skrb

TREATMENT OUTCOMES AND ORGANIZATION OF ONCOLOGY CARE, COMPARISON OF CROATIA AND SURROUNDING COUNTRIES

In extenso article attached

ANUŠKA BUDISAVLJEVIĆ[1], Renata Kelemenić-Dražin[2]

abudisavljevic@obpula.hr

[1] General Hospital Pula
• *Department of Medical Oncology and Hematology*
[2] General Hospital Varaždin
• *Department of Medical Oncology and Hematology, Clinical Immunology*

Introduction: During the last three decades, cancer mortality in Europe shows favorable patterns. For most eastern European countries, including Croatia those trends are not that good. We wanted to analyze, which factors are responsible for the poor outcomes of cancer treatment in Croatia compared to surrounding countries.

Methods: Data from the National Institute of Statistics, the Croatian Institute of Public Health, the International Agency for Cancer Research, and the European Commission were used for this purpose.

Results: Croatia has the highest percentage of obese people in Europe, 64.8%, while the prevalence of smokers in the adult population ranks 5th and air pollution parameters are 50% higher than the European average. The response rate to screening mammography in Croatia is 63% (EU 66%). Preventive screening for the early detection of colon cancer in rural areas have a response rate of only 17% (EU 30%). In terms of the number of oncologists, Croatia is below the EU average; in 2020, there were 3.1 oncologists per 100000 inhabitants, which is 10% lower than the EU average for 2015. The number of linear accelerators is 0.4/100000 inhabitants, (EU 0.8/100000). Expenditures for healthcare in HR are lower than the EU (HR 7.0% of GDP; EU 9.9%), while total costs for cancer treatment are higher than the EU average (HR 7%; EU 6%). Reduced productivity due to illness accounted for 44% of cancer treatment costs in Croatia, for the EU it amounted to 13%. On the other hand, 26% of the total expenditure on cancer in Croatia refers to expenditure on health care (including medicines), while the EU average is 49%.

Conclusion: If we want to improve outcomes of treatment of malignant diseases, it is necessary to invest additional efforts in improving all segments of oncology care.

Keywords: cancer, outcomes of cancer treatment, oncology care

SEKCIJA TUMORI SŽS, GLAVE I VRATA / CNS, HEAD AND NECK SESSION

NOVOSTI S ASCO I ESMO KONGRESA U LIJEČENJU TUMORA GLAVE I VRATA

LJUBICA VAZDAR

ljubica.vazdar@gmail.com

Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*

Temeljeno na pozitivnim rezultatima imunoterapije u liječenju rekurentnog/metastatskog (r/m) raka pločastih stanica glave i vrata (HNC) nova ispitivanja daju i pozitivne rezultate u ranim stadijima bolesti. Za izdvojiti je DEPEND ispitivanje u HPV negativnog lokoregionalnog HNC s primjenom anti PD-1, nivolumaba, u kombinaciji s paklitakselom i karboplatinom u neoadjuvantnom, a potom nakon kemoradiopterapije i adjuvantnom liječenju tijekom 9 mjeseci. U ispitivanju je 54% bolesnika imalo smanjenje tumora > 50% nakon neoadjuvatne imunokemoterapije, uz naknadnu aplikaciju prilagođene, manje doze zračenja u odnosu na suboptimalni neodjuvantni odgovor (<50%) s potrebom standardne doze zračenja. Uz dubok terapijski odgovor na neoadjuvantno liječenje bolje je preživljenje i lokalna kontrola bolesti uz manju akutnu toksičnost. Ispitivanje nam daje mogućnost stratifikacije bolesnika ovisno o neoadjuvantnom odgovoru i potrebitoj manjoj dozi zračenja uz koju se postiže dobra učinkovitost uz manju toksičnost.

Za bolesnike koji nisu pogodni za terapiju cisplatinom ispitivanje FRAIL-IMMUNE pokazalo je dobru učinkovitost anti PD-L1 durvalumaba u kombinaciji s tjednim paklitakselom i karboplatinom u prvo linijskom liječenju bolesnika s r/m HNC. Postignut je medijan ukupnog preživljenja (OS) 18 mjeseci i medijan preživljenja bez progresije bolesti (PFS) od 7 mjeseci.

U lokoregionalnoj bolesti, ispitivanje faze III, u bolesnika neprikladnih za cisplatin, docetaksel kao radiosenzibilizator je potencijalna terapijska opcija uz dobru učinkovitost. 2-godišnji PFS postignut je u 42% bolesnika (kemoradioterapija) naspram radioterapije, 30,3%. Dvogodišnji OS s docetakselom iznosilo je 25,5 mjeseci naspram 15,3 mjeseca za radioterapiju.

Za izdvojiti je i adjuvantno liječenje nazofaringealnog raka gemcitabinom i cisplatinom s boljom učinkovitošću u odnosu na standardno liječenje cisplatinom i 5-fluorouracilom. Trogodišnji PFS za gemcitabin iznosi 83,9% naspram 71,5% za kontrolnu skupinu uz redukciju rizika progresije za 46%. Učinkovitost se postiže i u preživljenju bez lokalnog relapsa kao i preživljenju bez udaljenih metastaza ali uz veću hematološku toksičnost.

NEWS ON HEAD AND NECK CANCER FROM ASCO AND ESMO CONGRESS

LJUBICA VAZDAR

ljubica.vazdar@gmail.com

University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors Zagreb, Department of Medical Oncology*

Based on positive results of immunotherapy in treatment of recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC), new trials offer positive results in early-stage disease. DEPEND trial in HPV-negative locoregional HNSCC used anti-PD-1 nivolumab, in neoadjuvant and adjuvant treatment, after chemo-radiation (CRT), in combination with paclitaxel and carboplatin, for 9 months. 54% of patients had tumor regression >50% after neoadjuvant immunochemotherapy, therefore received adapted and reduced radiation dose, in comparison to those with suboptimal treatment response (<50%) and standard-dose radiation. Patients with deep response rate to neoadjuvant treatment had favorable survival and locoregional disease control, also decreased acute toxicities. The trial has provided a possibility for patient stratification based on neoadjuvant treatment response and reduced radiation dose, with achievement of good efficacy and reduced toxicity.

In first-line treatment of R/M HNSCC, the FRAIL-IMMUNE trial has demonstrated good efficacy of anti-PD-1 durvalumab in combination with weekly paclitaxel and carboplatin in patients not eligible for cisplatin. Overall survival (OS) median of 18 months, and progression free survival (PFS) median of 7 months were achieved. In locoregional disease in patients not eligible for cisplatin, a phase III trial has shown that use of docetaxel as radiosensitizer is a possible therapeutic option with good efficacy. The 2-year PFS was reached in 42% of patients in chemoradiation arm in contrast with radiotherapy (RT) arm (30.3%). The 2-year OS with docetaxel was 25.5 months compared with 15.3 months (RT). Also, an adjuvant treatment with gemcitabine and cisplatin for nasopharyngeal carcinoma has shown better efficacy compared to standard treatment with cisplatin and 5-fluorouracil. 3-year PFS in the gemcitabine group was 83.9% and 71.5% in the control group with overall 46% reduction of progression risk. Efficacy was achieved also in local recurrence-free survival, as well as distant metastasis-free survival, but with greater hematological toxicity observed.

LEPTOMENINGEAL CARCINOMATOSIS: A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

MARIJA SKOBLAR VIDMAR

mskoblarvidmar@gmail.com

Institute of Oncology Ljubljana, Slovenia
• *Division of Radiotherapy*

In September, The EANO-ESMO guidelines for the diagnosis, treatment, and follow-up of leptomeningeal disease were published. This text is based on those guidelines.

Leptomeningeal metastasis (LM) is defined as the spread of tumor cells within the leptomeninges and the subarachnoid space. It typically occurs in approximately 10% of patients with solid cancers, often in the context of progressive systemic disease. The incidence of central nervous system metastasis, including LM, appears to be increasing. This may be attributed to improved patient survival related to the development of new systemic agents that are potentially less effective within the central nervous system than outside it, as well as advancements in diagnostic assessment. Breast cancer, lung cancer, and melanoma are the main primary tumors in patients with LM. The diagnosis of LM is based on clinical evaluation, cerebrospinal magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) analysis.

Cerebrospinal MRI, without and with contrast enhancement, is the gold-standard imaging method. The MRI presentation can be divided into five main subtypes: linear leptomeningeal disease (Type A), nodular leptomeningeal disease (Type B), a combination of linear and nodular leptomeningeal disease (Type C), hydrocephalus only (Type D – hydrocephalus), or no neuroimaging evidence of leptomeningeal metastasis (Type D – normal).

Lumbar punctures should be performed after neuroimaging to avoid any potential risks to the patients. CSF analysis results are typically categorized as positive (the presence of malignant cells), equivocal (suspicious or atypical cells), or negative (the absence of malignant or potentially malignant cells).

The treatment needs to be individualized. It is guided by factors such as the primary tumor, and its systemic treatment options, as well as the clinical, imaging, and cytological presentation of LM. The treatment approach often involves a combination of intrathecal therapy, systemic pharmacotherapy, and focal radiotherapy.

PRIMJENA IMUNOTERAPIJE U NEMETASTATSKOM PLANOCELULARNOM RAKU GLAVE I VRATA

MARIN PRPIĆ[1], Neva Purgar Levarda[1], Dora Franceschi[1], Davor Kust[1], Ana Fröbe[1]

marin.prpic@kbcsm.hr

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za onkologiju i nuklearnu medicinu*

U više od 60% bolesnika kod kojih je postavljena dijagnoza planocelularnog karcinoma glave i vrata (engl. kratica HNSCC) radi se o lokalno uznapredovaloj bolesti. Standard radikalnog liječenja ove skupine bolesnika predstavlja operacija s postoperativnom radioterapijom (s ili bez kemoterapije) ili radioterapija u radikalnoj dozi (s ili bez kemoterapije). Usprkos navedenom multimodalnom liječenju, 5-godišnje stope preživljenja su niske i iznose oko 40-50%. U bolesnika s metastatskom/rekurentnom bolesti, medijan preživljenja je još niži. Uvođenje imunoterapije, odnosno inhibitora imunosnih kontrolnih točaka je nepovratno promijenilo paradigmu liječenja raka u prethodnom desetljeću. Trenutno se u kliničkoj praksi koriste 2 inhibitora imunosnih kontrolnih točaka, konkretno inhibitori PD-1 (eng. Programmed Death 1) signalnog puta – nivolumab i pembrolizumab. U tijeku je provođenje mnogobrojnih klinički studija, uključujući studije imunoterapije u kombinaciji s operacijom, kemoterapijom i radioterapijom u bolesnika s nemetastatskim HNSCC. Nekoliko studija je pokazalo obećavajući potencijal u primjeni imunoterapije u navedenoj indikaciji. Inhibitori kontrolnih točaka se istražuju u neoadjuvantnom liječenju, kako bi se izazvala dugotrajna imunosna antitumorska aktivnost, postiglo smanjenje volumena bolesti što bi dovelo do manjeg opsega kirurške resekcije i posljedičnog morbiditeta te smanjenje potrebe za kasnijim adjuvantnim liječenjem u vidu (kemo)radioterapije. U studiji faze I/II CheckMate 358 primijenjene su neoadjuvantno dvije aplikacije nivolumaba, nakon čega su bolesnici operirani, a patološka regresija je viđena u 23,5% HPV-pozitivnih HNSCC-a i 5,9% HPV-negativnih tumora. Schoenfeld i sur. su u studiji faze 2 s neliječenim HNSCC-om usne šupljine sa stadijima T2 ili višim, davali neoadjuvantni nivolumab sam ili u kombinaciji s ipilimumabom. Rezultati ukazuju na bolji patološki odgovor kod primjene dvostruke imunoterapije. U zaključku se može reći kako je potrebno više studija faze III, bolja selekcija bolesnika obzirom na stadij bolesti, PD-L1 i HPV status kako bi se točno definirala uloga i pozicija imunoterapije u liječenju nemetastatskog planocelularnog raka glave i vrata

APPLICATION OF IMMUNOTHERAPY IN NON-METASTATIC SQUAMOUS CELL CANCER OF THE HEAD AND NECK

MARIN PRPIĆ[1], Neva Purgar Levarda[1], Dora Franceschi[1], Davor Kust[1], Ana Fröbe[1]

marin.prpic@kbcsm.hr

[1] University Hospital Centre Sestre milosrdnice
• *Department of Oncology and Nuclear medicine*

More than 60% of patients diagnosed with squamous cell carcinoma of the head and neck (HNSCC) have locally advanced disease. The standard of radical treatment for this group of patients is surgery with postoperative radiotherapy (with or without chemotherapy) or radical dose radiotherapy (with or without chemotherapy). Despite the mentioned multimodal treatment, the 5-year survival rates are low and amount to around 40–50%. In patients with metastatic/recurrent disease, median survival is even lower. The introduction of immunotherapy, i.e., inhibitors of immune checkpoints, irreversibly changed the paradigm of cancer treatment in the previ-

ous decade. Currently, 2 immune checkpoint inhibitors are used in clinical practice, specifically PD-1 (Programmed Death 1) signalling pathway inhibitors – nivolumab and pembrolizumab. Numerous clinical studies are underway, including studies of immunotherapy in combination with surgery, chemotherapy, and radiotherapy in patients with non-metastatic HNSCC. Several studies have shown promising potential in the application of immunotherapy in this indication. Checkpoint inhibitors are being investigated in neoadjuvant treatment, to induce long-term immune antitumor activity, to achieve a reduction in the volume of the disease, which would lead to a smaller extent of surgical resection and consequent morbidity, and to reduce the need for subsequent adjuvant treatment in the form of (chemo)radiotherapy. In the phase I/II CheckMate 358 study, two applications of nivolumab were applied neoadjuvantly, after which the patients underwent surgery, and pathological regression was seen in 23.5% of HPV-positive HNSCC and 5.9% of HPV-negative tumors. In conclusion, more phase III studies, better selection of patients regarding disease stage, PD-L1 and HPV status are needed to accurately define the role and position of immunotherapy in the treatment of non-metastatic squamous cell cancer of the head and neck.

SEKCIJA TUMORI PLUĆA / LUNG TUMORS SESSION

LOKALNO UZNAPREDOVALI RAK PLUĆA

IVA SKOČILIĆ[1], Dragan Trivanović[2]

iskocilic@gmail.com

[1] Klinički bolnički centar Rijeka
• *Klinika za tumore*
[2] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*

Uvod: Nedavne registracije lijekova promijenila su standard skrbi za pacijente s kliničkim stadijem raka pluća nemalih stanica I-III koji se liječe kirurškom resekcijom ili definitivnom terapijom zračenjem. Standardne mogućnosti skrbi za ove pacijente sada uključuju dodatak check point inhibitora ili ciljanu terapiju. Suvremene terapije, koje danas predstavljaju standard liječenja s relativno dobrim toksičnim profilom, značajno su produžile preživljenje bez progresije bolesti i 5-godišnje preživljenje. Razvojem adjuvantnog, neoadjuvantnog i perioperativnog liječenja otvorila su se nova pitanja, ne samo kome dati adjuvantnu terapiju, već i potpuna promjena paradigme koja sve više ide u smjeru precizne medicine. Durvalumab kao konsolidativna monoterapija nakon konsolidirajuće kemoradioterapije (cCRT) postao je standardni tretman za bolesnike s neoperabilnim rakom pluća nemalih stanica stadija III (NSCLC) koji je nedvojbeno poboljšao prognozu mnogih bolesnika s lokalno uznapredovalom bolešću u smislu preživljenja bez progresije bolesti i ukupnog preživljenja.

Prikaz slučaja: Ovdje prezentiramo slučaj 57-godišnjeg muškarca, bivšeg pušača, kojemu je dijagnosticiran adenokarcinom gornjeg lijevog režnja pluća i lijeva medijastinalna limfadenopatija, te je uspješno liječen multimodalnim pristupom. Klinički stadij bolesti bio je T2bN2, III A. Ekspresija PD-L1 bila je 50%. Pacijent je podvrgnut radioterapiji moduliranom intenzitetom (frakcionirana radioterapija do 66 Gy u dnevnim frakcijama od 2 Gy) istodobno s dublet kemoterapijom na bazi platine. Durvalumab je započet 14 dana nakon završetka cCRT-a. Nakon 12 mjeseci konsolidacijske imunoterapije došlo je do potpunog odgovora primarnog karcinoma pluća i djelomične regresije medijastinalnih limfnih čvorova. U ovom slučaju pacijent je vrlo rano započeo imunoterapiju i nije doživio ozbiljne nuspojave povezane s imunološkim sustavom, što dokazuje sigurnost primjene durvalumabom nakon cCRT-a.

Zaključak: Optimalni slijed liječenja adjuvantne i/ili neoadjuvantne ili postperioperativne terapije ostaje važno pitanje koje zahtjeva odgovore u budućnosti. Razina ekspresije PD-L1 prije početka liječenja, serijski cirkulirajući DNA za minimalno praćenje rezidualne bolesti i drugi čimbenici potencijalni su biomarkeri čiju uskoro očekujemo jasniju definiciju.

LOCALLY ADVANCED LUNG CANCER

IVA SKOČILIĆ[1], Dragan Trivanović[2]

iskocilic@gmail.com

[1] University Hospital Centre Rijeka
• *Department of Radiotherapy and Oncology*
[2] General Hospital Pula
• *Department of Medical Oncology and Hematology*

Introduction: Recent immunotherapy approvals have changed the standard of care for patients with clinical stage I-III non–small cell lung cancer treated with surgical resection or definitive radiation therapy. Standard-of-care options for these patients now include the addition of an immune checkpoint inhibitor or targeted therapy. With the development of adjuvant, neoadjuvant and perioperative treatment, new questions appeared, not only to whom to give adjuvant therapy, but a complete change of paradigm, which is increasingly moving in the direction of precision medicine. Durvalumab as consolidative monotherapy following concurrent chemoradiotherapy (cCRT) became the standard treatment for patients with unresectable stage III NSCLC which undoubtedly improved the prognosis of many patients with locally advanced disease in terms of progression- free and overall survival.

Case Report: Here we describe a case of 57-year-old male, former smoker, who was diagnosed with adenocarcinoma of the upper left lobe of the lung and left mediastinal lymphadenopathy and was successfully treated with multimodal approach. The clinical stage of disease was T2bN2, III A. The PD-L1 expression was 50%. Patient underwent intensity modulated radiotherapy (fractionated radiotherapy to 66 Gy in 2 Gy daily fractions) concurrent with platinum-based doublet chemotherapy. Durvalumab was initiated 14 days after finishing cCRT. After 12 months of consolidation immunotherapy there was complete response of primary lung cancer and partial regression in mediastinal lymph nodes and experienced no severe immune-related adverse events.

Conclusion: The optimal treatment sequence of adjuvant and/or neoadjuvant or post perioperative therapy remains an important unanswered question, including the optimal regimen in the adjuvant setting and whether adjuvant therapy following neoadjuvant treatment will improve outcomes. Also, we need standardized predictive and prognostic biomarkers to guide the standard of care like PD-L1 expression before treatment initiation, serial circulating DNA for MRD monitoring and other factors.

SEKCIJA PROBAVNI TUMORI / DIGESTIVE TUMORS SESSION

LOKALNO UZNAPREDOVALI KARCINOM GUŠTERAČE – PRIKAZ SLUČAJA

DORA TOMEK HAMZIĆ[1], Domina Kekez[1], Borislav Belev[1,2]

doratomek@icloud.com

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Sveučilište u Zagrebu
• *Medicinski fakultet*

Uvod: Karcinom pankreasa je jedan od najsmrtonosnijih karcinoma. Čak i u lokalno uznapredovalom stadiju medijan preživljenja ostaje kraći od 18 mjeseci. Standard liječenja lokalno uznapredovalog karcinoma pankreasa je multimodalitetno liječenje koja uključuje kiruršku resekciju, kemoterapiju i radioterapiju u određenim okolnostima.

Prikaz slučaja: Bolesniku starom 53 godine je krajem 2021. godine sklopu obrade mršavljenja, bolova u trbuhu i žutice postavljena dijagnoza lokalno uznapredovalog adenokarcinoma glave pankreasa. Obzirom da je

tumor je infiltrirao gornju mezenteričnu arteriju i venu, nije bio operabilan. Zbog žutice i dilatacije žučnih vodova postavljen je plastični stent u pankreatični vod. Od komorbiditeta za izdvojiti je šećerna bolest neovisna o inzulinu, arterijska hipertenzija, infarkt miokarda i preboljela duboka venska tromboza. Inicijalno je liječen kemoterapijom po FOLFIRINOX protokolu. Primio je ukupno 9 ciklusa. Obzirom da nije postignuta resektabilnost, u kolovozu 2022. provedena SBRT tvorbe u pankreasu. Od tada je bio bez simptoma i bez znakova povrata bolesti do studenog 2022. godine kada je opet razvio žuticu. CT-om je opisan lokalni recidiv uz dilataciju žučnih vodova. Sada je postavljen metalni stent u glavni pankreatični vod. Po oporavku bilirubina nastavljeno je sustavno onkološko liječenje, primio je još 6 ciklusa po FOLFIRINOX protokolu, čime je postignuta kontrola bolesti, bez diseminacije bolesti. U lipnju 2023. ponovo je provedena SBRT lokalnog recidiva. Dalje se liječenje kompliciralo se krvarenjem u probavnu cijev i progresijom lokalnog recidiva, zbog čega je započeta druga linija liječenja po protokolu nabpaklitaksel-gemcitabine. Primio je jedan ciklus liječenja no danji tijek liječenja kompliciralo se pancitopenijom, pogoršanjem ascitesa i općeg stanja. Nakon kolovoza 2023. godine bolesnik je izgubljen iz praćenja.

Zaključak: Ishodi liječenja lokalno uznapredovalog adenokarcinoma pankreasa ostaju loši unatoč svim modernim terapijama, no multidisciplinarnim pristupom koji uključuje radiologa, kirurga, gastroenterologa i internističkog i radioterapijskog onkologa mogu se poboljšati.

LOCALLY ADVANCED PANCREATIC CANCER – CASE PRESENTATION

DORA TOMEK HAMZIĆ[1], Domina Kekez[1], Borislav Belev[1,2]

doratomek@icloud.com

[1] University Hospital Centre Zagreb
• *Department of Oncology*
[2] University of Zagreb
• *School of Medicine*

Introduction: Pancreatic cancer is one of the deadliest cancers. Even in the locally advanced stage, the median overall survival remains less than 18 months. The standard of care for locally advanced pancreatic cancer is multimodal treatment that includes surgical resection, chemotherapy, and radiotherapy in certain circumstances.

Case Report: A 53-year-old patient, with diabetes, hypertension, myocardial infarction, and deep vein thrombosis was diagnosed with locally advanced adenocarcinoma of the pancreas in December of 2021. Tumor was not operable, because it infiltrated superior mesenteric artery and vein. Due to jaundice a plastic stent was placed in the pancreatic duct. He was initially treated with 9 cycles of FOLFIRINOX chemotherapy protocol. As resectability was not achieved SBRT was performed in August 2022. Until November 2022 he was fine without signs of relapse, when he developed jaundice because of local recurrence. A metal stent was placed in the main pancreatic duct. After the recovery of bilirubin, systemic oncology treatment was continued. He received 6 more cycles of FOLFIRINOX protocol. As local disease was stable, without systemic dissemination, in June 2023 SBRT of local recurrence was performed again. Further treatment was complicated with bleeding into duodenum and progression. Second line of treatment was started with nabpaclitaxel-gemcitabine protocol, he received only one cycle. Further treatment was complicated with pancytopenia, ascites, and deterioration. After August 2023, the patient was lost to follow-up.

Conclusion: Treatment outcomes for locally advanced pancreatic adenocarcinoma remain poor despite all modern therapies but can be improved with a multidisciplinary approach that includes a radiologist, surgeon, gastroenterologist and medical and radiation oncologist.

PRIKAZ SLUČAJA – HCC – KOJI JE OPTIMALNI KONCEPT LIJEČENJA?

DOMINA KEKEZ

domina.kekez@gmail.com

Klinički bolnički centar Zagreb
• *Klinika za onkologiju*

Uvod: Hepatocelularni karcinom je najčešći podtip primarnih tumora jetre te je treći vodeći uzrok smrti od raka u svijetu. Liječenje, ovisno o proširenosti bolesti, može biti transplantacija jetre, lokalno ablativne metode ili sistemsko liječenje. Sorafenib je do recentno bio jedina sistemska opcija liječenja u ovih bolesnika. Objavom rezultata studije ImBrave 150 zlatni standard liječenja je postao atezolizumab u kombinaciji s bevacizumabom.

Prikaz slučaja: Bolesniku starom 62 godine je u 10/2022 započela obrada zbog bolova pod desnim rebrenim lukom te febriliteta. Postavljena sumnja na neplastični proces jetre, a biopsijom dokazan hepatocelularni karcinom. Učinjenom obradom nađeno da se radi od multiplim konfluirajućim lezijama (segment V i VI, rubno u VII i VIII) s trombozom u desnoj grani vene porte. Na MSCT toraksa se opisuje nodozna lezija od 6 mm u donjem desnom plućnom režnju uz parakardijalno uvećane limfne čvorove. Markeri virusnog hepatitisa su bili negativni, a obradom probavne cijevi se isključi postojanje varikoziteta jednjaka. AFP 41372,0, sintetska funkcija jetre održana, CP A5. Od komorbiditeta poznat prethodni abuzus alkohola. Prikazan na MDT te je odlučeno započeti sistemsku terapiju atezolizumabom uz bevacizumab. Od 11/2022 do 7/2023 bolesnik dobio ukupno 12 ciklusa navedene terapije s gotovo potpunom regresijom vijabilnog tumora intrahepatalno te stacionarnim nalazom metastaze pluća i limfnih čvorova, AFP 13,2. U srpnju 2023 radi porasta vrijednosti aminotransferaza hospitaliziran te je učinjenom biopsijom jetre potvrđeno da se radi o autoimunom hepatitisu posljedično imunoterapiji atezolizumabom. U terapiju uveden steroid na što nakon mjesec dana terapije dolazi do gotovo potpune normalizacije vrijednosti jetrenih aminotrasnferaza. Daljnji tijek liječenja se komplicira razvojem celulitisa i posljedično tome kompartment sindroma lijeve potkoljenice što je zahtijevalo kirurško liječenje. U trenutku pisanja ovog prikaza slučaja bolesnik hospitaliziran u JIL Klinike za kirurgiju s kompliciranim postoperativnim oporavkom.

Zaključak: Kombinacija imnunoterapije uz bevacizumab je donijela veliki napredak u liječenju bolesnika s HCC.

CASE PRESENTATION – HCC – WHAT IS THE OPTIMAL TREATMENT CONCEPT?

DOMINA KEKEZ

domina.kekez@gmail.com

University Hospital Centre Zagreb
• *Department of Oncology*

Introduction: Hepatocellular carcinoma is the most common subtype of primary liver tumors and the third leading cause of cancer-related death worldwide. Treatment options, depending on the extent of the disease, include liver transplantation, local ablative methods, or systemic treatment. Until recently, sorafenib was the only systemic treatment option. With the publication of the ImBrave 150 study results, the gold standard of treatment has become atezolizumab in combination with bevacizumab.

Case Report: A 62-year-old patient began treatment in October 2022 due to right-sided abdominal pain and fever. Suspected liver neoplasm was diagnosed, and a liver biopsy confirmed hepatocellular carcinoma. Further evaluation revealed multiple confluent lesions (in segments V, VI, VII and VIII) with thrombosis in the right branch of the portal vein. A 6mm nodular lesion in the lower right lung lobe and enlarged paracardial lymph nodes were described on chest MSCT. Viral hepatitis markers were negative, and EGDS found no oesophageal varices. AFP was 41372.0, synthetic liver function was maintained, and the Child-Pugh class was A5. Comorbidities included a history of alcohol abuse. The case was discussed in a MDT meeting, and systemic therapy with atezolizumab and bevacizumab started. From November 2022 to July 2023, the patient received a total of 12 cycles of therapy, resulting in almost complete regression of the intrahepatic viable tumor and stable findings in lung and lymph node metastases, AFP levels 13.2. In July 2023, the patient was hospitalized due to elevated aminotransferase levels, and a liver biopsy confirmed autoimmune hepatitis as a consequence of immunotherapy.

Steroids were introduced, leading to almost complete normalization of liver aminotransferase values after one month of therapy. Subsequently, the treatment course was complicated by cellulitis and compartment syndrome in the left leg, requiring surgical treatment. At the time of writing this case report, the patient is hospitalized in the Surgical ICU with a complicated postoperative recovery.

Conclusion: Atezolizumab and bevacizumab represents a significant advancement in the treatment of patients with HCC.

NOVOSTI S AACR, KOJI NAM NOVI LIJEKOVI DOLAZE U BUDUĆNOSTI?

DRAGAN TRIVANOVIĆ

dtrivanovic@obpula.hr

Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*

Multidisciplinarni pristup liječenju malignih bolesti je direktno povezan sa smjernicama koje objavljuju onkološka društva na osnovu *peer-reviewed* znanstvenih radova i projekata. Smjernice su jasne uz isticanje razine dokaza i jačine preporuke. Istovremeno veliki je broj novih akademski vođenih i/ili industrijom praćenih pretkliničkih i kliničkih radova odnosno kolaboracija koje donose nove informacije o mogućnostima stvaranja novih načina liječenja malignih bolesti bilo iskorištavajući nove mehanizme ili razvojem novih lijekova. Američko udruženje kliničkih istraživača raka AACR (puno ime: *American Association for Cancer Research*) značajan je skup pretkliničara i onih koji su uključeni u razvoj novih lijekova te će se tijekom prezentacije prikazati najbitnije novosti o uzbudljivim lijekovima koji dolaze u budućnosti sa nedavnog godišnjeg kongresa AACR i nekih drugih znanstvenih skupova. Novi pristupi se temelje na poboljšanju imunološkog odgovora u prepoznavanju i borbi protiv tumora, nove biomarkerom vođene molekularne ciljane lijekove, bispecifična antitijela i drugo.

Biti će prikazane osnovne novosti o statusu personalizirane mRNA vakcine u kombinacijama sa lijekovima kao što su vibostolimab, gebasaxturev ili u kombinaciji s imunoterapijom odnosno kombiniranje intratumoralne IL-12 mRNA u protokolima s imunoterapijom. Značajnu perspektivu pokazuju i novi pristupi liječenju poput inhibitora *yes-associated* proteina (YAP)/*transcriptional enhancer activator domain* (TEAD), *dual targeting* BiTE® molecule, alogene anti-CD70 CAR T-cell terapije kao i novog zamaha u razvoju anti-drug konjugata, bispecifičnih antitijela te *an-mutant isoform selective* panPI3Kα inhibitora. Posljednjih godina svjedoci smo i razvoja inhibicije do sada *undruggable* RAS puta. Kao svi novi lijekovi vremenom se pojavljuju ograničenja u obliku rezistencije na prvu generaciju KRAS inhibitora koja se sada nastoje premostiti razvojem novih RAS inhibitora koristeći RAS-ON principe ili KRAS G12D specifičnu inhibiciju. Dolazi uzbudljivo vrijeme i za kliničare te će vjerojatno biti zahtjevno odvagnuti što je optimalno u liječenju bolesnika s malignim bolestima.

NEWS FROM AACR, WHAT NEW DRUGS ARE COMING OUR WAY IN THE FUTURE?

DRAGAN TRIVANOVIĆ

dtrivanovic@obpula.hr

General Hospital Pula
• *Department of Medical Oncology and Hematology*

The multidisciplinary approach to the treatment of malignant diseases is directly related to the guidelines published by oncology societies based on peer-reviewed scientific papers and projects. The guidelines are clear, emphasizing the level of evidence and strength of recommendation. There is a large number of new academically led and/or industry-monitored preclinical and clinical works, i.e., collaborations that bring new information about the possibilities of creating new ways of treating malignant diseases, either by exploiting new mechanisms or developing new drugs. The presentation will feature highlights of exciting drugs coming from the recent AACR Annual Congress and some other scientific meetings. New approaches are based on improving the immune response to recognize and fight tumors, new biomarker-driven molecularly targeted drugs, bispecific antibodies, and more.

Scientific news about the status of personalized mRNA vaccine in combinations with drugs such as vibostolimab, gebasaxturev or in combination with immunotherapy, i.e., combining intratumoral IL-12 mRNA in protocols with immunotherapy, will be presented. New approaches to treatment such as yes-associated protein (YAP)/transcriptional enhancer activator domain (TEAD) inhibitors, dual targeting BiTE® molecule, allogeneic anti-CD70 CAR T-cell therapy, as well as new momentum in the development of anti-drug conjugates show a significant perspective, bispecific antibodies, and an-mutant isoform selective panPI3Kα inhibitor etc. In recent years, we have also witnessed the development of inhibition of the hitherto undruggable RAS pathway. Like all new drugs, limitations appear over time in the form of resistance to the first generation of KRAS inhibitors, which are now being overcome by the development of new RAS inhibitors using RAS-ON principles or KRAS G12D specific inhibition. An exciting time is coming for clinicians as well, and it will probably be demanding to weigh what is optimal in the treatment of patients with malignant diseases.

SEKCIJA MELANOM, MEZENHIMALNI I RIJETKI TUMORI / MELANOMA, SARCOMA AND RARE TUMORS SESSION

ISKUSTVA JEDNOG CENTRA U LIJEČENJU LOKALIZIRANOG OSTEOSARKOMA

TATJANA LADENHAUSER

tladenhauser@gmail.com

Klinički bolnički centar Osijek
• *Zavod za onkologiju*

Uvod: Osteosarkom (OS) je najčešći koštani sarkom, najveće incidencije u drugom desetljeću života, češći kod muškog spola, kod mladih u kostima ekstremiteta. Dijagnoza se postavlja radiografski i biopsijom, a mandatoran je inicijalni staging (CT/scintigrafija skeleta/ MR cijelog tijela ili FDG-PET-CT) s LDH i ALP. Revizija histološkog nalaza obavezna je za sve ustanove izvan mreže ekspertize. Princip liječenja lokaliziranog *high-grade* OS je neoadjuvantna kemoterapija, resekcija i adjuvantna kemoterapija s kurativnim ciljem.

Prikaz slučaja: Pacijent iz prikaza je adolescent (19 godina), negativne onkološke anamneze. Tri mjeseca nakon udarca u proksimalnu lijevu tibiju nastaje bolna oteklina. Promptno je učinjena radiološka obrada, biopsija s revizijom PHD, *staging*. Nađena je lokalizirana bolest, histološki *high-grade* OS (teleangiektatični tip), započinje se neoadjuvantno doksorubicin, cisplatin i visokodozni metotreksat (MAP). Odmah nakon početka kemoterapije nastupa spontana patološka fraktura kosti. Od planirane *limb-sparing* resekcije se odustaje i obavlja se egzartikulacija potkoljenice, ranije od predviđenoga. Protokol MAP nastavljen je kao adjuvantni kroz 6 ciklusa. Od 11.5.2023. pacijent prima i mifamurtid uz kemoterapiju. U rujnu 2023. na kontrolnom PET-CT nema znakova proširenosti bolesti niti recidiva.

Mifamurtid (muramil-tripeptid, Mepact) je sintetski analog sastojka iz stanične stijenke *Mycobacterium sp*., imunostimulans, registriran u EU za adjuvantno liječenje kompletno reseciranog *high-risk* OS kod mlađih od 30 godina, zajedno s adjuvantnom kemoterapijom, a sve na temelju prospektivne randomizirane studije faze III skupine *Children's Oncology Group* iz 2007. godine. Studija je provedena na 662 pacijenta. U skupini s Mepactom postojao je trend k boljem EFS (P =.08), a značajno je poboljšano ukupno šestogodišnje preživljenje sa 70 na 78% (P =.03), HR 0.71. Lijek se primjenjuje kao intravenska infuzija 1 sat, u dozi 2mg/m2, prvih 12 tjedana 2 dana u tjednu, a iduća 24 tjedna jedan dan u tjednu.

Zaključak: Za ovako mlade onkološke pacijente opravdano je i potrebno uključiti i nove modalitete liječenja s dokazanim benefitom u ukupnom preživljenju.

SINGLE CENTER EXPERIENCE – LOCALIZED OSTEOSARCOMA TREATMENT

TATJANA LADENHAUSER

tladenhauser@gmail.com

University Hospital Centre Osijek
• *Department of Oncology*

Introduction: Osteosarcoma (OS) is the most common bone sarcoma, with peak incidence in second decade, more frequent in males, in younger predominantly in extremity bones. Diagnosis is obtained radiographically and through biopsy. An initial staging is mandatory (CT, bone scan, whole body MRI or PET/CT scan) as well as histology report review for all institutions outside the expertise network. The principle of localized OS treatment is neoadjuvant chemotherapy, resection, and adjuvant chemotherapy, with curative intent.

Case Report: The case patient is a male adolescent, 19 years, with negative oncologic history. He experienced a painful swelling of the left proximal tibia – localization of the previous kick three months before. Radiologic assessment, biopsy and staging were performed promptly and localized high-grade telangiectatic OS was found. Neoadjuvant chemotherapy (MAP) was initiated, but few days after cisplatin and doxorubicin, the left tibia fractured. Limb-sparing surgery had to be converted to urgent amputation. He continued with MAP in adjuvant setting for 6 cycles, with mifamurtide from 11th of May 2023. In September 2023, there is no dissemination or local relapse on PET-CT scan.

Mifamurtide (muramyl tripeptide, Mepact) is a synthetic analogue of a compound from the Mycobacterium sp. cell wall, an immunostimulant. It is registered in EU for adjuvant treatment of completely resected high-risk OS in younger than 30 years, given with adjuvant chemotherapy. The registration arrived after the results from a prospective randomized clinical trial phase III (Children's Oncology Group, 2007). It comprised 662 patients. In Mepact group, there was a trend towards improvement in EFS (P =.08), but the 6-year overall survival improvement from 70 to 78% was statistically significant (P =.03), HR 0.71. It is administered as one-hour intravenous infusion, 2mg/m2. First 12 weeks, it is administered twice and next 24 weeks once a week.

Conclusion: There is a strong legitimacy and necessity of adding novel treatment modalities with benefit in overall survival to such young oncologic patients.

SEKCIJA RAK DOJKE / BREAST CANCER SESSION

TRENUTNE MOGUĆNOSTI LIJEČENJA I NOVI HORIZONTI U LIJEČENJU TROSTRUKO NEGATIVNOG RAKA DOJKE

KARLA ZEKULIĆ[1], Anamarija Kovač Peić[2]

karla.mircevski@gmail.com

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*
[2] Opća bolnica „dr. Josip Benčević" Slavonski Brod
• *Odjel za onkologiju i hematologiju*

Uvod: Trostruko negativni rak dojke smatra se najagresivnijim podtipom raka dojke i povezan je s najvišim stopama povrata bolesti. U novije se vrijeme govori o zasebnom entitetu unutar trostruko negativnog podtipa, a to je HER-2 low podtip koji bi mogao biti liječen novim terapijskim opcijama. Tijekom prezentacije bit će prikazan proces donošenja terapijskih odluka te će se učiniti pregled dostupnih terapijskih opcija, ali i onih koje se potencijalno očekuju u budućnosti.

Prikaz slučaja: Bolesnici je prvi puta u 46-oj godini života dijagnosticiran rani stadij trostruko negativnog karcinoma dojke 2007.g. Tada je liječena operativno, a potom adjuvantnom kemoterapijom prema protokolu

ddAC-T (trotjedni) i radioterapijom. Nakon 13 godina praćenja ustanovljen je povrat bolesti u istoj dojci, ponovo trostruko negativnog podtipa. Provedeno je 6 ciklusa neoadjuvantne kemoterapije prema TC protokolu, a postoperativno kapecitabinom tijekom 6 mjeseci. Vrlo brzo nakon završetka adjuvantne terapije, bolesnici je dijagnosticiran trostruko negativni karcinom u drugoj dojci. CT-om toraksa, abdomena i zdjelice isključena je diseminacija. Bolesnici je ponovno ponuđen neoadjuvantni pristup u liječenju čemu je ona sklona, no s obzirom na kumulativne doze doksorubicina provedeno je liječenje ddACx2 + PDL x2 -T(12xtjedni). Postoperativnim je PHDom potvrđen pCR te je nastavljeno praćenje u tijeku kojega se verificira diseminacija bolesti u jetru i pluća. Učinjenom biopsijom jetre potvrđena metastaza TNBC, PD-L1 poz., HER2 1+. Upućena je na BRCA testiranje, a liječenje započeto prvo linijskom terapijom nabpaklitaksel i atezolizumab koje se komplicira sumnjom na imunološki posredovan hepatitis. Nakon progresije bolesnica liječenje nastavlja olaparibom koje je u tijeku obzirom na pristigao pozitivan nalaz BRCA 1.

Zaključak: Iako se trostruko negativni rak dojke i dalje smatra prognostički lošim, dolaskom imunoterapije, PARPi te istraživanjem HER-2 low podtipa u ovom se području otvaraju potencijalne nove terapijske opcije te se vraća u fokus istraživanja.

CURRENT TREATMENT OPTIONS AND NEW HORIZONS IN THE TREATMENT OF TRIPLE NEGATIVE BREAST CANCER

KARLA ZEKULIĆ[1], Anamarija Kovač Peić[2]

karla.mircevski@gmail.com

[1] University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors Zagreb, Department of Medical Oncology*
[2] General Hospital „dr. Josip Benčević" Slavonski Brod
• *Department of Oncology and Hematology*

Introduction: Triple-negative breast cancer is considered the most aggressive subtype of breast cancer and is associated with the highest recurrence rates. More recently, there is talk of a separate entity within the TNBC subtype, namely the HER-2 low subtype. During the presentation, we will discuss the process of making therapeutic decisions and provide an overview of the available treatment options, as well as those expected in the future.

Case Report: The patient was diagnosed with early stage triple negative breast cancer (TNBC) in 2007 at the age of 46. She was treated surgically, followed by adjuvant chemotherapy-ddAC-T protocol (three weekly) and radiotherapy. After 13 years of follow-up, the disease reoccurred in the same breast, again a triple negative subtype. 6 cycles of TC protocol as neoadjuvant chemotherapy were applied and then she was treated postoperatively with capecitabine for 6 months. Soon after the completion of adjuvant therapy, the patient was diagnosed with TNBC in the other breast. Dissemination was ruled out by CT of the thorax, abdomen, and pelvis. Again, the neoadjuvant treatment was discussed to which she was prone, but considering the cumulative doses of doxorubicin, the treatment was carried out with ddACx2 + PDL x2 -T (12x weekly). pCR was confirmed by postoperative PHD. During the follow-up the dissemination of the disease in the liver and lungs is suspected. Liver biopsy confirmed TNBC metastasis, PD-L1+, HER2 1+. She was referred for BRCA testing, and treatment started with first-line therapy with nabpaclitaxel and atezolizumab, which was complicated by the possibility of immune-mediated hepatitis. After progression, the patient's treatment continues with olaparib, which is ongoing due to positive BRCA 1 finding.

Conclusion: Although triple negative breast cancer is still considered to have a poor prognosis, with the arrival of immunotherapy, PARPi and research into the HER-2 low subtype, potential new therapeutic options are opening up in this area.

HR+ POZITIVAN RAK DOJKE, PRIKAZ SLUČAJA I RASPRAVA

IVANA MATANIĆ[1], Iva Kukal Gjergjaj[2], Nikolina Lonjak[3], Natalija Dedić Plavetić[4,5], Tajana Silovski[4], Stela Bulimbašić[6]

ivana.matanic@gmail.com

[1] Opća bolnica Karlovac
• *Odjel interne medicine, onkologije i hematologije*
[2] Klinički bolnički centar Zagreb
• *Klinika za ženske bolesti i porode, Zavod za ginekološku onkologiju*
[3] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*
[4] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[5] Sveučilište u Zagrebu
• *Medicinski fakultet*
[6] Klinički bolnički centar Zagreb
• *Klinički zavod za patologiju i citologiju*

Uvod: Hormonski ovisan HER2 negativan najčešći je podtip raka dojke, a u metastatskoj bolesti ima povoljniju prognozu u odnosu na ostale podtipove. Otkriće novih lijekova, prvenstveno inhibitora o ciklinu D ovisnih kinaza (CDK4/6i), unaprijedilo je liječenje i ishode bolesnica, no uz i dalje prisutan neizbježan problem razvitka endokrine rezistencije. Ne postoji standard liječenja nakon progresije na CDK4/6i, no terapijski se sve više pokušava usmjereno djelovati na ciljane mutacije.

Prikaz slučaja: Bolesnici u dobi od 50 godina u svibnju 2011. godine učinjena je mastektomija i disekcija limfnih čvorova pazuha zbog invazivnog duktalnog karcinoma lijeve dojke T2N0M0 stadija Luminal B, Her2 negativnog fenotipa. Provedeno je adjuvantno liječenje sa 6 ciklusa kemoterapije po FEC protokolu te antihormonskom terapijom tamoksifenom tijekom 5 godina. U svibnju 2018. godine verificirane su multiple jetrene metastaze, a biopsijom jetre verificirana je ista biologija bolesti. Bolesnica se prezentirala sa žuticom i hiperbilirubinemijom te je odlučeno započeti kemoterapiju tjednim paklitakselom, a nakon postignute parcijalne regresije nastavljena je terapija održavanja letrozolom. Zbog progresije bolesti u jetri liječenje je nastavljeno kombinacijom fulvestranta i palbocikliba, a nakon 3 mjeseca je reinducirana terapija tjednim paklitakselom zbog gubitka kontrole nad bolesti. Nakon 30 aplikacija terapije došlo je do daljnje progresije bolesti, a u međuvremenu su dobiveni i rezultati genskog testiranja kojima je utvrđeno da se radi o nositeljici mutacije *PIK3C*A gena i patogene varijante *u PALB2* genu, što je bolesnicu učinilo kandidatom za liječenje PARP inhibitorom talazoparibom koji je tada bio dostupan u vidu milosrdne primjene te je u ožujku 2020. godine započeto liječenje. Zbog daljnje progresije bolesti, godinu dana kasnije, liječenje je nastavljeno PI3K inhibitorom alpelisibom u kombinaciji s fulvestrantom, potom ponovno kemoterapijom (paklitaksel, kapecitabin) koja je u tijeku.

Zaključak: Optimiziranje liječenja bolesnica s metastatskim hormonski ovisnim karcinomom dojke predstavlja sve veći izazov u svakodnevnoj kliničkoj praksi s otvaranjem novih mogućnosti liječenja.

HR+ BREAST CANCER; CASE REPORT AND PANEL DISCUSSION

IVANA MATANIĆ[1], Iva Kukal Gjergjaj[2], Nikolina Lonjak[3], Natalija Dedić Plavetić[4,5], Tajana Silovski[4], Stela Bulimbašić[6]

ivana.matanic@gmail.com

[1] General Hospital Karlovac
• *Department of Internal Medicine, Medical Oncology and Hematology*
[2] University Hospital Centre Zagreb
• *Clinical Department of Gynaecology and Obstetrics, Department of Gynaecologic Oncology*
[3] University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors Zagreb, Department of Medical Oncology*
[4] University Hospital Centre Zagreb
• *Department of Oncology*
[5] University of Zagreb
• *School of Medicine*
[6] University Hospital Centre Zagreb
• *Department of Pathology and Cytology*

Introduction: Hormone-dependent HER2-negative is the most common subtype of breast cancer, and it has a more favorable prognosis compared with other subtypes. The discovery of new drugs, primarily inhibitors of cyclin D-dependent kinases (CDK4/6i), improved the treatment and outcomes of patients, however, an inevitable problem of endocrine resistance is still present. There is no standard treatment after progression to CDK4/6i so there are more attempts to develop drugs for target mutations.

Case Report: A 50-year-old patient underwent mastectomy and axillary lymph node dissection in May 2011 due to invasive ductal carcinoma of the left breast (T2N0M0 stage Luminal B, Her2 negative immunophenotype). The patient received adjuvant treatment, chemotherapy according to the FEC protocol and antihormonal therapy with tamoxifen for 5 years. In May 2018, MSCT showed multiple liver metastases and liver biopsy revealed the matching immunophenotype. The patient presented with jaundice and hyperbilirubinemia, so it was decided to start chemotherapy with weekly paclitaxel. After partial regression, maintenance therapy with letrozole continued. Due to the progression of the disease, the treatment continued with a combination of fulvestrant and palbociclib then, due to further progression, with 30 applications of weekly paclitaxel. In the meantime, the results of genetic testing were obtained, which showed that she was a carrier of a mutation in the *PIK3CA* gene and a pathogenic variant in the *PALB2* gene, that made the patient a candidate for treatment with the PARP inhibitor talazoparib, then available in the form of compassionate use, and treatment started in March 2020. Due to further progression, one year later, treatment continued with the PI3K inhibitor alpelisib in combination with fulvestrant, then again with chemotherapy (paclitaxel then capecitabine), which is ongoing.

Conclusion: Optimizing the treatment of patients with metastatic hormone-dependent breast cancer represents an increasing challenge in everyday clinical practice with the opening of new treatment options.

IZAZOVI U LIJEČENJU HER2 POZITIVNOG RAKA DOJKE U SVAKODNEVNOJ KLINIČKOJ PRAKSI – PRIKAZ SLUČAJA

JURICA VRBANEC[2], Marina Popović[1]

jvrbanec@gmail.com

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*

Uvod: U otprilike 15–20% svih slučajeva raka dojke radi se o HER2 pozitivnom tumoru, pri čemu je dobno standardizirana stopa HR+HER2+ raka dojke 12,9, a HR-HER2+ 5,2 nova slučaja na 100 000. Liječenje HER2 pozitivnog raka dojke je iz temelja promijenjeno otkrićem lijekova koji blokiraju HER2 receptor. Kroz prikazani slučaj bit će raspravljene specifičnosti liječenja HR+HER2+ raka dojke od rane bolesti do metastatskog povrata. Tijekom prezentacije bit će opisan proces donošenja odluka u ključnim trenutcima liječenja, potkrijepljen dokazima iz najrelevantnijih kliničkih studija.

Prikaz slučaja: Premenopauzalnoj bolesnici u dobi od 47 godina dijagnosticiran je inflamatorni HR+HER2+ rak dojke sa zahvaćanjem pazušnih limfnih čvorova, bez znakova diseminacije bolesti. Napravljena je modificirana radikalna mastektomija i provedena adjuvantna kemoterapija po ddAC-T protokolu uz blokadu HER2 receptora trastuzumabom. Nakon završetka kemoterapije provedeno je adjuvantno zračenje i nastavljena endokrina terapija tamoksifenom. Dvije godine kasnije dijagnosticiran je metastatski povrat bolesti s metastazama u plućima, jetri i kostima. Nakon indukcijske kemoterapije docetakselom uz dvojnu HER2 blokadu, liječenje je nastavljeno aromataznim inhibitorom uz daljnju primjenu trastuzumaba i pertuzumaba. U trećoj godini liječenja metastatske bolesti zabilježena je progresija bolesti intrakranijalno uz ekstrakranijalno stabilnu bolest. Provedena je iradijacija mozga i reinducirana kemoterapija. Kad se intrakranijalno postigla regresija bolesti, zbog izraženih nuspojava kemoterapije liječenje je nastavljeno fulvestrantom uz dvojnu HER2 blokadu. Posljednja slikovna obrada u listopadu 2023. pokazuje progresiju bolesti u mozgu uz i dalje stacionaran nalaz na drugim organima.

Zaključak: Metastaze u mozgu još uvijek predstavljaju klinički izazov u onkologiji. Liječenje se uglavnom temelji na postizanju kontrole bolesti lokalno ablativnim pristupom ili radioterapijom. Nove terapijske opcije u liječenju metastatskog HER2 pozitivnog raka dojke pokazuju obećavajuću intrakranijalnu učinkovitost. Ipak, ograničena dostupnost lijekova otežava liječenje prema smjernicama u svakodnevnoj kliničkoj praksi i iziskuje terapijske pristupe koji nisu testirani u kliničkim studijama.

CHALLENGES IN THE TREATMENT OF HER2-POSITIVE BREAST CANCER IN EVERYDAY CLINICAL PRACTICE – A CASE PRESENTATION

JURICA VRBANEC[2], Marina Popović[1]

jvrbanec@gmail.com

[1] University Hospital Centre Zagreb
• *Department of Oncology*
[2] General Hospital Pula
• *Department of Medical Oncology and Hematology*

Introduction: HER2 is overexpressed in 15–20% of primary breast cancers (BC), with an age-adjusted rate of 12.9 for HR+HER2+ BC, and 5.2 new cases per 100,000 women for HR-HER2+ BC. The discovery of drugs that block HER2 receptor has changed the treatment paradigm for HER-2 positive BC. The management of HR+HER2+ BC from early-stage disease to metastatic recurrence will be discussed through this patient case-based presentation. Clinical reasoning at key points in treatment decision-making will be analyzed in accordance with evidence from the most relevant clinical studies.

Case Report: A 47-year-old premenopausal woman was diagnosed with inflammatory HR+HER2+ BC with axillary lymph node involvement and no evidence of metastasis at presentation. She underwent a modified radical mastectomy, followed by ddAC-T adjuvant chemotherapy with one year of adjuvant trastuzumab. After chemotherapy cessation, adjuvant radiotherapy was preformed, and adjuvant tamoxifen was started. Two years later, metastatic recurrence was diagnosed in the lungs, liver, and bones. Following induction chemotherapy with docetaxel and dual HER2 blockade, maintenance aromatase inhibitor was introduced with continuation of trastuzumab and pertuzumab. In the third year of metastatic disease treatment, intracranial involvement was identified, with otherwise stable disease. Whole-brain irradiation was performed, and chemotherapy was reintroduced. Due to pronounced side effects of chemotherapy, after the confirmed regression of the intracranial disease, a transition from chemotherapy to fulvestrant was performed without changing the anti-HER2 therapy. The latest CT-scan done in October 2023 showed intracranial progression with other metastatic sites responding to treatment.

Conclusion: Brain metastases remain a clinical challenge in oncology. Treatment approaches include surgical resection and radiation therapy. Newer generations of HER2 targeted agents have shown promising intracranial activity. However, the limited availability of these drugs prevents treatment according to the latest guidelines in daily clinical practice and encourages therapeutic approaches that have not been validated in clinical trials.

SEKCIJA MLADIH ONKOLOGA / YOUNG ONCOLOGISTS SESSION

ŠTO JE UOPĆE „SURVIVORSHIP" I ZAŠTO JE VAŽAN?

IVA NIKLES

marincic.iva@gmail.com

Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*

„Život s rakom" (eng. *cancer survivorship*) je višedimenzionalan koncept koji obuhvaća fizičke, emocionalne i psihosocijalne aspekte života nakon postavljanja dijagnoze i liječenja raka. Počinje u trenutku postavljanja dijagnoze i proteže se kroz cijeli život pojedinca, neovisno o fazi liječenja u kojoj se bolesnik nalazi. Sve veći uspjeh u liječenju malignih bolesti doveo je do rastuće populacije bolesnika koji žive s rakom, čije zbrinjavanje danas postaje ključni fokus u onkologiji.

Fizički aspekti života s rakom odnose se na upravljanje dugoročnim posljedicama same bolesti, ali i posljedicama liječenja. Dugoročne posljedice često uključuju umor, bol, disfunkciju organa i veći rizik od razvoja sekundarnih malignih bolesti. Osobe koje žive s rakom često zahtijevaju stalnu medicinsku skrb, praćenje i rehabilitaciju. Mnogi bolesnici s rakom doživljavaju niz emocija, od olakšanja i zahvalnosti do tjeskobe, tuge i straha od povrata bolesti. Vještine suočavanja, emocionalna podrška i očuvanje mentalnog zdravlja ključni su za rješavanje ovih psiholoških izazova. Psihosocijalni aspekti obuhvaćaju utjecaj na društveni život i međuljudske odnose bolesnika s rakom. Odnosi se često mijenjaju, a bolesnici se gotovo svakodnevno bore s problemima koji uključuju doživljaj vlastitog tijela, samopoštovanje i intimnost. Grupe za podršku, savjetovanje i programi namijenjeni bolesnicima s rakom imaju značajnu ulogu prevladavanju navedenih teškoća.

Nadalje, sam koncept naglašava važnost promjena načina života, uključujući zdravu prehranu, tjelovježbu i izbjegavanje čimbenika rizika poput pušenja, kako bi se promicala dugoročna dobrobit. Također potiče redovito praćenje zdravstvenog stanja, održavanje zdravog životnog stila i razvoj planova skrbi koji su prilagođeni jedinstvenim potrebama pojedinca.

Ukratko, koncept „života s rakom" nadilazi početnu dijagnozu i liječenje, obuhvaćajući cjeloživotno putovanje upravljanja fizičkim, emocionalnim i psihosocijalnim aspektima. S napretkom u liječenju raka, važno je osvijestiti potrebu za sveobuhvatnom podrškom bolesnicima s rakom, putem koordinacije i individualizacije zdravstvene skrbi.

WHAT IS SURVIVORSHIP ANYWAY AND WHY IS IT IMPORTANT?

IVA NIKLES

marincic.iva@gmail.com

University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors Zagreb, Department of Medical Oncology*

Cancer survivorship is a multifaceted concept that encompasses the physical, emotional, and psychosocial aspects of life after cancer diagnosis and treatment. It begins at the time of diagnosis and extends throughout the individual's lifetime. The increasing success of cancer treatments has led to a growing population of cancer survivors, making survivorship a critical focus within the field of oncology.

Physical aspects of cancer survivorship involve managing the long-term effects of cancer and its treatments. These effects can include fatigue, pain, organ dysfunction, and a higher risk of secondary cancers. Cancer survivors often require ongoing medical care, monitoring, and rehabilitation to address these issues. Emotionally, cancer survivorship can be a complex journey. Many survivors experience a range of emotions, from relief and gratitude to anxiety, depression, and fear of recurrence. Coping strategies, emotional support, and mental health services are crucial for addressing these psychological challenges. Psychosocial aspects encompass the impact of cancer on a survivor's social and interpersonal life. Relationships may change, and survivors often grapple with

issues related to body image, self-esteem, and intimacy. Support groups, counselling, and survivorship programs play a significant role in helping survivors navigate these challenges. Furthermore, cancer survivorship emphasizes the importance of lifestyle changes, including healthy eating, exercise, and avoiding risk factors like smoking, to promote long-term well-being. It also encourages regular follow-up care, health maintenance, and a survivorship care plan tailored to an individual's unique needs.

In summary, cancer survivorship extends beyond the initial diagnosis and treatment, encompassing a lifelong journey of managing physical, emotional, and psychosocial aspects. With advancements in cancer care, survivorship is becoming increasingly central, highlighting the importance of comprehensive support, healthcare coordination, and individualized care plans to help cancer survivors lead fulfilling lives after their cancer journey.

PSIHOLOŠKI, SOCIJALNI I EKONOMSKI ASPEKTI RAKA

IVANA KUKEC[1], Ivona Poljak[1]

ikukec@kbc-zagreb.hr

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*

Život s rakom odnosi se na osobe koje su izliječene od raka i one koje žive s metastatskim rakom. Onkologija nije samo liječenje raka s najboljim dostupnim lijekovima, nego poboljšanje sveukupnog života bolesnika. Kao onkolozi imamo etičku dužnost prilikom odabira liječenja bolesnika razmotriti koji utjecaj ima sama bolest i njezino liječenje na život bolesnika. Zapitajmo se što je važno toj osobi? Što je ono u čemu joj u kratkom roku možemo pomoći? Rak utječe na sve aspekte osobnosti bolesnika, te je nužna cjelovita procjena njegovog stanja (fizičkih, psiholoških, socijalnih, ekonomskih, duhovnih i drugih aspekata). Zatim je važno zajedno s bolesnikom identificirati njegove osobne ciljeve i prema tome prilagoditi liječenje i ponuditi rehabilitaciju. U ovom radu usredotočit ćemo se na razumijevanje psiholoških aspekata raka, ključnu ulogu socijalne podrške i često zanemarene ekonomske posljedice života s rakom. Na kraju ćemo dati kratak osvrt na prava osoba s rakom u Hrvatskoj u okviru zdravstvenog, socijalnog i mirovinskog osiguranja.

Potrebna su daljnja istraživanja i političke inicijative kako bi se poboljšali uspostavljeni sustavi potpore osobama koje žive s rakom.

Ključne riječi: život s rakom, psihološki aspekt, socio-ekonomski aspekt

PSYCHOSOCIAL AND ECONOMIC ASPECTS OF CANCER SURVIVORSHIP

IVANA KUKEC[1], Ivona Poljak[1]

ikukec@kbc-zagreb.hr

[1] University Hospital Centre Zagreb
• *Department of Oncology*

Cancer survivors refers to persons who have been cured of cancer and those living with metastatic illness. Oncology is not just about treating cancer with the best available therapies; it is about making the lives of our patients better. As oncologists, we have an ethical duty not only to treat the cancer but also to consider the impact of the disease and treatment on each patient's life". Let's ask ourselves what is important to that person? What can we help her with in the short term? Cancer affects all aspects of the patient's personality, and it is necessary to do a holistic assessment of his condition (physical, psychological, social, economic, spiritual, and other aspects). Then it is important to identify personal goals of each person and to adjust the treatment accordingly and offer rehabilitation. In this paper, we will focus on understanding the psychological aspects of cancer, the key role of social support and the often-overlooked economic consequences of living with cancer. In the end, we will give a brief overview of the rights of cancer patients in Croatia within the framework of health, social and pension insurance.

Further research and policy initiatives are needed to improve established support systems for people living with cancer.

Keywords: cancer survivor, psychological aspect, socio-economic aspect

SEKCIJA GINEKOLOŠKIH TUMORA / GYNECOLOGICAL TUMORS SESSION

NOVI MOLEKULARNI BIOMARKERI U KARCINOMU ENDOMETRIJA – POGLED PATOLOGA

MARIJA MILKOVIĆ PERIŠA[1,2]

mmperisa@gmail.com

[1] Klinički bolnički centar Zagreb
• *Klinički zavod za patologiju i citologiju*
[2] Sveučilište u Zagrebu
• *Medicinski fakultet*

Uvod: Endometralni karcinom je najčešća zloćudna novotvorina ženskog spolnog sustava. Histološki razlikuju se endometrioidni karcinom, serozni karcinom, svijetlo-stanični karcinom, nediferencirani karcinom, dediferencirani karcinom, miješani karcinom i karcinosarkom. Endometrioidni endometralni karcinom (EEC) je najčešći histološki tip karcinoma obuhvaćajući 80% slučajeva. Prognostički čimbenici za endometralni karcinom uključuju histološki gradus, dubinu invazije miometrija, zahvaćanje seroze, cervikalne strome, vagine ili adneksa te limfovaskularnu invaziju i zahvaćenost limfnih čvorova. Usprkos postojećim prognostičkim čimbenicima, teško je predvidjeti agresivnost endometrioidnog karcinoma u skupini karcinoma istog histološkog gradusa i istih prognostičkih čimbenika. Iz tog razloga, potrebni su dodatni prognostički parametri kako bismo otkrili tumore s lošom prognozom.

Predmet predavanja: Zadnja Klasifikacija tumora ženskog spolnog sustava Svjetske zdravstvene organizacije objavljena 2020. godine dijeli endometrioidne adenokarcinome endometrija (EEC) u četiri molekularna podtipa. Ti podtipovi su: POLE (patogene somatske mutacije krivog smisla u egzonukleaznoj domeni epsilon DNA polimeraze) mutirani endometrioidni adenokarcinom, endometrioidni adenokarcinom s deficijencijom proteina za popravak krivo sparenih baza (*eng. mismatch repair deficient* MMRd), p53-mutirani endometrioidni adenokarcinom i endometrioidni adenokarcinom nespecifičnog molekularnog profila (NSMP). Podtip p53-mutirani endometrioidni adenokarcinom čini 2–5% svih EEC niskog gradusa i 20% svih EEC visokog gradusa i predstavlja podtip s najlošijom prognozom i najkraćim vremenom do povrata bolesti. Promjene MMR i p53 proteina mogu se određivati imunohistokemijski. Molekularna klasifikacija endometrioidnog karcinoma je uključena u FIGO 2023 klasifikaciju endometralnih tumora.

Zaključak: Otkrivanje molekularnih biomarkera, poput molekularnih podtipova karcinoma endometrija, je ključno u predviđanju agresivnosti tumora i odgovarajućeg onkološkog liječenja. Takva perspektiva otvara vrata sljedećim istraživanjima u otkrivanju novih parametara koji će omogućiti još bolju perspektivu za potvrdu dijagnoze i odabir adekvatnog onkološkog liječenja.

NEW MOLECULAR BIOMARKERS IN ENDOMETRIAL CARCINOMA – VIEW OF PATHOLOGIST

MARIJA MILKOVIĆ PERIŠA[1,2]

mmperisa@gmail.com

[1] University Hospital Centre Zagreb
• *Department of Pathology and Cytology*
[2] University of Zagreb
• *School of Medicine*

Introduction: Endometrial carcinoma is the most common malignant tumor occurring in the female genital tract. Histologically, it can be endometrioid carcinoma, serous carcinoma, clear cell carcinoma, undifferentiated carcinoma, dedifferentiated carcinoma, mixed carcinoma and carcinosarcoma. Endometrioid endometrial carcinoma is the most prevalent type, accounting for 80% of cases. The prognostic factors for endometrial carci-

noma include histological grade, depth of myometrial invasion, serosal, cervical stromal, vaginal, or adnexal invasion, along with lymphovascular invasion and lymph node status. However, it is challenging to predict tumor aggressiveness in endometriod carcinoma with the same histological grade and prognostic factors. Therefore, additional prognostic parameters are essential to identify tumors with a poor prognosis.

Objectives: The latest WHO Classification of female genital tumors from 2020 divides endometrioid endometrial carcinoma (EEC) into four molecular subtypes. These subtypes include: endometrioid adenocarcinoma of mutated DNA polymerase epsilon (POLE ultramutated), endometrioid adenocarcinoma with mismatch repair deficiency (MMRd), p53-mutated endometrioid adenocarcinoma, and endometrioid adenocarcinoma with nonspecific molecular profile (NSMP). The p53-mutated endometrioid adenocarcinoma subtype is present in 2–5% of all low-grade EEC and 20% of high-grade EEC, making it the subtype with the worst prognosis and the shortest time to relapse. Changes in MMR and p53 proteins can be determined with immunohistochemistry. The molecular classification has been included in the 2023 FIGO classification of endometrial tumors.

Conclusion: The identification of molecular biomarkers, such as the subtypes of EEC, is crucial in determining the tumor aggressiveness and the appropriate oncological treatment. This perspective opens doors for further research to discover other prognostic parameters and offer promising prospects for improving the diagnosis and treatment of endometrial carcinoma.

LIJEČENJE METASTATSKOG KARCINOMA VRATA MATERNICE – ULOGA IMUNOTERAPIJE

TIHANA BORASKA JELAVIĆ[1,2]

tihana_boraska@yahoo.com

[1] Opća bolnica Dubrovnik
• *Odjel za onkologiju*
[2] Sveučilište u Splitu
• *Sveučilišni odjel zdravstvenih studija*

Rak vrata maternice jest jedan od vodećih globalnih javnozdravstvenih problema s 604 000 novooboljelih žena u svijetu i oko 342 000 smrti u 2020. godini. Postoje velike varijacije u incidenciji i ishodima liječenja raka vrata maternice, pri čemu se većina slučajeva događa u zemljama niske stope rasta odnosno slabije socioekonomske moći.

Metastatski rak vrata maternice se najčešće razvija nakon liječenja lokalizirane bolesti i dijagnosticira se učestalo u kontekstu peristirajuće/recidivirajuće bolesti s udaljenim metastazama. Osnovu liječenja čini kemoterapija temeljena na platini u kombinaciji s paklitakselom (TC protocol), s ili bez bevacizumaba. Triplet, TC protokol s bevacizumabom, je polučio medijan ukupnog preživljenja od 17 mjeseci. Nakon neuspjeha liječenja s prvo linijskim protokolom temeljenim na platini uobičajeno se primjenjuje sekvencijsko liječenje monokemoterapijskim opcijama s palijativnim ciljem.

Temeljem uspjeha primjene imunoterapije inhibitorima kontrolne točke u nizu sijela solidnih tumora započelo je istraživanje navedenih lijekova i u liječenju uznapredovalog raka vrata maternice. Prvi ovakav lijek odobren od američke *The Food and Drug Administration* (FDA) je pembrolizumab u 2. liniji liječenja metastatskog raka vrata maternice na osnovu rezultata studije Keynote – 158. Ovo istraživanje 2. faze uključilo je među ostalima i 98 pacijentica s metastatskim rakom vrata maternice, a pembrolizumab je polučio objektivnu stopu odgovora (ORR) od 12%, ali s dugim trajanjem odgovora pri čemu je u više od 75% bolesnica on trajao dulje od 9 mjeseci. Jedini objavljeni rezultati istraživanja faze 3 su iz studije EMPOWER- Cervical 1 koja je pokazala prednost cemiplimaba, anti PD-1 protutijela, pred monokemoterapijom prema izboru istraživača u 2. linijskom liječenju, u medijanu ukupnog preživljenja (medijan 12 mjeseci vs 8.5 mjeseci s kemoterapijom, $p < 0.001$). Cemiplimab je u studenom 2022. godine odobren od Europske medicinske agencije (EMA) u ovoj indikaciji.

Keynote-826 (KN 826) je kliničko istraživanje faze 3 koje je usporedilo primjenu prvolinijske kemoterapije po TC protokolu s ili bez bevacizumaba s istim protokolom uz dodatak pembrolizumaba u bolesnica s perzistirajućim/recidivirajućim i/ili metastatskim rakom vrata maternice. Kombinacijska kemoimunoterapija je postigla dulji PFS i OS u odnosu na kontrolnu granu, neovisno jeli ili nije primijenjen bevacizumab, i pembrolizumab je dobio i FDA i EMA odobrenje u ovoj indikaciji. Nažalost, u Republici Hrvatskoj nemamo odobrenu primjenu nijednog od navedenih inhibitora kontrolnih točaka u liječenju uznapredovalog raka vrata maternice.

U tijeku je i cijeli niz istraživanja s drugim inhibitorima kontrolnih točaka, dualnim kombinacijama anti-PDL1 i anti-CTLA 4 lijekovima, a eksploriraju se i lijekovi koji ciljaju nove točke imunološkog nadzora rasta tumora (TIGIT, LAG- 3, TIM- 3, VISTA).

Humanim papilloma virusom (HPV) vođena karcinogeneza u raku vrata maternice dovodi do izbjegavanja imunuloškog nadzora kroz nekoliko mehanizama, ne samo povećanjem izražaja PD-1 receptora na tumorskim stanicama. Drugi načini su stvaranje imunosupresivnog tumorskog mikrookruženja utišavanjem kritičnih signalnih puteva za pokretanje imunološke reakcije, kao i izbjegavanje imunog nadzora preko E7 onkoproteina koji antigen prezentirajuće stanice ne prepoznaju kao strani antigen što dovodi do imune tolerancije. Sve ovo, zajedno s činjenicom da bolesnice oboljele od HIV-a razvijaju 6 puta češće rak vrata maternice, je rezultiralo nizom istraživanja primjene i drugih formi imunoterapije u raku vrata maternice: terapije tumorskim vakcinama, T- stanicama, dendritičkim stanicama, imunomodulatorima.

Najdalje su poodmakla istraživanja učinkovitosti primjene žive, irevezibilno utišane bakterije Listerie monocytogenes (lijek Axalimogene filolisbac (AXAL, ili ADXS11-001), te je Lm-LLO-E7 imunoterapija specifično dizajnirana za liječenje karcinoma povezanih s HPV- om. Također su u tijeku istraživanja liječenja tumor infiltrirajućim limfocitima i CAR-T stanicama za HPV-om inducirane karcinome, te ispitivanja učinkovitosti peptidnih i DNA temeljenih vakcina.

Zaključno, imunoterapija metastatskog raka vrata maternice je nezaobilazna točka terapijskog pristupa ovim bolesnicama, s odobrenom primjenom inhibitora kontrolnih točaka u prvoj i drugoj liniji liječenja. U tijeku su i brojna istraživanja primjene ovih lijekova u ranijim fazama bolesti, kao i eksploriranje novih meta i novih terapijskih pristupa.

THE TREATMENT OF METASTATIC CERVICAL CANCER – THE ROLE OF IMMUNOTHERAPY

TIHANA BORASKA JELAVIĆ[1,2]

tihana_boraska@yahoo.com

[1] General Hospital Dubrovnik
• *Department of Oncology*
[2] University of Split
• *University Department of Health Studies*

Cervical cancer is one of the leading global public health problems with 604,000 newly diagnosed women in the world and about 342,000 deaths in 2020. There are large variations in the incidence and treatment outcomes of cervical cancer, with most cases occurring in countries with low growth rates or lower socioeconomic power.

Metastatic cervical cancer most often develops after treatment of localized disease and is often diagnosed in the context of persistent/recurrent disease with distant metastases. The basis of treatment is chemotherapy based on platinum salt in combination with paclitaxel (TC protocol), with or without bevacizumab. The triplet, TC protocol with bevacizumab, achieved a median overall survival of 17 months. After treatment failure with a first-line platinum-based protocol, sequential treatment with monochemotherapy options with a palliative goal is commonly used.

Based on the success of the use of immunotherapy with checkpoint inhibitors in several solid tumor types, the research of the mentioned drugs also began in the treatment of advanced cervical cancer. The first drug of this kind approved by the US Food and Drug Administration (FDA) is pembrolizumab in the 2nd line of treatment for metastatic cervical cancer based on the results of the Keynote-158 study. This phase 2 study included, among others, 98 patients with metastatic cervical cancer, and pembrolizumab achieved an objective response rate (ORR) of 12%, but with a long duration of response, with more than 75% of responses lasting longer than 9 months. The only published phase 3 research results are from the EMPOWER-Cervical 1 study, which showed the advantage of cemiplimab, an anti-PD-1 antibody, over investigator-selected monochemotherapy in 2nd-line treatment, in median overall survival (median 12 months vs 8.5 months with chemotherapy, $p < 0.001$). Cemiplimab was approved in November 2022 by the European Medicines Agency (EMA) in this indication.

Keynote-826 is a phase 3 clinical study that compared the use of first-line chemotherapy with TC protocol with or without bevacizumab with the same protocol with the addition of pembrolizumab in patients with persistent/recurrent and/or metastatic cervical cancer. Combination chemoimmunotherapy achieved longer PFS and OS compared to the control arm, regardless of whether bevacizumab was administered, and pembrolizumab received

both FDA and EMA approval in this indication. Unfortunately, in the Republic of Croatia, we do not have an approved application of any of the mentioned checkpoint inhibitors in the treatment of advanced cervical cancer.

A whole series of research is underway with other checkpoint inhibitors, dual combinations of anti-PDL1 and anti-CTLA 4 drugs, and drugs that target new points of immune control of tumor growth are also being explored (TIGIT, LAG-3, TIM-3, VISTA).

Human papilloma virus (HPV)-driven carcinogenesis in cervical cancer leads to evasion of immunological surveillance through several mechanisms, not only by increasing PD-1 receptor expression on tumor cells. Other ways are the creation of an immunosuppressive tumor microenvironment by silencing critical signaling pathways for initiating an immune reaction, as well as avoiding immune surveillance via the E7 oncoprotein, which is not recognized by antigen-presenting cells as a foreign antigen, leading to immune tolerance. All this, together with the fact that patients with HIV develop cervical cancer 6 times more often, has resulted in a series of research on the application of other forms of immunotherapy in cervical cancer: therapy with tumor vaccines, T-cells, dendritic cells, immunomodulators.

Research on the effectiveness of the use of live, irreversibly silenced Listeria monocytogenes bacteria (axalimogene filolisbac (AXAL, or ADXS11-001)) has advanced farthest, and Lm-LLO-E7 immunotherapy is specifically designed for the treatment of HPV-related cancers. There is also ongoing research with tumor-infiltrating lymphocytes and CAR-T cells for HPV-induced carcinomas and testing the effectiveness of peptide and DNA-based vaccines.

In conclusion, immunotherapy of metastatic cervical cancer is an indispensable point of therapeutic approach for these patients, with the approved use of checkpoint inhibitors in the first and second line of treatment. There are also ongoing numerous studies on the use of these drugs in the earlier stages of the disease, as well as the exploration of new targets and new therapeutic approaches.

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SEKCIJA UROGENITALNI TUMORI / UROGENITAL TUMORS SESSION

POZITRONSKA EMISIJSKA TOMOGRAFIJA SPECIFIČNIM MEMBRANSKIM ANTIGENOM PROSTATE (PSMA PET/CT) U BOLESNIKA S BIOKEMIJSKIM POVRATOM BOLESTI NAKON PROVEDENOG LOKALNOG LIJEČENJA: PRIKAZ SLUČAJA

IVAN VIČIĆ[1], Maja Baučić[1]

ivan.vicic1@gmail.com

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*

Uvod: Rak prostate je najčešća novootkrivena maligna bolest muškaraca u Hrvatskoj, a treća po mortalitetu. Prema podacima Hrvatskog zavoda za javno zdravstvo (HZJZ) u 2020. godini dijagnosticirano je 2299 novooboljelih. Opcije liječenja lokalne bolesti su radikalna prostatektomija ili radikalna radioterapija sa ili bez dodatka androgen deprivacijske terapije (ADT). Biokemijski relaps se javlja kod gotovo trećine bolesnika nakon provedenog lokalnog liječenja, a pozitronska emisijska tomografija specifičnim membranskim antigenom prostate (PSMA PET/CT) kao sve dostupnija dijagnostička metoda omogućuje raniju detekciju daljnje progresije bolesti.

Prikaz slučaja: Godine 2017. u 60-godišnjeg bolesnika učinjena je biopsija prostate zbog povišenog prostata specifičnog antigena (PSA) 6 ng/mL. Verificiran je adenokarcinom prostate, Gleasonovog zbroja 4+3 u 8/12 cilindara. U sklopu inicijalne obrade učinjen je CT toraksa, abdomena i zdjelice te scintigrafija skeleta kojima nije nađena proširena bolest. U lipnju 2017. učinjena je radikalna prostatektomija te ekstirpacija 3 limfna čvora zdjelice. Prema patohistološkom nalazu ustanovljena je infiltracija kapsule prostate tumorom bez zahvaćanja sjemenih mjehurića i čisti operacijski rubovi. U izoliranim limfnim čvorovima nije bilo tumorskog tkiva. Vrijednost poslije operacijskog PSA bila je <0,002 ng/mL te je bolesnik praćen. Zbog porasta vrijednosti PSA 0,494 ng/mL u siječnju 2023. bolesnik je upućen na PSMA PET/CT kojim je potvrđeno patološko nakupljanje radiofarmaka u limfnom čvoru pararektalno lijevo veličine 0,6 x 0,5 cm. Sljedivo tome provedena je spasonosna radioterapija ležišta prostate i limfnih čvorova zdjelice uz pojačanje doze na PSMA PET/CT pozitivan limfni čvor uz kratkotrajnu ADT goserelinom.

Zaključak: PSMA PET/CT predstavlja praktičan dijagnostički alat u obradi biokemijskog relapsa raka prostate te potencijalno mijenja terapijske odluke, a u budućnosti vjerojatno i službene smjernice, zbog mogućnosti rane detekcije povrata bolesti pri niskim vrijednostima PSA, što dosada nije bilo moguće. Ovaj slučaj je praktični primjer vrijednosti primjene PSMA PET/CT-a u bolesnika s povratom bolesti u limfni čvor nominalne fiziološke veličine.

Ključne riječi: rak prostate, biokemijski relaps, PSMA PET/CT

PROSTATE-SPECIFIC MEMBRANE ANTIGEN POSITRON EMISSION TOMOGRAPHY SCAN (PSMA PET/CT) IN A PATIENT WITH A BIOCHEMICAL RECURRENCE AFTER DEFINITIVE LOCAL THERAPY: CASE REPORT

IVAN VIČIĆ[1], Maja Baučić[1]

ivan.vicic1@gmail.com

[1] University Hospital Centre Zagreb
• *Department of Oncology*

Introduction: Prostate cancer is the most common malignancy of men in Croatia and the third in terms of mortality, with 2299 new cases in 2020. Treatment options for localized disease are radical prostatectomy or radical radiotherapy with or without the addition of androgen deprivation therapy (ADT). Biochemical recurrence occurs in approximately a third of patients after local therapy, and prostate-specific membrane antigen positron emission tomography scan (PSMA PET/CT) is an increasingly available diagnostic tool in that setting.

Case Report: In 2017, a 60-year-old patient underwent a prostate biopsy due to an elevated prostate-specific antigen (PSA) of 6 ng/mL. The histology report verified prostate adenocarcinoma with a Gleason score of 4+3 in 8/12 cylinders. No distant metastases were found on initial staging. In June 2017, a radical prostatectomy was performed, and 3 pelvic lymph nodes were removed. According to the pathohistological findings, surgical margins were clean, the tumor infiltrated the prostate capsule without the involvement of the seminal vesicles, and lymph nodes were normal. The postoperative PSA value was <0.002 ng/mL. After a follow-up period PSA increased to the value of 0.494 ng/mL in January 2023. The patient was referred for a PSMA PET/CT. Abnormal PSMA uptake was reported in the left pararectal lymph node measuring 0.6 x 0.5 cm. Prostate bed and pelvic lymph node salvage radiotherapy was performed with a boost on a PSMA PET/CT positive lymph node. Short-term ADT with goserelin was initiated as well.

Conclusion: PSMA PET/CT is a practical diagnostic tool for prostate cancer biochemical recurrence workup. The possibility of an earlier disease recurrence detection at lower PSA levels can change treatment decisions and potentially official guidelines in the future. This case is an example of the PSMA PET/CT imaging use in a patient with disease recurrence in a morphologically normal-sized lymph node.

Keywords: prostate cancer, biochemical recurrence, PSMA PET/CT.

METASTATSKI HORMON – OSJETLJIVI KARCINOM PROSTATE – KAKO ODABRATI ADT PARTNERA?

In extenso rad u prilogu

MARTINA MLADINOVIĆ[1], Milena Gnjidić[2]

martina.mladinovic@hotmail.com

[1] Opća bolnica „dr. Josip Benčević" Slavonski Brod
• *Odjel za onkologiju i hematologiju*
[2] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*

Uvod: Metastatski hormonski osjetljivi rak prostate (mHSRP) imaju bolesnici koji nisu na androgen deprivacijskoj terapiji (ADT) u trenutku pojave ili progresije bolesti. Osnova liječenja je rana kontinuirana androgen deprivirajuća terapija ili kirurška kastracija uz dodatak antiandrogena nove generacije (ARTA) i/ili kemoterapije.

Prikaz slučaja: Osamdesetogodišnjem bolesniku je u 11/2021 postavljena dijagnoza adenokarcinoma prostate, Gleason broj 5+4=9, inicijalni prostata specifični antigen (PSA) 93. Radiološki suspektni sekundarizmi u jetri uz brojne u kostima. Plan liječenja bio je ADT uz docetaksel. Prije kemoterapije bolesnik je učinio UZV srca koji je pokazao ejekcijsku frakciju 25–30%. S ozirom na kardiomiopatiju te epilepsiju započeto liječenje abirateronom uz prednizon na što je imao zadovoljavajući klinički i biokemijski odgovor. U 11/2022 diskretan porast PSA, radiološki regresija promjena u jetri i ne značajna progresija u kostima uz dobro opće stanje. Nastavljena terapija abirateronom, a prednizon zamijenjen deksametazonom na što dolazi do pada PSA. Od 5/2023 bilježi se porast PSA.

Bolesnik star 77 godina u 7/2022 hospitaliziran zbog febriliteta i pancitopenije. Zbog PSA od 2680 učinjena biopsija prostate potvrdila je adenokarcinom prostate, Gleason broj 4+5=9, sa suspektnim sekundarizmima u jetri, slezeni te kostima uz infiltraciju koštane srži malignim stanicama. S obzirom na lošije opće stanje u 8/2022 započeta samo ADT. Nakon mjesec dana značajan pad vrijednosti PSA 224. Pet mjeseci kasnije došlo je do značajnog kliničkog i biokemijskog poboljšanja i oporavka krvne slike. Započeto liječenje abirateronom uz prednizolon na što dolazi do pada vrijednosti PSA uz daljnje kliničko poboljšanje.

Zaključak: U nedostatku boljih dokaza, za sada odabir lijeka uz ADT za pacijente s mHSRP ovisi o volumenu bolesti, biologiji tumora, općem stanju, dobi, komorbiditetima i profilu toksičnosti lijeka.

METASTATIC HORMONE – SENSITIVE PROSTATE CANCER – HOW TO CHOOSE AN ADT PARTNER?

In extenso article attached

MARTINA MLADINOVIĆ[1], Milena Gnjidić[2]

martina.mladinovic@hotmail.com

[1] General Hospital „dr. Josip Benčević" Slavonski Brod
• *Department of Oncology and Hematology*
[2] University Hospital Centre Zagreb
• *Department of Oncology*

Introduction: Metastatic hormone-sensitive prostate cancer (mHSPC) occurs in patients who are not on androgen deprivation therapy (ADT) at the time of onset or progression of the disease. The cornerstone of treatment is early continuous ADT or surgical castration with the addition of next-generation antiandrogens and/or chemotherapy.

Case Report: An eighty-year-old patient was diagnosed with prostate adenocarcinoma in 11/2021, with a Gleason score of 5+4=9 and initial PSA of 93. Diagnostic workup showed suspect liver metastases and numerous bone metastases. The treatment plan was combination of ADT and docetaxel chemotherapy. Before the chemo-

therapy treatment patient did echocardiogram that showed ejection fraction of 25–30%. Due to cardiomyopathy and epilepsy, treatment with abiraterone with prednisone was initiated instead with satisfactory clinical and biochemical response. In 11/2022, there was a slight increase in PSA, radiological regression of liver lesions, insignificant progression in bones, and overall good condition. The abiraterone therapy was continued, and prednisone was replaced with dexamethasone, leading to a decline in PSA. As of 5/2023, there was an observed rise in PSA.

A 77-year-old patient was hospitalized in 7/2022 due to fever and pancytopenia. A PSA value of 2680 led to a prostate biopsy, confirming prostate adenocarcinoma with a Gleason score of 4+5=9 and suspect liver, spleen, and bone metastases with infiltration of the bone marrow. Considering overall condition, ADT alone was initiated in 8/2022. After one month, there was a significant decline in PSA to 224. Five months later, there was significant clinical and biochemical improvement and recovery of blood counts. Treatment with abiraterone plus prednisolone was initiated, resulting in a decline in PSA levels and further clinical improvement.

Conclusion: In practice, because lack of known biomarkers and mutually compared studies, drug selection (with concomitant ADT) for patients with mHSPC is individualized considering disease volume, tumor biology, overall health, age, comorbidities, and the drug's toxicity profile.

NOVOSTI U LIJEČENJU UROTELNOG KARCINOMA

ZRNA ANTUNAC GOLUBIĆ

zrna.antunac@gmail.com

Klinički bolnički centar Zagreb
• *Klinika za onkologiju*

Urotelni karcinom je deseti najčešći tumor u svijetu te iako se u 75 % slučajeva prezentira kao mišićno-neinvazivni tumor, unatoč agresivnoj lokalnoj terapiji povrat bolesti te progresija su česti. Posljednjih godina došlo je do nagle pojave novih opcija u liječenju metastatskog urotelnog karcinoma prvenstveno razvojem imunoterapije, a u zadnje vrijeme pojavom ciljane terapije. Unatoč tome kemoterapija bazirana na cisplatini ostaje osnova liječenja metastatske bolesti. Terapija održavanja avelumabom u bolesnika koji nisu progredirali na kemoterapiju današnji je standard liječenja za one bolesnike koji su pogodni za terapiju baziranu na platini. Velik dio bolesnika, međutim, ne može primiti terapiju baziranu na platini te je u takvih bolesnika imunoterapija jedina opcija liječenja. Liječenje bolesnika nakon progresije na kemoterapiju te PD1/PDL1 inhibitore predstavlja veliki izazov te do nedavno nije bilo učinkovitih opcija. Pojavom ciljane terapije otvorile su se nove mogućnosti i za ovu populaciju. Enfortumab vedotin (konjugat protutijela i lijeka) ciljana je terapija koja je pokazala učinkovitost u liječenju ove skupine bolesnika uz prihvatljivu toksičnost. Erdafitinib je prva odobrena terapija u liječenju metastatskog urotelnog karcinoma usmjerena na specifični biomarker odnosno *FGFR2/FGFR3* mutaciju koja je pokazala učinkovitost. Sve više se istražuje i kombinacija imunoterapije i ciljane terapije osobito u populaciji bolesnika nepogodnih za cisplatinu kod kojih su mogućnosti liječenja skromne. Unatoč razvoju imunoterapije i ciljane terapije metastatski urotelni karcinom i dalje ostaje neizlječiva bolest te su potrebni bolji prediktivni molekularni markeri kako bi se odabrala najbolja opcija za pojedinog bolesnika. Osim toga, ranija dijagnostika i pravovremeno liječenje u ranijoj fazi bolesti omogućava manju stopu povrata bolesti i povećava šanse za izlječenjem. Radikalna cistektomija uz primjenu neoadjuvantne kemoterapije bazirane na cisplatini standard je liječenja mišićno-invazivnog raka mokraćnog mjehura no nedovoljno se koristi, mnogi bolesnici za nju nisu pogodni, a neki niti ne odgovore na nju. Budući da se imunoterapija pokazala učinkovitom u liječenju uznapredovale bolesti te uzimajući u obzir njen mehanizam djelovanja istraživanja su usmjerena i na primjenu imunoterapije u perioperativnom liječenju te liječenju mišićno-neinvazivnog urotelnog karcinoma. Za izdvojiti je nivolumab koji je pokazao produljenje perioda bez bolesti u adjuvantnoj primjeni u usporedbi s placebom, u indikaciji u kojoj do sada kemoterapija nije pokazala jednaku učinkovitost kao u neoadjuvantoj primjeni. Iako je radikalna cistektomija i dalje zlatni standard u liječenju mišićno-invazivne bolesti mnogi bolesnici nisu skloni radikalnom zahvatu niti su kandidati za zahvat. Stoga je potrebno razvijati metode s ciljem očuvanja mokraćnog mjehura uz dobar onkološki ishod. Ove metode se za sada preporučaju samo u sklopu kliničkog ispitivanja.

NEWS IN THE TREATMENT OF UROTHELIAL CANCER

ZRNA ANTUNAC GOLUBIĆ

zrna.antunac@gmail.com

University Hospital Centre Zagreb
• *Department of Oncology*

Urothelial cancer is the tenth most common cancer worldwide and although usually presents as non-muscle invasive cancer tends to relapse and progress to advanced stage despite aggressive local therapy. In the last years new treatment options have emerged dominantly with the development of immunotherapy, and more recently with targeted therapy. Despite this platinum-based chemotherapy remains the mainstay of therapy for metastatic urothelial cancer. Maintenance therapy with avelumab is the standard therapy for patients not progressing on platinum-based therapy. Large number of patients is platinum ineligible and for those immunotherapy remains the only option. Treatment after progression on chemotherapy and PD1/PDL1 inhibitors remains a challenge and till recently there were no available effective options. Targeted therapy is a new option for this population and enfortumab vedotin (antibody-drug conjugate) is the first approved therapy showing efficacy and safety. Erdafitinib was the first effective biomarker-directed therapy to be approved for metastatic urothelial carcinoma targeting *FGFR2/FGFR3* mutation. Targeted therapy and immunotherapy combinations are being investigated in cisplatin-ineligible patients with bladder cancer in which treatment options are modest. Despite the development of immunotherapy and targeted therapy metastatic urothelial cancer remains an incurable disease so better molecular predictive biomarkers are needed to guide the therapy. Earlier diagnosis and timely treatment in earlier stages can decrease the recurrence rate and improve the cure rate. Radical cystectomy with cisplatin based neoadjuvant chemotherapy is the standard of treatment for muscle-invasive disease but is underused, many patients are ineligible and some of them do not respond. Since immunotherapy has shown efficacy in advanced disease and considering its mechanism of action many investigations focus on its role in perioperative treatment as well as in treatment of non-muscle invasive disease. Nivolumab has shown prolonged disease-free survival compared with the placebo, in the setting in which chemotherapy is not as effective as in the neoadjuvant setting. Although radical cystectomy remains the gold standard in treatment of muscle invasive disease many patients are non- cystectomy candidates or refuse the operation. Therefore bladder-preserving options need to be developed but without compromising the oncological outcome. For now, these options should be performed within the clinical trial.

IZAZOVI I ISKUSTVA U LIJEČENJU UROONKOLOŠKIH BOLESNIKA U NEKLINIČKIM CENTRIMA

ANAMARIJA KOVAČ PEIĆ

akovacpeic@gmail.com

Opća bolnica „dr. Josip Benčević" Slavonski Brod
• *Odjel za onkologiju i hematologiju*

Uspješno liječenje bolesnika s onkološkim bolestima temelji se na odlučivanju u sklopu multidisciplinarnih timova. Po uzoru na kliničke bolničke centre i opće bolnice u RH koje pružaju skrb onkološkim bolesnicima s ciljem unaprjeđenja liječenja su osnovale multidisciplinarne timove koji okupljaju sve medicinske specijalnosti koje sudjeluju u dijagnosticiranju, te kirurškom odnosno sistemskom liječenju određenih sijela malignih bolesti. Kao nužnost pri osnivanju smatrali smo neophodnim da su sve medicinske struke koje sudjeluju predstavljene s minimalno dva člana kako bi samo odlučivanje bilo transparentnije. Također cilj kojim zajednički težimo bio je prikaz svih bolesnika kojima je patohistološki dokazana maligna bolest s ishodištem urološkog sustava. Kod uroonkoloških bolesti, primjerice kod karcinoma prostate jedna od prepreka pri uspješnom utvrđivanju stupnja proširenosti bolesti za visoko rizične bolesnike sa sumnjom na uznapredovalu metastatsku bolest koja nije dokazana konvencionalnim metodama kao što su CT i scintigrafija bila je dužina čekanja na PET/CT. Termine za dijagnostičke metode primjerice PSMA PET ostvarivali smo prikazom naših bolesnika na Timu KBC Zagreb, gdje su nam slanje dijagnostičkih nalaza telemedicinom, te e-uputnice za MDT uvelike koristile. Od listopada 2020. odlukom HZZO nekliničkim bolničkim centrima je omogućena primjena imunoterapije nakon prikaza na MDT kliničkog centra i početka liječenja u Klinikama do prve reevaluacije. Zahvaljujući odličnoj suradnji s dvije

ustanove KBC Zagreb i KBC Osijek bolesnici s urotelnim i karcinomom bubrega su prema indikacijama nastavljali liječenje u našim ustanovama. Izazov u liječenju u zadnjih nekoliko godina bili su i bolesnici s karcinomom mokraćnog mjehura koji su zahtijevali neoadjuvantnu kemoterapiju, a neki od operativnih zahvata uz mentorstvo urologa iz tercijarnog centra su obavljeni u našoj ustanovi. Individualizirani pristup bolesniku s oligometastatskom bolesti u dijagnostičkom ili potencijalno kurativnom pristupu podrazumijevao je suradnju s klinikama.

CHALLENGES AND EXPERIENCES IN THE TREATMENT OF URO-ONCOLOGY PATIENTS IN NON-CLINICAL CENTERS

ANAMARIJA KOVAČ PEIĆ

akovacpeic@gmail.com

General Hospital „dr. Josip Benčević" Slavonski Brod
• *Department of Oncology and Hematology*

Successful treatment of patients with oncological diseases is based on decision-making within multidisciplinary teams (MDT). Following the example of clinical hospital canters, general hospitals in the Republic of Croatia that provide care to oncological patients with the aim of improving treatment established multidisciplinary teams. They are bringing together all medical specialties involved in diagnostics, surgical and systemic treatment of specific malignant diseases. We considered it necessary that all participating medical professions are represented with a minimum of two members to make decision-making more transparent. The goal that we jointly strive for was the presentation of all patients who have pathohistologically proven malignant disease. In treating prostate cancer, one of the obstacles to successfully determining the extent of disease spread for high-risk patients with suspected advanced metastatic disease that has not been proven by conventional methods (CT and scintigraphy) was the wait time for PET/CT. We scheduled diagnostic procedures, such as PSMA PET, by presenting our patients to the MDT at KBC Zagreb, where telemedicine was used for sending diagnostic reports and e-referrals for the MDT greatly helped. Since October 2020, according to the decision of the Croatian Institute for Health Insurance, non-clinical hospital centers have been allowed to administer immunotherapy after presentation at the MDT of a clinical center and the start of treatment in the clinics until the first reevaluation. Thanks to the excellent collaboration with two institutions, KBC Zagreb and KBC Osijek, patients with urothelial and renal cancer continued treatment in our institutions according to indications. In recent years, a challenge was treating patients with bladder cancer who required neoadjuvant chemotherapy, and some of the surgical procedures under the guidance of urologists from the tertiary center was performed in our institution. An individualized approach to patients with oligometastatic disease in potentially curative approach involved collaboration with clinics.

SEKCIJA POTPORNE I PALIJATIVNE MEDICINE / SUPPORTIVE AND PALLIATIVE TREATMENT SESSION

ŠTO ZNAČI DOBRA SMRT ZA HRVATE?

ANA BOROVEČKI

abor@mef.hr

Sveučilište u Zagrebu
• *Medicinski fakultet*

Kada je riječ o donošenju odluka na kraju života i palijativnoj skrbi važno je razumjeti stavove određenog društva o "dobroj smrti". U Republici Hrvatskoj nije do sada bilo provedeno sustavno istraživanje stavova opće populacije o konceptu "dobre smrti". Ovdje je prikazano presječeno istraživanje provedeno je na slučajnom uzorku u tri faze, stratificiranom po regijama, županijama i lokacijama unutar tih županija (N=1203) tijekom

studenog i prosinca 2019. U istraživanju je korišten posebno pripremljeni upitnik koji se sastojao od 62 čestice. Najvažnije karakteristike dobre smrti koje su istaknuli ispitanici bile su: odsutnost boli, prisutnost i neopterećenost obitelji i voljenih, važnost osjećaja ispunjenosti i smisla života, pomirenje s Bogom, prisutnost svijesti i prisebnosti te mogućnost liječenja.

WHAT IS CONSIDERED "GOOD DEATH" FOR CROATS?

ANA BOROVEČKI

abor@mef.hr

University of Zagreb
• *School of Medicine*

When it comes to decision-making at the end of life and palliative care, it is important to understand the attitudes of a certain society about "good death". In the Republic of Croatia, no systematic research on the attitudes of the general population about the concept of "good death" has been carried out. Herer a cross-section study is presented done on a random sample in three phases, stratified by regions, counties, and locations within these counties (N: 1203) during November and December 2019. The research used a specially prepared questionnaire consisting of 62 items. The most important characteristics of a good death that were highlighted by respondents were the absence of pain, the presence of family not to be burden to family and loved ones, the importance of a sense of fulfillment and meaning in life, reconciliation with God, the presence of consciousness and sobriety, and the possibility of treatment.