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SAŽETCI PREDAVANJA | LECTURE ABSTRACTS

IZAZOVI ONKOLOGIJE KROZ PRIZMU HRVATSKIH ONKOLOŠKIH PROFESIONALACA – REZULTATI ISTRAŽIVANJA

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Uvod: Nakon istraživanja Europskog društva za medicinsku onkologiju (ESMO W4O) iz 2016. i 2021. koja su pokazala kako postoji rodni jaz u onkološkoj karijeri proveli smo istraživanje u hrvatskoj onkološkoj zajednici s ciljem identificiranju izazova s kojima se onkološki profesionalci susreću u svojoj karijeri.

Materijali i metode: Putem Google forms *online* ankete dizajnirane analizom sadržaja literature provedeno je istraživanje s pitanjima o utjecaju političke pripadnosti, seksualne orijentacije, vjere i spola na razvoj karijere. Rezultati su analizirani prema spolu i dobi ispitanika.

Rezultati: Prikupljeno je 206 odgovora od čega je 74% ispitanika bilo ženskog, a 26% muškog spola. U istraživanje su bili uključeni svi profesionalci koji se bave onkologijom. Najviše, 55% je bilo internističkih onkologa i onkologa radioterapeuta, potom slijede specijalisti patologije i citologije (15%), kirurški onkolozi (5%), radiolozi (4%) i ostali. Značajan udio ispitanika (41%) je imao ≤40 godina i nalazi se u ranoj fazi svoje karijere (18% specijalizanata, 43% ispitanika se onkologijom bavi manje od 10 godina). Ispitanici su gotovo jednako podijeljeni između rada u kliničkim bolničkim centrima (42%) i općim/županijskim bolnicama (39%), a 19% ispitanika radi u farmaceutskoj/biotehnološkoj tvrtki. Spol je u trećine ispitanika imao umjeren (22%) ili velik utjecaj (10%) na razvoj karijere, za razliku od političke ili vjerske pripadnosti ili seksualne orijentacije. Ispitanici kao glavne prepreke za postizanja ravnopravnosti spolova navode: nedostatak ravnoteže između poslovnog i privatnog života (69%), društvene pritiske (46%), nesvjesnu pristranost (44%) i nedostatak razvoja vodstva za žene (33%). 35% ispitanika je izjavilo kako je zbog spola doživjelo diskriminaciju na radnom mjestu dok je 34% ispitanika navelo spol i kao diskriminirajući faktor u interakciji s pacijentima. Čak 38% ispitanika je doživjelo uznemiravanje ili je svjedočilo (47%) uznemiravanju na radnom mjestu, ali ga je prijavilo samo 11% ispitanika (znatno manje u odnosu provedeno istraživanje ESMO W4O; 2016. 41%, 2021. 50%). Iako je većini ispitanika (80%) važno napredovanje u karijeri čak trećina ispitanika (34%) je tek djelomično zadovoljno ili uopće nije zadovoljno napredovanjem u svojoj karijeri. Također se većina ispitanika (86%) suočila s preprekama u napredovanju u karijeri pri čemu je najčešća pronalaženja ravnoteže između posla i obiteljskog života (56%), a čak 28% ispitanika je kao prepreku navelo neprijateljsko okruženje na radnom mjestu i mobing. 59% ispitanika smatra kako je značajno opterećeno administracijom. U prilog opterećenosti onkologa govori i podatak kako 61% ispitanika radi više od 8 radnih sati dnevno, a samo 14% ispitanika ne radi vikendom ili slobodnim danima.

Zaključak: Spol ostaje glavna prepreka napredovanju u karijeri u onkologiji, kako u onkološkoj zajednici u svijetu, tako i u Hrvatskoj. Spol je također značajan diskriminirajući faktor na radnom mjestu, ali i u interakciji s pacijentima. Nedostatak ravnoteže između poslovnog i privatnog života najveći je izazov u karijeri i glavna prepreka za postizanje ravnopravnosti spolova. Zabrinjava visoka stopa uznemiravanja na radnom mjestu i niska stopa prijavljivanja neprikladnog ponašanja. Administracija uz prekovremeni rad te rad vikendom i slobodnim danima predstavlja značajno opterećenje onkologa. Rezultati istraživanja pružaju nove dokaze i naglašavaju područja za buduće intervencije za podršku jednakosti i raznolikosti u onkološkom razvoju karijere.

Ključne riječi: rodni jaz, onkologija, anketa, karijera, uznemiravanje na radnom mjestu

CHALLENGES OF ONCOLOGY THROUGH THE PRISM OF ONCOLOGISTS – RESEARCH RESULTS

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Background: Following the 2016 and 2021 European Society for Medical Oncology (ESMO W4O) surveys, which showed a gender gap in the oncology career, we surveyed the Croatian oncology community to identify challenges facing oncology professionals.

Materials and methods: Through an online Google Forms survey designed by analyzing the content of the literature, research was conducted with questions about the influence of political affiliation, sexual orientation, religion and gender on career development. The results were analyzed according to the gender and age of the respondents.

Results: 206 responses were collected, of which 74% were women and 26% were men. All oncology specialists were involved in the research. At most, 55% were medical oncologists and radiation oncologists, followed by specialists in pathology and cytology (15%), surgical oncologists (5%), radiologists (4%) and others. A significant proportion of respondents (41%) were ≤40 years old and were in the early phase of their career (18% of residents, 43% of respondents have been working in oncology for less than 10 years). Respondents are almost equally divided between working in a Clinical Hospital Center (42%) and a General/County Hospital (39%), and 19% of respondents work in a pharmaceutical/biotechnology company. Gender had a moderate (22%) or large (10%) influence on career development for a third of respondents, in contrast to political or religious affiliation or sexual orientation. Respondents cited as the main obstacles to achieving gender equality: lack of balance between work and private life (69%), social pressures (46%), unconscious bias (44%) and lack of leadership development among women (33%). 35% of respondents state that they have experienced discrimination in the workplace because of their gender, while 34% of respondents state that gender is a discriminatory factor in their interactions with patients. 38% of respondents experienced harassment or witnessed (47%) harassment in the workplace, but only 11% of respondents reported it (significantly less compared to the ESMO W4O survey; 41% in 2016, 50% in 2021). Although career advancement is important to the majority of respondents (80%), a third of respondents (34%) are only partially or not at all satisfied with their career advancement. Also, the majority of respondents (86%) encountered obstacles in career advancement, the most common of which was finding a balance between work and family life (56%). 28% of respondents cited a hostile workplace environment and mobbing as an obstacle. 59% of respondents believe that they are significantly burdened by the administration. In support of the workload of oncologists is the fact that 61% of respondents work more than 8 working hours a day, and only 14% of respondents do not work on weekends or days off.

Conclusions: Gender remains the main obstacle to advancement in the oncology career, both in the oncology community in the world and Croatia. Gender is also a significant discriminating factor in the workplace, but also in interaction with patients. The lack of balance between work and private life is the biggest challenge in a career and the main obstacle to achieving gender equality. The high rate of harassment in the workplace and the low rate of reporting inappropriate behavior is a concern. Administration along with overtime work and work on weekends and days off represents a significant burden for oncologists. The research findings provide new evidence and highlight areas for future interventions to support equity and diversity in oncology career development.

Keywords: gender gap, oncology, survey, career, workplace harassment

SEKCIJA POTPORNE I PALIJATIVNE MEDICINE / SUPPORTIVE AND PALLIATIVE TREATMENT SESSION

TERAPIJA KUĆNIM LJUBIMCIMA U OSOBA S RAKOM

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Terapija kućnim ljubimcima (engl. PET therapy; Animal-assisted therapy, AAT) koristi trenirane životinje, najčešće pse, za pružanje terapijskih interakcija koje mogu ublažiti bol i poboljšati emocionalnu dobrobit bolesnika.

AAT se pokazala korisnom u smanjenju boli kod pacijenata s rakom kroz smanjenje anksioznosti i stresa, što može umanjiti percepciju boli. Terapija životinjama potiče otpuštanje hormona poput oksitocina i endorfina, što doprinosi osjećaju opuštenosti i smanjenju boli. Studije su pokazale da pacijenti uključeni u AAT programe ponekad trebaju manje lijekova protiv bolova, što naglašava potencijal ove terapije kao komplementarne metode u liječenju boli.

AAT dovodi i do poboljšanje emocionalnog stanja pacijenata, smanjuje umor i osjećaja depresije, smanjuje emocionalni distres, te poboljšava kvalitetu života u osoba s rakom.

AAT može se primjenjivati u onkološkim odjelima, dnevnim bolnicama, hospicijima i odjelima za palijativnu skrb.

Zaključno, terapija uz pomoć životinja nudi obećavajući pristup u upravljanju boli kod osoba s rakom, uz minimalne nuspojave i potencijalno smanjenje upotrebe lijekova protiv bolova.

Ključne riječi: terapija životinjama, bol, onkološki pacijenti, suportivna terapija

PET THERAPY IN PERSONS WITH CANCER

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Pet therapy (also known as Animal-assisted therapy, AAT) involves using trained animals, most commonly dogs, to provide therapeutic interactions that can alleviate pain and improve patients' emotional well-being.

AAT has proven beneficial in reducing pain in cancer patients by lowering anxiety and stress levels, which can decrease the perception of pain. Animal therapy stimulates the release of hormones such as oxytocin and endorphins, contributing to relaxation and pain relief. Studies have shown that patients participating in AAT programs sometimes require less pain medication, highlighting the potential of this therapy as a complementary method in pain management.

AAT also leads to an improvement in patients' emotional state, reduces fatigue and feelings of depression, decreases emotional distress, and enhances the quality of life in persons with cancer.

AAT can be applied in oncology wards, day hospitals, hospices, and palliative care units.

In conclusion, animal-assisted therapy offers a promising approach to pain management in cancer patients, with minimal side effects and the potential to reduce the use of pain medication.

Keywords: pet therapy, pain, cancer patient, supportive therapy

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

RECURRENT GLIOMA: A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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Molecular biomarkers have fundamentally changed the understanding of glioma over the last decade. Accordingly, the fifth edition of the World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS5) incorporates numerous molecular biomarkers with clinicopathologic utility that are important for more accurate classification of CNS neoplasms. Molecular biomarkers also improve diagnostic accuracy and influence the course of treatment by changing treatment recommendations. A marker of particular importance is isocitrate dehydrogenase (IDH). Mutations in genes encoding *IDH* are known to play a crucial role in the classification of gliomas. IDH mutant (IDHm) glioma generally exhibits a better disease outcome than IDH wild type (IDHwt). In adults, diffuse gliomas have been divided into three types according to the new classification: (1) astrocytoma, IDHm; (2) oligodendroglioma, IDHm and 1p/19q-codeleted; and (3) glioblastoma, IDHwt.

The treatment of gliomas includes maximal surgical resection, possibly followed by radiotherapy (RT) and chemotherapy with either procarbazine/lomustine/vincristine (PCV) or temozolomide (TMZ). Due to the proliferative, radioresistant, and chemoresistant nature of the gliomas and high levels of intratumoral heterogeneity, the disease often recurs, and the possibilities of additional treatment are very limited.

The evaluation of treatment response remains a challenge in glioma cases because the neuro oncological therapy can lead to the development of treatment-related changes (TRC) that mimic true progression (TP). Positron emission tomography (PET) using O-(2-[^{18}F] fluoroethyl-)-L-tyrosine (^{18}F-FET) has been shown to be a useful tool for detecting TRC and TP.

The results of our published study indicated that the diagnostic value of static and dynamic biomarkers of ^{18}F-FET PET for discrimination between TRC and TP depends on the IDH mutation status of the tumor. Dynamic ^{18}F-FET PET acquisition proved helpful in the IDHwt subgroup, as opposed to the IDHm subgroup, providing an early indication to discontinue dynamic imaging in the IDHm subgroup.

Keywords: glioma, isocitrate dehydrogenase, positron emission tomography, biomarkers

CILJANA TERAPIJA

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Ozbiljnije poglavlje o ciljanoj terapiji tumora mozga počinje 2022. odobravanjem BRAF/MEK inhibitora temeljem *BRAF V*600E mutacije neovisno o primarnom sijelu tumora. U gotovo 90% pedijatrijskih glijalnih tumora dolazi do alteracije u MAPK signalnom putu s time da je u većine prisutna *BRAF* fuzija (35%), potom *BRAF* V600E mutacija (17%) i *NF1* alteracija (17%). U adolescenata i mladih odraslih mutacija *BRAF*V600E prisutna je u oko 10% bolesnika. Temeljem studija ROAR, NCI MATCH i CTMT212X2101 uočena je visoka stopa odgovora od 33% za gliome visokog gradusa i 50% za gliome niskog gradusa. BRAF/MEK inhibitori od iznimne su važnosti u djece, bolesnika s difuznim gliomima gdje resekcija nije moguća, gdje je zračenje velikog volumena povezano s nuspojavama i kod leptomeningealnih tumora. U bolesnika s progresijom bolesti u travnju 2024. odobren je lijek tovorafenib koji djeluje kao pan-RAF inhibitor uz ukupnu stopu odgovora od 51% (FIREFLY-1). Gliomi niskog gradusa pojavljuju se u mlađim dobnim skupinama, prosječno između 30. i 50.

godine. Većina glijalnih tumora niskog gradusa ima *IDH1* mutaciju u kodonu R132, a 10–15% oboljelih mlađih od 55 godina imaju *IDH2* mutaciju u kodonu R172. Posljedica mutacija je intracelularno nakupljanja 2-hidroksiglutarata, metabolita koji potiče proliferacijsku aktivnost stanice. Gliome niskog gradusa dijelimo na tumore niskog i visokog rizika. Tumori visokog rizika nadalje su predmet radioterapije i kemoterapije. Kako tumori niskog rizika imaju dulje očekivano trajanje života veća je briga o akutnim i kasnim posljedicama zračenja i kemoterapije koje smanjuje kvalitetu života. INDIGO je randomizirana studija faze 3 koja pozicionira vorasidenib u prvu liniju liječenja IDH mutiranih glijalnih tumora gradusa 2. Primarni cilj studije PFS je 27,7 mjeseci u odnosu na 11,1. mj u skupini koja je dobivala placebo (HR 0.39, P=0,000000067). Ključni sekundarni cilj studije je vrijeme do sljedeće intervencije i statistički značajno favorizira vorasidenib (HR, 0,26, *P*=0,000000019). Registracijski postupak je u tijeku.

Ključne riječi: gliomi, BRAF, izocitrat dehidrogenaza, ciljana terapija

TARGETED THERAPY

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BRAF/MEK inhibitors are approved based on the *BRAF* V600E mutation, regardless of the primary tumor site. In almost 90% of pediatric glial tumors there is an alteration in the MAPK signaling pathway, with *BRAF* fusion, *BRAF* V600E mutation, and *NF1* alteration present in the majority. In adolescents and young adults, the *BRAF* V600E mutation is present in about 10% of patients. Based on the ROAR, NCI MATCH, and CTMT212X2101 studies, a high response rate of 33% for high-grade gliomas and 50% for low-grade gliomas (LGG) was observed. In patients with disease progression, a pan-RAF inhibitor tovorafenib was approved in April 2024. Overall response rate is 51% (FIREFLY-1).

LGG appears in younger patients, between the ages of 30 and 50. Most LGG have an *IDH1* mutation in codon R132, and 10–15% of patients under the age of 55 have an IDH2 mutation in codon R172. LGG are divided into low- and high-risk tumors. High-risk tumors are further subject to radiotherapy and chemotherapy. Since low-risk tumors have a longer life expectancy, there is greater concern about the consequences of radiation and chemotherapy. In these tumors, efforts are made to postpone radiotherapy and chemotherapy, and start targeted therapy. Vorasidenib is an *IDH1* and *IDH2* inhibitor with significantly better distribution and a 1:1 ratio between plasma and brain parenchyma. INDIGO is a randomized phase 3 study that positions vorasidenib in the first-line treatment of IDH-mutated grade 2 glial tumors. The primary objective of the study is PFS 27.7 months compared to 11.1. month in the placebo group (HR 0.39, P=0.000000067). The key secondary objective of the study is the time to the next intervention and statistically significantly favors vorasidenib (HR, 0.26, P=0.000000019). The registration procedure is in progress.

Keywords: glioma, *BRAF,* isocitrate dehydrogenase, targeted therapy

IMA LI DALJNJEG NAPRETKA U LIJEČENJU REKURENTNOG I/ILI METASTATSKOG PLANOCELULARNOG KARCINOMA GLAVE I VRATA?

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Promjena paradigme u liječenju rekurentnog/metastatskog (R/M) karcinoma skvamoznih stanica glave i vrata (HNSCC) s uvođenjem inhibitora imunoloških kontrolnih točaka (anti-PD1) sa ili bez kemoterapije, u početku u okruženju otpornom na platinu, a zatim u prvoj liniji R/M bolesti dovela je do poboljšanja u preživljenju. Unatoč ovom terapijskom napretku, samo 15%–19% bolesnika doživi četiri godine te postoji nezadovoljena potreba za novim terapijama za R/M HNSCC. Nove terapijske mogućnosti uključuju terapijska cjepiva, bispecifična protutijela, fuzijske proteine, multitargetirane inhibitori kinaza te konjugate protutijela i lijeka (ADC).

Nove imunoterapijske strategije uključuju terapijska cjepiva koja ciljaju epitope specifične za humani papiloma virus (HPV), cjepiva koja nisu usmjerena na HPV te personalizirana neoantigenska cjepiva. Od 2011. provedena su brojna klinička ispitivanja terapijskih cjepiva kao monoterapije ili u kombinaciji s drugim lijekovima, najčešće inhibitorima imunoloških kontrolnih točaka usmjerenih na PD1, a HPV je glavna terapijska meta. Cjepiva su pokazala značajnu kliničku dobrobit u ispitivanjima faze II i III.

ISA 101 cilja epitope E6 i E7 virusnog proteina i inducira CD4+ i CD8+ T-stanične odgovore. U ispitivanju faze II, u kombinaciji s nivolumabom postignuta je objektivna stopa odgovora (ORR) od 33% s medijanom PFS-a 10,3 mjeseca. PDS0101 u kombinaciji s pembrolizumabom u prvolinijskom liječenju, ispitivanje VERSATILE 002, dovelo je do smanjenja tumora u 67,6% bolesnika s medijanom PFS-a 10,4 mjeseci, a jednogodišnji OS bio je 87,1%. U ispitivanju su i druga kombinacijska cjepiva usmjerena na HPV, u kombinaciji s pembrolizumabom BNT113,CUE-101,HB-200 te INO-3112 u kombinaciji s durvalumabom.

Terapijska cjepiva koja nisu usmjerena na HPV kao UV1 koje je usmjereno na reverznu transkriptazu ljudske telomeraze (hTERT), odnosno ribonukleoproteinski enzim koji može produžiti telomere i igra značajnu ulogu u napredovanju raka. U tijeku je ispitivanje FOCUS – randomizirano ispitivanje faze II, UV1 s pembrolizumabom u usporedbi sa samim pembrolizumabom u prvolinijskom liječenju bolesnika s PD-L1-pozitivnim HNSCC-om. Personalizirano cjepivo, MVX-ONCO-1, kombinira ozračene autologne tumorske stanice s kolonijom granulocitnih makrofaga, pokazalo je ohrabrujući odgovor u prethodno liječenih i otpornih na nivolumab s medijanom OS-a 11,4 mjeseci, a stope OS-a od 12 i 18 mjeseci bile su 49,2% i 31,6%. Terapijska cjepiva imaju povoljan sigurnosni profil u kojemu dominira umor, artralgije i infuzijske reakcije.

Druga nova oružja, uključujući bispecifična protutijela, fuzijske proteine i multitargetirane inhibitore kinaza, iskorištavaju istodobno višestruke mete i modulaciju mikrookruženja tumora kako bi se iskoristio antitumorski imunitet i inhibicija protumorogenih signalnih putova s novim obećavajućim rezultatima. Petosemtamab, IgG1 je bispecifično protutijelo za EGFR i transmembranski receptor LGR5, prisutan u 89% stanica raka glave i vrata. Bolesnici koji su napredovali ili nisu podnosili anti– PD-(L)1 i terapiju baziranu na platini pokazali su ORR od 37%, s medijanom trajanja odgovora od 6 mjeseci. BCA 101 je bifunkcionalan fuzijski protein, monoklonsko protutijelo usmjereno na EGFR i transformirajući faktor rasta beta, u kombinaciji s pembrolizumabom u prvoj liniji liječenja ima ORR 46%.

Inhibitori multikinaza kao što je lenvantinib u kombinaciji s pembrolizumabom u odnosu na pembrolizumab, faza III ispitivanja LEAP-010, u prvolinijskom liječenju PD-L1 CPS ≥1, ima ORR-u 46,1% vs 25,4 % i poboljšanje medijana PFS-a sa 2,8 na 6,2 mjeseca uz više stope nuspojava povezanih s liječenjem, stupnja ≥3 (61,4% vs 17,8%), veće stope prekida liječenja zbog nuspojava (28% vs 8%) i brojčano više stope smrtnih slučajeva povezanih s liječenjem. OS nije poboljšan s ovom kombinacijskom terapijom. U tijeku je ispitivanje LEAP-009 koje procjenjuje lenvatinib sa ili bez pembrolizumaba u odnosu na standardnu kemoterapiju nakon progresije na inhibitoru PD-1 i kemoterapiju na bazi platine. Cabozantinib u kombinaciji s pembrolizumabom u populaciji PD-L1 CPS ≥1,u prvoj liniji liječenja pokazuje ORR od 52%, medijan PFS-a 12,8 mjeseci, 2-godišnji PFS 32,6% i 2-godišnji OS 54,7 %. U tijeku je ispitivanje STELLAR-305, kombinacije zanzalintiniba i pembrolizumaba, također u prvolinijskom liječenju u PD-L1 pozitivnom R/M HNSCC.

Od konjugata protutijela i lijeka (ADC) objavljeni su preliminarni podaci za tisotumab vedotin (TV), enfortumab vedotin (EV) i SGN-B6A, u pretretiranih bolesnika s najmanje dvije linije prethodne sustavne terapije sa ORR oko 20%, medijanom PFS-a 4 mjeseca i OS-a oko 9 mjeseci. Sacituzumab govitekan (SG) je Trop-2-usmjereni ADC, ispitivan je u TROPiCS-03 (faza II) u 43 bolesnika otpornih na platinu i inhibitore kontrolnih točaka, 68% je primilo ≥2 linije sustavne terapije u metastatskom okruženju. ORR je bio 16% s medijanom PFS-a od 4,2 mjeseca. Nuspojave povezane s liječenjem stupnja ≥3 zabilježene su u 44% bolesnika, od kojih najčešće gastrointestinalne, s jednim smrtnim slučajem septičkog šoka, koji se smatrao povezanim s liječenjem.

Trenutačni podaci o ADC-ima u bolesnika s HNSCC-om usmjereni su na bolesnike koji su otporni na platinu i imunoterapiju, a rani rezultati su ohrabrujući. Za populaciju koja je prethodno intenzivno liječena stope odgovora su varirale od 16% do 40% uz relativno dobru podnošljivost. Međutim, regulatorne agencije nisu odobrile nijedan od ovih lijekova za liječenje HNSCC-a iako višestruka klinička ispitivanja trenutno procjenjuju različite ADC-e za ovu populaciju.

Uz rano oduševljenje novim terapijama u R/M HNSCC-u, željno se očekuju rezultati većih randomiziranih ispitivanja u R/M HNSCC-u.

Ključne riječi: planocelularni karcinomi glave i vrata, konjugati lijeka i protutijela,, imunoterapija, antitumorska cjepiva

IMPROVEMENTS IN THE TREATMENT OF RECURRENT AND/OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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The paradigm shift in the treatment of recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (HNSCC) with the introduction of immune checkpoint inhibitors (anti-PD1) with or without chemotherapy, initially in platinum-refractory settings and later in the first line of R/M disease, has led to improved survival. Despite this therapeutic improvement, only 15%–19% of patients survive four years, underlining the unmet need for new therapies for R/M HNSCC. New therapeutic options include therapeutic vaccines, bispecific antibodies, fusion proteins, multitargeted kinase inhibitors, and antibody-drug conjugates (ADC).

New immunotherapeutic approaches include therapeutic vaccines targeting epitopes specific to human papillomavirus (HPV), non-HPV-targeted vaccines, and personalized neoantigen vaccines. As the primary therapeutic target, HPV has been the subject of multiple clinical trials since 2011 involving therapeutic vaccinations either as monotherapy or in combination with other medications, most frequently immune checkpoint inhibitors targeting PD1. These vaccines have shown significant clinical benefits in phase II and III trials.

ISA 101 targets the E6 and E7 viral protein epitopes, inducing CD4+ and CD8+ T-cell responses. In a phase II trial, a median progression-free survival (PFS) of 10.3 months was attained with an objective response rate (ORR) of 33% when in combination with nivolumab. In the VERSATILE 002 study, PDS0101 plus pembrolizumab as first-line treatment resulted in tumor decrease in 67.6% of patients, with a median progression-free survival (PFS) of 10.4 months and a one-year overall survival (OS) of 87.1%. Other HPV-targeted combination vaccines in trials include pembrolizumab with BNT113, CUE-101, HB-200, and INO-3112 with durvalumab.

Human telomerase reverse transcriptase (hTERT), a ribonucleoprotein enzyme that can lengthen telomeres and is substantial in cancer development, is the target of non-HPV-targeted therapeutic vaccinations like UV1. The FOCUS trial is a randomized phase II study that compares pembrolizumab alone to UV1 plus pembrolizumab as first-line therapy for patients with PD-L1-positive HNSCC. With a median overall survival (OS) of 11.4 months and OS rates of 49.2% and 31.6% at 12 and 18 months, respectively, the personalized vaccine MVX-ONCO-1, which combines irradiated autologous tumor cells with a granulocyte-macrophage colony, has demonstrated an encouraging response in previously treated and nivolumab-resistant patients. Therapeutic vaccines have a favorable safety profile, with fatigue, arthralgia, and infusion reactions being the most common side effects.

With encouraging new results, other novel medicines like fusion proteins, bispecific antibodies, and multitargeted kinase inhibitors use several simultaneous targets and tumor microenvironment modification to harness anticancer immunity and disrupt protumorigenic signaling pathways. Petosemtamab, an IgG1 bispecific antibody for EGFR and the transmembrane receptor LGR5, present in 89% of head and neck cancer cells, showed an ORR of 37%, with a median duration of response of 6 months in patients who progressed on or could not tolerate anti–PD-(L)1 and platinum-based therapy. BCA 101, a bifunctional fusion protein, a monoclonal antibody directed at EGFR and transforming growth factor beta, in combination with pembrolizumab in first-line treatment, has an ORR of 46%.

In first-line treatment for PD-L1 CPS ≥1, multikinase inhibitors such as lenvatinib in combination with pembrolizumab showed an ORR of 46.1% versus 25.4% and an improvement in median PFS from 2.8 to 6.2 months in the phase III LEAP-010 trial. There were also higher rates of treatment-related adverse events of grade ≥3 (61.4% vs 17.8%), higher rates of treatment discontinuation due to adverse events (28% vs. 8%), and numerically higher rates of treatment-related deaths. OS was not improved with this combination therapy. In the ongoing LEAP-009 trial, lenvatinib in combination with or without pembrolizumab is being compared to conventional chemotherapy following progression on PD-1 inhibitor and platinum-based chemotherapy. Cabozantinib in combination with pembrolizumab in a PD-L1 CPS ≥1 population in first-line treatment showed an ORR of 52%, median PFS of 12.8 months, 2-year PFS of 32.6%, and 2-year OS of 54.7%. The STELLAR-305 trial of zanzalintinib and pembrolizumab combination in first-line treatment in PD-L1-positive R/M HNSCC is ongoing.

Preliminary data have been published for antibody-drug conjugates (ADCs) such as tisotumab vedotin (TV), enfortumab vedotin (EV), and SGN-B6A in pre-treated patients with at least two lines of prior systemic therapy, with ORR around 20%, median PFS of 4 months, and OS of about 9 months. In TROPiCS-03 (phase II), sacituzumab govitecan (SG), a Trop-2-targeted ADC, was investigated in 43 platinum- and checkpoint-resistant patients; 68% of these patients received at least two lines of systemic therapy in the context of metastatic disease. The ORR was 16%, with a median PFS of 4.2 months. Treatment-related adverse events of grade ≥3 were reported in 44% of patients, most commonly gastrointestinal, with one treatment-related death from septic shock. The patients with HNSCC resistant to immunotherapy and platinum are the focus of current data on ADCs, and the initial findings are promising. Response rates for the population that received extensive pretreatment have ranged from 16% to 40%, with a generally acceptable level of tolerability. However, regulatory agencies have not yet approved any of these medications for the treatment of HNSCC, even though numerous clinical trials are presently assessing different ADCs for this demographic.

Larger randomized trials in R/M HNSCC are widely anticipated, given the early enthusiasm for potential therapeutics in this condition.

Keyword: head and neck squamous cancer, antibody drug conjugate, immunotherapy, cancer vaccines

SEKCIJA PROBAVNI TUMORI / DIGESTIVE TUMORS SESSION

AVAPRITINIB U ČETVRTOJ LINIJI LIJEČENJA METASTATSKOG GASTROINTESTINALNOG STROMALNOG TUMORA – PRIKAZ SLUČAJA

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Uvod: GIST je najčešći mezenhimalni tumor probavne cijevi, ali samo 1–2% svih probavnih tumora. Cajalove stanice mišićnog sloja odgovorne za peristalitiku najvjerojatnije su ishodište. GIST uzrokuju aktivirajuće mutacije u *KIT i PDGFRA* genima za receptore tirozinskih kinaza. Najčešća je mutacija KIT u egzonu 11 (60–70%).

PDGFRA D842V u egzonu 18 prisutna je kod 10–15% slučajeva. Avapritinib je peroralni TKI registriran za liječenje uznapredovalog *PDGFRA* egzon 18 mutiranog GIST-a i za sistemske mastocitoze.

Prikaz slučaja: Kod muškarca, 1948. godište, bez značajnih komorbiditeta, je u svibnju 2021. dijagnosticiran *high-risk* GIST želudca 21x31x28 cm. Učinjena je resekcija te je upućen onkologu. Uveden je imatinib 400 mg, a nakon 7 mjeseci pojavljuju se metastaza jetre i peritoneja. Na imatinib 800 mg pacijent je bez progresije bolesti 15 mjeseci, kada progrediraju jetrene i peritonejske metastaze. Druga linija sunitinibom i treća regorafenibom trajale su 5 i 3 mjeseci, uz mršavljenje i klinički i radiološki porast izraslina trbušne stijenke. U 10/2023. pristiže nalaz SGP-a tumora i mutacija *PGDFRA D842V* sa sugestijom terapije avapritinibom. Putem NPLVSGP-a nabavljen je avapritinib – prva primjena lijeka u RH, a procedura SGP, odobrenja i uvoza potrajala je tri mjeseca. Od veljače 2024. pacijent redovno uzima avapritinib 300 mg do danas (8 ciklusa). Rađene su dvije CT reevaluacije, svaka s parcijalnom regresijom, opće se stanje poboljšava, udebljao se 14 kg. Nuspojave terapije nema, nema alteracija kognitivnog statusa, u EKG-u se otprije prati graničan QTc, koji je tijekom liječenja minimalno produljen na 490ms. Kardiolog smatra da ne postoji realna opasnost od malignih aritmija. U listopadu se planira kontrolna reevaluacija.

Zaključak: Pacijent je idealan za ilustraciju važnosti inicijalne molekularne dijagnostike, jer imatinib i sunitinib na *PDGFRA D842V* mutirani GIST ne djeluju, kao i za uvid u djelotvornost avapritiniba u dugotrajnoj kontroli metastatskog *PDGFRA D842V* mutiranog tumora.

Ključne riječi: gastrointestinalni stromalni tumori, *PGDFRA D842V,* avapritinib,molekularna dijagnostika

AVAPRITINIB IN FOURTH-LINE TREATMENT FOR METASTATIC GASTROINTESTINAL STROMAL TUMORS – A CASE REPORT

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Introduction: GIST is the most common digestive tract mesenchymal tumor, but only 1–2% gastrointestinal cancers are GIST. Probable origin is Cajal's cells of the muscular layer facilitating peristalsis. GIST is driven by activating mutations in *KIT* and P*DGFRA* genes for TK receptors with KIT exon11 being the most frequent (60–70%). *PDGFRA D842V* exon18 is present in 10–15% only gastric GISTs. Avapritinib is an oral TKI registered for advanced *PDGFRA D842V* mutated GIST and systemic mastocytosis treatment.

Case Report: In May 2021, a high-risk gastric GIST measuring 21x31x28cm, was diagnosed in a male patient born 1948. It was radically resected, and the patient was referred to an oncologist. After 7 months of adjuvant imatinib 400 mg, liver and peritoneal metastases emerged on CT scan. Disease is stable for 15 months of subsequent imatinib 800 mg, then liver and peritoneal metastases progress. Second line sunitinib and third line regorafenib control the disease for 5 and 3 months, the patient loses weight and registers abdominal wall protuberance growth. CT records peritoneal and subcutaneous progression. In October 2023 tumour molecular profiling resulted in PDGFRA D842V mutation finding, with the suggestion of avapritinib treatment. Avapritinib was obtained *via* a special health insurance fund, whilst this medication is not routinely available in Croatia. Therefore, the procedure of genetic testing, granting and acquisition of the first avapritinib in the country, took roughly 3 months. Patient is taking avapritinib 300mg from February 2024, 8 months by now, with two interim CTs, both showing partial regression. Patient's general condition improved, he gained 14 kg of body mass, with no treatment side-effects, no cognitive alterations. There was a borderline QTc in ECG from before, and it has slightly prolonged during treatment to 490 ms. Cardiologist finds no threats of malignant arrhythmias. Next CT scan is in October 2024.

Conclusion: This case is illustrative of the initial molecular profiling importance, because imatinib and sunitinib have no effect on *PDGFRA D842V* mutated GIST. It is also beneficial for the direct insight on this targeted drug's effect in control of metastatic disease.

Keywords: gastrointestinal stromal tumors, *PGDFRA D842V,* avapritinib, molecular diagnostic

SEKCIJA TUMORI DOJKE / BREAST CANCER SESSION

NOVOSTI U LIJEČENJU KARCINOMA DOJKE

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Rak dojke područje je neprestanog razvoja. Svake godine objavljuju se brojna istraživanja koja oblikuju terapijski pristup liječenju raka dojke. Kliničari i pacijenti u potrazi za optimalnim liječenjem traže ravnotežu između eskalacije i deeskalacije liječenja.

Kirurzi prednjače u procesu deeskalacije. Rezultati ispitivanja SENOMAC podržavaju izostavljanje aksilarne disekcije (ALND) u svim subpopulacijama pacijenata s do dva pozitivna sentinel limfna čvora (SLNB), uključujući pacijente s mastektomijom te one s ekstranodalnim širenjem. Jedno retrospektivno (EUBREST-06/OMA) i jedno prospektivno (NEOSENTITURK) ispitivanje pokazalo je da, u pacijenata s inicijalno pozitivnom aksilom, koja se nakon neoadjuvantne kemoterapije (NAKT) konvertirala u negativnu aksilu, SLNB i ciljana aksilarna disekcija (kombinacija SLNB i ekscizija prethodno označenog pozitivnog čvora) imaju slične rezultate u smislu lokoregionalnog recidiva. ALND je i dalje indicirana kod rezidualne bolesti nakon NAKT. ICARO ispitivanje ipak sugerira da je SLNB razuman pristup ako se pronađu samo zaostale izolirane tumorske stanice. U tijeku su ispitivanja koja testiraju može li se ALND zamijeniti zračenjem limfne drenaže (RNI) ako se u konačnom patohistološkom nalazu pronađe više rezidualne bolesti (mikro ili makrometastaza). Čak je i uloga SLNB-a upitna. Ispitivanje SOUND pokazalo je da u bolesnika s luminalnim karcinomom dojke, veličine do 2 cm, s negativnim aksilarnim ultrazvukom, preživljenje bez invazivne bolesti (IDFS) jednako bez obzira napravimo li SLNB ili ne.

Klinički onkolozi ne zaostaju za kirurzima. Ispitivanje NSABP 51 pokazalo je da nema potrebe za zračenjem limfne drenaže u slučaju inicijalno pozitivne aksile, koja se nakon NAKT konvertirala u negativnu aksilu. Potreban je oprez kod subpopulacije pacijenata s mastektomijom kod kojih RNI povećava IDFS za 3%. Prema objavljenim podacima studija LUMINA i PRIME II, izostavljanje radioterapije nakon poštedne operacije dojke (BSC) u bolesnika s T1N0 ne-lobularnim luminalnim tumorima, gradus 1–2, ne utječe na ishode preživljenja, ali povećava stopu lokoregionalnih recidiva na 10 godina s 1 na 10 %. Potrebna je individualna odluka za svakog pacijenta o potrebi za adjuvantnom radioterapijom nakon BSC.

Nažalost, internistički onkolozi ne prate trendove u kirugiji i radioterapiji. Utjecaj farmaceutske industrije i mnoštvo novih ispitivanja koja predlažu nove terapijske mogućnosti rezultiraju eskalacijom terapije.

Nije bilo većih promjena u liječenju HER 2 (epidermalni faktor rasta dva) pozitivnog karcinoma dojke. U završnoj analizi ispitivanja Katherine, trastuzumab emtanzin (TDM-1), u usporedbi s trastuzumabom, u bolesnica s rezidualnom bolesti nakon NAKT, statistički je značajno poboljšao IDFS za 13,7% (67,1 vs 80%, HR 0.54) kao i ukupno preživljenje (OS) za 4,7% (84,1 vs 89,9%, HR 0.66). Glavna dilema u metastatskoj bolesti je optimalno liječenje nakon progresije na drugolinijsko liječenje trastuzumab derukstekanom (TDx). Dodatak tukatiniba trastuzumab emtanzinu, u HER2CLIMB-02 istraživanju produljilo je preživljenje bez progresije bolesti (PFS) sa 7,4 na 9,5 mjeseci HR 0,76 (p=0,0163). Retrospektivna analiza bolesnica s pneumonitisom uzrokovanim s TDx, pokazala je sigurnost reindukcije terapija s Tdx u slučaju pneumonitisa stupnja 1, uz prijedlog smanjenja doze TDx-a kod reindukcije.

U trostruko negativnom raku dojke (TNBC), dodatak pembrolizumaba NAKT (ispitivanje KEYNOTE 522) značajno je povećao stopu kompletnog patološkog odgovora te stopu bez povrata bolesti. Subanaliza KEYNOTE-522 pokazala je korist pembrolizumaba čak i kod tumora manjeg rizika kao T2N0 TNBC.

U metastatskoj bolesti obećavaju prvolinijski rezultati kombinacije konjugata antitijela i lijeka (ADC) te imunoterapije. datopotamab-derukstekan (Dato-TDx) i durvalumab u primarno ligand programiranoj staničnoj smrti 1 (PD-L1) negativnih pacijenata postigli su visoku stopu objektivnog odgovora od 79% te PFS od 13,8 mjeseci. U malom randomiziranom ispitivanju MORPEHUS-pan BC, u PD-L1 pozitivnih bolesnica, atezolizumab i sacituzimab govitekan produljili su PFS spram atezolizumaba i nab-paklitaksela (12,2 vs 5,9 mjeseci). U tijeku su mnoga randomizirana ispitivanja faze III čije rezultate željno iščekujemo.

Estrogen receptor (ER) pozitivni rak dojke je najčešći rak dojke, te je i većina objavljenih ispitivanja provedena u ovoj subpopulaciji.

Pitanje potrebe za adjuvantnom kemoterapijom jedno je od većih kliničkih dilema. Pojava Oncotpye DX multigenetskog testa olakšala je kliničku praksu uz i dalje nerazriješenu dilemu potrebe za kemoterapijom u premenopauzalnih žena s pozitivnim limfnim čvorovima. Subanaliza ispitivanja RxPONDER pokazala je da kod žena u pre/perimenopauzi s do tri pozitivna limfna čvora te Oncoytpe rezultatom < 25, nizak anti-mullerov hormon može razlikovati žene koje neće imati koristi od kemoterapije.

Dvije godine adjuvantne terapije inhibitorom ciklin-ovisnih kinaza 4 i 6 (CDK 4/6) abemaciklib je zlatni standard u visokorizičnih luminalnih tumora (4 ili više pozitivnih limfnih čvorova ili pozitivni čvorovi uz tumor > 5 cm ili tumor gradus 3). Ispitivanje NATALEE, testira tri godine ribocikliba, u dozi 400 mg, na široj populaciji pacijentica. Uključene su sve bolesnice s pozitivnim limfnim čvorovima, kao i bolesnice s negativnim čvorovima uz uvjet tumor gradus 3 ili T3 tumor ili tumor gradus 2 uz KI 67 > 20% ili visoki genomski rizik. Nakon medijana praćenja od 36 mjeseci, ribociklib je statistički značajno poboljšao IDFS (90,7 vs 87,6 %, HR 0,749).

Dva ispitivanja KEYNOTE-756 (pembrolizumab) i CA-209-7FL (nivolumab) testiraju ulogu neoadjuvantno-adjuvantne imunoterapije u luminalnom karcinomu dojke. Sve bolesnice su imale tumor gradus 3, uz pozitivne limfne čvorove ili T3 tumor. Dodatak imunoterapije povećao je stopu kompletnog patološkog odgovora. Učinak imunoterapije bio je veći kod PD-L1-pozitivnih i tumora niske ER ekspresije. Dugoročni rezultati nisu dostupni.

Inhibitori CDK 4/6 prvolinijski su standard u liječenju metastatskog luminalnog raka dojke. Ispitivanje MONARCH 3 pokazalo je da abemaciklib poboljšava OS za 13 mjeseci (66,8 vs 53,7 mjeseci, HR 0,80), ali bez postizanja statističke značajnosti. Među tri CDK 4/6 inhibitora jedino je ribociklib produžio OS.

Dodatak novog inhibitora fosfatidilinozitol 3-kinaze (PI3K) inavolisiba palbociklibu i fulvestrantu u bolesnika s PI3K mutacijom koji su progredirali tijekom ili unutar 12 mjeseci od završetka adjuvantne endokrine terapije udvostručilo je vrijeme do progresije bolesti (15,7 vs 7,3 mj., HR 0,43, P < 0,0001). Inavolisib je očekivano povećao toksičnost karakterističnu za PI3K inhibiciju (mukozitis, hiperglikemija, osip, proljev), ali s niskom stopom prekida (6%). Čekamo podatke o preživljenju.

Nakon što je nekoliko manjih ispitivanja sugeriralo benefit nastavka terapijom CDK 4/6 inhibitorom nakon progresije na iste, ispitivanje NEXTMONARCH, prvo ispitivanje faze III, pokazalo je da za pacijente koji su progredirali na terapiju palbociklib ili ribociklib, nastavak CDK 4/6 inhibitora uz prelazak na abemaciklib produžio PFS za manje od mjesec dana (6,0 naspram 5,3 mj. HR 0,73, p = 0,02).

Kada se razvije endokrina rezistencija, liječenje se najčešće nastavlja s kemoterapijom. Ispitivanje DESTINY BREAST-06 odgovorilo je na dva pitanja: Može li Tdx, nakon neuspjeha endokrine terapije, postati prva opcija u luminalnom karcinomu dojke s niskom ekspresijom HER 2, te možemo li proširiti primjenu TDx-a na populaciju luminalnih bolesnica s HER 2 ultraniskom ekspresijom (definirano kao HER 2 (0) ekspresija ali s primjetnim bojanjem na HER 2). TDx je spram kemoterapije produžio PFS i to vrlo slično u pacijenata s niskom HER 2 (13,2 vs 8,1 mj. HR 0,62) kao i HER 2 ultraniskom ekspresijom HER 2 (13,2 vs 8,3 mj., HR 0,83).

Prošla godina u području raka dojke obilježena je daljnjim naporima u deeskalaciji kirurgije i radioterapije. Studije su međutim kreirane bez koordinacije između disciplina te ostaje pitanje možemo li paralelno deeskalirati kirurgiju i radioterapiju. U sustavnom liječenju, potencijalna primjena adjuvantnog ribocikliba, triplet terapija s inavolisibom u bolesnika s endokrinom rezistencijom, te ranija i šira uporaba TDx-a u luminalnom raku dojke glavne su inovacije, bez većih napredaka u deeskalaciji ili boljoj selekciji pacijenata za sistemno liječenje.

Ključne riječi: rak dojke, imunoterapija, inhibitori o ciklinima ovisnih kinaza 4/6, eskalacija, deeskalacija

YEAR IN REVIEW – BREAST CANCER

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Breast cancer is an ever-evolving field with the publication of numerous trials that shape the breast cancer treatment landscape. Clinicians and patients searching for optimal treatment struggle to find the right balance between treatment escalation and de-escalation.

Surgeons are leading the way in the de-escalation process. The results of the SENOMAC trial further support the omission of axillary dissection (ALND) in all subpopulations of patients with up to two positive sentinel lymph nodes (SLNB), most importantly mastectomy patients and those with extranodal extension. For patients with clinically positive axilla who undergo neoadjuvant chemotherapy (NACT) and convert to negative axilla, SLNB only is a reasonable approach. One retrospective (EUBREST-06/OMA) and one prospective (NEOSENTI-TURK) trial showed that SLNB and Targeted axillary dissection (combination of SLNB and excision of the clipped positive node) have similar results in terms of local recurrence, questioning the need for clipping. ALND is still indicated for residual disease after neoadjuvant treatment. The ICARO trial suggests that SLNB only, is a reasonable approach if only residual isolated tumor cells are found. Many trials are underway to see if ALND can be replaced with nodal irradiation if more residual disease (micro or macrometastases) is found on the final surgical report. Even the role of SLNB is questioned. SOUND trial proved that in patients with luminal breast cancer, up to 2 cm, with a negative axillary ultrasound, invasive disease-free survival (IDFS) is the same whether or not we perform SLNB.

Clinical oncologists are right up there with surgical colleagues. NSABP 51 trial showed no need for nodal irradiation in the case of an initially positive axilla, which converts to a negative axilla after NACT. Caution should be taken for a subpopulation of mastectomy patients for whom nodal irradiation provides a 3 % IDFS benefit. According to LUMINA and PRIME II trials published data, omission of RT after breast-conserving surgery (BSC) in patients with T1N0 non lobular luminal tumors, grade 1–2, does not affect survival outcomes but increases locoregional recurrence in 10 years from 1 to 10%. This results in shared decision-making with every patient about the need for adjuvant radiotherapy.

Unfortunately, medical oncologists are falling behind. The impact of the pharmaceutical industry and a plethora of new trials that suggest new therapeutic options result in therapy escalation.

There were no groundbreaking trials in epidermal growth factor receptor two positive (HER 2+) breast cancer. In the final analysis of Katherine trial, trastuzumab emtansine (TDM-1), compared to trastuzumab, in patients with residual disease after NACT, statistically significantly improved both IDFS by 13.7% (67.1 vs 80 %, HR 0.54) and overall survival (OS) by 4.7% (84.1 vs 89.9 % HR 0.66). The main dilemma in the metastatic setting is optimal treatment after second-line progression on trastuzumab deruxtecan (TDx). The addition of tucatinib to TDM-1 in HER2CLIMB-02 modestly increased progression-free survival (PFS) from 7.4 to 9.5 months HR 0.76 (p=0.0163). According to a retrospective analysis of pneumonitis pattern with TDx, it is safe to rechallenge with TDx in case of pneumonitis grade 1, with a suggestion to reduce the dose of TDx.

In triple-negative breast cancer (TNBC), the addition of pembrolizumab to NACT (KEYNOTE-522 trial) significantly increased complete pathological response and event-free survival. There has been a press release about positive OS results. Subanalysis showed that pembrolizumab is beneficial even in smaller-risk tumors such as T2N0 TNBC. In the metastatic settings, there are promising results for first-line antibody-drug conjugates (ADC) – immunotherapy combinations. datopotamab-deruxtecan (Dato-TDx) and durvalumab in primarily programmed death-ligand 1 (PD-L1) negative patients achieved a high objective response rate of 79% and PFS of 13.8 months. In a small randomized trial MORPEHUS-pan BC trial in PD-L1 positive patients, atezolizumab and sacituzimab govitecan prolonged PFS to atezolizumab and nab-paclitaxel (12.2 vs 5.9 months). Many randomized phase III trials are underway, and we eagerly await the results.

Estrogen receptor positive (ER) breast cancer is the most frequent breast cancer, and most published trials were conducted in this subpopulation.

To give or not to give adjuvant chemotherapy that is the question. With the emergence of Oncotype DX; this question is mainly answered except for premenopausal women with node-positive disease. A subanalysis of the

RxSPONDER trial showed that in pre/perimenopausal women with node-positive disease and Oncotype score of < 25, low anti-Mullerian hormone could differentiate women who will not benefit from chemotherapy.

Two years of adjuvant Cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor abemaciclib is an established standard in high-risk luminal tumors (4 or more positive nodes or positive nodes with either tumor > 5 cm or grade 3 tumor). In the NATALEE trial, ribociclib was tested in a broader patient population. All patients with node-positive disease and selected node-negative patients (grade 3 or T3 tumors, or grade 2 tumors with KI 67 > 20% or high genomic risk) were randomized to 3 years of 400 mg daily ribociclib or placebo. At a median follow-up of 36 months, ribociclib statistically significantly increased IDFS 90.7 vs 87.6 %, HR 0.749.

Neoadjuvant-adjuvant immunotherapy is emerging, with two trials, KEYNOTE-756 (pembrolizumab) and CA-209-7FL (nivolumab), reporting an increased pathological response rate with the addition of immunotherapy. Patients had grade 3 disease with either node-positive or T3 tumors. The impact of immunotherapy was higher in PD-L1-positive and ER-low tumors. Long-term results are unavailable.

CDK 4/6 inhibitors are the mainstay treatment for first-line metastatic luminal breast cancer. The MONARCH 3 trial reported that abemaciclib prolonged OS by 13 months (66.8 vs 53.7 months, HR 0.80), but without reaching statistical significance. We conclude that among three CDK 4/6 inhibitors, only ribociclib consistently prolonged OS.

Adding new phosphatidylinositol 3-kinase (PI3K) inhibitor inavolisib to palbociclib and fulvestrant for patients with PI3K mutation who progress during or under 12 months of end-of-adjuvant-endocrine therapy doubled PFS time (15.7 vs 7.3 mo., HR 0.43, P < 0.0001). inavolisib expectedly increased toxicities common to PI3K inhibition (mucositis, hyperglycemia, rash, diarrhea) but with a lower-than-expected discontinuation rate (6%). We are waiting for OS data.

After several smaller trials suggested some benefit of CDK 4/6 inhibition beyond progression but only if CDK 4/6 is switched, the NEXTMONARCH trial, first phase III trial, showed that for patients who progressed on mostly palbociclib or ribociclib, continuing CDK 4/6 and switching to abemaciclib prolonged PFS for less than a month (6.0 vs 5.3 mo. HR 0.73, p = 0.02).

When endocrine resistance develops, patients are mostly switched to chemotherapy or ADCs. DESTINY BREAST-06 trial answered two questions: Can Tdx in luminal, HER 2 low patients become the preferred therapeutic option after ET failure, and can we broaden the TDx population from HER2 low to HER 2 ultralow patients defined as HER 2 zero, but with some positive staining. TDx prolonged PFS, to a similar degree, over chemotherapy in both HER 2 low (13.2 vs. 8.1 mo. HR 0.62) and HER 2 ultralow patients (13.2 vs. 8.3 mo., HR 0.83).

Last year in breast cancer was marked by further efforts in the de-escalation of surgery and radiotherapy, which is still discipline-specific and needs more coordination between disciplines. In systemic treatment, escalation efforts of adjuvant ribociclib and inavolisib in endocrine resistance metastatic settings and earlier and broader use of TDx in luminal breast cancer have been the most echoing improvements in the oncology community.

Keywords: breast cancer, immunotherapy, cyclin dependent kinase 4/6 inhibitor, escalation, deescalation

HER2 POZITIVAN RANI RAK DOJKE: NOVI STANDARDI U PRISTUPU AKSILI U RANOM RAKU DOJKE

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Uvod: Pojačana izraženost HER2 receptora prisutna je u 15–20 % slučajeva raka dojke koji često pokazuju agresivnije ponašanje u usporedbi s drugim tipovima, predstavljajući dodatne izazove u procesu liječenja. U kontekstu neoadjuvantnog liječenja operabilnih HER2+ tumora, danas se neoadjuvantno liječi većina HER2+ tumora >2 cm i/ili s pozitivnim limfnim čvorovima. Standard u neoadjuvantnom liječenju HER2+ bolesnica uključuje kemoterapiju temeljenu na kombinaciji antraciklina i taksana te dualnu anti-HER2 blokadu pertuzumabom i trastuzumabom. Nakon operativnog zahvata slijedi adjuvantna radioterapija (ovisno o indikaciji), nastavak anti-HER2 terapije (ovisno o stopi odgovora) i endokrina terapija ako se radi o hormonski ovisnim tumorima. Neoadjuvantnim pristupom znatno se povećava broj poštednih operacija te se bitno smanjuje broj potrebnih disekcija aksile.

Prikaz slučaja: Bolesnici u dobi od 51 godine dijagnosticiran je luminal B, hormon receptor pozitivan (HR+), HER2+ tumor sa zahvaćanjem pazušnih i infraklavikularnih limfnih čvorova. Provedena je neoadjuvantna kemoterapija po ddAC-wPT protokolu uz blokadu HER2+ receptora. Uslijedila je segmentektomija uz SLNB te disekcija aksile. Prema PHD-u postignut je potpuni patološki odgovor (pCR) primarnog tumora i limfnih čvorova, dok su u jednom limfnom čvoru bili prisutni znakovi deplecije limfocita i fibrozne reakcije. Nakon operacije provedeno je adjuvantno zračenje te je nastavljena aplikacija dvojne anti-HER terapije do ukupno 18. ciklusa. Nastavljena je endokrina terapija tamoksifenom uz LHRH agonist.

Zaključak: Optimalan klinički pristup u aksili nakon neoadjuvantne kemoterapije još uvijek je neizvjestan i aktivno se istražuje. Odluka o izostavljanju disekcije aksile ili SLNB-a, te postavljanje indikacije za zračenje, ovisi o kombinaciji kliničkih, patoloških i terapijskih čimbenika. Multidisciplinarni tim i točna dijagnostika igraju ključnu ulogu u sigurnom i uspješnom provođenju deeskalacije.

Ključne riječi: aksila, rani rak dojke, HER2, disekcija

HER2 POSITIVE EARLY BREAST CANCER: NEW STANDARDS IN TREATMENT OF AXILLA IN EARLY BREAST CANCER

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Introduction: Increased expression of the HER2 receptor is present in 15–20% of breast cancer (BC) cases and often exhibits more aggressive behavior compared to other types, presenting additional challenges in the BC treatment. In the context of neoadjuvant treatment (NACT) for operable HER2+ BC, tumors larger than 2cm

and/or with positive lymph nodes are treated in neoadjuvant setting. The current standard NACT of HER2+ patients includes chemotherapy based on a combination of anthracyclines and taxanes, and dual anti-HER2 blockade with pertuzumab and trastuzumab. This is followed by surgical intervention and adjuvant radiotherapy (if indicated), continuation of anti-HER2 therapy (the choice depends on the response rate), and endocrine therapy in HR+ tumors. The neoadjuvant approach significantly increases the number of breast-conserving surgery and greatly reduces the number of necessary axillary dissections.

Case Report: A 51-year-old patient was diagnosed with a HR+/HER2+ BC with involvement of the axillary and infraclavicular lymph nodes. Neoadjuvant chemotherapy was administered according to the ddAC-wPT protocol with HER2+ receptor blockade. Additionally, a segmentectomy was performed along with SLNB and axillary dissection. According to the pathology findings, a complete pathological response (pCR) was achieved in the primary tumor and lymph nodes, while in one lymph node, there were signs of lymphocyte depletion and fibrous reaction. After the surgery, adjuvant radiation was administered, and the application of dual anti-HER2 therapy was continued for a total of 18 cycles. Endocrine therapy with tamoxifen has been continued along with an LHRH agonist.

Conclusion: The optimal clinical approach of the axilla after NACT is still a matter of ongoing research. The decision to omit axillary dissection or SLNB depends on clinical, pathological, and therapeutic factors. A multidisciplinary approach and accurate diagnosis play a key role in the safe and successful implementation of de-escalation in axillary surgery.

Keywords: axila, early breast cancer, HER2, dissection

GUŽVA U 16-STERCU, IZAZOVI SEKVENCIRANJA TERAPIJE HORMON RECEPTOR POZITIVNOG RANOG RAKA DOJKE: INHIBITORI O CIKLINIMA OVISNIH KINAZA 4/6, INHIBITORI POLI ADP-RIBOZA POLIMERAZE I INHIBITORI KONTROLNIH TOČAKA

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Uvod: Luminalni rak najčešći je podtip te predstavlja oko 70% svih slučajeva raka dojke. Standardno liječenje ranog raka dojke uključuje antihormonalnu, a u određenim slučajevima i kemo- i radioterapiju. Novija istraživanja su također u određenim slučajevima visokog rizika dokazala djelotvornost CDK 4/6 inhibitora, abemacikliba i ribocikliba kao i PARP inhibitora olapariba u *BRCA* mutiranih, u adjuvantnom liječenju luminalnog HER2 negativnog raka dojke. Međutim, ne postoje jasne preporuke odabira i sekvenciranja ovih lijekova u neoadjuvantnom i adjuvantnom liječenju.

Prikaz slučaja: Predmenopauzalna bolesnica u dobi od 33 godine započela je obradu zbog palpabilne tvorbe u desnoj dojci. Kliničkim pregledom i radiološkom obradom utvrđena su dva tumora od 3,1 i 1,5 cm, u desnoj dojci te uvećani limfni čvorovi u desnom pazuhu. Biopsijom je potvrđen luminalni B, HER2 negativni invazivni lobularni rak gradusa 3. Napravljena je i citološka punkcija limfnog čvora pazuha koja je bila negativna. Provedena je neoadjuvantna kemoterapija po ddAC-T protokolu, nakon koje je učinjena mastektomija i biopsija limfnog čvora čuvara. Konačni patohistološki nalaz potvrdio je ostatni tumor u dojci veličine 2,1 cm te fibrozu u dva limfna čvora koja najvjerojatnije predstavlja odgovor na neoadjuvantnu terapiju. Zbog pozitivne obiteljske anamneze na rak dojke, provedeno je genetsko testiranje kojim je potvrđen status nositeljice patogene mutacije *BRCA2* gena. Postoperativno je provedena adjuvantna radioterapija. Daljnje liječenje je nastavljeno adjuvantnom antihormonalnom terapijom letrozolom i LHRH agonistom. Bolesnica je kandidat za adjuvantno liječenje abemaciklibom i olaparibom.

Zaključak: Odabir i sekvencioniranje terapije u liječenju bolesnica s ranim hormonski ovisnom rakom dojke su posebno važni obzirom da se radi o izlječivoj bolesti s visokom prevalencijom povrata.

Ključne riječi: hormon receptor pozitivan, rani rak dojke, inhibitori o ciklinima ovisnih kinaza 4/6, inhibitori poli ADP-riboza polimeraze, imunoterapija

CROWD IN PENALTY AREA, CHALLENGES OF SEQUENCING HORMONE RECEPTOR POSITIVE EARLY BREAST CANCER THERAPY: CYCLIN DEPENDENT KINASE 4/6 INHIBITORS, POLY ADP-RIBOSE POLYMERASE INHIBITORS, AND CHECKPOINT INHIBITORS

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Introduction: Luminal subtype is the most common and represents about 70% of all breast cancers. Standard treatment of early breast cancer includes endocrine therapy and, in certain cases, chemo- and radiotherapy. Recent research has also proven the effectiveness of CDK 4/6 inhibitors, abemaciclib and ribociclib, as well as PARP inhibitor, olaparib in *BRCA* mutated in the adjuvant treatment of luminal HER2-negative high-risk tumors. However, there are still no standard guidelines for selecting and sequencing these drugs in the neoadjuvant and adjuvant treatment.

Case Report: A 33-year-old premenopausal patient started work-up due to a palpable lesion in the right breast. Clinical examination and imaging revealed 2 tumors, 3.1 and 1.5 cm in size, in the right breast and enlarged lymph nodes in the right axilla. The biopsy confirmed luminal B, HER2-negative, grade 3 invasive lobular carcinoma. A cytological puncture of the lymph node was also performed and was negative. Neoadjuvant chemotherapy according to the ddAC-T protocol was administered, and afterward, a mastectomy and sentinel lymph node biopsy were performed. Pathohistological examination showed a residual tumor of 2.1 cm in the right breast and fibrosis in two lymph nodes, which most likely corresponds to a response to neoadjuvant therapy. Due to a family history of breast cancer, genetic testing was performed, which showed that the patient was a carrier of a pathogenic mutation in the *BRCA2* gene. She underwent adjuvant radiotherapy. Further treatment was continued with adjuvant endocrine therapy – letrozole and an LHRH agonist. The patient is a candidate for adjuvant treatment with abemaciclib and olaparib.

Conclusion: Selection and sequencing of treatment in patients with hormone-dependent tumors are extremely important considering that it is a curable disease with a high prevalence of recurrence.

Keywords: Hormone receptor positive, early breast cancer, cyclin dependent kinase 4/6 inhibitors, poly ADP-ribose polymerase inhibitors, immunotherapy

TERAPIJA RANOG TROSTRUKO NEGATIVNOG RAKA DOJKE, ESKALACIJA I DEESKALACIJA, KADA JE MANJE – VIŠE?

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Trostruko negativni rak dojke (TNBC) je heterogen tumor i najagresivniji podtip raka dojke. Mutacije u Breast Cancer gene (BRCA) najčešće su prisutne u TNBCte se preporučuje, sukladno kriterijima, odrediti BRCA status pri dijagnozi. Unatoč mnoštvu klasifikacija temeljenih na genomici, transkriptomici i epigenomici, njihova klinička primjena zasad nije utvrđena te nisu integrirane u rutinsku kliničku praksu.

Smjernice sugeriraju neoadjuvantnu kemoimunoterapiju za tumore veće od 2 cm ili one s pozitivnom aksilom. Za manje tumore rezervirana je kirurgija uz adjuvantnu sistemsku terapiju ovisno o riziku. Temeljem studije KEYNOTE-522, perioperativna primjena imunoterapije pembrolizumabom u kombinaciji s polikemoterapijom povećala je stopu kompletnog patohistološkog odgovora (pCR), smanjila stopu povrata bolesti i povećala

ukupno preživljenje te predstavlja današnji standard liječenja. Neoadjuvatni pristup je ključan budući su rezultati primjene imunoterapije u adjuvantnom setingu negativni. Translacijska istraživanja su za sada izostala te nemamo prediktivnih biljega za potencijalnu deeskalaciju ovog toksičnog protokola. Trenutno nije jasna sekvenca postneoadjuvantne terapije. Inače, standard je adjuvantni pembrolizumab do godine dana. Inhibitori poli (ADP-riboza) polimeraze se preporučuju kod pacijenata s patogenom gBRCA1/2 mutacijom i rezidualnom bolesti. Za ostale s nepostignutim pCR-om, može se primijeniti kapecitabin, posebno kod nebazalnog fenotipa. Ostaje kontroverza istodobne primjene pembrolizumaba s olaparibom ili kapecitabinom.

Retrospektivne opservacijske studije pokazuju benefit adjuvantne kemoterapije i kod manjih pT1a TNBC-a. Nekoliko retrospektivnih studija ukazuje na mogućnost izbjegavanja kemoterapije u stadiju I kod obilnog prisustva limfocita koji infilititraju tumor, tzv. TILs. Potrebna su prospektivna randomizirana ispitivanja za dodatne potvrde.

Multimodalna terapija poboljšala je ishode liječenja, ali istovremeno povećala toksičnost. Ispituju se specifični biomarkeri za precizniju identifikaciju kandidata za manje intenzivnu terapiju. Iščekujemo studije OPT-PEMBRO i OPTIMICE-pCR za postneoadjuvantni pembrolizumab. Kod bolesnika s rezidualnom bolesti velika su očekivanja od konjugata antitijelo-lijek. Možda su nam na horizontu i druge strategije liječenja ili nove terapijske opcije drugačijih mehanizama.

Ključne riječi: rani rak dojke, trostruko negativni rak dojke, imunoterapija, geni BRCA1/2

TAILORING THERAPY FOR EARLY TRIPLE NEGATIVE BREAST CANCER, ESCALATION AND DE-ESCALATION, WHEN IS LESS – MORE?

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Triple-negative breast cancer (TNBC) is a heterogeneous tumor and the most aggressive subtype of breast cancer. Mutations in the Breast Cancer gene (*BRCA*) are most commonly found in TNBC, and it is recommended, according to guidelines, to determine BRCA status at diagnosis. Despite various genomic, transcriptomic, and epigenomic classifications, their clinical use remains unclear and not part of routine practice.

Guidelines suggest neoadjuvant chemoimmunotherapy for tumors larger than 2 cm or those with positive axillary nodes. For smaller tumors, surgery is combined with adjuvant systemic therapy depending on the risk. The KEYNOTE-522 study shows that perioperative pembrolizumab with chemotherapy improves complete pathological response (pCR), reduces disease recurrence, and enhances overall survival, setting the current standard of care. The neoadjuvant approach is essential since adjuvant immunotherapy has yielded negative results. Currently, there is no translational research or predictive biomarkers for de-escalating this toxic protocol. The sequence of post-neoadjuvant therapy is currently unclear. Adjuvant pembrolizumab is standard for up to a year. PARP inhibitors are recommended for patients with pathogenic g*BRCA1/2* mutations and residual disease, while capecitabine is an option for those without pCR, particularly in non-basal phenotypes. The concurrent use of pembrolizumab with olaparib or capecitabine remains controversial.

Retrospective observational studies show a benefit of adjuvant chemotherapy even for smaller pT1a TNBCs. Several retrospective studies suggest that chemotherapy might be avoidable in stage I with high levels of tumor-infiltrating lymphocytes (TILs). Prospective randomized trials are needed for further confirmation.

Multimodal therapy has improved outcomes but also increased toxicity. Specific biomarkers are being studied to more precisely identify candidates for less intensive therapy. We're awaiting results from the OPT-PEMBRO and OPTIMICE-pCR studies on post-neoadjuvant pembrolizumab. In patients with residual disease, antibody-drug conjugates are highly anticipated. Other treatment strategies or new therapeutic options with different mechanisms may also be on the horizon.

Keywords: early breast cancer, triple negative breast cancer, immunotherapy, BRCA1/2 genes

SEKCIJA UROGENITALNIH TUMORA / UROGENITAL TUMORS SESSION

LIJEČENJE LOKALNOG VISOKORIZIČNOG KARCINOMA PROSTATE

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Uvod: Rak prostate je najčešći zloćudni tumor u muškaraca, a drugi po mortalitetu nakon karcinoma pluća u Hrvatskoj. Rak prostate u većini slučajeva se dijagnosticira u ranom stadiju. Opcije liječenja lokalne bolesti su radikalna prostatektomija ili radikalna radioterapija sa ili bez dodatka androgen deprivacijske terapije i nove generacije anti-androgene terapije u slučaju lokalnog visokorizičnog karcinoma prostate.

Prikaz slučaja: Godine 2013. u 62-godišnjeg bolesnika učinjena je biopsija prostate zbog povišenog prostata specifičnog antigena (PSA) 90 ng/mL, a patohistološki verificiran je adenokarcinom prostate, Gleasonovog zbroja 4+3. Inicijalnom obradom ne nađe se znakova diseminirane bolesti te je učinjena radikalna prostatektomija s limfadenektomijom. Patohistološkom analizom utvrdi se adenokarcinom prostate Gleasonovog zbroja 4+5 sa zahvaćanjem sjemenih mjehurića, pozitivnim regionalnim limfnim čvorovima i pozitivnim resekcijskim rubovima. Vrijednost postoperativnog PSA bila je 27 ng/mL. Započeto je liječenje androgen deprivacijskom terapijom LHRH agonistom i bikalutamidom. Nakon 10 mjeseci liječenja zabilježen je nadir vrijednosti PSA od 0,07 ng/mL. Za vrijeme trajanja terapije prati se diskretan porast PSA, a u studenom 2019. godine PET CTom s kolinom verificiran je povrat bolesti u zdjeličnom limfnom čvoru. Obzirom na razvoj kastracijski rezistentnog karcinoma prostate započeta je terapija enzalutamidom na što se inicijalno prati dobar odgovor. Tijekom razdoblja od 32 mjeseca ponovo se prati blagi porast PSA uz radiološki stabilnu bolest, te je nastavljena ista terapija. U ožujku 2024. godine PET CTom s kolinom verificirana je progresija bolesti u zdjelične i retroperitonealne limfne čvorove te je provedeno stereotaksijsko zračenje (SBRT) navedenih limfnih čvorova.

Zaključak: Liječenje i praćenje bolesnika s lokalnim visokorizičnim karcinomom prostate predstavlja veliki izazov. Multidisciplinarni pristup koji uključuje operativni zahvat, zračenje i sistemsku terapiju smatra se optimalnim načinom liječenja lokalnog visokorizičnog karcinoma prostate s dugoročno najboljim ishodima.

Ključne riječi: rak prostate, metastatski, kastracijski rezistentan, PET CT s kolinom

MANAGEMENT AND TREATMENT OF LOCALISED HIGH-RISK PROSTATE CANCER

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Introduction: Prostate cancer is the most common cancer in men and the second leading cause of cancer-related death after lung cancer in Croatia. The majority of patients are diagnosed in the early stage. Treatment options for localized disease are radical prostatectomy or radical radiotherapy with or without the addition of androgen deprivation therapy (ADT) and the new generation of antiandrogen therapy in high risk localized disease.

Case Report: In 2013, a 62 year-old patient underwent a prostate biopsy due to an elevated prostate-specific antigen (PSA) of 90 ng/mL. The histology report verified prostate adenocarcinoma with Gleason score of 4+3. No distant metastases were found on initial staging. Radical prostatectomy and lymphadenectomy was performed. Pathohistological examination revealed Gleason score 4+5 with positive surgical margins, seminal vesicles involvement and positive regional lymph nodes. The postoperative PSA value was 27 ng/mL and androgen deprivation therapy with LHRH agonist and bicalutamide was initiated. PSA nadir was 0.07 ng/mL after 10

months of therapy. While the therapy was ongoing, PSA started to rise and in November 2019 choline PET detected a recurrent disease in one pelvic lymph node. Therapy with enzalutamide was initiated for castration resistant disease with good biochemical response. During the period of 32 months there was a continuously rising trend of PSA value with radiological stable disease until March 2024 when choline PET confirmed lymph node disease progression. SBRT of PET positive retroperitoneal lymph node was performed.

Conclusion: The management of patients with high-risk, early-stage prostate cancer represents a major challenge. However, multimodal treatment strategies including surgery, radiation therapy, and systemic therapy offer a great potential for improved long-term outcomes for patients with high-risk prostate cancer who may harbor occult metastatic disease.

Keywords: prostate cancer, metastatic, castration-resistant, choline PET CT

KAKO SEKVENCIONIRATI LIJEČENJE U METASTATSKOM KASTRACIJSKI REZISTENTNOM KARCINOMU PROSTATE?

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Uvod: Rak prostate drugi je najučestaliji tumor u muškaraca u svijetu. Iako je udio bolesnika s kastracijski rezistentnom bolešću mali u odnosu na ukupan broj bolesnika (1,2 – 2,1 %), ti bolesnici čine populaciju s visokim morbiditetom, te značajno kraćim preživljenjem.

Prikaz slučaja: Godine 2018. bolesniku u dobi od 67 godina utvrđen je adenokarcinom prostate Gleasonovog zbroja 4+3 u 9/18 cilindara uz inicijalni PSA 20,6 ng/mL te bez udaljenih presadnica u standardnoj obradi. Učinjena je radikalna prostatektomija i zdjelična limfadenektomija. Zbog biokemijskog relapsa nakon 3 mjeseca učinjena je „spasonosna" radioterapija ležišta prostate. Dva mjeseca nakon radioterapije bilježi se ponovno porast PSA. Na pozitronskoj emisijskoj tomografiji s kolinom verificira se patološko nakupljanje radiofarmaka u limfnom čvoru opturatorne regije lijevo. Započeta ADT uz stereotaksijsku ablativnu radioterapiju (SBRT) zahvaćenog limfnog čvora. Nakon 6 mjeseci bilježi se biokemijski relaps uz kastracijsku razinu testosterona. Kompjuteriziranom tomografijom utvrdi se sklerotična lezija u tijelu kralješka L3 karakteristike presadnice. Započeta terapija enzalutamidom uz zolendronat kao prvolinijsko liječenje metastatskog kastracijski rezistentnog raka prostate uz SBRT presadnice u kralježnici. Nakon 15 mjeseci utvrđena radiološka koštana progresija te se započinje kemoterapija docetakselom. Nakon 6 ciklusa terapija prekinuta zbog nuspojava te daljnjeg porasta PSA. Nastavljeno liječenje kabazitakselom no nakon 3 ciklusa bilježi se porast PSA uz radiološku progresiju koštanih presadnica i novonastale presadnice u retroperitonealnim limfnim čvorovima. Kemoterapija karboplatinom provedena je u 6 ciklusa, nakon čega je verificirana klinička i radiološka progresija s novonastalim jetrenim metastazama. Zbog kliničke deterioracije stanja bolesnika nastavljeno je simptomatsko i palijativno liječenje.

Zaključak: U kastracijski rezistentnoj bolesti na raspolaganju stoje inhibitori androgene signalizacije novije generacije, kemoterapija, radionuklidna terapija, PARP inhibitori te imunoterapija. Bolesnik prikazan u ovom slučaju s obzirom na brzu progresiju na više linija liječenja dobar je kandidat za multigensko testiranje što može pružiti dodatne prognostičke i prediktivne informacije.

Ključne riječi: rak prostate, multimodalna terapija, sekvencioniranje terapije, antiandrogena terapija

HOW TO SEQUENCE TREATMENT IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER ?

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Introduction: Prostate cancer is the second most common cancer in men worldwide. Although the proportion of patients with castration-resistant disease is small (1.2–2.1%), these patients have high complication rates and significantly shorter survival.

Case report: In 2018, a 67-year-old patient was diagnosed with Gleason score 4+3 prostate adenocarcinoma in 9/18 cylinders with an initial PSA of 20.6 ng/mL and no metastases on standard radiological workup. Radical prostatectomy and pelvic lymphadenectomy were performed. Due to a biochemical relapse after three months, salvage radiotherapy of the prostate bed was performed. Two months after radiotherapy, a significant PSA rise was observed. Positron emission tomography with choline verified the left obturator lymph node metastasis. ADT was started, and stereotactic ablative radiotherapy (SBRT) of the affected lymph node was performed. After six months, a biochemical relapse was observed. Computed tomography revealed a metastatic sclerotic lesion in the L3 vertebra. Enzalutamide and zoledronate as first-line treatment of metastatic castration-resistant prostate cancer was initiated, and SBRT of spinal metastasis was performed. After 15 months, radiological bone progression was detected, and docetaxel chemotherapy was started. After six cycles, the therapy was discontinued due to side effects and biochemical progression. Treatment with cabazitaxel continued, but after 3 cycles, an increase in PSA was noted along with the radiological progression of bone metastases and newly formed metastases in the retroperitoneal lymph nodes. Chemotherapy with carboplatin was continued for six cycles, after which clinical and radiological progression with new liver metastases was verified. Due to the clinical deterioration of the patient's condition, palliative treatment was continued.

Conclusion: Next-generation androgen receptor inhibitors, chemotherapy, radionuclide therapy, PARP inhibitors, and immunotherapy are available in castration-resistant disease treatment. This patient was a good candidate for multigene testing, which may have provided additional prognostic and predictive information.

Keywords: prostate cancer, multimodal treatment, treatment sequencing, anti-androgenic therapy

NOVOSTI U LIJEČENJU UROTELNOG KARCINOMA – PRIKAZ SLUČAJA

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Uvod: Urotelni karcinom u uznapredovalom i metastatskom stadiju poznat je kao jedan od onih s najlošijom prognozom, odnosno preživljenjem. Nedavno je kombinacija pembrolizumaba i enfortumab-vedotina (EV) postala najbolja opcija liječenja u prvoj liniji. U Hrvatskoj je trenutno dostupna kemoterapija uz terapiju održavanja avelumabom što je bio donedavni standard prvolinijskog liječenja. Velika nezadovoljena potreba su i opcije drugolinijskog kao i daljnjeg tretmana, iza progresije na liječenje kemoterapijom i inhibitorima kontrolnih točaka. Enfortumab vedotin, konjugat lijeka i protutijela usmjeren na Nektin-4, pokazao se učinkovitim za takvu populaciju progresora, a odnedavno je dostupan i u našoj zemlji.

Prikaz slučaja: Kod 65-godišnjeg bolesnika je u srpnju 2023. godine, nakon verificiranog pT3bN0 urotelnog karcinoma mokraćnog mjehura, učinjen radikalni operativni zahvat. Već kod prvog planiranog ciklusa adjuvantne kemoterapije ddMVAC protokolom, suspektna je proširena bolest, a nakon četiri ciklusa navedenog protokola sigurna progresija bolesti kontrolnom radiološkom obradom, te slijedi liječenje nivolumabom u drugoj liniji. Nakon 16 provedenih ciklusa liječenja utvrđena je daljnja progresija bolesti. Započinje se terapija EV-om u

srpnju 2024. Već nakon prve aplikacije, dolazi do razvoja makuloznog eritematoznog osipa po koži trupa i udova bolesnika (zahvaćajući 30% površine tijela). Uz kortikosteroidnu terapiju regresija osipa, te je uz odgodu i redukciju doze nastavljena terapija. U drugom je ciklusu, s obzirom na ponovno javljanje kožne nuspojave po smanjenju doze kortikosteroida, dodatno reducirana doza. Osim kožnih promjena, bolesnik liječenje dobro podnosi.

Zaključak: Enfortumab vedotin, jedan od novijih konjugata lijeka i antitijela, etablirao se u liječenju urotelnih karcinoma u uznapredovalim fazama. Usmjeren je na Nektin-4, adhezijsku molekulu koja je osim u određenim vrstama karcinoma, visoko izražena u epidermalnim keratinocitima i kožnim adneksama. Dolaskom novijih terapija, konjugata lijeka i antitijela, u kliničkoj se praksi susrećemo s novim profilom nuspojava.

Ključne riječi: urotelni karcinom, enfortumab-vedotin, pembrolizumab, nektin-4

ADVANCES IN THE TREATMENT OF UROTHELIAL CARCINOMA – A CASE REPORT

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Introduction: Advanced and metastatic urothelial carcinoma is known for its poor prognosis and survival rates. Recently, the combination of pembrolizumab and enfortumab vedotin (EV) has emerged as the best first-line treatment option. In Croatia, chemotherapy combined with avelumab maintenance therapy is currently available, which was the previous first-line treatment standard. There remains a significant unmet need for second line and further treatment options following progression after chemotherapy and checkpoint inhibitors. Enfortumab vedotin, a drug-antibody conjugate targeting Nectin-4, has proven effective for this patient population with disease progression and has recently become available in our country.

Case Report: In July 2023, a 65-year-old patient underwent radical surgery following the confirmation of pT3bN0 urothelial carcinoma of the bladder. At the first planned cycle of adjuvant chemotherapy with the ddMVAC protocol, there was suspicion of disease spread. After four cycles of the protocol, radiological evaluation confirmed disease progression, and second-line treatment with nivolumab was initiated. After 16 cycles of treatment, further disease progression was detected. Therapy with EV was initiated in July 2024. After just one application, the patient developed a macular erythematous rash on the skin of the trunk and limbs, covering 30% of the body surface. With corticosteroid therapy, the rash regressed, and treatment continued with delayed administration and dose reduction. In the second cycle, due to the recurrence of skin side effects following the reduction of corticosteroid dose, the EV dose was further reduced. Aside from skin changes, the patient tolerated the treatment well.

Conclusion: Enfortumab vedotin, one of the newer drug-antibody conjugates, has established itself in the treatment of advanced stages of urothelial carcinoma. It targets Nectin-4, an adhesion molecule that is highly expressed not only in certain types of cancer but also in epidermal keratinocytes and skin adnexa. With the advent of newer therapies, including drug-antibody conjugates, clinical practice is encountering a new profile of side effects.

Keywords: urothelial carcinoma, enfortumab vedotin, pembrolizumab, Nectin-4

ADRENOKORTIKALNI KARCINOM – IZAZOVI LIJEČENJA

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Uvod: Kao iznimna rijetka, „orphan" bolest, adrenokortikalni karcinom (ACC) još uvijek predstavlja enigmu u pogledu adekvatne terapije. S obzirom na nisku incidenciju (<1 slučaj na milijun ljudi u godini) te kratko vrijeme preživljavanja, za sada postoji vrlo mali broj prospektivnih istraživanja, što većinu terapijskih preporuka bazira na retrospektivnim podacima.

Klinička slika i dijagnostika: Ovisno o hormonskoj proizvodnji ACC se dijele u funkcionalne i nefunkcionalne. U skladu s tim, 40–60% pacijenata se inicijalno prezentira simptomima prekomjerne razine hormona, u vidu Cushingovog sindroma, virilizacije, hiperaldosteronizma. Ostali pacijenti se prezentiraju ili nespecifičnim znakovima tumorske bolesti ~30 % (bolovi u trbuhu, konstitucijski znakovi maligniteta) ili slučajno nađenom tumorskom masom pri slikovnoj dijagnostici ~20–30%.

Slikovna dijagnostika (MSCT, MR) je osnova primarnog razlučivanja karaktera žarišne tvorbe nadbubrežne žlijezde, s diferencijalnom dijagnozom koja uključuje adenome, metastatske lezije, feokromocitom, odnosno ACC. Uloga FDG-PET je prvenstveno korisna u isključenju koštanih metastaza. Opći je konsenzus da se ne radi preoperativno perkutano uzorkovanje tkiva, s obzirom na malu količinu materijala koja onemogućuje konkluzivnu potvrdu maligniteta, česte komplikacije procedure te rizik lokalnog širenja („*seeding*") tumora. Nakon kirurške resekcije, Weiss klasifikacija koja uzima u obzir 9 mikroskopskih karakteristika, je osnova diferenciranja benigne od maligne tvorbe.

Određivanje stadija i prognoza: TNM (tumor, node, metastasis) klasifikacijski sistem je osnova određivanja stadija ACC-a. Od ostalih faktora, Ki-67 proliferacijski indeks se pokazao kao pojedinačno najsnažniji prediktor povrata bolesti nakon resekcije. Većina pacijenata s ACC-om se inicijalno prezentira s uznapredovalom bolesti, gdje su najčešća sijela metastaza jetra, pluća, limfni čvorovi i kosti. Sveukupno 5-godišnje preživljenje pacijenata s ACC-om je <35 %, sa stopom povrata bolesti do 70–80%, s razmjerno manjim postotkom u nižim stadijima bolesti.

Liječenje: *Lokalizirana bolest:* Radikalna kirurška resekcija je osnova terapije za bolesnike u I. i II., te za određene u III. stadiju bolesti. Postizanje negativnih rubova resekcije je preduvjet minimiziranja rizika povrata bolesti, što često implicira resekciju ipsilateralnog bubrega, gušterače, slezene te dijela jetre i ošita.

Čak i nakon R0 resekcije, ovisno o stadiju, stopa povrata bolesti se kreće od 40–70 %. U nedostatku randomiziranih studija ne postoje čvrste preporuke za neoadjuvantno liječenje, te većina autora predlaže primarno kiruršku resekciju.

Za sada jedini FDA odobreni adrenokortikalni citotoksični lijek mitotan čini osnovu adjuvantnog liječenja ACC-a. Sistematski pregledni članak Tang Y i sur., koji je analizirao 1249 pacijenata, pokazao je da adjuvantno primijenjeni mitotan značajno smanjuje stopu povrata bolesti i smrtnost nakon resekcije ACC-a kod pacijenata bez metastaza. Recentne studije su pokazale da korist adjuvantno primijenjenog mitotana imaju prvenstveno pacijenti s visokim rizikom povrata bolesti nakon resekcije, što uključuje slučajeve s velikom tumorskom masom, pozitivnim rubovima resekcije, rupturiranom kapsulom tumora te visokim Ki-67 indeksom (>10 %). Navedeno je značajno prvenstveno iz aspekta izbjegavanja potencijalno ozbiljih nuspojava mitotana kod pacijenata s niskim rizikom povrata bolesti nakon resekcije.

Konkluzivnije informacije o opravdanosti primjene mitotana kod bolesnika s niskim rizikom povrata bolesti, te o kombinaciji mitotana s cisplatinom/etopozidom za bolesnike s vrlo visokim rizikom povrata bolesti, trebali bi dobiti iz trenutno aktivne Adiuvo-2 studije.

S obzirom na činjenicu da adjuvantna radioterapija nema značajnog učinka u sistemnoj kontroli bolesti, pa tako i ukupnom preživljenju, a i ACC se smatra radiorezistentnim tumorom, taj modalitet liječenja nije preporučen u rutinskoj kliničkoj praksi.

Metastatska bolest: S 5-godišnjim preživljenjem od 0–17%, metastatski ACC spada u malignitete s najlošijom prognozom. Trenutno ne postoji kurativna sistemna terapija za takve bolesnike, a u određenim slučajevima s oligometastatskom bolesti (pluća, jetra) u obzir dolazi i kirurška resekcija.

S obzirom da monoterapija mitotanom u metastatskoj bolesti ima vrlo nisku stopu ukupnog odgovora (ORR) od 10–30%, kombinirana terapija koja uključuje i etopozid, doksorubicin te cisplatinu (EDP) je općenito preporučena. U randomiziranoj studiji na 304 bolesnika s proširenim ACC-om (FIRM-ACT) pokazana je značajna razlika i u odgovoru (RR) i preživljenju bez povrata bolesti (PFS) pacijenata na terapiji EDP i mitotanom, u usporedbi s onima koji su primali mitotan i streptozotocin.

Za sada ne postoji konsenzus o drugoj liniji liječenja metastatskog ACC-a. U tom kontekstu postoji veći broj studija o ulozi imunoterapije u liječenju bolesnika s metastatskim ACC-om, čiji rezultati još generalno nisu previše entuzijastični. Navedeno bi se potencijalno moglo objasniti imunosupresivnim djelovanjem lokalno izlučenih glukokortikoida i disreguliranom Wnt/β- kateninskom signalizacijom.

Najekstenzivnije evaluirani imunoterapijski protokol je monoterapija pembrolizumabom, koji je naveden u NCCN smjernicama kao terapijska opcija u metastatskom ACC-u, uključujući i prvu liniju liječenja. On bi bio izbor liječanja prvenstveno za pacijente koji ne toleriraju EDP kemoterapiju te za one koji su oligosimptomatski i imaju sporiju kinetiku tumora.

Od ostalih terapijskih protokola za spomenuti je primjenu tirozin kinaznog inhibitora (TKI) kabozantiniba kod pacijenata s progresijom bolesti nakon mitotana. U retrospektivnoj studiji na 16 pacijenata postignuta su 3 djelomična odgovora te 5 slučajeva stabilne bolesti 4 mjeseca i duže. Također, u tijeku je klinička studija faze II (CaboACC) s analizom utjecaja kabozantiniba u proširenoj bolesti te studije kombinacije kabozantiniba s različitim imunoterapeuticima.

Iako još uvijek u ranim fazama, postoji opravdana nada za etabliranjem ciljane terapije ACC-a. Navedeno se bazira na novim prospektivnim istraživanjima te identifikaciji biomarkera koji bi pouzdano predviđali njihovu efektivnost uz testiranje nove generacije (NGS) koje bi identificiralo mutacije pogodne za terapijsko djelovanje.

Ključne riječi: adrenokortikalni karcinom, kemoterapija, imunoterapija, metastatski

ADRENOCORTICAL CARCINOMA – TREATMENT CHALLENGES

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Introduction: As an extremely rare, "orphan" disease, adrenocortical carcinoma (ACC) still represents an enigma in terms of adequate therapy. Considering the low incidence (<1 case per million people per year) and the short survival time, there is currently a very small number of prospective studies, which bases most therapeutic recommendations on retrospective data.

Clinical picture and diagnostics: Depending on hormonal production, ACC is divided into functional and non-functional. Accordingly, 40–60% of patients initially present with symptoms of excessive hormone levels, in the form of Cushing's syndrome, virilization, hyperaldosteronism. Other patients present either with non-specific signs of tumor disease ~30% (abdominal pain, constitutional signs of malignancy) or with a tumor mass found accidentally during imaging ~20–30%.

Imaging diagnostics (MSCT, MR) is the basis of primary differentiation of the character of focal formation of the adrenal gland, with a differential diagnosis that includes adenomas, metastatic lesions, pheochromocytoma or ACC. The role of FDG-PET is primarily useful in excluding bone metastases. The general consensus is that preoperative percutaneous tissue sampling is not performed, given the small amount of material that prevents conclusive confirmation of malignancy, the frequent complications of the procedure, and the risk of local tumor seeding. After surgical resection, the Weiss classification, which takes into account 9 microscopic characteristics, is the basis for differentiating a benign from a malignant formation.

Staging and prognosis: The TNM (tumor, node, metastasis) classification system is the basis for determining the stage of ACC. Among other factors, the Ki-67 proliferation index was shown to be the single most powerful predictor of disease recurrence after resection. Most patients with ACC are initially presented with advanced disease, where liver, lung, lymph nodes and bone metastases are the most common sites. The overall 5-year survival of patients with ACC is <35%, with a relapse rate of up to 70–80%, with a relatively lower percentage in lower disease stages.

Treatment: *Localized disease:* Radical surgical resection is the basis of therapy for patients in stage I and II, and for certain stage III patients. Achieving negative resection margins is a prerequisite for minimizing the risk of disease recurrence, which often implies resection of the ipsilateral kidney, pancreas, spleen, and part of the liver and diaphragm.

Even after R0 resection, depending on the stage, the disease recurrence rate ranges from 40–70%. In the absence of randomized studies, there are no solid recommendations for neoadjuvant treatment, and most authors suggest primarily surgical resection.

So far, the only FDA-approved adrenocortical cytotoxic drug mitotane forms the basis of adjuvant treatment of ACC. A systematic review article by Tang Y et al., which analyzed 1249 patients, showed that adjuvant mitotane significantly reduced the rate of disease recurrence and mortality after ACC resection in patients without metastases. Recent studies have shown that the benefit of adjuvantly administered mitotane is primarily for patients with a high risk of disease recurrence after resection, which includes cases with a large tumor mass, positive resection margins, ruptured tumor capsule and a high Ki-67 index (>10%). This is significant primarily from the aspect of avoiding potentially serious side effects of mitotane in patients with a low risk of disease recurrence after resection.

More conclusive information on the justification of the use of mitotane in patients with low risk of disease recurrence, and on the combination of mitotane with cisplatin/etoposide for patients with a very high risk of disease recurrence, should be obtained from the currently active Adiuvo-2 study.

Given the fact that adjuvant radiotherapy does not have a significant effect in systemic disease control, including overall survival, ACC is considered a radioresistant tumor and this modality of treatment is not recommended in routine clinical practice.

Metastatic disease: With a 5-year survival rate of 0–17%, metastatic ACC is among the malignancies with the worst prognosis. Currently, there is no curative systemic therapy for such patients, and in certain cases with oligometastatic disease (lung, liver) surgical resection is also considered.

Given that mitotane monotherapy in metastatic disease has a very low overall response rate (ORR) of 10–30%, combination therapy including etoposide, doxorubicin, and cisplatin (EDP) is generally recommended. A randomized study of 304 patients with advanced ACC (FIRM-ACT) showed a significant difference in both response (RR) and disease-free survival (PFS) of patients treated with EDP and mitotane compared to those treated with mitotane and streptozotocin.

So far, there is no consensus on the second line of treatment for metastatic ACC. In this context, there are a large number of studies on the role of immunotherapy in the treatment of patients with metastatic ACC, whose results are still generally not too enthusiastic. The above could potentially be explained by the immunosuppressive effect of locally secreted glucocorticoids and dysregulated Wnt/β-catenin signaling.

The most extensively evaluated immunotherapy protocol is pembrolizumab monotherapy, which is listed in NCCN guidelines as a therapeutic option in metastatic ACC, including first-line treatment. It would be the treatment choice primarily for patients who do not tolerate EDP chemotherapy and for those who are oligosymptomatic and have slower tumor kinetics.

Other therapeutic protocols worth mentioning, include the use of the tyrosine kinase inhibitor (TKI) cabozantinib in patients with disease progression after mitotane. In a retrospective study of 16 patients, 3 partial responses and 5 cases of stable disease for 4 months or longer were achieved. Also, a phase II clinical study (CaboACC) is underway with the analysis of the impact of cabozantinib in advanced disease and studies of the combination of cabozantinib with different immunotherapeutic agents.

Although still in early stages, there is reasonable hope for the establishment of a targeted therapy for ACC. The aforementioned is based on new prospective research and the identification of biomarkers that would reliably predict their effectiveness with new generation testing (NGS) that would identify mutations suitable for therapeutic action.

Keywords: adrenocortical carcinoma, chemotherapy, immunotherapy, metastatic

SEKCIJA GINEKOLOŠKIH TUMORA / GYNECOLOGICAL TUMORS SESSION

NOVOSTI U LIJEČENJU LOKALNO UZNAPREDOVALOG KARCINOMA VRATA MATERNICE – INTERLACE STUDIJA

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Prema zadnjim podatcima Hrvatskog registra za rak, u 2018. godini su u Hrvatskoj zabilježena 274 nova slučaja karcinoma vrata maternice, što čini 2% od ukupnog broja slučajeva raka u žena. Podatci o mortalitetu pokazuju da je iste godine od karcinoma vrata maternice umrlo 125 žena. Bolest najviše pogađa žene u dobi od 35 do 55 godina.

U posljednjih 10 godina bilježi se trend pada standardizirane stope incidencije karcinoma vrata maternice, dok je mortalitet stabilan, što čini ovu bolest velikim javnozdravstvenim problemom.

U liječenju lokalno uznapredovalog karcinoma vrata maternice bilo je vrlo malo novosti u zadnjih 25 godina, od kada je kao standard brige za pacijentice uvedena primarna kemoradioterapija, (tjedna primjena cisplatine uz radioterapiju vanjskim snopom na područje zdjelice, minimalno 3D konformalnom tehnikom) nakon čega slijedi intrakavitarna/intersticijska brahiterapija (unutar 8 tjedana). Međutim, cijelo vrijeme se poteže pitanje što još možemo učiniti da se preživljenje pacijentica produlji.

Studija INTERLACE je randomizirana studija faze III koja je ispitivala učinkovitost uobičajene konkomitantne kemoradioterapije, u odnosu na indukcijsku kemoterapiju (6 tjednih aplikacija karboplatine i paklitaksela) nakon koje slijedi konkomitantna kemoradioterapija. Podatci ukazuju na značajno poboljšanje ukupnog preživljenja i vremena do progresije bolesti u pacijentica koje su primale indukcijsku kemoterapiju prije standardnog liječenja.

Primjena istog kemoterapijskog protokola (karboplatina i paklitaksel) adjuvantno nije pokazala benefit, prema OUTBACK studiji.

Pitanje je trena kada će indukcijska kemoterapija prije kemoradioterapije postati standard brige za pacijentice sa lokalno uznapredovalim karcinomom vrata maternice.

Ključne riječi: karcinom vrata maternice, kemoradioterapija, indukcijska kemoterapija, lokalno uznapredovali

NEWS IN THE TREATMENT FOR LOCALLY ADVANCED CERVICAL CANCER – INTERLACE STUDY

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According to the latest data from the Croatian Cancer Registry, 274 new cases of cervical cancer were registered in Croatia in 2018, which represents 2% of the total number of cancer cases in women. Mortality data show that 125 women died from cervical cancer in the same year. The disease mainly affects women between the ages of 35 and 55.

Over the past 10 years, the standardized incidence rate of cervical cancer has decreased while the mortality rate has remained stable, making this disease a major public health concern.

There have been few innovations in the treatment of locally advanced cervical cancer over the last 25 years since primary chemoradiotherapy was introduced as the standard treatment for patients (weekly application of cisplatin with external beam radiotherapy to the pelvic area, minimally with 3D conformal technique), followed by intracavitary/interstitial brachytherapy (within 8 weeks). However, the question always arises as to what else we can do to prolong patient survival.

The INTERLACE trial is a randomized phase III trial that investigated the efficacy of conventional adjuvant chemoradiotherapy compared to induction chemotherapy (6 weekly doses of carboplatin and paclitaxel) followed by adjuvant chemoradiotherapy. The data indicate a significant improvement in overall survival and progression free survival in patients who received induction chemotherapy prior to standard treatment.

Adjuvant use of the same chemotherapy protocol (carboplatin and paclitaxel) has shown no benefit according to the OUTBACK study.

It is only a matter of time before induction chemotherapy prior to chemoradiotherapy becomes the standard of care for patients with locally advanced cervical cancer.

Keywords: cervical cancer, chemoradiotherapy, induction chemotherapy, locally advanced

NE-EPITELNI KARCINOMI JAJNIKA

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Ne-epitelni karcinomi jajnika (engl. NEOC) su histološki i klinički različiti rijetki tumori. Oni čine približno 10% svih karcinoma jajnika. NEOC uključuju tumore zametnih stanica (engl. GCT), tumore spolnog tračka i strome (engl. SCST) i karcinome malih stanica jajnika. Početni simptomi su obično subakutna bol u zdjelici, osjećaj pritiska zbog mase u zdjelici i menstrualne nepravilnosti. Oko 10% pacijenata doživi akutni abdomen kao posljedicu torzije, krvarenja ili rupture tumora. Dijagnostička obrada treba uključiti UZ zdjelice, MSCT abdomena i zdjelice, RTG prsnog koša, i PET snimak u odabranim slučajevima. Određivanje tumorskih biljega kao što su serumski beta humani korionski gonadotropin (β-hCG), alfa fetoprotein (αFP), inhibin B, anti-Müllerov hormon (AMH) i laktat dehidrogenaza (LDH), uz kompletnu krvnu sliku, te prikaz funkcije jetre i bubrega, treba preporučiti. Definiranje stadija bolesti preuzeto je od epitelnog karcinoma jajnika kojeg je izvorno definirala Međunarodna federacija ginekologije i opstetricije (FIGO). Kirurški pristup može se provesti otvorenim putem ili, u odabranim slučajevima, minimalno invazivnim pristupima, kako bi se izbjegla ruptura tumora tijekom operacije. Potreban je pažljiv pregled trbušne šupljine. Kirurgija koja čuva plodnost – jednostrana salpingooforektomija uz očuvanje kontralateralnog jajnika i maternice (engl. FSS) i kemoterapija na bazi platine ostaju standard skrbi, pružajući visoku stopu izlječenja u svim fazama. Kod žena u postmenopauzi i bolesnica s uznapredovalim stadijem bolesti ili obostrano zahvaćenim jajnicima preporučuje se abdominalna histerektomija i bilateralna salpingooforektomija.

GCT kod žena čine 2–5% svih malignih tumora jajnika. Dijagnosticiraju se uglavnom u prva tri desetljeća života s najvećom incidencijom u mladih djevojaka u dobi od 15 do 19 godina. GCT nastaje iz primordijalnih zametnih stanica embrionalne gonade. Svjetska zdravstvena organizacija (WHO) histološki je klasificirala GCT jajnika u nekoliko kategorija: disgerminome, embrionalne karcinome, tumore žumanjčane vrećice (engl. YST), negestacijske koriokarcinome, zrele i nezrele teratome i miješane tumore zametnih stanica. Ovisno o histologiji, stadiju i molekularnim značajkama GCT, nakon operacije slijedi aktivno praćenje ili adjuvantna kemoterapija. Postoperativno se nastavljaju pratiti samo disgerminomi ograničeni na jajnik i nezreli teratom stupnja I. Svi bolesnici sa stadijem I YST liječe se adjuvantnom kemoterapijom nakon operacije. Nedavni podaci upućuju na pomno praćenje stadija I YST nakon kompletne kirurške resekcije i urednog postoperativnog αFP, ali ovaj stav nije široko prihvaćen i o odluci treba razgovarati s pacijentima. BEP (bleomicin, etopozid i cisplatin) najpopularniji je protokol, dok se EP protokol (etopozid, cisplatin) može razmotriti u bolesnika koji nisu podobni za bleomicin (poodmakla dob i plućni komorbiditet). Otprilike će 15–20% pacijenata s uznapredovalom bolešću,

većina unutar prve dvije godine primarnog liječenja, doživjet recidiv. Terapija povrata bolesti uključuje operaciju i kemoterapiju. U bolesnika s relapsom osjetljivim na platinu (progresija > 4–6 tjedana nakon završetka kemoterapije) IP/TIP (ifosfamid, platina sa ili bez paklitaksela) treba razmotriti kao drugu liniju liječenja. Drugi kemoterapijski protokoli uključuju: gemcitabin-TIP, TE/TP (paklitaksel, etopozid/paklitaksel, cisplatin), vinblastin, ifosfamid, cisplatin (VeIP) i cisplatin, vinblastin, bleomicin (PVB). Bolesnici rezistentni na terapiju baziranu na platini primaju vinkristin, aktinomicin D, ciklofosfamid (VAC) ili paklitaksel, gemcitabin ili gemcitabin, oksaliplatin. Studija faze III koja je u tijeku, TIGER, definitivno će procijeniti ulogu kemoterapije visokim dozama (engl. HDCT) kod recidiva tumora zametnih stanica kod muškog spola u usporedbi sa standardnom konvencionalnom kemoterapijom. GCT može izraziti KRAS, BRCA1/2 i c-KIT mutacije. Do sada nijedna ciljana terapija nije pokazala klinički značajnu učinkovitost u neseletiranim populacijama pacijenata u nekoliko kliničkih ispitivanja, iako je normalizacija tumorskog biljega ili kratkoročni odgovor na liječenje opisana nakon primjene sunitiniba, imatiniba i brentuksimab vedotina. Uloga inhibitora kontrolnih točaka imunološkog sustava u tumorima zametnih stanica tek treba biti definirana.

Tumori spolnog tračka i strome jajnika uključuju i benigne i maligne tumore koji potječu od spolnog tračka, stromalnih stanica, ili oboje. Prema klasifikaciji WHO, SCST uključuju čiste tumore spolnog tračka (juvenilni i adultni granuloza stanični tumori – GrCTs), čiste stromalne tumore (fibromi, tekomi, fibrosarkomi, tumori Leydigovih stanica, tumori stromalnih stanica i tumori steroidnih stanica) i miješane SCST (Sertoli-Leydigovi tumori – SLCTs). SCST se javljaju u različitim dobnim skupinama, pri čemu se GrCT javljaju uglavnom u žena u peri- ili postmenopauzi, a SLCT u žena u dobi između 20 i 40 godina. Većina njih se javlja u ranoj fazi, uglavnom su jednostrani. SCST su često funkcionalni, luče estrogen i testosteron, što uzrokuje preuranjeni pubertet i virilizaciju. Zbog proizvodnje estrogena, hiperplazija endometrija i karcinom endometrija mogu se vidjeti u do 10% pacijenata. GrCT mogu lučiti inhibin i AMH. Liječenje SCST uključuje operaciju, kemoterapiju i ciljanu terapiju. Za pacijente sa stadijem IA GrCT, sama operacija daje izvrsnu prognozu. Mladim pacijentima koji imaju stadij IA dobro diferenciranog SLCT bez heterolognih elemenata, i u reproduktivnoj su dobi, nudi se FSS. Onima sa slabo diferenciranom malignom bolešću nudi se adjuvantna kemoterapija (BEP). Za GrCT i SLCT stadija većeg od IA, nudi se operacija i adjuvantna kemoterapija bez obzira na diferencijaciju tumora. GOG trenutno provodi randomizirano ispitivanje faze II koje uspoređuje BEP s kombinacijom paklitaksela i karboplatina za pacijentice s novodijagnosticiranim i kemoterapijski naivnim rekurentnim metastatskim SCST jajnika. Alternativne kemoterapijske opcije uključuju: PVB, EP, CAP, VAC i tjedni paklitaksel za pacijente s relapsom. Pokazalo se da hormonska terapija ima ulogu u GrCT-a koji izražavaju steroidne receptore. Ovi tumori odgovaraju na primjenu agonista gonadotropina, tamoksifena, progestina i inhibitora aromataze. Anastrozol je polučio kliničku dobit kod 41 pacijentice s recidivirajućim GrCT u prospektivnom multicentričnom ispitivanju faze II PARAGON. Unatoč ograničenim dostupnim podacima, čini se da je hormonska terapija koristan alternativni tretman za pacijente s uznapredovalim stadijem ili rekurentnim odraslim GrCT. Angiostatski agensi su također ispitivani u bolesnika s rekurentnim adultnim GrCT zbog prekomjerne ekspresije vaskularnog faktora rasta. ALIENOR/ENGOT ov-7/GINECO je randomizirana studija koja je istraživala istovremenu primjenu bevacizumaba i tjednog paklitaksela te terapiju održavanja bevacizumabom naspram tjedne primjene paklitaksela i praćenja u 60 bolesnica s relapsom SCST. Dodatak bevacizumaba tjednom paklitakselu nije polučio kliničku dobit mjerenu 6-mjesečnim PFS-om (71% vs 72%).

Karcinomi jajnika malih stanica – hiperkalcijemičnog tipa (SCCOHT) se javljaju u adolescenata i mladih žena s najvećom incidencijom u trećem desetljeću života. Razine kalcija u serumu mogu poslužiti u procjeni odgovora na liječenje te pomoći u dijagnozi recidiva. Prognoza SCCOHT-a je vrlo loša jer je rizik širenja izvan jajnika visok. Karcinomi jajnika malih stanica – plućnog tipa (SCCOPT) pogađaju pacijentice u peri- ili postmenopauzi. SCCOPT je pretežno jednostran i ima lošu prognozu čak i kad se rano dijagnosticira. U liječenju se preporuča kombinacija više modaliteta koji podrazumijevaju kirurški debulking kojeg slijedi kemoterapija i eventualno radioterapija. Terapija na bazi cisplatina i etopozida općenito se smatra najprikladnijom. Nedavno je predložena HDCT za pacijente koji su postigli R0 nakon operacije i/ili potpuni odgovor nakon kemoterapije. Navedena terapijska opcija koju slijedi autologna transplantacija matičnih stanica povezana je s boljim preživljavanjem. Liječenje relapsa bolesti često je vrlo izazovno budući kemoterapijom postižemo kratku remisiju. Do danas nijedna ciljana terapija nije ispitana u SCCOHT-u. Obećavajući rezultati anti-PD1 antitijela ekstrapolirani su iz studija s karcinomom pluća malih stanica.

Ključne riječi: ne-epitelni rak jajnika, kemoterapija, hormonska terapija, ciljana terapija

NON-EPITHELIAL OVARIAN CANCER

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Non-epithelial ovarian cancers (NEOCs) are histologically and clinically distinct rare tumors. They account for approximately 10% of all ovarian cancers. NEOCs include germ cell tumors (GCTs), sex cord-stromal tumors (SCSTs) and small cell carcinomas of the ovary. The initial symptoms of NEOCs are usually subacute pelvic pain, feeling of pressure due to a pelvic mass and menstrual irregularities. About 10% of patients experience an acute abdomen as a result of a torsion, hemorrhage or tumor rupture. Diagnostic work-up include pelvic ultrasound, an abdomino-pelvic computed tomography scan, chest X-ray and positron emission tomography scan in selected cases. Tumors markers such as serum beta human chorionic gonadotropin (β-hCG), alpha fetoprotein (αFP), inhibin B, anti-Müllerian hormone (AMH) and lactate dehydrogenase (LDH) levels, along with full blood count, liver and renal functions, should be recommended. The staging system for NEOCs is generally adopted from the epithelial ovarian cancer originally defined by the International Federation of Gynecology and Obstetrics (FIGO). A surgical approach can be carried out through an open route or, in selected cases, by minimally invasive approaches, to avoid tumor rupture during surgery. A careful examination of the abdominal cavity is required. Fertility-sparing surgery – unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus (FSS) and platinum–based chemotherapy remains the standard of care, providing a high chance of cure at all stages. In postmenopausal women and in patients with advanced-stage disease or with bilateral ovarian involvement, abdominal hysterectomy and bilateral salpingo-oophorectomy is recommended.

Female GCTs account for 2–5% of all ovarian malignancies. They are diagnosed principally in the first three decades of life with peak incidence in young girls aged 15 to 19 years old. GCT originates from the primordial germ cell of the embryonic gonad. The World Health Organization (WHO) has classified ovarian GCTs histologically into several categories: dysgerminomas, embryonal carcinomas, yolk sac tumors (YSTs), non-gestational choriocarcinomas, mature and immature teratomas and mixed germ cell tumors. Depending on the histology, staging and molecular features of the GCTs, surgery will be followed by active surveillance or adjuvant chemotherapy. Only dysgerminomas confined to the ovary and grade I immature teratoma are managed with surveillance post-operatively. All patients with stage I YSTs are treated with adjuvant chemotherapy after surgery. Recent data suggest close surveillance for stage I YSTs with complete surgical staging and negative postoperative αFP, but this policy is not widely accepted and needs to be discussed with the patients. BEP (bleomycin, etoposide and cisplatin) is the most popular regimen while EP protocol (etoposide, cisplatin) can be considered in patients ineligible to bleomycin (advanced age and pulmonary comorbidity). Around 15–20% patients with advanced disease, majority within the first two years of primary treatment, will experience relapse. Salvage treatment includes surgery and chemotherapy. In patients with platinum-sensitive relapse (progression > 4–6 weeks after completion of chemotherapy), IP/TIP (ifosfamide, platinum with or without paclitaxel) should be considered as second line treatment. Further chemotherapy regimens include: gemcitabine-TIP, TE/TP (paclitaxel, etoposide/paclitaxel, cisplatin), vinblastine, ifosfamide, cisplatin (VeIP) and cisplatin, vinblastine, bleomycin (PVB). Patients resistant to a platinum-based therapy receive vincristine, actinomycin D, cyclophosphamide (VAC) or paclitaxel, gemcitabine or gemcitabine, oxaliplatin as salvage therapy. Ongoing trial phase 3, TIGER, will definitively assess the role of high dose chemotherapy (HDCT) in relapse male germ cell tumors by comparing with standard conventional-dose chemotherapy. GCT can acquire *KRAS, BRCA1/2 and c-KIT* mutations. So far, no molecularly targeted treatment has shown clinically meaningful activity in unselected patient populations across several clinical trials, though tumor marker stabilization or short-term treatment responses have been described after treatment with sunitinib, imatinib and brentuximab vedotin. The role of immune checkpoint inhibitors in germ cell tumors still needs to be elucidated.

Ovarian sex cord stromal tumors include both benign and malignant cancers which originate from either the sex cord or stromal cells, or both. According to WHO classification, SCSTs include pure sex cord tumors (juvenile and adult granulosa cell tumors – GrCTs), pure stromal tumors (fibromas, thecomas, fibrosarcomas, Leydig

cell tumors, stromal cell tumors and steroid cell tumors) and mixed SCST (Sertoli-Leydig cell tumors – SLCTs). SCSTs occur in different age groups, with GrCTs occurring mainly in peri- or postmenopausal women, and SLCT in women aged between 20 to 40. The majority of these present at an early stage, mostly unilateral. SCSTs are often functional, secreting oestrogen and testosterone, which causes precocious puberty and virilization. Due to oestrogen production, endometrial hyperplasia and endometrial carcinoma can be seen in up to 10% of patients. GrCTs can secrete inhibin and AMH. Treatment of SCST involves surgery, chemotherapy and targeted therapy. For patients with stage IA GrCT, surgery alone provides an excellent prognosis. For young patients who have stage IA well-differentiated SLCT without heterologous elements, and are of reproductive age, FSS is offered. Those with poorly differentiated malignancy are offered adjuvant chemotherapy (BEP). For GrCT and SLCT staging greater than IA, surgery and adjuvant chemotherapy are offered irrespective of tumor differentiation. The GOG is currently conducting a randomized phase II trial which investigates the BEP protocol with the combination of paclitaxel and carboplatin for patients with newly diagnosed and chemotherapy-naïve recurrent metastatic SCSTs of the ovary. Alternative options include: PVB, EP, CAP, VAC and weekly paclitaxel for relapsed patients. Hormone therapy has been shown to have a role in GrCTs which express steroid hormone receptors. Response to gonadotropin-releasing hormone agonists, tamoxifen, progestin and aromatase inhibitors (AIs) has been reported. Anastrozol achieved clinical benefit in 41 patients with recurrent GrCTs in the prospective multicentre phase II PARAGON trial. Despite limited available data, hormone therapy appears to be a useful alternative treatment for patients with advanced-stage or recurrent adult GrCTs. Anti-angiogenic agents have also been investigated in patients with recurrent adult GrCT, due to the overexpression of vascular endothelial growth factor. ALIENOR/ENGOT ov-7/GINECO is a randomized study that investigated the concomitant use of bevacizumab and weekly paclitaxel and maintenance therapy with bevacizumab versus weekly paclitaxel and follow-up in 60 patients with relapsed SCST. Addition of bevacizumab to weekly paclitaxel did not result in clinical benefit as measured by 6-month PFS (71% vs 72%).

Small cell carcinomas of the ovary hypercalcemic type (SCCOHT) occur in adolescents and young women with a peak incidence in the third decade of life. Serum calcium levels may serve as a marker for treatment response and recurrences. The prognosis of SCCOHT is very poor and the risk of extra-ovarian spread is high. Small cell carcinomas of the ovary pulmonary type (SCCOPT) affect peri- or postmenopausal patients. SCCOPT are predominantly unilateral and have dismal prognosis even when diagnosed early. A combination of treatment modalities, consisting of debulking surgery, followed by chemotherapy and possibly radiotherapy is recommended. Cisplatin and etoposide-based therapy is generally considered most appropriate. More recently, HDCT for patients who achieved a complete response after surgery and/or chemotherapy with autologous stem cell transplantation (ASCT) rescue has been proposed and is associated with better survival. The management of relapsed disease is often very challenging, since we achieve short remission with chemotherapy. To date, no targeted therapies have been tested in SCCOHT. The promising results of the anti-PD1 antibodies are extrapolated from trials of the small-cell lung cancers.

Keywords: Non-epithelial ovarian cancer, chemotherapy, hormonal therapy, targeted therapy