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Sažetci liječničkih predavanja | Physicians lectuar abstracts

EPIDEMIOLOGIJA RAKA I EUROPSKI REGISTAR NEJEDNAKOSTI U PODRUČJU RAKA

ŠEKERIJA M.[1,2], Čukelj P.[1]

[1] Hrvatski zavod za javno zdravstvo
• *Odjel za maligne bolesti*
[2] Sveučilište u Zagrebu
• *Medicinski fakultet*
mario.sekerija@hzjz.hr

Uvod: Na epidemiološke trendove malignih bolesti utječe mnogo čimbenika, između ostalog i primjena primarnih i sekundarnih mjera prevencije te kvaliteta zdravstvene skrbi. Ovisno o sijelu raka u Hrvatskoj postoje razlike u incidenciji i mortalitetu između Kontinentalne i Jadranske Hrvatske, pa i između pojedinih županija. Osim razlika unutar država, postoje i značajne razlike u vrijednostima pojedinih indikatora vezanih za zloćudne bolesti između zemalja članica EU.

Materijali i metode: Veliki javnozdravstveni teret kojeg rak predstavlja u svim zemljama Europske Unije potaknuo je Europsku komisiju da 2021. godine donese Europski plan za borbu protiv raka (engl. Europe's Beating Cancer Plan). Plan je strukturiran oko 4 glavna područja djelovanja: prevencije, ranog otkrivanja, jednakosti u dostupnosti rane dijagnostike i pravovremenog liječenja te poboljšanja kvalitete života pacijenata. Jedna od inicijativa, čiji je cilj smanjenje nejednakosti u području raka između zemalja članica i veće razumijevanje snaga i slabosti pojedine zemlje je i uvođenje europskog registra nejednakosti u raku. Tematska područja prevencije, ranog otkrivanja, dijagnoze i liječenja, kvalitete života i smrtnosti od raka obrađena su kroz moguće dimenzije u kojima se pojavljuju nejednakosti: države u kojima osoba živi, spola, urbanizacije, razine prihoda, obrazovanja i dobi.

Rezultati: U Hrvatskoj su maligne bolesti čest uzrok pobola, i drugi po redu uzrok smrti. Prema podacima Hrvatskog registra za rak u 2019. godini dijagnosticirana su 25 352 slučajeva raka (stopa 623,6/100 000) (isključujući nemelanomski rak kože), dok je prema posljednjim podacima mortalitetne statistike u 2020. godini od zloćudnih bolesti umrlo 13 138 (stopa 324,6/100 000) osoba. Općenito, incidencija raka u Hrvatskoj je u porastu, dok smrtnost blago pada.

Zaključak: Koristeći podatke iz zadnjeg vala Europske zdravstvene ankete (European Health Interview Survey, EHIS), podatke o smrtnosti te ostale relevantne informacije Eurostata u izlaganju su prikazani odnosi gore navedenih područja i dimenzija nejednakosti.

CANCER EPIDEMIOLOGY AND THE EUROPEAN CANCER INEQUALITIES REGISTRY

ŠEKERIJA M.[1,2], Čukelj P.[1]

[1] Croatian Institute of Public Health
• *Department for malignant diseases*
[2] University of Zagreb
• *School of Medicine*

Introduction: There are multiple causes of cancer incidence and mortality, such as primary and secondary prevention and the quality of health care. Depending on the cancer site, in Croatia we observed a difference in incidence and mortality between Continental and Adriatic region, even between individual counties. In addition to differences within countries, there is also significant variability in values of specific malignant disease indicators between the EU countries.

Materials and methods: Public health burden that cancer presents in all EU countries has motivated the European Commission to establish the Europe's Beating Cancer Plan in 2021. The Plan is structured around 4 main areas: prevention, early detection, equity in availability of early diagnostics and timely treatment and improvement of patient quality of life. One of the initiatives is the European Cancer Inequalities Registry with

the goal to reduce inequalities in cancer care between member states and to develop greater understanding in strengths and weaknesses of individual countries. Thematic areas of prevention, early detection, diagnosis and treatment, patient quality of life and cancer mortality are shown through dimensions in which inequalities can be present: by country, sex, age, degree of urbanization, income and degree of education.

Results: Cancer is a common cause of morbidity in Croatia and the second most common cause of death. According to data from the Croatian National Cancer Registry, in 2019 there was 25 352 (rate 623.6/100 000) recorded new cancer cases (excluding non-melanoma skin cancer), while in 2020 13 138 people (rate 324.6/100 000) died from cancer. Cancer incidence in Croatia is rising, while mortality is in slight decline.

Conclusion: The relationship of above-mentioned indicators is analysed and displayed in the presentation using the Eurostat data on cancer mortality, data on health care, and data from the European Health Interview Survey.

In extenso rad u privitku | In extenso article attached

UKLJUČIVANJE SEKVENCIRANJA NOVE GENERACIJE (NGS) U RUTINSKU KLINIČKU PRAKSU – TRENUTNI IZAZOVI I POGLED U BUDUĆNOST

KELEMENIĆ-DRAŽIN R.[1], Budisavljević A.[2]

[1] Opća bolnica Varaždin
• *Odjel za hematologiju, onkologiju i kliničku imunologiju i alergologiju*
[2] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*
renata.kelemenicdrazin@optinet.hr

Unatoč ograničenjima koja postoje u korištenju molekularnih biomarkera u kliničkoj praksi naša onkološka zajednica živi u eri precizne medicine u kojoj raste broj pacijenata koji se podvrgavaju tumorskom genomskom profiliranju, kao i broj novih odobrenih lijekova za rak usmjerenih na specifične genetske promjene.

Sekvenciranje sljedeće generacije (Next generation sequencing – NGS) omogućuje brze, pristupačne i djelotvorne informacije o molekularnom profilu tumora pri čemu se NGS može provesti korištenjem ciljanih genskih panela, sekvenciranjem cijelog egzoma ili sekvenciranjem cijelog genoma. Rezultati NGS-a mogu utjecati na kliničke odluke tj. otvaraju opcije molekularno vođenog liječenja (molecularly guided treatment options – MGTOs) za svakog pacijenta ponaosob rezultat čega je visoko personalizirano liječenje.

Prve preporuke znanstvenog društva o korištenju NGS-a izdalo je ESMO u kolovozu 2020. godine s namjerom da se objedini donošenje odluka o tome kako bi se NGS trebao koristiti u osam sijela raka odgovornih za najveći broj smrtnih slučajeva u svijetu (rak dojke, pluća, kolorektalni rak, rak gušterače, prostate, želuca, jetre i kolangiokarcinom). Pri tome je korištena ESMO ljestvica kliničke djelotvornosti molekularnih ciljeva (ESCAT – rangira podudaranje između lijeka i genomskih promjena prema djelotvornosti) kao i prevalencija genomskih promjena te je temeljem toga donijeta preporuka koji bi pacijenti trebali biti testirani NGS-om. Tako bi, iz perspektive javnog zdravlja, prema ESMO-u, NGS rutinski trebalo koristiti kod bolesnika s metastatskim adenokarcinomom pluća, metastatskim rakom prostate, jajnika te kod metastatskog kolangiokarcinoma.

Unatoč rastućoj podršci genomskom testiranju kroz smjernice, implementacija NGS-a, a time i pristup pacijentima, razlikuje se diljem Europe i svijeta što posljedično negativno utječe na standard onkološke skrbi i unapređenje personalizirane medicine.

No usprkos trenutnim poteškoćama u provođenju NGS-a u kliničkoj praksi smatra se kako će uskoro tumor specifičnu terapiju zamijeniti tumor agnostička terapija gdje bolesnike nećemo liječiti prema sijelu bolesti već prema onkogenim driverima odgovornim za rast i širenje tumora.

IMPLEMENTATION OF NEXT-GENERATION SEQUENCING (NGS) INTO ROUTINE CLINICAL PRACTICE – CURRENT CHALLENGES AND A VIEW TO THE FUTURE

KELEMENIĆ-DRAŽIN R.[1], Budisavljević A.[2]

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

Despite the limitations in the use of molecular biomarkers in clinical practice, our oncology community lives in an era of precision medicine in which the number of patients undergoing tumor genomic profiling is increasing, as well as the number of newly approved cancer drugs targeting specific genetic changes. Next-generation sequencing (NGS) provides fast, affordable, and practical information on the molecular profile of tumors, whereby NGS can be performed using targeted gene panels, whole exome sequencing, or whole genome sequencing. The results of NGS can influence clinical decisions, i.e. they open molecularly guided treatment options (MGTOs) for each patient, resulting in highly personalized treatment. ESMO issued the first scientific society recommendations on the use of NGS in August 2020 to unify decision-making on how NGS should be used in the eight cancers responsible for the highest number of deaths worldwide (breast, lung, colorectal cancer, pancreatic, prostate, stomach, liver, and cholangiocarcinoma). In doing so, the ESMO scale of the clinical effectiveness of molecular targets (ESCAT – ranks the match between the drug and genomic changes according to point), as well as the prevalence of genomic changes, was used and based on this, a recommendation was made which patients should be tested with NGS. Thus, from a public health perspective, according to ESMO, NGS should be routinely used in patients with metastatic lung adenocarcinoma, metastatic prostate cancer, ovarian cancer, and metastatic cholangiocarcinoma. Despite growing support for genomic testing through guidelines, the implementation of NGS, and thus access to patients, vary across Europe and the world, which consequently negatively affects the standard of oncology care and the advancement of personalized medicine. However, despite the current difficulties in implementing NGS in clinical practice, it is believed that tumor-specific therapy will soon be replaced by tumor-agnostic treatment, where patients will not be treated according to the tumor sites, but according to the oncogenic drivers responsible for tumor growth and spread.

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

NEOADJUVANTNA KEMOTERAPIJA UZNAPREDOVALOG KARCINOMA LARINKSA

KOCIĆ L.[1]

[1] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*
lidija.kocic@gmail.com

Iako karcinom larinksa čini 0,8% slučajeva raka, ima značajnu društvenu važnost zbog uloge u glasovnoj produkciji, gutanju i kvaliteti života. Zbog morbiditeta povezanog s karcinomom larinksa i njegovim multimodalnim liječenjem, istraživanja su usmjerena na očuvanje funkcije larinksa kroz poboljšanja u jednom modalitetu liječenja.

Od uvođenja operacije očuvanja, IC igra značajnu ulogu. Cilj je „shrink or downstage" primarnog karcinoma u slučajevima potencijalno resektabilnih lezija. Cilj daljnjih ispitivanja je procjena uloge IC kod resektabilnih karcinoma grkljana. Iz metaanalize randomiziranih kontroliranih ispitivanja vidljivo je da nema razlike u lokoregionalnoj kontroli između bolesnika koji prime ili ne prime IC, ali skupina (IC) pokazuje manju sklonost udaljenim metastazama za 11,7%.

Prvo izdanje ispitivanja RTOG 9111 razjasnilo je da je CRT bolja od IC nakon koje slijedi RT. Kasniji rezultati istog pokazuju trend lošijeg OS-a s CRT u odnosu na IC unatoč višoj stopi očuvanja larinksa i lokoregionalne kontrole uz CRT.

IC PF nakon koje slijedi RT je prvo odobrena u potencijalno operabilnih koji zahtijevaju totalnu laringektomiju. GORTEC 2000-01 ispitivanje donosi superiornost TPF indukcije u liječenju laringealnih karcinoma koji ispunjavaju uvjete strategije očuvanja organa. Za bolesnike s T3, T4 bolešću IC nudi mogućnost očuvanja organa bez ugrožavanja OS-a. Za bolesnike s velikim T3 ili T4a i / ili lošom laringealnom funkcijom, bolje stope OS i QOL postižu se totalnom laringektomijom.

NCCN smjernice uključuju IC s TPF nakon čega slijedi samo RT ili CRT kao validirano liječenje. Rezultati su visoke stope ORR, brzog gubitka simptoma, no s druge strane visok rizik od teške toksičnosti sa stopom smrtnosti do 6,7%. Identificirani su prediktivni čimbenici toksičnosti: nutritivni status i jetrena disfunkcija. Revizijom ispitivanja TTCC 2503, 7 godina nakon, IC-CRT nije dokazao značajnu prednost učinkovitosti u odnosu na samu CRT u bolesnika s LAHNSCC. Posebno se izdvaja subpopulacija bolesnika larinks primarnog tumora gdje je IC pokazala korist u smislu TTF-a i PFS-a. Imali su dulji med. PFS od onih koji su primali samo CRT (16,9 – 11,3 mj).

TPF ostaje zlatni standard kao IC u raku larinksa ako se izvodi u iskusnim centrima u kontekstu kvalificiranog MDT.

NEOADJUVANT CHEMOTHERAPY OF ADVANCED LARYNGEAL CANCER

KOCIĆ L.[1]

[1] General Hospital Pula
• *Department of Medical Oncology and Hematology*

Although laryngeal carcinoma accounts for 0.8% of cancer cases, it has significant social importance due to its role in voice production, swallowing, and quality of life. Because of the morbidity associated with laryngeal cancer and its multimodal treatment, research is focused on preserving laryngeal function through improvements in a single treatment modality.Since the introduction of the conservation operation, the IC has played a significant role. The goal is to "shrink or downstage" the primary cancer in cases of potentially resectable lesions. The aim of further studies is to evaluate the role of IC in resectable laryngeal cancers. From the meta-analysis of randomized controlled trials, it is evident that there is no difference in locoregional control between patients who receive or do not receive IC, but the group (IC) shows a lower tendency for distant metastases by 11.7%. The first edition of the RTOG 9111 trial clarified that CRT is superior to IC followed by RT. Later results of the same trial shows a trend of worse OS with CRT compared to IC despite a higher rate of larynx preservation and locoregional control with CRT.IC PF followed by RT is first approved in potentially operable requiring total laryngectomy. The GORTEC 2000-01 trial demonstrates the superiority of TPF induction in the treatment of laryngeal cancers that meet the conditions of an organ preservation strategy. For patients with T3, T4 disease, IC offers the possibility of organ preservation without jeopardizing OS. For patients with large T3 or T4a and/or poor laryngeal function, better OS and QOL rates are achieved with total laryngectomy.NCCN guidelines include IC with TPF followed by RT or CRT alone as a validated treatment. The results are a high rate of ORR, rapid relief of symptoms, but on the other hand a high risk of severe toxicity with a mortality rate of up to 6.7%. Predictive factors of toxicity were identified: nutritional status and liver dysfunction. A review of the TTCC 2503 trial, 7 years later, did not demonstrate a significant efficacy advantage of IC-CRT over CRT alone in patients with LAHNSCC. In particular, the subpopulation of patients with larynx primary tumor where IC showed a benefit in terms of TTF and PFS stands out. They had a longer median PFS than those who received CRT alone (16.9 – 11.3 months). TPF remains the gold standard as IC in laryngeal cancer if performed in experienced centers in the context of skilled MDT.

PRIMARNA KEMORADIOTERAPIJA LOKOREGIONALNO UZNAPREDOVALOG KARCINOMA LARINKSA

SOČE M.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
majana.soce@gmail.com

Liječenje lokalno uznapredovalog karcinoma larinksa se značajno promijenilo u posljednjim desetljećima. Sve do 1980-ih, standardno liječenje se sastojalo od totalne laringektomije (TL) praćene postoperativnom radioterapijom. Ovakav agresivni pristup polučio je zadovoljavajuće rezultate preživljenja, ali uz doživotne posljedice kao što je gubitak govora, te stvaranja trajne cervikalne stome.

Današnje liječenje usmjereno je ka kontroli bolesti, ali uz održanu dobru kvalitetu života, u smislu liječenja očuvanjem organa/larinksa (organ/larinx preservation treatment). Takvo liječenje temelji se na dvije strategije: upotreba indukcijske kemoterapije za razlikovanje bolesnika pogodnih za radioterapiju ili konkomitantna kemoradioterapija.

Inicijalna studija koja je utvrdila prihvatljivost primarne radioterapije kod karcinoma larinksa je Veteran's Affair (VA). Nakon toga, RTOG 91-11 pokazao je da kombinacija kemoterapije na bazi platine s radioterapijom je dodatno poboljšala ishode i nudi najbolje stope preživljenja bez laringektomije. Međutim, preživljenje nakon dijagnoze karcinoma larinksa smanjilo se tijekom istog vremenskog razdoblja, što se povezalo s uvođenjem kemoradioterapije kao opcije liječenja. Te retrospektivne analize imaju svoja ograničenja u analizi konkomitantne kemoradioterapije; većina ne uzima u obzir dozu RT, ne isključuje bolesnike koji nisu primili kurativnu dozu cisplatine, neusklađenost T stadija tumora (lokalno uznapredovala bolest obuhvaća T2N1 do T4N3). Kemoradioterapija je povezana s lošijim ukupnim preživljenjem u odnosu na TL u bolesnika s T4 bolešću; međutim, nema razlike među bolesnicima s T3 bolešću.

Novije metaanalize pokazuju da kod dobro odabranih bolesnika, strategija liječenja očuvanjem larinksa je dobra i prihvatljiva metoda liječenja. Odluke o liječenju se trebaju donositi multidisciplinarno, uzimajući u obzir status bolesnika, volumen bolesti, plućnu funkciju. Volumen bolesti je iznimno važan prilikom odluke, TL se preporučuje kao primarni modalitet liječenja za T4a tumore. Primarnu TL također treba razmotriti za T3 bolesnike s teškim i nepovratnim oštećenjem funkcije grkljana, s velikim subglotičnim širenjem koje zahvaća krikoidnu hrskavicu ili s kontraindikacijom za optimalnu kemoradioterapiju (prethodna RT na vratu, kontraindikacija za kemoterapiju).

PRIMARY CHEMORADIOTHERAPY FOR LOCOREGIONALLY ADVANCED LARYNGEAL CANCER

SOČE M.[1]

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

The treatment of locally advanced laryngeal cancer has changed significantly in the last decades. Until the 1980s, the standard treatment consisted on total laryngectomy (TL) followed by postoperative radiotherapy. his aggressive approach yielded satisfactory survival results, but induced lifelong sequelae, such as the loss of speech, and the creation of a permanent cervical stoma.

Today's treatment is aimed at disease control, but with maintained good quality of life, in terms of organ/larynx preservation treatment. Two main strategies were devised: the use of induction chemotherapy to differentiate those patients eligible for a preservative treatment with radiotherapy and the use of concomitant chemoradiotherapy.

The initial study that established the acceptability of primary radiotherapy in laryngeal cancer was the Veteran's Affair (VA). Subsequently, RTOG 91-11 showed that combination platinum-based chemotherapy with radiotherapy further improved outcomes and offering the best laryngectomy-free survival rates.

However, survival after a diagnosis of LSCC has declined over the same time period, which has been associated with the introduction of chemoradiotherapy as a treatment option. These retrospective studies are limited

in their analysis of concomitant chemoradiotherapy; the majority do not consider RT dose, do not exclude patients who did not receive curative dose of cisplatin, tumor T stage mismatch (locally advanced disease includes T2N1 to T4N3). The chemoradioterapy is associated with worse OS relative to TL is in patients with T4 disease; however, no difference is seen among patients with T3 disease.

Recent meta-analyses show that in well selected patients, the treatment strategy of preserving the larynx is a good ant acceptable treatment method. Treatment decisions should be made in a multidisciplinary team, taking into account the patient's status, disease volume and lung function. Disease volume is a extremely important in the decision, TL is recommended as the primary treatment modality for patients with T4a LC. Primary TL should also be considered for T3 LC patients with severe and irreversible impairment of laryngeal function, with large subglottic extension invading the cricoid cartilage, or with contraindication to an optimal chemoradiotehrapy (previous RT to the neck, contraindication to CT).

STANDARDI I NOVOSTI U LIJEČENJU TUMORA GLAVE I VRATA

VAZDAR LJ.[1]

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*
ljubica.vazdar@gmail.com

Terapijski pristup u liječenju raka glave i vrata dramatično se mijenja uvođenjem imunoterapije checkpont inhibitorima, posebice u rekurentnom/metastatskom raku glave i vrata pločastih stanica (r/m SCHNC). U lokalno proširenoj bolesti okosnica liječenja i dalje su cisplatin, zračenje (RT) i operacija uz visoki rizik toksičnosti u kombiniranom liječenju. U r/m SCHNC imunoterapija je novi modalitet liječenja uz bolju učinkovitost i manju toksičnost u odnosu na raniji standardni pristup. Prije ere imunoterapije r/m SCHNC bila je bolest izrazito loše prognoze s medijanom ukupnog preživljenja manjim od godine dana. Palijativni sustavni tretman r/m bolesti ima niz ciljeva od kojih su najvažniji kontrola simptoma, utjecaj na kvalitetu života (QoL), kontrola bolesti i produženo ukupno preživljenje (OS). Izbor terapije ovisi o performans statusu, komorbiditetu, prethodnim terapijama, simptomima, preferencama bolesnika i podrški te biomarkerima. U kontekstu vremena, EXTREME protokol bio je okosnica prvolinijskog liječenja do 2016. s benefitom od 3 mjeseca u ukupnom preživljenju kombinacijom cetuksimaba i kemoterapijskog doubleta (OS 10,1 mjeseci) u odnosu na kemoterapijski doublet (OS 7,4 mjeseca) i stopom ukupnog odgovora (ORR) 35% naspram 18% u korist cetuksimaba. Na temelju rezultata istraživanja KEYNOTE-048, 2019. godine novi standard prvolinijskog liječenja za PD-L1 pozitivne bolesnike je monoterapija pembrolizumabom ili kombinacija pembrolizumaba s kemoterapijom (ciplatin/karboplatin+5-FU) ovisno o PD-L1 ekspresiji i tumorskom opterećenju. Rezultati CheckMate-651 kombinacije nivolumaba+ipilimumaba u odnosu na EXTREME režim je negativna studija, nema statistički signifikantnog povećanja OS u ukupnoj randomiziranoj populaciji (HR 0.95) i CPS≥20 (HR 0.78) uz signifikantni prijelazak na novolumab+ ipilimumab tretman (crossover).

Do unazad nekoliko godina standard druge linije nije postojao, a primjenjivala se monoterapija (metotreksat, docetaksel, cetuximab) s medijanom preživljenja 4–6 mjeseci. Godine 2017. na osnovu rezutata ispitivanja CheckMate -141 checkpoint inhibitor nivolumab postaje standard druge linije liječenja za bolesnike koji su progredirali tijekom ili unutar 6 mjeseci od zadnje doze platine s redukcijom rizika smrtnosti za 30% i ukupnim preživljenjem od 7,7 mjeseci, neovisno o PD-L1 statusu, HPV pozitivitetu, dobi, prethodnoj primjeni cetuximaba. Benefit pembrolizumaba (KEYNOTE-040) u 2L je vidljiv samo u bolesnika s PD-L1 ekspersijom (CPS≥1).

Nove strategije liječenja r/m bolesti su ciljanje angiogeneze ili HGF(hepatocyte growth factor) /Met signalnog puta. Ovime se povećava produkcija antigena i mikrookoliš tumora postaje povoljniji za checkpoint inhibiciju. U tijeku su studije faze 1 i 2, kombinacija pembrolizumaba s lenvantinibom (multikinazni inhibitor VEGFR 1-3, FGFR 1-4, PEGRF, RET i KIT), pembrolizumab i cabozantinib u refraktornoj bolesti i ficlatuzumab (anti HGF IgG1 protutijelo) u kombinaciji s cetuksimabom.

U tijeku su ispitivanja racionala dodatka imunoterapije kemoradioterapiji (CRT), radioterapiji (RT) i/ili kiruškom liječenju u definitivnom liječenju, lokalno proširenoj bolesti, lokalnom recidivu ili metastatskoj bolesti. Inicijalna ispitivanja (GORTEC 2017-01, KEYNOTE-412, HN004, KEYNOTE-689, HN003/RTOG 1216 etc.) demonstriraju izvedivost i sigurnost administracije imunoterapije tijekom ili nakon CRT/RT. Trenutni podaci ne

podupiru inkorporaciju imunoterapije u CRT ili RT kao standarda tretmana lokalno proširenog raka glave i vrata. I dalje ostaju neodgovorena pitanja oko primjene imunoterapije u ranom raku u kombinacijskom liječenju, kao što su selekcija bolesnika i biobiljezi, doza i frakcije zračenja, kada i koliko imunoterapije, izbor kombinacije ili pojedinačnog modaliteta liječenja. Nova ispitivanja pokazuju napore uključivanja imunoterapije u rane stadije liječenja uz očekivanje povoljnih i jasnih rezultata.

STANDARDS AND NEW APPROACHES IN THE TREATMENT OF HEAD AND NECK TUMORS

VAZDAR LJ.[1]

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

The therapeutic approach in the treatment of head and neck cancer changed dramatically with the introduction of immunotherapy with checkpont inhibitors, especially in recurrent/metastatic squamous cell and neck cancer (r/m SCHNC). In the locally advanced disease combined therapy, including cisplatin, irradiation (RT) and surgery, remained the standard of treatment with high risk of toxicity. In r/m SCHNC immunotherapy presents a new treatment modality with better effectiveness and lower toxicity compared to the earlier standard approach. Before the era of immunotherapy, r/m SCHNC was a disease of extremely poor prognosis with a median overall survival (OS) of less than a year. Goals of palliative systemic treatment used in r/m disease are symptom control, improvement of quality of life (QoL), disease control and prolonged overall survival. The choice of therapy depends on patients performance status, comorbidity, previous therapies, symptoms, preferences and biomarkers. In the context of time, the EXTREME protocol was the backbone of first-line (1L) treatment until 2016. It showed survival benefit of 3 months with a combination of cetuximab and chemotherapy doublet (OS 10.1 months) in comparison to the chemotherapy doublet (OS 7.4 months) and the total response rate (ORR) of 35% vs 18% in favor of cetuximab. Based on the results of the KEYNOTE-048 study, in 2019 the new standard of 1L treatment for PD-L1 positive patients is pembrolizumab monotherapy or a combination of pembrolizumab with chemotherapy (ciplatin/carboplatin+5-FU) depending on PD-L1 expression and tumor load. The CheckMate-651 study, which compared combination of nivolumab and ipilimumab with EXTREME regimen, showed no statistically significant increase in OS in the total randomized population (HR 0.95) and CPS ≥20 population (HR 0.78) with a significant patient crossover to nivolumab+ipilimumab treatment.

Until the last few years the second line (2L) standard did not exist and monotherapy (methotrexate, docetaxel, cetuximab) with median survival of 4–6 months was applied. In 2017, based on the results of the CheckMate – 141 study, checkpoint inhibitor nivolumab became the standard of 2L treatment for patients who progressed during or within 6 months of the last dose of platinum with a 30% reduction in risk of mortality and total survival of 7.7 months, regardless of PD-L1 status, HPV positivity, age and prior use of cetuximab. The benefit of pembrolizumab (KEYNOTE-040) in 2L was visible only in patients with PD-L1 expression (CPS≥1).

New treatment strategies for r/m diseases are targeting angiogenesis or HGF (hepatocyte growth factor)/Met signaling pathway. This increases the production of antigens and the microenvironment of the tumor becomes more favorable for checkpoint inhibition. Ongoing phase 1 and 2 studies are investigating combination of pembrolizumab with lenvantinib (multikinase inhibitor VEGFR 1-3, FGFR 1-4, PEGRF, RET and KIT), pembrolizumab and cabozantinib in refractory disease and ficlatuzumab (anti HGF IgG1 antibody) in combination with cetuximab.

Trials investigating addition of immunotherapy to chemoradiotherapy (CRT), radiotherapy (RT) and/or surgery in definitive treatment, locally advanced disease, local relapse or metastatic setting are still ongoing. Initial studies (GORTEC 2017-01,KEYNOTE-412, HN004, KEYNOTE-689,HN003/RTOG 1216 etc.) demonstrate the feasibility and safety of immunotherapy administration during or after CRT/RT. Current data do not support the incorporation of immunotherapy into CRT or RT as a standard of treatment for locally advanced disease.Use of immunotherapy in combination treatment for early stage disease still raises a lot of questions: patient selection and biomarkers, radiation doses and fractions, when and how much immunotherapy to apply, choice of combination or individual treatment modality etc. New trials show efforts to incorporate immunotherapy into the early stages of treatment with the expectation of favorable and clear results.

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SEKCIJA RAK PLUĆA / LUNG CANCER SESSION

IMUNOTERAPIJA U RAKU PLUĆA U KLINIČKOJ PRAKSI – KOJI SU ISKLJUČNI KRITERIJI IZVAN KLINIČKIH STUDIJA?

TRIVANOVIĆ D.[1]

[1] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*
dtrivanovic@obpula.hr

Rezultati kliničkih studija su temelj uključivanja novih lijekova u kliničku praksu dokazujući njihovu djelotvornost i sigurnost. Da bi razvoj lijeka slijedio u potpunosti ove principe potrebno je biti siguran da će ishodi dobiveni u studijama biti istovjetni i u „real life" uvjetima.

Bolesnici koji su uključeni u kliničke studije često nisu istovjetni bolesnicima s kojima se svakodnevno susrećemo u liječenju te postoji opravdana bojazan da rezultati iz kliničkih studija se neće moći jednakovrijedno iskazati u stvarnoj kliničkoj praksi. Najčešće isključni kriteriji su loš performans status, visoka životna dob i višestruki komorbiditeti. Imunocheckpoint inhibitori osim iznimne uspješnosti dodali su čitav niz novih isključnih kriterija koji ranije nisu bili toliko važni i često nisu bili isključivi u kliničkih studijama poput postojanje autoimunih bolesti ili korištenje imunomodulatorskih lijekova.

Slijedi prikaz nekoliko najvažnijih studija u posljednje vrijeme koji su bili fokusirane na real world data ili su dizajnirane ciljano na bolesnicima koji su obično isključeni iz kliničkih studija i koji su usporedili učinkovitost i sigurnost imunocheckpoint inhibitora u liječenju raka pluća bolesnika koji su lošijih performans stausa, starije životne dobi ili imaju izražene komorbiditete.

Uz sve bolje rezultate u ishodima liječenja susrećemo se i sa sve češćim problemom tzv. „rechellange setting-a" odnosno zabrinutošću zbog eventualnih dugoročnih imunoloških nuspojava primjerice poput ubrzanja ateroskleroze o čemu smo zbog kratkog preživljenja bolesnika ranije puno manje brinuli.

IMMUNOTHERAPY IN LUNG CANCER IN CLINICAL PRACTICE – WHAT ARE EXCLUSION CRITERIA OUT OF CLINICAL TRIALS?

TRIVANOVIĆ D.[1]

[1] General Hospital Pula
• *Department of Medical Oncology and Hematology*

The results of clinical studies are the basis for the inclusion of new drugs in clinical practice, proving their effectiveness and safety. For this to be possible, trials must evaluate outcomes that genuinely reflect real-world settings and concerns.

The patients involved in clinical studies are often not identical to the patients we encounter every day in treatment, and there is a justified fear that the results from clinical studies will not be able to be equally expressed in real clinical practice. The most common exclusion criteria are poor performance status, older age and multiple comorbidities. In addition to their exceptional success, immunocheckpoint inhibitors added a whole series of new exclusion criteria that were not so important before and were often not exclusive in previous clinical studies, such as the existence of autoimmune diseases or the use of immunomodulatory drugs.

The following is a presentation of several of the most important recent studies that were focused on real world data or were designed to target patients who are usually excluded from clinical studies and that compared the efficacy and safety of immunocheckpoint inhibitors in the treatment of lung cancer in patients with poorer performance status, older age or have significant comorbidities.

Along with the increasingly better results in treatment outcomes, we also encounter the increasingly common problem of the so-called Rechellange setting, that is, concern about possible long-term immune side effects, for example, acceleration of atherosclerosis, which we used to worry much less about due to the short survival of the patient.

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SEKCIJA RAK DOJKE / BREAST CANCER SECTION

In extenso rad u privitku | In extenso article attached

PREGLED NOVOSTI U LIJEČENJU RAKA DOJKE – SABCS, ASCO, ESMO

NALBANI M.[1]

[1] Opća bolnica Dubrovnik
• *Odjel za onkologiju*
marion@bolnica-du.hr

Uvod: Karcinom dojke je najčešći tumor te drugi uzrok smrtnosti od tumora u žena. Veliki je javnozdravstveni problem, stoga ne čudi veliki trud medicinske zajednice u prevenciji, ranom otkrivanju i liječenju karcinoma dojke. Liječenje karcinoma dojke rapidno evoluira. Stalna dostupnost rezultata iz novih studija opetovano rezultira ažuriranim preporukama i smjernicama. Prikazat ćemo standarde u liječenju karcinoma dojke te kako se novosti uklapaju u algoritme liječenja.

Materijali i metode: Učinjen je sveobuhvatni pregled literature na engleskom jeziku uključujući i ASCO, ESMO i NCCN smjernice o liječenju karcinoma dojke. Uključena su mišljenja eksperata kao i potencijalne nove strategije liječenja prezentirane unatrag dvije godine na međunarodnim kongresima: ESMO, ASCO, San Antonio breast cancer, ESMO breast.

Rezultati: Liječenje ranog hormon receptor pozitivnog (HR+) karcinoma dojke obilježila je eskalacija terapije sa abemaciklibom (MonarchE) u bolesnica s visokim rizikom od povrata bolesti kao i olaparibom (Olympia)

u gBRCA pozitivnih bolesnica. Uspješno je smanjena potreba za kemoterapijom u postmenopauzalnih bolesnica s jednim do tri pozitivna limfna čvora (Rxsponder). U liječenju metastatskog HR+ karcinoma stvorila se diskrepanca između različitih o ciklinima ovisnih kinaza 4/6. Pozitivne studije za ukupno preživljenje (OS) sa ribociklibom (Monaleesa 2,3,7) te abemaciklibom (Monarch 2,3) naspram negativnih studije s palbociklibom (Paloma 2,3) promijenile su ravnotežu među CDK 4/6 inhibitorima. U post CDK 4/6 eri težimo boljim endokrinim terapijama. Izuzev alpelisiba u bolesnica s PI3K mutacijom za sada su ostale endokrine terapije dale skromne rezultate. Najdalje su napredovali oralni degradatori estrogenog receptora, s djelovanjem ponajprije u bolesnica sa *ESR*1 mutacijom. Inovativni pristup PADA studije pokazao je da ako dokažemo mehanizam rezistencije u cirkulirajućoj DNA (ESR1 mutacija) i prije kliničke progresije, te promijenimo inhibtore aromataze u fulvestrant, možemo značajno produljiti vrijeme do progresije bolesti.

Karboplatina (BRIGHTNESS) se pozicionirala u neoadjuvantnom liječenju ranog trostruko negativnog karcinoma dojke (TNBC). Ipak najveća revolucija u liječenju ranog TNBC-a je neoadjuvantna primjena imunoterapije (Keynote522) koja je značajno produljila vrijeme do povrata bolesti. Olaparib (0lympia) je pokazao svoje djelovanje ne samo kod HR+ veći kod i TNBC, (g)*BRCA* mutiranih bolesnica. U metastatskom TNBC-u određene nedoumice o ulozi imunoterapije u bolesnica sa pozitivnom ekspresijom liganda programirane stanične smrti 1 (PDL-1), proizašle su iz oprečnih rezultata dviju studija sa atezolizumabom (IMpassion130, IMpassion131) razriješila je Keynote 355 studija sa pembrolizumabom koja je značajno produljila preživljenje u PDL-1 pozitivnih bolesnica. Pri odabiru imunoterapije bitno je paziti na metodologiju testiranja na PLD-1 pozitivitet.

U receptor za humani epidermalni čimbenik rasta (HER 2) pozitivnim karcinomu dojke trastuzumab deruxtecan je snažno „porazio" trastuzumab emntasin u drugoj liniji metastatskog HER 2+ karcinoma dojke (DESTINY-Breast04) i time promijenio slijed sekvencioniranja terapija.

Ipak najveća promjena u liječenju karcinoma dojke koja je transformirala paradigmu liječenja su konjugati protutijela i lijeka (ADC). Nova generacija ADC-a se odlikuje „bystander effectom" odnosno mogućnošću djelovanja i na okolne tumorske stanice koje možda i nemaju ekspresiju antigena za koje se veže protutijelo te time nadilaze tradicionalnu podjelu karcinoma dojke.

Trastuzmab deruxtecan je pokazao djelovanje i u HER 2 „low" bolesnica (DESTINY-Breast04) te je proširio svoje indikacije i u pretretiranih formalno HR+ i TNBC bolesnica koje ipak imaju određenu ekspresiju HER 2. Sacituzimab govitecan dokazao je svoje djelovanje u TNBC-u kao i u HR+ karcinomu (TROPiCS-02)dojke. Mnogobrojni novi ADC-ovi su u različitim fazama istraživanja.

Zaključak: Liječenje karcinoma dojke je rapidno evoluiralo. Intenzivno se istražuju mehanizmi rezistencije u želji za razvojem novih terapija. Mnogobrojne terapije, dokazane u bolesnica s proširenom bolesti, pokazale su svoje djelovanje i u lokalnim stadijima. Konjugati protutijela i lijeka sa svojim "pan" djelovanjem, neovisnom o podtipu karcinoma dojke, promijenili su paradigmu liječenja karcinoma dojke te su trenutno predmet najvećeg broja istraživanja.

OVERIEW OF NEWS IN BREAST CANCER – SABCS, ASCO, ESMO

NALBANI M.[1]

[1] General Hospital Dubrovnik
• *Department of Oncology*

Introduction: Breast cancer is the most common cancer and the second cause of death from cancer in women. It is a major public health problem, so it is not surprising that the medical community is making great efforts in the prevention, early detection and treatment of breast cancer. Breast cancer treatment is rapidly evolving. The constant availability of results from new studies repeatedly results in updated recommendations and guidelines. We will show the standards in the treatment of breast cancer and how the novelties fit into the treatment algorithms.

Materials and methods: A comprehensive review of the literature was performed, including ASCO, ESMO and NCCN guidelines on breast cancer treatment. We included the opinions of experts, as well as potential new treatment strategies presented in the last two years at international congresses: ESMO, ASCO, San Antonio breast cancer, ESMO breast.

Results: The treatment of early hormone receptor positive (HR+) breast cancer was marked by the escalation of therapy with abemaciclib (MonarchE) in patients with a high risk of disease recurrence as well as olaparib (Olympia) in gBRCA positive patients. The need for chemotherapy was successfully reduced in postmenopausal patients with one to three positive lymph nodes (Rxsponder). A discrepancy between different cyclin-dependent kinases 4/6 has arisen in the treatment of metastatic HR+ cancer. Positive overall survival (OS) studies with ribociclib (Monaleesa 2,3,7) and abemaciclib (Monarch 2,3) versus negative studies with palbociclib (Paloma 2,3) shifted the balance among CDK 4/6 inhibitors. In the post CDK 4/6 era, we strive for better endocrine therapies. With the exception of alpelisib in patients with a PI3K mutation, other endocrine therapies have so far produced modest results. Oral estrogen receptor degraders have progressed the farthest, with action primarily in patients with ESR1 mutation. The innovative approach of the PADA TRIAL showed that if we prove the mechanism of resistance in circulating DNA (ESR1 mutation) even before clinical progression, and change aromatase inhibitors to fulvestrant, we can significantly extend the time to disease progression.Carboplatin (BRIGHTNESS) has positioned itself in the neoadjuvant treatment of early triple-negative breast cancer (TNBC). However, the biggest revolution in the treatment of early TNBC is the neoadjuvant application of immunotherapy (Keynote522), which has significantly extended disease-free survival. Olaparib (0lympia) showed its effect not only in HR+, but also in TNBC, (g)BRCA positive patients. In metastatic TNBC, certain doubts about the role of immunotherapy in patients with positive expression of programmed cell death ligand 1 (PDL-1), arising from conflicting results of two trials with atezolizumab (IMpassion130, IMpassion131), were resolved by the Keynote 355 study trial with pembrolizumab, which significantly prolonged survival in PDL-1 positive patients. When choosing immunotherapy, it is important to pay attention to the methodology of testing for PLD-1 positivity.In human epidermal growth factor receptor (HER 2) positive breast cancer, trastuzumab deruxtecan strongly "defeated" trastuzumab emtansin in second line of metastatic HER 2+ breast cancer (DESTINY-Breast04) and thus changed the sequencing of therapies.However, the biggest change in the treatment of breast cancer that has transformed the treatment paradigm are antibody-drug conjugates (ADC). The new generation of ADCs is characterized by the "bystander effect", i.e. the ability to act on surrounding tumor cells that may not have the expression of the antigen to which the antibody binds, thus surpassing the traditional subtypes division of breast cancer. Among ADC trastuzmab deruxtecan also showed activity in HER 2 "low" patients (DESTINY-Breast04) and expanded its indications in pretreated, formally HR+ and TNBC patients who still have some HER 2 expression. Sacituzimab govitecan proved its activity in TNBC as well as in HR+ breast cancer (TROPiCS-02). Numerous new ADCs are in various stages of research.

Conclusion: Breast cancer treatment has evolved rapidly. Mechanisms of resistance are intensively researched in the desire to develop new therapies. Numerous therapies, proven in patients with advanced disease, have shown their effectiveness in local stages as well. Conjugates of antibodies and drugs with their "pan" action, independent of the subtype of breast cancer, have changed the paradigm of breast cancer treatment and are currently the subject of the largest number of studies.

RANI RAK DOJKE – KEMOTERAPIJA DA ILI NE?

KARDUM FUCAK I.[1], Mladinović M.[2]

[1] Opća bolnica „dr. Tomislav Bardek" Koprivnica
• *Odjel za gastroenterologiju, onkologiju i hematologiju*
[2] Opća bolnica „dr. Josip Benčević" Slavonski Brod
• *Odjel za onkologiju i hematologiju*
ikardum@gmail.com

Rak dojke najčešća je maligna bolest u žena u svijetu i većina slučajeva invazivnog raka dojke dijagnosticira se u ranom stadiju. U 70–80% slučajeva radi se o raku dojke s pozitivnim hormonskim receptorima (HR+) i negativnom ekspresijom humanog epidermalnog faktora rasta 2 (HER 2-). U većini slučajeva povezan je s dobrom prognozom te ovisno o jačini hormonske ekspresije, kliničkim i patohistološkim karakteristikama tumora najčešće zahtijeva lokalni tretman te adjuvantnu endokrinu terapiju. Dodatak adjuvantne kemoterapije adjuvantnoj endokrinoj terapiji, u slučajevima kada je ona potrebna, može smanjiti rizik od recidiva i povećati izlječenje bolesnika. Odluka o dodatku kemoterapije prvenstveno ovisi o klasičnim kliničko patološkim karakteristikama – veličini, stupnju diferencijacije tumora, limfovaskularnoj invaziji, statusu limfnih čvorova, dobi bole-

snica i komorbiditetima ali i o rezultatima profila ekspresije gena dobivenog iz dostupnih multigenskih testova. Obje adjuvantne terapije – endokrina kao i kemoterapija, imaju nuspojave pri čemu je ipak kemoterapija povezana sa većom toksičnošću, narušavanjem svakodnevne kvalitete života, radnom nesposobnosti te oštećenjem gonadalne funkcije i neplodnosti. Danas u sve većem broju slučajeva susrećemo mlade, premenopauzalne bolesnice s ovim podtipom raka dojke (HR+, HER2-). One se češće prezentiraju složenim oblicima bolesti i u usporedbi sa skupinama postmenopauzalnih bolesnica sa istim oblicima bolesti imaju značajno lošije ishode liječenja. Mlade bolesnice zahtijevaju sveobuhvatni pristup liječenju.

U cilju što bolje procjene ishoda i očekivane koristi od adjuvantnog sustavnog liječenja stvorene su kombinacije kliničkopatoloških i prognostičkih faktora u obliku medicinskih kalkulatora. To su uglavnom prognostički alati koji neizravno provjenjuju moguću korist od sustavne terapije ali bez dodanog prediktivnog značaja. Revoluciju u donošenju odluka o adjuvantnom liječenju žena s hormon receptor pozitivnim ranim rakom dojke donijeli su multigenski testovi. Trenutno je dostupno nekoliko testova – Oncotype DX, MammaPrint, Prosigna, BCI, EndoPredict.

Oncotype DX validiran je za premenopauzalne bolesnice s HR+/Her2- rakom dojke i negativnim pazušnim limfnim čvorovima. Omogućuje određivanje zbroja rizika povrata bolesti (recurrence score – RS) čime definira prediktivne vrijednosti dodavanja adjuvantne kemoterapije. Ovo je pokazano u TAILORx studiji gdje su bolesnice mlađe od 50 godina s RS-om 16–25 dobile adjuvantnu kemoterapiju uz adjuvantnu endokrinu terapiju. Rezultat je značajno niža stopa udaljenog povrata bolesti dodatkom adjuvantne kemoterapije. Benefit dodatka kemoterapije u mladih bolesnica sa zahvaćenim ograničenim brojem limfnih čvorova u pazuhu (1–3) i RS zbrojem manjim od 25 ispitivan je u studiji RxPONDER.

Skupina mladih žena s tim karakteristikama bolesti i RS manjim od 25 dodatkom kemoterapije endokrinom liječenju pokazala je 45% redukciju rizika od povrata invazivne bolesti. MammaPrint zajedno s Oncotype DX spada u testove prve generacije. Validan je u skupini postomenopauzalnih bolesnica za testiranje H+/Her2- tumora s 0–3 pozitivnih pazušnih limfnih čvorova. Druga generacija testova u koju pripadaju EndoPredict te Prosigna dizajnirana je za postmenopauzalne bolesnice.

Rastuća briga o reproduktivnom zdravlju uz rizike koje nosi adjuvantno liječenje u posljednje vrijeme vodi razvoju onkofertiliteta kao izdvojene discipline. Očuvanje fertiliteta dobiva sve veći značaj najviše zahvaljujući napretku u liječenju pacijentica s rakom koje vodi sve dužem preživljenju. Dostupne strategije za očuvanje fertiliteta u vrijeme prije početka sustavne kemoterapije su supresija ovarijelne funkcije krioprezervacija jajnih stanica i embrija kao i krioprezervacija ovarijelnog tkiva.

EARLY BREAST CANCER – CHEMOTHERAPY YES OR NO?

KARDUM FUCAK I.[1], Mladinović M.[2]

[1] General Hospital „dr. Tomislav Bardek" Koprivnica
• *Department of Gastroenterology, Oncology and Hemathology*
[2] General Hospital „dr. Josip Benčević" Slavonski Brod
• *Department of Oncology and Hemathology*

Breast cancer is the most common malignancy diagnosed in women worldwide and the majority of breast cancer cases have early-stage disease at the time of diagnosis. Approximately 70 – 80% of cases are hormone receptor-positive (HR +) and human epidermal factor 2 negative (HER2-) and as such is associated with a good overall prognosis. Depending on hormonal expression level, and clinical and pathological characteristics adjuvant treatment is in majority of cases call for definitive local and endocrine treatment. The addition of chemotherapy to adjuvant treatment can help reduce the risk of relapse and cure patients. The decision whether or not to administer adjuvant chemotherapy in patients with HR-positive, HER2-negative tumors is based on classical clinical and pathological factors such as size, grade, lymphovascular invasion, lymph node status, age, comorbid conditions as well as the results of a gene expression profile test using multigene assays. Both treatment modalities – endocrine therapy as well as chemotherapy are associated with frequent side effects however, chemotherapy is associated with greater toxicity, impairment of everyday quality of life, work incapacity, and damage to gonadal function which can result in infertility. These days the number of young, premenopausal patients with hormone receptor-positive and HER 2 negative diseases is increasing. Premenopausal women withhormone receptor-positive breast cancer present with complex disease and compared to their postmenopausal counter-

parts have inferior survival outcomes. Young patients ask for a multimodal approach in deciding on treatment options. To improve the ability to accurately predict the prognosis of breast cancer patients and the benefit of adjuvant systemic therapy combinations of several clinicopathological prognostic factors have been tailored in form of medical calculators. Those were mainly prognostic tools that indirectly estimate the possible benefits of chemotherapy in adjuvant settings but without any predictive significance. Multiparameter gene expression assays have revolutionized adjuvant therapy decision-making for women with early-stage, hormone receptor-positive breast cancer. Several genomic tests are available – Oncotype DX, MammaPrint, Prosigna, BCI, and EndoPredict.Oncotype DX was first validated in the group of premenopausal patients who have HR-positive HER 2 negative and axillary node-negative diseasse. It provides us with a numerical value – recurrence score that gives us an estimation of the risk of disease relapse and defines the added benefit of adjuvant chemotherapy. The benefits of chemotherapy addition were shown in TAILORx trial for a subset of patients younger than the age of 50 with RS of 16–25. Those patients had a lower distant recurrence rate in the group that received adjuvant chemo. RxPONDER trial addressed also the group of young patients with a limited number (1–3) of positive axillary lymph nodes that had a recurrence score of less than 25 according to Oncotype results. A subgroup of young patients had a 45% risk reduction for invasive disease relapse. Another genomic, first-generation test is MammaPrint which is as well as other second-generation tests, EndoPredict and Prosigna, validated for post-menopausal patients. Oncofertility arises as a new discipline as a result of growing concern for reproductive health. Fertility preservation in cancer patients has been gaining ever greater attention, largely thanks to the progress in cancer care which leads to significantly higher survival rates and life expectancy. Available strategies for preservation of fertility in young patients prior to administration of chemotherapy include ovarian suppression during cytotoxic therapy, cryopreservation of oocytes and embryos, and the cryopreservation of ovarian tissue.

PRIKAZ SLUČAJA BOLESNICE S RANIM RAKOM DOJKE – KEMOTERAPIJA DA ILI NE?

MLADINOVIĆ M.[1], Kardum Fucak I.[2], Silovski T.[3]

[1] Opća bolnica „dr. Josip Benčević" Slavonski Brod
• *Odjel za onkologiju i hematologiju*
[2] Opća bolnica „dr. Tomislav Bardek" Koprivnica
• *Odjel za gastroenterologiju, onkologiju i hematologiju*
[3] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
martina.mladinovic@hotmail.com

Uvod: Mlade odrasle žene u dobi od 15 do 39 godina najčešće obolijevaju od raka dojke. Invazivni rak dojke u toj populaciji čini 5,6% svih karcinoma dojke kod žena. Mlađe žene češće imaju predispozicijske gene obiteljskog raka, veće tumore s nepovoljnim biološkim karakteristikama, metastatsku bolest pri dijagnozi kao i nepovoljnije ishode. Preporuke za adjuvantno liječenje razlikuju se za pre i postmenopauzalne žene. Liječenje mladih žena zahtijeva koordiniranu multidisciplinarnu skrb i modalitete liječenja koji minimiziraju kasne učinke liječenja. Potrebno je proaktivno praćenje psihološkog i seksualnog zdravlja u tijeku i nakon liječenja uz neophodno savjetovanje o očuvanju fertilnosti.

Prikaz slučaja: Mlada bolesnica, stara 34 godine, udana, majka jednog djeteta, u redovnom programu praćenja je radi pozitivne obiteljske anamneze za karcinom dojke i druge tumore po majčinoj liniji. Magnetskom rezonancom u 2/2022 te potom ultrazvučno i mamografski dva mjeseca kasnije opisan je obostrano suspektan nalaz. Učinjena je biopsija obostrano i u bioptirane tvorbe postavljeni tkivni markeri. PHD nalaz biopsije tumora u desnoj dojci govori u prilog invazivnom karcinomu dojke, NST, hormonski pozitivnom, Her2 negativnom karcinomu s proliferacijskim indeksom 38%, imunofenotipa Luminal B. Ostale promjene u dojkama citološki i histološki su bez malignih stanica. S nalazom kontrolne magnetske rezonance koja pokazuje progresiju nalaza i uvećanje tvorbe u desnoj dojci na ukupnu veličinu od 19 x 22 mm prikazana je na multidisciplinarnom timu za tumore dojke. Odlukom Tima indicirano je onkološko liječenje započeti operativnim zahvatom desne dojke (SNSM) s rekonstrukcijom uz biopsiju limfnog čvora čuvara te markaciju mastektomiranog materijala. Operativni zahvat učinjen u 7/2022. Konačni patohistološki nalaz potvrdio je invazivni karcinom dojke, veličine 1.9 x 1.7 cm, uobičajenog tipa, gradusa II, sa visokim estrogenskim i nižim progesteronskim receptorima (ER 100%, PR 50%), Her2 negativan sa proliferacijskim indeksom Ki 67 35%, bez limfogene diseminacije.

S obzirom na patološki nalaz tumora, biologiju tumora, dob bolesnice, pozitivnu obiteljsku anamnezu, indicirano je provođenje genetskog testiranja, genetsko profiliranje tumora Oncotype DX kao i provođenje postupka onkofertiliteta. Rezultati Oncotype DX su pokazali 23% rizik udaljenog povrata bolesti nakon 9 godina uz benefit od kemoterapije veći od 15%. Prema nalazu testa indicirano je provođenje adjuvantne kemoterapije po TC protokolu (docetaxel + ciklofosfamid) u trajanju od 4 ciklusa te LHRH agonist.

Zaključak: Važnost redovitog samopregleda dojki kao i obavljanja dijagnostičkih pretraga uvelike doprinosi ranom otkrivanju raka dojke. Liječenje zahtijeva multidisciplinarni pristup i poštivanje želja pacijentica. Prije konačne odluke o vrsti sustavne adjuvantne terapije u mlađih bolesnica od 50 godina s hormonski ovisnim, Her2 negativnim tumorima i negativnim aksilarnim limfnim čvorovima preporuča se određivanje genskog profila primjenom Oncotype DX. Preporučuje se očuvanje fertilnosti koje se provodi u dogovoru s bolesnicom.

CASE REPORT OF A PATIENT WITH EARLY BREAST CANCER – CHEMOTHERAPY YES OR NO?

MLADINOVIĆ M.[1], Kardum Fucak I.[2], Silovski T.[3]

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

Introduction: Young adult women between the ages of 15 and 39 are most often affected by breast cancer. Invasive breast cancer in young adults accounts for 5.6% of all invasive breast cancers in women. Younger women are more likely to have familiar cancer predisposition genes, larger breast tumors with unfavorable biological characteristics, metastatic disease at diagnosis, and unfavorable outcomes. Recommendations for use of adjuvant therapy in premenopausal and postmenopausal women are different. Treatment of younger patients requires coordinated multidisciplinary care and treatment modalities that minimize late effects of chemotherapy. Proactive monitoring of psychological and sexual health is necessary during and after treatment, along with necessary counseling on preserving fertility.

Case report: A young patient, aged 34, married and a mother of one child was screened regularly due to positive family history of breast cancer and other tumors on her mother's side. Magnetic resonance imaging in 2/2022, followed by ultrasound and mammography two months later revealed suspicious findings in both breasts. A biopsy of bilateral tumors was performed, and tissue markers were placed in the biopsied formations. Pathohistological diagnosis revealed a usual type of invasive breast cancer with positive hormonal receptors, negative HER 2 receptors and proliferation index of 38% – Luminal B immunophenotype. The other biopsied formations were not malignant. Control breast MRI performed in June 2022 revealed increase in size of the lesion to 19 x 22 mm. Multidisciplinary team for breast cancer discussed optimal treatment strategies and suggested primary surgical treatment – skin and nipple sparing mastectomy and sentinel lymph node biopsy with final decision on adjuvant treatment based on patohistology findings and lymph node status. The operation was performed in July 2022. Patohystology confirmed invasive breast cancer of usual type, grade II with positive estrogen receptors (100%) and lower progesterone receptors (50%) proliferation index of 35% and Her2 negative tumor without lymph node affection. Considering pathological finding of the tumor as well as biology of the tumor, age of the patient and positive family history genetic profiling with a gene expression test – Oncotype DX was performed together with discussing the oncofertility procedures with the patient. Oncotype DX results showed a score of RS 35, the risk of distant disease recurrence after 9 years was 23%, and the benefit of chemotherapy was more than > 15%. Four cycles of adjuvant chemotherapy according to TC protocol (docetaxel + cyclophosphamide) were indicated along with LHRH agonist.

Conclusion: The importance of regular breast self-examination as well as performing diagnostic tests greatly contributes to the early detection of breast cancer. Treatment requires a multidisciplinary approach and the desire of the patient. Before the final decision on the type of systemic adjuvant therapy in patients younger than 50 years with hormone-dependent, Her2-negative tumors and negative axillary lymph nodes, it is recommended to determine the gene profile using Oncotype DX. Fertility preservation in young patients is highly recommended and the procedures are carried out in agreement with patients.

OPTIMALNA SEKVENCIJA U LIJEČENJU METASTATSKOG HORMONSKI OVISNOG, HER2 NEGATIVNOG RAKA DOJKE

KRIŽIĆ M.[1], Jazvić M.[2], Dedić Plavetić N.[1,3]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Klinički bolnički centar Sestre milosrdnice
• *Klinika za onkologiju i nuklearnu medicinu*
[3] Sveučilište u Zagrebu
• *Medicinski fakultet*
mkrizic13@gmail.com

Iako je u posljednje vrijeme ostvaren ogroman napredak u liječenju metastatskog karcinoma dojke, i dalje se smatra neizlječivom bolesti. Hormonski ovisni HER2-negativni metastatski rak dojke je najčešći podtip koji ima povoljniju prognozu u odnosu na ostale podtipove zbog mogućnosti djelovanja na estrogenski receptor. U posljednje vrijeme prognoza se dodatno poboljšala otkrićem novih lijekova, prvenstveno inhibitora o ciklinu D ovisnih kinaza (CDK4/6 inhibitora) koji su u kombinaciji s endokrinom terapijom udvostručili medijan vremena do progresije bolesti (mPFS) u odnosu na endokrinu terapiju samu te se etablirali kao današnji standard liječenja hormon receptor (HR) pozitivnog metastatskog karcinoma dojke. Nekoliko randomiziranih kliničkih studija potvrdilo je učinkovitost tri različita CDK 4/6 inhibitora i u endokrino senzitivnoj i u endokrino rezistentnoj bolesti. Najvažniji faktori koji utječu na odluku o inicijalnom liječenju su: prethodna osjetljivost na endokrinu terapiju (de novo vs rekurentna bolest, vrijeme proteklo od završetka endokrinog liječenja za rani rak, menopauzalni status i komorbiditeti pacijenta). Unatoč prosječnom značajnom benefitu u mPFS-a od 25 mj., ipak 17% bolesnika progredira na terapiju CDK4/6 inhibitorima već nakon 12 mjeseci, a nakon 18 mjeseci progredira ih 38%. Mehanizmi rezistencije na CDK4/6 inhibitore nisu dovoljno razjašnjeni te se ubrzano istražuju, a postojeće studije su utvrdile razliku između intrinzičnih i kasnije stečenih mehanizama rezistencije. Najčešći mehanizam rezistencije na endokrinu terapiju je prisustvo ESR1 mutacije. Većina pacijenata s tom mutacijom rezistentna je na terapiju inhibitorima aromataze i tamoksifen. Recentno objavljena studija faze 3 PADA-1 istraživala je bolesnike koji su liječeni palbociklibom i inhibitorom aromataze u 1. liniji. U tijeku liječenja 1. linijom, pomoću ctDNA je utvrđen status ESR1 mutacije, te je bolesnicima s mutacijom aromatazni inhibitor zamijenjen u fulvestrant. Ova studija je utvrdila benefit u PFS-u zamjene endokrinog partnera u fulvestrant nakon detekcije ESR1 mutacije te je izvjesno kako će se ova strategija nastaviti dalje razvijati i uskoro postati dio kliničke prakse. Napredak u otkrivanju mehanizama rezistencije na CDK4/6 inhibitore dovodi do razvoja novih lijekova koji će biti učinkovitiji u sljedećim linijama terapije. Nakon progresije na prvu liniju liječenja CDK4/6 inhibitorima sve je više mogućnosti ciljanog liječenja, a s obzirom na manjak kvalitetnih dokaza još uvijek ostaje otvoreno pitanje optimalne sekvence liječenja. Neki od poznatih mehanizama rezistencije su aktivacija/disregulacija PI3K/Akt/mTOR signalnog puta što je dovelo do razvoja ciljanih lijekova koji djeluju više razina ovog signalnog puta. Trenutno odobrene opcije endokrine terapije u 2. liniji su PI3K inhibitor alpelisib u kombinaciji s fulvestrantom za bolesnice koje imaju PIK3CA mutaciju te mTOR inhibitor everolimus u kombinaciji s endokrinom terapijom. Ostale moguće opcije u 2. liniji terapije su monoterapija fulvestrantom, tamoksifenom ili inhibitorima aromataze. Većina dostupnih opcija liječenja registrirana je na temelju randomiziranih kliničkih istraživanja koja su rađena prije ere CDK4/6 inhibitora, tako da njihova učinkovitost u stvarnom svijetu tek treba biti dokazana. Podaci koji imamo za sada, većinom iz subanalize randomiziranog kliničkog istraživanja PALOMA 3 te više retrospektivnih studija govore u prilog tome da prethodno liječenje CDK4/6 inhbitorima ne narušava učinkovitost endokrine terapije u sljedećim linijama. Studija faze 2, BYLieve također je potvrdila održanu učinkovitost terapije alpelisibom u kombinaciji s fulvestrantom kod pacijenata s PIK3CA mutacijom nakon progresije na endokrinu terapiju CDK4/6 inhibitorima. Uzimajući u obzir sve dostupne podatke većina eksperata se slaže da je preferirana opcija nakon progresije na CDK4/6 inhibitore endokrina terapija sama ili u kombinaciji s drugim lijekom. U slučaju izražene brze progresije bolesti i/ili izražene kliničke progresije smjernice zagovaraju korištenje kemoterapije, a izbor kemoterapeutika baziran je na individualnom pristupu i ovisi o ranijoj terapiji u (neo) adjuvantnom liječenju i komorbiditetima bolesnika. Nekoliko je novih opcija na vidiku za koje se očekuje da bi vrlo skoro mogle ući u svakodnevnu kliničku praksu nakon progresije na 1. liniju terapije CDK4/6 inhibitorima. U studiji faze 3, EMERALD, oralni SERD elacestrant je ostvario značajan benefit u PFS-u te smanjio za 30% rizik od progresije bolesti u odnosu na standardnu endokrinu terapiju (inhibitor aromataze ili fulvestrant), a u pod-

skupini pacijenata s ESR1 mutacijom rizik od progresije bolesti smanjen je za čak 45%. U tijeku je više studija koje istražuju učinkovitost CDK4/6 inhibitora u kombinaciji s drugim endokrinim partnerom nakon progresije na prethodnu terapiju CDK 4/6 inhibitorima. Trenutno dostupni podaci iz studije faze 2, MAINTAIN, pokazali su benefit u PFS-u terapije ribociklibom i drugim endokrinim parterom nakon progresije na prethodnu terapiju CDK 4/6 inhibitorima. Velika prekretnica ove godine dogodila se u liječenju pretretiranih bolesnica, tj. onih bolesnica koje su refraktorne na endokrinu terapiju i progredirale na barem jednu liniju kemoterapije. Na ovogodišnjoj ASCO konferenciji objavljeni su rezultati DESTINY 04 studije koja je pokazala značajan benefit trastuzumab derukstekana u PFS-u i u OS-u kod bolesnica s HER2 low (IHC 1+ ili 2+/ISH neg) tumorima te tako ušla u standard liječenja kod ove podskupine bolesnica. Studija TROPICS-2 pokazala je učinkovitost konjugat-protutijela i lijeka sacituzumab govitekana u odnosu na kemoterapiju kod vrlo pretretiranih bolesnica s 12-mjesečnim preživljenjem u 21% bolesnica. Ostaje i pitanje kako će na dosadašnje odluke o optimalnom sekvenciranju 1. linije utjecati uvođenje CDK4/6 inhibitora abemacikliba u adjuvantnu terapiju kod visoko rizičnih bolesnica u ranom stadiju HR pozitivnog HER2 negativnog raka dojke. Od novosti s ovogodišnjeg ESMO kongresa još je za izdvojiti studiju faze 2, AMEERA-3, koja je pokazala da oralni SERD amcenestrant nije ostvario značajan benefit u PFS-u u odnosu na terapiju po izboru istraživača kod bolesnica koje su progredirale na endokrinu terapiju. Studija ELAINE 1 pokazala je da lasoksifen u usporedbi s fulvestrantom ima numerički, ali ne i statistički značajan benefit u PFS-u nakon progresije na CDK 4/6 inhibitore i inhibitore aromataze. Objavljeni su i rezultati studije DAWNA-2 koja je pokazala benefit u PFS-u novog CDK 4/6 inhibitora dalpicikliba u kombinaciji s inhibitorima aromataze u 1. liniji metastatskog HR pozitivnog raka dojke. I dok su se CDK 4/6 inhibitori etablirali kao standard 1. linije metastatskog HR pozitivnog HER2 negativnog raka dojke, opcije endokrine terapije u 2. liniji se i dalje ubrzano razvijaju. Razvoj novih lijekova općenito doprinosi savladavanju mehanizama rezistencije, odgodi primjene kemoterapije, boljem ishodu liječenja i poboljšanju kvalitete života bolesnika.

OPTIMAL SEQUENCE OF TREATMENT IN METASTATIC HORMONAL POSITIVE/ HER2 NEGATIVE BREAST CANCER

KRIŽIĆ M.[1], Jazvić M.[2], Dedić Plavetić N.[1,3]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
[2] University Hospital Centre Sestre milosrdnice
• *Department of Oncology and Nuclear medicine*
[3] University of Zagreb
• *School of Medicine*

Although tremendous progress has recently been made in treating metastatic breast cancer, it is still considered an incurable disease. Hormone receptor-positive HER2-negative metastatic breast cancer is the most common subtype with a favorable prognosis compared to other subtypes, due to the possibility of acting on estrogen receptors. Recently, the prognosis has been further improved by discovering new drugs, primarily inhibitors of cyclin D-dependent kinases (CDK4/6 inhibitors). In combination with endocrine therapy (ET), CDK4/6 inhibitors doubled the median progression-free survival (mPFS) compared to ET alone and are established as the current standard of care for HR-positive metastatic breast cancer. Several randomized clinical trials have confirmed the efficacy of three different CDK 4/6 inhibitors in both endocrine-sensitive and endocrine-resistant disease. The most important factors influencing the decision on initial treatment are previous sensitivity to endocrine therapy, menopausal status, and patient comorbidities. Despite the average significant benefit in mPFS of 25 months, 17% of patients progressed to therapy with CDK 4/6 inhibitors already after 12 months, and 38% progressed after 18 months. Mechanisms of resistance to CDK 4/6 inhibitors are not sufficiently elucidated and are being rapidly investigated, existing studies have determined the difference between intrinsic and later acquired resistance mechanisms. The most common mechanism of resistance to endocrine therapy is the presence of an ESR1 mutation. Most patients with this mutation are resistant to therapy with aromatase inhibitors (AI) and tamoxifen. The recently published phase 3 PADA-1 study investigated first line treatment with palbociclib and an AI. During first-line treatment, the ESR1 mutation status was determined using ctDNA, and the AI was replaced with fulvestrant in patients with the mutation. Changing the endocrine partner in fulvestrant after detecting an ESR1 mutation demonstrated improvement in PFS, making it evident that this strategy will certainly continue to

develop and soon become part of clinical practice. Progress in discovering the mechanisms of resistance to CDK 4/6 inhibitors leads to the development of new drugs that will be more effective in the subsequent lines of therapy. After progression to 1st line treatment with CDK 4/6 inhibitors, there are numerous options for targeted treatment, and given the lack of quality evidence from research, the question of the optimal treatment sequence remains open. Some known mechanisms of resistance are the activation/dysregulation of the PI3K/Akt/mTOR signaling pathway, which has led to the development of targeted drugs that act at multiple levels of this signaling pathway. Currently approved endocrine therapy options in the 2nd line are the PI3K inhibitor alpelisib in combination with fulvestrant for patients with a *PIK3CA* mutation and the mTOR inhibitor everolimus in combination with ET. Other options in the 2nd line of treatment are monotherapy with fulvestrant, tamoxifen, or AI. Most of the available treatment options are based on randomized clinical trials that were conducted before the era of CDK 4/6 inhibitors, so their effectiveness in the real world has yet to be proven. The data we have so far, mainly from the subanalysis of the PALOMA-3 randomized clinical trial and several retrospective studies, support the fact that previous treatment with CDK4/6 inhibitors does not impair the effectiveness of endocrine therapy in the subsequent lines. The phase 2 study, BYLieve, also confirmed the sustained efficacy of alpelisib therapy in combination with fulvestrant in patients with PIK3CA mutation after progression on endocrine therapy with CDK 4/6 inhibitors. Considering all the available data, most experts agree that the preferred option after progression to CDK 4/6 inhibitors is endocrine therapy alone or in combination with another drug. In the case of rapid progression of the disease or pronounced clinical symptoms, the guidelines suggest the use of chemotherapy. The choice of chemotherapeutics is based on an individual approach and depends on the previous therapy in the (neo)adjuvant setting and the patient's comorbidities. Several new options are on the horizon after progression to first-line CDK 4/6 inhibitor therapy, which is expected to enter daily clinical practice very soon. In the Phase 3 EMERALD study, the oral SERD elacestrant achieved a significant benefit in PFS and reduced the risk of disease progression by 30% compared to standard ET (AI or fulvestrant), and in the subgroup of patients with ESR1 mutation, the risk of disease progression was reduced by 45%. Multiple studies are underway investigating the efficacy of CDK4/6 in combination with another endocrine partner after progression on prior CDK 4/6 inhibitor therapy. The currently available data from the MAINTAIN phase 2 study showed a benefit in PFS of ribociclib and other endocrine partners after progression to prior therapy with CDK 4/6 inhibitors. This year, a significant turning point occurred in treating overtreated patients, i.e., those who are refractory to endocrine therapy and have progressed to at least one line of chemotherapy. At this year's ASCO conference, the results of the DESTINY 04 study were published, which showed a significant benefit of trastuzumab deruxtecan in terms of PFS and OS in patients with HER2 low (IHC 1+ or 2+) tumors, thus entering the standard of treatment for this subgroup of patients. The TROPICS-2 study showed the efficacy of the conjugate-antibody sacituzumab govitecan-hziy compared to chemotherapy in highly pre-treated patients with 12-month survival in 21%. There remains the question of how the introduction of the CDK 4/6 inhibitor abemaciclib into adjuvant therapy in high-risk patients in the early stage of HR-positive HER2-negative breast cancer will affect the decisions made so far regarding optimal 1st-line sequencing. Out of this year's ESMO congress novelties, we could single out the phase 2 study, AMEERA-3, which showed that the oral SERD amcenestrant failed to show significant benefit in PFS compared to the therapy of the researcher's choice in patients who progressed to ET. The ELAINE 1 study showed that lasofoxifene, compared with fulvestrant, had a numerical but not statistically significant benefit in PFS after progression on CDK 4/6 inhibitors and AI. The results of the DAWNA-2 study were also published, which showed a benefit in PFS of the new CDK 4/6 inhibitor dalpiciclib in combination with AI in 1st-line metastatic HR+ breast cancer. And while CDK 4/6 inhibitors have been established as the standard of first-line treatment for metastatic HR-positive HER2 negative breast cancer, second-line endocrine therapy options are still rapidly developing. In addition, the development of new drugs contributes to overcoming resistance mechanisms, delaying chemotherapy use, and improving patients' overall quality of life.

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SEKCIJA TUMORI PROBAVNIH ORGANA / GASTROINTESTINAL TUMORS SECTION

MOLEKULARNO PROFILIRANJE U GASTROINTESTINALNIM TUMORIMA

BALEN M.[1]

[1] Opća bolnica „dr. Josip Benčević" Slavonski Brod
• *Odjel za onkologiju i hematologiju*
balenmatea@gmail.com

Personalizirana onkologija omogućuje primjenu visoko specifične ciljanje terapije za određeni tumor pomoću metoda analize tumorskih stanica kao je sekvencioniranje slijedeće generacije (NGS) koje omogućuje analiziranje stotine gena ili cijelog genoma. Gastrointestinalni tumori se na globalnoj razini javljaju s incidencijom od 26% te su uzrokom i do 35% smrtnosti uzrokovane tumorima zbog čega je potreba za ciljanom terapijom izrazito velika.

Mogućnosti molekularnog ispitivanja u metastatskom kolorektalnom karcinomu do nedavno su uključivale određivanje mutacije KRAS i NRAS gena, mutacije BRAF V600E, te proteina za popravak DNA (MMR). Danas znamo kako 2–6% bolesnika sa metastatskim kolorektalnim karcinomom ima izraženu i prekomjernu ekspresiju HER2 zbog amplifikacije *ERBB2* gena, a koja zajedno sa promjenama u drugim genima kao što su PI3KCA i *PTEN* dovodi do rezistencije na anti-EGFR terapiju. Isto tako, dostupni su rezultati studija koje su pokazale dobre stope odgovora istražujući anti-HER2 terapiju u liječenju metastatskog kolorektalnog karcinoma.

Nove terapijske opcije dostupne su i u liječenju bolesnika sa tumorima bilijarnog trakta zahvaljujući njihovoj molekularnoj heterogenosti. Najčešće dokazane promjene u lokalno uznapredovalih, neresektabilnih i metastatskih kolangiokarcinoma su mutacija IDH1 gena te fuzija gena FGFR2. Učinkovitost u liječenju bolesnika sa dokazanom fuzijom gena FGFR2 u studijama faze II pokazali su infigratinib sa stopom odgovora od 23.1% te pemigatinib sa stopom odgovora 35.5%, dok je ivosidenib pokazao svoju učinkovitost u liječenju bolesnika s mutacijom gena IDH1 u studiji faze III poboljšanjem PFS-a.

Sa druge strane, bolesnici sa adenokarcinomom gušterače nisu pokazali odgovor na do sada testirane ciljane terapije kao što su MEK inhibitori, mTOR inhibitori ili anti-HER2 terapija. Izuzetak u ovoj skupini tumora čine bolesnici sa dokazanom zametnom mutacijom BRCA gena, koja je prisutna u oko 5–7% bolesnika s adenokarcinomom gušterače, a kod kojih su odlične rezultate u terapiji održavanja pokazali PARP inhibitori temeljem POLO studije.

Poznavanje prediktivnih biomarkera temeljem kojih je moguće ciljano odabrati odgovarajuću terapiju može poboljšati ishode liječenja bolesnika sa gastrointestinalnim tumorima, uz optimalnu kvalitetu života.

MOLECULAR PROFILING IN GASTROINTESTINAL TUMOURS

BALEN M.[1]

[1] General Hospita l„dr. Josip Benčević" Slavonski Brod
• *Department of Oncology and Hemathology*

Personalized oncology enables the application of highly specific targeting therapy for a particular tumour using cell analysis methods such as next generation sequencing (NGS) which allow analysis of hundreds of genes or the entire genome. Gastrointestinal tumours occur at a global level with an incidence of 26% and are the cause of up to 35% of mortality caused by all tumours, which is why the need for targeted therapy is extremely high. Until recently, molecular testing options in metastatic colorectal cancer included determination of *KRAS* and gene mutation, *BRAF* V600E mutation, and for mismatch repair (MMR). Today we know that 2–6% of patients with metastatic colorectal cancer have pronounced and overexpressed HER2 due to amplification of the ERBB2 gene, which together with changes in other genes such as PI3KCA and PTEN leads to resistance to anti-EGFR therapy. Likewise, results are available from studies that have shown good response rates investigating anti-HER2 therapy in the treatment of metastatic colorectal cancer.New therapeutic options are also available in the treatment of patients with tumours of the biliary tract thanks to their molecular heterogenicity. The most frequently

proven changes in locally advanced, unresectable, and metastatic cholangiocarcinoma are IDH1 gene mutation and FGFR2 gene fusion. Efficacy in the treatment of patients with a proven FGFR2 gene fusion in phase II studies was demonstrated by infigratinib with a response rate of 23.1% and pemigatinib with a response rate of 35.5%, while ivosidenib demonstrated its efficacy in the treatment of patients with an IDH1 gene mutation in a phase III study by improving PFS.On the other hand, patients with pancreatic adenocarcinoma have not shown a response to targeted therapies tested so far, such as MEK inhibitors, mTOR inhibitors or anti-HER2 therapy. An exception in this group of tumours are patients with a proven germline mutation of the *BRCA* gene, which is present in about 5–7% of patients with pancreatic adenocarcinoma, and in whom PARP inhibitors have shown excellent results in maintenance therapy based on the POLO study.On the basis of knowledge of predictive biomarkers it is possible to select appropriate therapy in a targeted manner, which can improve treatment outcomes for patients with gastrointestinal tumours, with optimal quality of life.

HCC – MIJENJA LI SE PARADIGMA DOSADAŠNJEG SUSTAVNOG LIJEČENJA?

ŠOŠIĆ HORVAT S.[1]

[1] Županijska bolnica Čakovec
• *Odjel za internističku onkologiju i hematologiju*
sara.sosic@gmail.com

Hepatocelularni karcinom najčešći je primarni tumor jetre. Incidencija mu je u porastu, a smrtnost i dalje visoka. U najvećem broju slučajeva razvija se na podlozi cirotične jetre, pa je kod ovih pacijenata u određenoj mjeri poremećena i jetrena funkcija. Interakcija između progresivne maligne bolesti i primarne bolesti jetre predstavlja veliki izazov u odabiru terapijske strategije.

Iako su rizični čimbenici za nastanak HCC-a dobro poznati, većina pacijenata prezentira se u uznapredovaloj fazi bolesti. Pri izradi terapijskog plana za svakog pojedinog pacijenta, moramo uzeti u obzir ne samo stupanj proširenosti bolesti, već njegovo opće stanje i funkciju jetrenog parenhima uključujući razvijene komplikacije, te ih na temelju navedenoga svrstavamo u prognostičke skupine, što nam omogućava bolju procjenu podobnosti za određene modalitete liječenja. Nekoliko nam je alata dostupno, a u svakodnevnom radu služimo se BCLC klasifikacijskim sustavom koji je nedavno ažuriran, a uključuje najbitnije parametre i preporučene terapijske opcije za svaki stadij.

Treba istaknuti važnost probira ciljne populacije i ranog otkrivanja čime se povećava mogućnost radikalnog liječenja. Takvi pacijenti kandidati su za potencijalno kurativni pristup – kiruršku resekciju ili transplantaciju. Pacijenti koji iz nekog razloga nisu podobni za operativni zahvat, mogu se tretirati lokalnim ablativnim metodama. Petogodišnja stopa povrata bolesti iznosi oko 60%, a za sada nema dokaza koji bi podupirali primjenu adjuvantne terapije. Najlošiju prognozu imaju pacijenti s uznapredovalim HCC-om. Za one s očuvanom jetrenom funkcijom indicirano je sistemsko liječenje. Kemoterapija se ovdje pokazala neučinkovitom, a godinama je sorafenib, multikinazni inhibitor, na osnovu rezultata SHARP studije bio jedini dokazano učinkovit lijek za ovu skupinu pacijenata. Kasnija istraživanja dovela su do upotrebe još nekih lijekova poput lenvatiniba, regorafeniba, ramucirumaba i kabozantiniba, što je pridonijelo liječenju ovih pacijenata.

Otkrićem imunoterapije svjedoci smo revolucionarnih rezultata u različitim tumorskim sijelima, stoga ne čudi porast zanimanja za njen učinak u liječenju HCC-a. Rezultati IMbrave150 studije donijeli su promjenu pokazavši značajnu korist u ukupnom preživljenju i preživljenju bez progresije bolesti kod kombinacije atezolizumaba i bevacizumaba u usporedbi sa sorafenibom, uz prihvatljiv sigurnosni profil. Vrlo brzo kombinacija je odobrena od strane FDA u prvoj liniji liječenja, a odnedavno je dostupna i kod nas.

Primjenom imunoterapije već sada se uvelike promijenio dosadašnji standard liječenja ovih pacijenata, a otvaraju se i brojna druga pitanja o ulozi imunoterapije i optimalnom sekvencioniranju dostupne terapije. U tijeku je nekoliko studija čiji rezultati će nam zasigurno odgovoriti na mnoga pitanja i pomoći u boljem donošenju terapijskih odluka u budućnosti kako bismo ovim pacijentima omogućili još bolje ishode.

HCC – IS THERE A CHANGE IN PRESENT SYSTEMIC TREATMENT PARADIGM?

ŠOŠIĆ HORVAT S.[1]

[1] County Hospital Čakovec
• *Department of Medical Oncology and Hematoogy*

Hepatocellular carcinoma is the most common primary liver cancer. The incidence is increasing and mortality rates are high. In most of the cases, HCC occurs in patients with underlying liver cirrhosis, and those patients often present with an impaired liver function. The interaction between progressive malignancy and chronic liver disease poses a big challenge in choosing treatment strategies.

Although risk factors for developing HCC are well known, most of the patients are diagnosed in advanced stage of disease. Before making any definitive treatment plans for every individual patient, we must take into account not only disease stage, but also his performance status and liver function. Based on this parameters we classify them into prognostic groups, which allows us to better understand patient suitability for certain treatment options. In everyday work we are using BCLC classification system which has recently been updated, and it includes the most important parameters and treatment recommendation across all stages.

There are screening options for high – risk population, which can help detect HCC in early stages. Those patients are candidates for a potentially curative approach – surgical resection or transplantation. If patients are not suitable for surgery, they can be treated with locally ablative methods. Five year recurrence rates are approximately 60%, and there is no current evidence to support the use of adjuvant therapy. The worst prognosis is observed in advanced stages of HCC. If the liver function is preserved, systemic therapy is required. Chemotherapy is ineffective here as the HCC is chemorefractory, and for many years sorafenib, a multikinase inhibitor, has been the only drug that has been proven to be clinically effective, based on results from SHARP trial. Later trials led to the approval of other drugs like lenvatinib, regorafenib, ramucirumab and cabozantinib, which contributed to treatment of this patients.Immunotherapy brought some revolutionary changes in treating different malignancies, so it doesn't surprise to see the growing interest for its role in HCC. The IMbrave150 trial results brought a change as well, by showing significantly better overall survival (OS) and progression – free survival (PFS) for atezolizumab plus bevacizumab combination when compared to sorafenib, with acceptable safety profile. Shortly after, the combination has been approved by FDA for the first – line treatment, and recently, it also became available in our country.

By using immunotherapy, the treatment paradigm in HCC already shifted significantly from the former standard of care, and there are some new questions raising about the role of immunotherapy and optimal sequencing of all available drugs. There are few ongoing trials that will surely answer many questions and also help us in making future treatment decisions so that we could ensure even better outcomes for our patients.

BILIJARNI KARCINOM – NA PRAGU NOVIH PROMJENA SUSTAVNE TERAPIJE

LIBRENJAK N.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
niksa.librenjak@gmail.com

Karcinomi bilijarnog trakta su heterogena i unatoč rastućoj incidenciji još uvijek rijetka skupina tumora vrlo loše prognoze, očekivano preživljenje u uzapredovalom stadiju je kraće od 12 mjeseci. Standard sustavne terapije u prvoj liniji liječenja već više od desetljeća je kombinacija cisplatine i gemcitabina. Usprkos brojnim pokušajima niti jedna ciljana ili biološka terapija u kombinaciji s ili bez kemoterapije nije postigla napredak u liječenju ovih bolesnika. No, početkom 2022. godine objavljeni su prvi rezultati TOPAZ –1 studije faze 3, koja je evaluirala učinkovitost i sigurnost dodatka durvalumaba naspram placebu stadndardnoj kemoterapiji te je pokazala dulje sveukupno preživljenje (engl. overall survivial – OS) kao i preživljenje bez progresije bolesti (engl. progression free survival – PFS) uz veću stopu odgovora (engl. response rate – RR). Učestalost neželjenih događaja između dvije skupine nije se statistički značajno razlikovala.

Nakon progresije na prvu liniju liječenja potencijalna opcija liječenja temeljem ABC-06 studije faze 3 jest kemoterapija po FOLFOX protkolu, no uz vrlo skroman utjecaj na sveukupno preživljenje. S obzirom na lošu

prognozu i razmjerno neučinkovitu kemoterapiju bilo je nekoliko pokušaja s primjenom ciljane terapije u neselekcioniranoj populaciji no bez uspjeha. Boljim razumijevanjem molekularne biologije bilijarnih karcinoma prepoznate su promjene koje mogu biti meta ciljane terapije. Dvije najčešće promjene su mutacija izocitrat dehidrogenaze 1 i 2 (IDH) i fuzija odnosno preuredba gena za receptor fibroblastnog čimbenika rasta 2 (FGFR2) te je svaka priustna u 10 do 15% intrahepatalnih kolangiocelularnih karcinoma. Rijeđe, no potencijalno targetabilne promjene su *BRAF* V600E mutacija i HER2 prekomjerna ekspresija.

Ivosidenib je oralni lijek koji inhibira IDH1 te je ispitan u studiji faze 3 (ClarIDHy) naspram placeba kod bolesnika koji su progredirali na prethodnu kemoterapiju, pokazavši značajno duži PFS uz trend i prema boljem OS.

Do danas je ispitana primjena nekoliko FGFR2 inhibitora, pemigatinib i infigratinib su reverzibilni FGFR 1–3 inhibitori, koji su u studijama faze 2 pokazali RR od 35,5% odnosno 23,1%. Za istaknuti je da je pemigatinib ispitan i kod drugih FGF/FGFR promjena kao i kod bolesnika bez FGF/FGFR promjena te nije pokazao objektivnog odgovora. S druge strane je futibatinib, ireverzibilni FGFR 1–4 inhibitor koji pokazuje FGFR2 inhibiciju i nakon razvoja rezistencije na reverzibilne FGFR inhibitore. U FOENIX-CCA2 studiji faze 2 postignuta je RR od 41,7% uz medijan trajanja odgovora 9,5 mjeseci te OS od 20 mjeseci.

Nedavno su objavljeni rezultati HERB studije faze 2 koja je pokazala obećavajuću aktivnost trastuzumab derukstekana u HER2 pozitivnim bilijarnim karcinomima uz RR od 36,4%.

Napretkom u razumijevanju molekularnih promjena u bilijarnim karcinomima otvorena su vrata novim terapijskim opcijama, te već danas možemo reći da je potrebno, kod svih bolesnika koji mogu primiti sustavnu terapiju, učiniti sveobuhvatno gensko profiliranje tumora. Navedeno predstavlja i novi izazov u dijagnostici i terapijskom odlukama kod tih bolesnika naglašavajući važnost multidisciplinarnog pristupa.

BILLIARY CARCINOMA – ON THE PATHWAY OF NEW SYSTEMIC TREATMENT IMPLEMENTATION

LIBRENJAK N.[1]

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

Biliary tract carcinomas are heterogeneous and, despite the growing incidence, still, a rare group of tumours with a very poor prognosis, the expected survival in an advanced stage is less than 12 months. For more than a decade, the standard of first-line systemic therapy has been the combination of cisplatin and gemcitabine. Despite numerous attempts, no targeted or biological therapy in combination with or without chemotherapy has achieved success in the treatment of these patients. However, at the beginning of 2022, the first results of the phase 3 TOPAZ-1 study were published, which evaluated the effectiveness and safety of the addition of durvalumab versus placebo to standard chemotherapy and showed longer overall survival (OS) as well as progression-free survival (PFS) with a higher response rate (RR). There was no statistically significant difference in adverse events between the two groups.After a progression to first-line treatment, a potential treatment option, based on the ABC-06 phase 3 study is FOLFOX chemotherapy, but with a very modest impact on OS. Given the poor prognosis and relatively ineffective chemotherapy, there were several attempts to apply targeted therapy in an unselected population, but without success. With a better understanding of the molecular biology of biliary cancers, targetable abberations have been identified. The two most common alterations are the mutation of isocitrate dehydrogenase 1 and 2 (IDH) and the fusion or rearrangement of the gene for the fibroblast growth factor receptor 2 (FGFR2), both present in 10 to 15% of intrahepatic cholangiocellular carcinomas. Less common but potentially targetable alterations are BRAF V600E mutation and HER2 overexpression.Ivosidenib is an oral drug that inhibits IDH1 and was examined in a phase 3 study (ClarIDHy) against placebo in patients who had progressed on previous chemotherapy, showing a significantly longer PFS with a trend towards better OS.Currently, several FGFR2 inhibitors are being investigated in biliary carcinomas, pemigatinib and infigratinib are reversible FGFR 1–3 inhibitors, which in phase 2 studies showed a RR of 35.5% and 23.1%, respectively. It should be emphasized that pemigatinib was tested in other FGF/FGFR changes as well as in patients without FGF/FGFR changes and did not show an objective response. On the contrary, futibatinib, an irreversible FGFR 1–4 inhibitor shows FGFR2 inhibition even after the development of resistance to reversible FGFR inhibitors. In phase 2 FOENIX-

CCA2 study, futibatinib achieved RR of 41.7% with a median duration of response of 9.5 months and an OS of 20 months.The results of the phase 2 HERB study were recently published, which showed the promising activity of trastuzumab deruxtecan in HER2-positive biliary carcinoma with an RR of 36.4%.Advances in the understanding of molecular changes in biliary cancers have opened the door to new therapeutic options, and we can already say today that it is necessary to perform comprehensive gene profiling of the tumour in all patients who can receive systemic therapy. The above represents a new challenge in diagnosis and therapeutic decisions for these patients, emphasizing the importance of a multidisciplinary approach.

TUMORI NEPOZNATOG PRIMARNOG SIJELA U VREMENU TEKUĆINSKIH BIOPSIJA I UMJETNE INTELIGENCIJE

TRIVANOVIĆ D.[1]

[1] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*
dtrivanovic@obpula.hr

Usprkos velikom razvoju u slikovnim pretragama, endoskopiji i raznim novim omics tehnologijama i dalje oboljeli od raka nepoznatog primarnog sijela čine 2–9% onkološke populacije.

Razvojem novih dijagnostičkih metoda rak nepoznatog primarnog sijela potvrđuje svoje posebnosti i zaseban entitet karakteriziran brzom progresijom, izrazitom kromosomskom nestabilnošću te nizom novih obilježja poput promjena fenotipske plastičnosti, nemutacijskog reprogramiranja, polimorfnih mikrobiomskih odnosa te senescent staničnih obilježja.

Rezultati ranijih studija nisu dokazali značajno preživljenje ovih bolesnika liječenim neselektivnim i neciljanim lijekovima no rezultati registracijskih studija koji su dizajnirane na tissue agnostic principu koristeći biomarkere tumor mutation burden-a i NTRK mutaciju ukazuju na novi smjer kojim se u budućnosti može primjeniti i kod ovih bolesnika.

Veliki napredak u dijagnostici i praćenju liječenja oboljelih od malignih bolesti postigle su ovođenje metoda poput likvidne biopsije i umjetne inteligencije o čijem statusu u borbi sa tumorima nepoznatog primarnog sijela je je dat prikaz u ovom radu.

TUMORS OF UNKNOWN PRIMARY ORIGIN IN THE ERA OF LIQUID BIOPSIES AND ARTIFICIAL INTELLIGENCE

TRIVANOVIĆ D.[1]

[1] General Hospital Pula
• *Department of Medical Oncology and Hematology*

Despite the robust development in imaging, endoscopy and various new omics technologies, cancer patients of unknown primary origin still make up 2–9% of the oncology population.

With the development of new diagnostic methods, cancer of unknown primary origin confirms its peculiarities and a separate entity characterized by rapid progression, marked chromosomal instability and with a series of new features such as changes in phenotypic plasticity, non-mutational reprogramming, polymorphic microbiome relationships and senescent cell features.

The results of previous studies did not prove a significant survival of these patients treated with non-selective and non-targeted drugs, but the results of registration studies that were designed on a tissue agnostic basis using biomarkers of tumor mutation burden and NTRK mutation point to a new direction that can be applied to these patients in the future.

Huge progress in the diagnosis and monitoring of the treatment of patients with malignant diseases has been achieved by the introduction of methods such as liquid biopsy and artificial intelligence, the status of which in the fight against cancer of unknown primary origin is presented in this presentation.

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SEKCIJA UROGENITALNI TUMORI / UROGENITAL TUMORS SECTION

ŠTO JE NOVO U LIJEČENJU METASTATSKOG HORMON-SENZITIVNOG RAKA PROSTATE (MHSRP)

GRUBIŠIĆ-ČABO F.[1], Jajac Bručić L.[1]

[1] Opća bolnica Šibenik
• *Odjel hematologije, onkologije i kliničke imunologije*
fgrubisic@yahoo.com

Pokušavajući napraviti pregled novosti u liječenju metastatskog hormon osjetljivog raka prostate, koje su se javile od jeseni 2021.godine, odlučili smo se za prikaz ARASENS studije, te novijih podataka dobivenih daljnjim praćenjem (engl. update) u studijama ENZAMET i STAMPEDE. ARASENS studija je objavljena na genitourinarnom simpoziju američkog udruženja kliničkih onkologa / engl. American Society of Clinical Oncology (ASCO), održanom u veljači 2022.godine. Radi se o studiji faze III koja je ispitivala liječenje darolutamidom, u odnosu na placebo, kod ispitanika sa metastatskim hormon osjetljivim rakom prostate, koji su u liječenju primali kombinaciju androgen deprivirajuće terapije /ADT/ i docetaksela. Primarni cilj studije bio je srednje preživljanje ispitanika. Dodatkom darolutamida, uz kombinaciju ADT-a i docetaksela, kod ispitanika oboljelih od metastatskog hormon osjetljivog raka prostate, postigla se 32,5% redukcija rizika od smrti, u odnosu na skupinu ispitanika koja je primala placebo. Poboljšanje srednjeg preživljanja postignuto je kako u onih sa „ de novo" metastatskom bolešću, tako i kod onih kod kojih se metastatska bolest pojavila kao povrat bolesti, nakon prethodnog lokalnog liječenja raka prostate. Potrebno je naglasiti kako su pojavnost i težina nuspojava liječenja bile usporedive u obje grupe ispitanika. Novi podatci iz ENZAMET studije, pokazali su kako i nakon 68 mjeseci praćenja skupina ispitanika koja je primala enzalutamid još nije dosegla srednje preživljenje, za razliku od skupine ispitanika u kontrolnoj grani koja je primala nesteroidne antiandrogene (NSAA), kod koje je bilo 73,2 mjeseca. To korenspodira sa omjerom rizika (engl. hazard ratio – HR) od smrti od 0,70 (95% CI 0,58–0,85, p<0,001). Prosječno 5 godišnje preživljenje u skupini ispitanika koja je primala enzalutamid bilo je 67%, a u skupini koja je primala NSAA 57%. Noviji podatci vezani uz STAMPEDE studiju, pokazali su kako dodatkom abirateron/acetata uz prednison/prednizolon (AAP) se postiglo bolje srednje preživljenje u odnosu na standardno liječenje, ali se dodatkom i enzalutamida AAP-u nije postiglo dodatno produženje srednjeg preživljenja, u odnosu na one koji su primali samo AAP. Ipak valja naglasiti kako se u obje grane studije postiglo duže srednje preživljenje, u odnosu na skupinu ispitanika koji su liječeni na standardan način. Za zaključiti je kako AAP ne treba kombinirati s enzalutamidom u liječenju mHSRP.

WHAT IS NEW IN METASTATIC HORMONE-SENSITIVE PROSTATIC CANCER (MHSPC) TREATMENT?

GRUBIŠIĆ-ČABO F.[1], Jajac Bručić L.[1]

[1] General Hospital Šibenik
• *Department of hematology, oncology and clinical immunology*

Trying to make an overview of the novelties in the treatment of metastatic hormone-sensitive prostate cancer, which have appeared since the fall of 2021, we have decided to present the ARASENS study, as well as more recent data obtained from further follow-up (update) in the ENZAMET and STAMPEDE studies. The ARASENS study was published at the Genitourinary Symposium of the American Association of Clinical Oncologists (ASCO)/, held in February 2022. It is a phase III study that examined treatment with darolutamide, compared to placebo, in subjects with metastatic hormone-sensitive prostate cancer, who were treated with a combination of androgen deprivation therapy /ADT/ and docetaxel. The primary objective of the study was the median survival of the subjects. With the addition of darolutamide, along with the combination of ADT and docetaxel, in subjects with metastatic hormone-sensitive prostate cancer, a 32.5% reduction in the risk of death was achieved, compared to the group of subjects who received a placebo. An improvement in median survival was achieved both in those with "de novo" metastatic disease, and in those in whom metastatic disease occurred as disease relapse, after previous local treatment of prostate cancer. It should be emphasized that the incidence and severity of treatment side effects were comparable in both groups of subjects. New data from the ENZAMET study showed that even after 68 months of follow-up, the group of subjects who received enzalutamide still did not reach median survival, in contrast to the group of subjects in the control arm who received non-steroidal antiandrogens (NSAA), where it was 73.2 month. This corresponds to a hazard ratio (HR) of death of 0.70 (95% CI 0.58–0.85, p<0.001). Average 5-year survival in the group of subjects receiving enzalutamide was 67%, and in the group receiving NSAA 57%. Newer data related to the STAMPEDE study showed that the addition of abiraterone/acetate to prednisone/prednisolone (AAP) achieved a better median survival compared to standard treatment, but the addition of enzalutamide to AAP did not achieve an additional prolongation of median survival, compared to those who received only AAP. However, it should be emphasized that in both branches of the study, a longer median survival was achieved, compared to the group of subjects who were treated in a standard way. It can be concluded that AAP should not be combined with enzalutamide in the treatment of mHSPC.

METASTATSKI HORMONSKI OSJETLJIV RAK PROSTATE – PRIKAZ SLUČAJA

VIČIĆ I.[1], Belev B.[1,3], Grubišić-Čabo F.[2]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Opća bolnica Šibenik
• *Odjel hematologije, onkologije i kliničke imunologije*
[3] Sveučilište u Zagrebu
• *Medicinski fakultet*
ivan.vicic1@gmail.com

Uvod: Karcinom prostate je drugi najčešći rak na svijetu u muškaraca. Od ukupnog broja novootkrivenih bolesnika 20% se inicijalno otkrije u metastatskom obliku dok se 60% otkrije u lokaliziranom, a 20% u lokalno uznapredovalom obliku. Petogodišnje preživljenje za metastatski oblik iznosi 29,8%. Do danas su za liječenje metastatskog oblika bolesti kao dodatak androgen deprivirajućoj terapiji (ADT) odobreni docetaksel, abirateron, apalutamid, enzalutamid te su prema recentnijim podatcima predloženi i abirateron s docetakselom i darolutamid s docetakselom.

Prikaz slučaja: 57-godišnjem bolesniku je 2017. godine u sklopu rutinskih pretraga verificiran povišen PSA te je nakon biopsije prostate dokazan adenokarcinom prostate (prema Gleason bodovanju 4+4=8). Na scintigrafiji je utvrđeno patološko nakupljanje radiofarmaka na petom rebru desno te u području sjedne kosti lijevo. Bolesnik je inicijalno bio asimptomatski. S obzirom na brzi porast PSA učinjen je PET/CT s kolinom kojim se utvrde presadnice u limfnim čvorovima uz ilijačne krvne žile obostrano, u sjednoj kosti lijevo, petom i prvom rebru desno te u trupu L4 kralješka. Započeta je ADT LHRH agonistom te kemoterapija docetakselom u ukupno

6 ciklusa (prosinac 2017. – ožujak 2018.). Provedena je i palijativna iradijacija koštanih presadnica zdjelice. Bilježi se dobar odgovor na terapiju uz pad PSA na 0,59 μg/mL te se nastavlja hormonska terapija LHRH agonistom. Ponovni se bilježi porast PSA (na 2,33 μg/mL) 13,5 mjeseci nakon početka terapije, no bez kliničke i radiološke progresije, a u terapiju se uvede bikalutamid. Provođena je i terapija zolendronatnom kiselinom. Ponovno se bilježi značajan porast PSA (23,38 μg/mL) uz kliničku progresiju 38 mjeseci nakon početka terapije (studeni 2020.) te je tada uveden enzalutamid.

Zaključak: Radi se o bolesniku s inicijalno metastatskim hormonski osjetljivim rakom prostate. Koristeći rezultate CHAARTED studije u ovog je bolesnika primijenjena terapija docetakselom uz ADT. Sljedeća linija terapije započeta je 38 mjeseci nakon početka liječenja (po CHAARTED studiji 14,9 mjeseci). Danas je pitanje odabira dodatka ADT-u, te bismo li u ovog bolesnika odabrali terapijski triplet što je predloženo u PEACE-1 i ARASENS studiji.

METASTATIC HORMONE-SENSITIVE PROSTATE CANCER – CASE REPORT

VIČIĆ I.[1], Belev B.[1,3], Grubišić-Čabo F.[2]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
[2] General Hospital Šibenik
• *Department of hematology, oncology and clinical immunology*
[3] University of Zagreb
• *School of medicine*

Introduction: Prostate cancer is the second most common cancer globally in men. Of the total number of newly diagnosed patients, 20% are initially detected as metastatic, 60% are detected as localized cancer, and 20% as locally advanced. Five-year survival for the metastatic disease is 29.8%. To date, docetaxel, abiraterone, apalutamide and enzalutamide have been approved for the treatment of the metastatic cancer as an adjunct to androgen deprivation therapy (ADT), and according to more recent data, abiraterone with docetaxel and darolutamide with docetaxel have also been proposed.

Case report: in 2017, a 57-year-old patient had an elevated PSA verified as part of routine tests, and after a prostate biopsy, he was diagnosed with prostate adenocarcinoma (Gleason score 4+4=8). The patient was initially asymptomatic. Bone scintigraphy detected an accumulation of radiopharmaceutical on the fifth rib on the right, and in the area of the inferior pubic ramus on the left. As PSA increased rapidly, a choline PET/CT detected abnormal metabolic activity in the iliac lymph nodes bilaterally, in the inferior pubic ramus on the left, in the fifth and the first rib on the right, and the L4 vertebral body. ADT with an LHRH agonist and chemotherapy with docetaxel for 6 cycles were started (December 2017 – March 2018). Palliative irradiation of pelvic bone metastases was also performed. PSA levels decreased to 0.59 ug/mL, followed by the continuation of the LHRH agonist. PSA increased (to 2.33 ug/mL) 13.5 months after the start of the treatment, without clinical and radiological progression, and bicalutamide was introduced. Zoledronic acid therapy was started. Significant increase in PSA level (23.38 ug/mL) was detected 38 months after the start of the therapy (November 2020), along with,clinical progression, and enzalutamide was introduced.

Conclusion: This patient was initially diagnosed with metastatic hormone-sensitive prostate cancer. Using the results of the CHAARTED study, docetaxel was added to ADT. The next line of therapy was started 38 months after the start of treatment (according to the CHAARTED trial 14.9 months). For patients like this, it remains to be decided whether the doublet combination (and which one) is preferred as opposed to the recently proposed triplet therapy (PEACE-1 and ARASENS studies).

KAKO POBOLJŠATI LIJEČENJE UROTELNOG KARCINOMA?

DOGAN K.[1], Antunac Golubić Z.[2]

[1] Opća bolnica Karlovac
• *Odjel interne medicine, onkologije i hematologije*
[2] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
katarinadogan@hotmail.com

Uvod: Urotelni karcinomi gornjeg trakta (UTUC) obuhvaćaju karcinome koji nastaju iz prijelaznih stanica kaliksa, bubrežne zdjelice ili uretera. Veoma su rijetki (čine 5–10% urotelnih karcinoma),često su multifokalni, te skloni recidivima.U 60% slučajeva su invazivni i imaju lošiju prognozu nego urotelni karcinom mokraćnog mjehura. Najčešće se prezentiraju hematurijom (70–80%) ili bolovima u lumbalnoj regiji (10–20%). Zlatni standard za postavljanje dijagnoze su CT urografija i ureteroskopija. UTUC su stratificirani u dvije kategorije rizika, tumore niskog i visokog rizika s različitim pristupom liječenju. Liječenje bolesnika sa UTUC-om je izazovno zbog nedostatka jasnih dokaza, što proizlazi iz ukupne rijetkosti bolesti. Liječenje je primarno kirurško. Budući da kirurški zahvat može uzrokovati pogoršanje bubrežne funkcije te onemogućiti primjenu adjuvantne kemoterapije, koja prema rezultatima POUT studije pokazala učinkovitost, u odabranih bolesnika treba razmotriti i neoadjuvantnu kemoterapiju. Za primjenu imunoterapije u adjuvantnoj nakani za sada nema dovoljno dokaza. U metastatskoj bolesti primjenjuju se isti principi liječenja kao kod urotelnih karcinoma mokraćnog mjehura što u prvoj liniji podrazumijeva kombiniranu kemoterapiju baziranu na platini te ukoliko nema znakova progresije bolesti terapiju održavanja avelumabom. Uz imunoterapiju postoje i nove mogućnosti liječenja ciljanom terapijom te primjenom konjugata lijeka i protutijela.

Prikaz slučaja: Prikazat ćemo bolesnika kojem je u travnju 2019. učinjena lijevostrana nefroureterektomija zbog urotelijalnog karcinoma lijevog uretera, pT3N1, s diseminacijom bolesti u ilijakalne limfne čvorove lijevo. Početak adjuvantnoga liječenja bio je planiran u svibnju 2019., no istovremeno je obrađivan radi nodozne promjene u lijevom režnju štitnjače, zbog čega je aplikacija kemoterapije bila odgođena do nakon operativnog rješavanja iste. Po postoperativnom oporavku verificira se lokalni recidiv te je liječen s četiri ciklusa ddMVAC kemoterapije uz kompletni odgovor na terapiju. Imunohistokemijskom analizom protutijelom na PDL-1 dobije se pozitivitet upalnih stanica na više od 5% analizirane tumorske površine. U ožujku 2021. otkriven je lokalni relaps bolesti te je odlučeno započeti liječenje kemoimunoterapijom, a provedeno je i zračenje mozga zbog multiplih moždanih metastaza. Četiri mjeseca kasnije dolazi do daljnje progresije bolesti u jetri, kostima i lokalno, te je započeto liječenje paklitkaselom, no ubrzo dolazi do izrazitog pogoršanja općega stanja bolesnika zbog čega se odustalo od daljnjeg specifičnog onkološkog liječenja.

Zaključak: Liječenje bolesnika s urotelnim karcinomom gornjega urotrakta predstavlja veliki izazov u liječenju zbog svoje rijetke zastupljenosti te bioloških karakteristika. Opisani slučaj prikazuje kako je unatoč primjeni kombinacije imunoterapije i kemoterapije došlo do brze progresije bolesti.

HOW TO IMPROVE THE TREATMENT OF UROTHELIAL CANCER?

DOGAN K.[1], Antunac Golubić Z.[2]

[1] General Hospital Karlovac
• *Department of Internal Medicine, Medical Oncology and Hematology*
[2] University Hospital Centre Zagreb
• *Department of Oncology*

Introduction: Urothelial carcinomas of the upper tract include carcinomas arising from transitional cells of the calyx, renal pelvis, or ureter. They are very rare (they make up 5–10% of urothelial cancers), often are multifocal, and tend to recur. In 60% of cases, they are invasive and have a worse prognosis than urothelial bladder cancer. They are most often presented with hematuria (70–80%) or pain in the lumbar region (10–20%). The gold standard for diagnosis is CT urography and ureteroscopy. They can be stratified into two risk categories, low-risk and high-risk tumors with different treatment approaches. The treatment of patients with urothelial carcinomas is challenging due to the lack of clear evidence, which results from the overall rarity of the disease. Treatment is primarily surgical. Since surgery can cause deterioration of renal function and prevent the use of adjuvant che-

motherapy, which according to the results of the POUT study has shown effectiveness, neoadjuvant chemotherapy should also be considered in selected patients. For the time being, there is not enough evidence for the use of immunotherapy in adjuvant setting. In metastatic disease, the same principles of therapy are applied as in urothelial carcinoma of the urinary bladder, which in the first line includes platinum-based chemotherapy and if there are no signs of disease progression, maintenance therapy with avelumab. In addition to immunotherapy, new treatment options with targeted therapy and the use of drug and antibody conjugates exist.

Case report: We will present a patient who underwent left nephroureterectomy in April 2019 due to urothelial carcinoma of the left ureter, pT3N1, with disseminatin of the disease to the left iliac lymph nodes. The start of adjuvant treatment was planned in May 2019, but at the same time he was treated for a nodular change in the left lobe of the thyroid gland, which is why the application of chemotherapy was postponed after surgical resolution. After postoperative recovery, local recurrence was verified and he was treated with four cycles od ddMVAC chemotherapy with a coplete response to therapy. Immunohistochemical analysis with an antibody to PDL-1 swovs the positivity of inflammatory cells on more than 5% of the analyzed tumor surface. In March 2021, a local relapse of the disease was detacted and we started a tretment with chemoimmunotherapy and brain radiation was also performed due to multiple brain metastases. Four months later futher progression of the disease occured in the liver, bones and locally, so we started the treatment with paclitaxel, but the patient condition soon gone worse, which is why further specific oncological treatment was abandoned.

Conclusion: The treatment of patients with urothelial carcinoma of the upper urinary tract represents a great challenge in treatment due to it is rare occurence an biological characteristics. This case shows how despite the application of a combination of immunotherapy and chemotherapy a rapid progression of the disease occured.

NUSPOJAVE IMUNOTERAPIJE. JESU LI UKLJUČENI DRUGI SPECIJALISTI?

MATANIĆ I.[1], Čonkaš M.[2], Antunac Golubić Z.[3]

[1] Opća bolnica Karlovac
• *Odjel interne medicine, onkologije i hematologije*
[2] Županijska bolnica Čakovec
• *Odjel za internističku onkologiju i hematologiju*
[3] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
ivana.matanic@gmail.com

Uvod: Imunoterapija zauzima sve veću ulogu u liječenju onkoloških bolesnika svih sijela. U našem prikazu slučaja osvrnut ćemo se na nuspojave inhibitora kontrolnih točaka. Ovi lijekovi djeluju tako da se vežu za antigene na površini stanice kojim tumorska stanica spriječava djelovanje T stanica protiv tumora. Dva su mehanizma djelovanja, preko CTLA-4 ili preko PD-1/PD-L1.

U liječenju metatstatskog karcinoma bubrega svijetlih stanica došlo je do značajnog napretka, poglavito za pacijente umjerenog i lošeg rizika prema IMDC kriterijima. Prema ESMO smjernicama prva linija liječenja za metastatski RCC umjererno i lošeg rizika je imunoterapija kombinacijom ipilimumaba i nivolumaba. Kombinacija nivolumaba i ipilimumaba je procijenjena u fazi tri Checkmate 214 studije u kojoj su prethodno neliječeni bolesnici s uznapredovalim ccRCC bili randomizirani za kombinaciju ili sunitinib. Rezultat je porast OS za 21.5 mjeseci.

Prikaz slučaja: Prikazat ćemo 62-godišnju pacijenticu kojoj je u sklopu obrade rezistentne arterijske hipertenzije otkrivena tumorska tvorba lijevog bubrega, te je učinjena radikalna lijevostrananefrektomija s adrenalektomijom. Patohistološka analiza je pokazala da se radi o karcinomu bubrega svijetlih stanica, pT3a, bez sarkomatoidne komponente. Nakon toga kontrolirana UZV-čno, tako da je kompletan staging bolesti učinjen tek nakon godinu dana. CT je pokazao tumorsku tvorbu u desnoj nadbubrežnoj žlijezdi veličine 5.2 x 2.5cm, koja je ranije mjerila 11mm, a u jetri su opisane dvije lezije veličine 7 i 11 mm, koje mogu odgovarati sekundarizmima. S obzirom da se radi o metastatskom raku bubrega umjerenog rizika prema IMDC kriterijima multidisciplinarni tim (MDT) je indicirao liječenje kombinacijom ipilimumaba 1mg/kg i nivolumaba 3mg/kg koje je započelo u srpnju 2021. Nakon dva ciklusa imunoterapije pacijentica se žalila na makulozni osip po koži trbuha, leđa i na obje potkoljenice. S obzirom da se radilo o dermatitisu gradusa 1 nastaviljeno je liječenje imunoterapijom, a osip je spontano regredirao. Nakon 4 ciklusa kombinacije nivolumab+ipilimumab nastavljeno je liječenju nivoluma-

bom kao monoterapijom. Nakon petog ciklusa pacijentica javlja opću slabost i nemogućnost ustajanja iz kreveta bez pomoći uz niske vrijednosti arterijskog tlaka. Bolesnici savjetovano da što prije učini laboratorijske nalaze koji su pokazali snižene vrijednosti kortizola i ACTH, sniženu vrijednost fT4 uz normalan TSH uz blaži porast transaminaza. Takav nalaz hormona uz blažu glavobolju upućivao je na razvoj hipokorticizma i smanjenu funkciju hipofize. Učinjen je MR hipofize kojim nije nađeno patoloških promjena. Konzultiran je endokrinolog koji je potvrdio da se radi o sekundarnoj adrenalnoj insuficijenciji i preporučio peroralnu terapiju hidrokortizonom 15mg + 5mg. UZV štitnjače je pokazao da se radi o nodoznoj strumu. Nakon 3 mjeseca imunoterapije učinjena je reevaluacija bolesti kojom se pokaže regresija veličine tvorbe desne nadbubrežne žlijezde, bez žarišnih promjena u jetri, te je nastavljeno liječenje nivolumabom. Tijek liječenja je bio kratko prekinut zbog blaže COVID-19 infekcije. Nakon ukupno 14 ciklusa nivolumaba kod pacijentice se posumnjalo na miozitis zbog bolova u mišićima. Hormoni štitnjače, kortizol i ACTH su bili unutar referentnih vrijednosti, CK i LDH bez porasta. S obzirom na kliničku sliku pacijentici je tada uveden prednizon 2x 20mg umjesto hidrokortizona 15+5mg. U daljnjim kontrolama endokrinologa otkrivena komplikacija liječenja kortikosteroidima – steroidni dijabetes, te je preporučeno uzimanje metformina ili smanjenje doze prednizona. U razdoblju od dva mjeseca pacijentica postepeno pokušavala sniziti dozu prednizona. U lipnju 2022. pacijentica počinje ponovno uzimati hidrokortizon 15mg+5mg. Nakon ukupno 16 ciklusa nivolumaba učinjena nova reevaluacija bolesti koje je pokazala progresiju veličine tumorske tvorbe desne nadbubrežne žlijezde i diskretno veću hipovaskularnu lezija u donjem polu desnog bubrega.

Pacijentica je prikazana na multidisciplinarnom timu koji je zaključio da je indicirano operativno liječenje tumorske tvorbe desne nadbubrežne žlijezde. U kolovozu 2022. učinjena je desnostrana adrenalektomija, a endokrinolog je preporučio stalno uzimanje nadomjesne terapije hidrokortizon 15 mg + 5 mg uz fludrokortizon. Pacijentica je nakon operativnog zahvata ponovno prikazana na mulltidisciplinarnom timu koji je preporučio reevaluacijsku radiološku obradu, odluka o nastavku liječenja će slijediti nakon očitanja. Do odluke multidisciplinarnog tima pacijentica je u pauzi liječenja imunoterapijom.

Zaključak: Radi optimalnog zbrinjavanja nuspojava imunoterapije potrebno je pažljivo pratiti bolesnika tijekom liječenja. U slučaju pojave nuspojava važno je pravovremeno početi liječenje kortikosteroidima i na vrijeme konzultirati druge specijaliste ovisno o vrsti nuspojave kako bi se pacijentu omogućila što kvalitetnija skrb.

IMMUNOTHERAPY SIDE-EFFECTS. ARE ALL OTHER SPECIALISTS INVOLVED AS WELL?

MATANIĆ I.[1], Čonkaš M.[2], Antunac Golubić Z.[3]

[1] General Hospital Karlovac
• *Department of Internal Medicine, Medical Oncology and*
[2] County Hospital Čakovec
• *Department of Medical Oncology and Hematoogy*
[3] University Hospital Centre Zagreb
• *Department of Oncology*

Introduction: Immunotherapy plays an increasingly important role in the treatment of cancer patients of all ages. In our case report, we will look at the side effects of checkpoint inhibitors. These drugs work by binding to antigens on the surface of the cell by which the tumor cell prevents the T cells from acting against the tumor. There are two mechanisms of action, via CTLA-4 or PD-1/PD-L1. Significant progress has been made in the treatment of metastatic clear cell renal carcinoma, especially for moderate and poor-risk patients according to the IMDC criteria. According to the ESMO guidelines, the first line of treatment for metastatic RCC of moderate and poor risk is immunotherapy with a combination of ipilimumab and nivolumab. The combination of nivolumab and ipilimumab was evaluated in the phase three Checkmate 214 study in which previously untreated patients with advanced ccRCC were randomized to the combination or sunitinib. The result is an increase in OS by 21.5 months.

Case report: We will present a 62-year-old patient who was diagnosed with a left kidney tumor as part of treatment for resistant arterial hypertension, and a radical left-sided nephrectomy with adrenalectomy was performed. Pathohistological analysis showed that it was clear cell renal carcinoma, pT3a, without a sarcomatoid component. After that, it was controlled by ultrasound, so that the complete staging of the disease was done only after one year. CT scan showed a tumor formation in the right adrenal gland of size 5.2 x 2.5 cm, which previously measured 11 mm, and two lesions of size 7 and 11 mm were described in the liver, which may correspond

to secondaries. Given that it is metastatic kidney cancer of moderate risk according to IMDC criteria, the multidisciplinary team (MDT) indicated treatment with a combination of ipilimumab 1mg/kg and nivolumab 3mg/kg, which began in July 2021. After two cycles of immunotherapy, the patient complained of a macular rash on the skin of the abdomen, back, and lower legs. Given that it was grade 1 dermatitis, immunotherapy treatment was continued, and the rash regressed spontaneously. After 4 cycles of the nivolumab+ipilimumab combination, treatment with nivolumab as monotherapy was continued. After the fifth cycle, the patient reports general weakness and the inability to get out of bed without help, along with low blood pressure values. The patient was advised to do laboratory tests as soon as possible, which showed decreased cortisol and ACTH values, decreased fT4 values with normal TSH, and a mild increase in transaminases. Such a finding of hormones together with a mild headache indicated the development of hypocorticism and reduced function of the pituitary gland. An MRI of the pituitary gland was performed, and no pathological changes were found. An endocrinologist was consulted, who confirmed that it was secondary adrenal insufficiency and recommended oral therapy with hydrocortisone 15mg + 5mg. Ultrasound of the thyroid showed that it was a nodular goiter. After 3 months of immunotherapy, the disease was re-evaluated, which showed a regression in the size of the formation of the right adrenal gland, without focal changes in the liver, and nivolumab treatment was continued. The course of treatment was briefly interrupted due to a milder COVID-19 infection. After a total of 14 cycles of nivolumab, myositis was suspected in the patient due to muscle pain. Thyroid hormones, cortisol, and ACTH were within reference values, CK and LDH without increase. Considering the clinical picture, the patient was then given prednisone 2x 20mg instead of hydrocortisone 15+5mg. In further controls by an endocrinologist, a complication of corticosteroid treatment was discovered – steroid diabetes, and it was recommended to take metformin or reduce the dose of prednisone. For two months, the patient gradually tried to lower the dose of prednisone. In June 2022, the patient starts taking hydrocortisone 15mg+5mg again. After a total of 16 cycles of nivolumab, a new reevaluation of the disease was performed, which showed progression in the size of the tumor formation of the right adrenal gland and a discreetly larger hypovascular lesion in the lower pole of the right kidney. The patient was presented to the multidisciplinary team, which concluded that surgical treatment of the tumor formation of the right adrenal gland is indicated. In August 2022, right-sided adrenalectomy was performed, and the endocrinologist recommended the constant use of replacement therapy hydrocortisone 15mg + 5mg with fludrocortisone. After the operation, the patient was seen again by the multidisciplinary team, which recommended a reevaluation of the CT scan, the decision to continue the treatment will follow after the reading. Until the decision of the multidisciplinary team, the patient is on a break from immunotherapy treatment.

Conclusion: To optimally manage the side effects of immunotherapy, it is necessary to carefully monitor the patient during treatment. In the event of side effects, it is important to start treatment with corticosteroids on time and to consult other specialists in time, depending on the type of side effect, in order to provide the patient with the best possible care.

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IZAZOV: LIJEČENJE KARCINOMA TESTISA LOŠE PROGNOZE – PRIKAZ SLUČAJA

BUŠELIĆ Š.[1], Gnjidić M.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
simebuselic@gmail.com

Uvod: Karcinom testisa najčešća je zloćudna novotvorina u mladih muškaraca. To je primjer zloćudne bolesti koja je, upotrebom kombinirane kemoterapije na temelju cisplatine i kirurgije, izlječiva i u metastatskoj fazi. Unatoč tome, 20–30% pacijenata neće biti izliječeno prvolinijskim PEB protokolom (cisplatina, etopozid, bleomicin). Primarni tumor u medijastinumu, prisutnost ne-plućnih presadnica te vrlo visoke vrijednosti tumorskih biljega bHCG, AFP i LDH, pretkazatelji su loše prognoze. Povrat bolesti nakon potpunog odgovora također

može ukazivati na lošiju prognozu, bez obzira na početnu kategoriju rizika. U višim linijama liječenja koriste se kombinacije cisplatine s ifosfamidom, vinblastinom i paklitakselom te kombinacija gemcitabina i oksaliplatine. U bolesnika koji su još osjetljivi na cisplatinu u prvom ili drugom relapsu, dolazi u obzir i primjena visokodozne kemoterapije uz potporu autolognim krvotvornim matičnim stanicama.

Prikaz slučaja: Kod 41-godišnjeg bolesnika dijagnoza germinativnog tumora postavljena je nakon patohistološke analize uklonjenog limfnog čvora na vratu, uz rasap u pluća te u medijastinalne i retroperitonealne limfne čvorove. Zbog sumnje na primarni proces u lijevom testisu učinjena je orhidektomija kojom se nije našlo tumora. Nakon četiri ciklusa PEB-a učinjena je resekcija ostatne bolesti u retroperitoneumu, mikroskopski bez tumorskog tkiva. Nakon nekoliko mjeseci dolazi do progresije bolesti u plućima te je započeta druga linija liječenja kombinacijom s ifosfamidom – protokol PEI. Nakon daljnje progresije odlučeno je liječenje nastaviti visokodoznom kemoterapijom. Periferne krvotvorne matične stanice su mobilizirane i prikupljene u dodatnom ciklusu kemoterapije uz čimbenik rasta granulocita. Uslijedila su dva ciklusa visokodozne kemoterapije uz reinfuziju vlastitih matičnih stanica. Drugi ciklus se kompliciran gram-pozitivnom sepsom u periodu aplazije, što je liječeno antibioticima širokog spektra. Nakon provedene terapije bilježi se dobra parcijalna regresija plućnih presadnica, veličinom stacionarnih u dosadašnjem praćenju, uz uredne tumorske biljege.

Zaključak: Dugogodišnje preživljenje bolesnika s relapsom karcinoma testisa moguće je postići primjenom konvencionalne ili visokodozne kemoterapije. Potreban je multidisciplinarni pristup u centrima s velikim iskustvom u liječenju takvih bolesnika.

Ključne riječi: germinativni tumor, loši rizik, povrat bolesti, visokodozna kemoterapija, autologna transplantacija krvotvornih matičnih stanica

CHALLENGE OF POOR PROGNOSIS TESTICULAR CANCER TREATMENT – CASE REPORT

BUŠELIĆ Š.[1], Gnjidić M.[1]

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

Introduction: Testicular cancer is the most common malignancy in young men. It's an example of a cancer that is curable even in the metastatic setting with the use of cisplatin-based combination chemotherapy and surgery. However, 20–30% of patients won't be cured by the first-line PEB regimen (cisplatin, etoposide, bleomycin). Mediastinal primary tumor, non-pulmonary metastases and very high serum tumor markers bHCG, AFP and LDH are predictors of a poor prognosis. Disease recurrence after a complete response may also indicate a worse prognosis, regardless of the initial risk category. In the subsequent lines of therapy, cisplatin-based combinations with ifosfamide, vinblastine and paclitaxel are used, as well as a combination of gemcitabine and oxaliplatin. In patients who are still cisplatin-sensitive at the time of first or second relapse, high-dose chemotherapy with the autologous hematopoietic stem cell support is considered.

Case report: In a 41-year-old patient, the diagnosis of a germ-cell tumor was confirmed after a histopathological analysis of the removed cervical lymph node, with dissemination to the lungs, mediastinal and retroperitoneal lymph nodes. Due to the suspected primary tumor of the left testicle, an orchiectomy was performed, in which no malignancy was found. After four cycles of PEB, the residual retroperitoneal disease was resected, microscopically no viable tumor was found. After a few months, the disease progressed in the lungs, and a second-line ifosfamide combination – PEI regimen, was initiated. After further progression, it was decided to continue the treatment with high-dose chemotherapy. Peripheral hematopoietic stem cells were mobilized and collected during an additional chemo-cycle with granulocyte-colony stimulating factor. Two cycles of high-dose chemotherapy followed, with reinfusion of autologous stem cells. The second cycle was complicated by gram-positive sepsis during aplasia, which was treated with broad-spectrum antibiotics. After completion of therapy, there was a good partial regression of the lung metastases, the size of which was stationary in the follow-up intervals so far, with normal tumor markers.

Conclusion: Long-term survival of patients with relapsed testicular cancer can be achieved using conventional or high-dose chemotherapy. A multidisciplinary approach is needed in centers with extensive experience in the treatment of such patients.

Keywords: germ-cell tumor, poor risk, disease recurrence, high-dose chemotherapy, autologous hematopoietic stem cell transplant

SEKCIJA MLADIH ONKOLOGA / YOUNG ONCOLOGISTS SECTION

UTJECAJ LIJEKOVA ZA ZAŠTITU ŽELUČANE SLUZNICE NA UČINKOVITOST I TOKSIČNOST ONKOLOŠKIH LIJEKOVA

JAKŠIĆ P.[1]

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*
petra.lepetic@gmail.com

Uvod: Obolijevanje od malignih bolesti predstavlja značajan javno zdravstveni problem kako diljem svijeta tako i u Hrvatskoj. Prema posljednje objavljenom Registru za rak Republike Hrvatske iz 2019. rak je bolest od koje obolijevaju starije. Ovaj podatak je indikativan s obzirom na očekivane prisutne komorbiditete i posljedičnu potencijalnu polipragmaziju u toj životnoj dobi. Lijekovi za zaštitu želučane sluznice – među kojima su najznačajniji inhibitori protonske pumpe (IPP-ovi), jedni su od najčešće propisivanih lijekova. Prema jednoj studiji, više od četvrtine oboljelih od malignih bolesti koriste IPP-ove na dnevnoj bazi i to najčešće dugotrajno. (1) Sve je veći broj lijekova koji se koriste u liječenju malignih bolesti; ne samo citotoksična kemoterapija već antihormonska, biološka i imunoterapija, a svi na neki način utječu na gastrointestinalni sustav.

Materijali i metode: Ovaj rad ima za cilj osvrnuti se na trenutno dostupne informacije o utjecaju lijekova koji suprimiraju želučanu kiselinu na učinkovitost i toksičnost onkološke terapije.

Rezultati: PH homeostaza tumora varira od one zdravih tkiva, upravo ta razlika čini je podobnom za razvoj malignog fenotipa čija su obilježja proliferacija i progresija. (2) Različita pred-klinička istraživanja pokazala su kako je mikrookoliš tumora kiseliji od onog zdravog tkiva što za posljedicu ima usmanjenu apsorpciju lijekova koji su slabe baze. Luciani i kolege svojim istraživanjem su pokazali kako bi liječenje IPP-ovima prije sustavnog antineoplastičnog liječenja moglo pospješiti učinkovitost nekih antineoplastika, primjerice cisplatine, 5-FU i vinblastina. (3) Pretpostavili su da je alkalizacija moguća nova strategija u prevladavanju otpornosti tumora na antineoplastike. S druge strane, sve je veći broj studija koje ističu kako lijekovi za zaštitu sluznice smanjuju biodostupnost lijekova koji se koriste u onkologiji, posebice peroralnih pripravaka poput inhibitora tirozin kinaza (TKI) ili inhibitora kontrolnih točaka. (4) Kao jedan od razloga neuspjeha sustavne antineoplastične terapije može biti interakcija među lijekovima pošto IPP-ovi imaju učinak na farmakologiju antineoplastika kao i na njihovu topljivost. Nekoliko studija ističe kako istodobno korištenje IPP-ova i CDK 4/6 inhibitora ima negativan utjecaj na vrijeme do progresije bolesti. (5,6) Smanjenjem lučenja želučane kiseline mijenja se sastav crijevnog mikrobioma, mogući je veći rizik enteralnih infekcija te je slabija apsorpcija mikronutijenata. Opisano se pretpostavlja uzrokom slabijeg odgovora na imunoterapiju. Dugotrajno uzimanje lijekova koji smanjuju lučenje želučane kiseline povećava rizik od koštanih lomova, pogoršava hipomagnezijemiju kao i deficijenciju željeza i vitamina B12.

Zaključak: Oprečni su podatci o utjecaju lijekova za zaštitu želučane sluznice na učinkovitost i toksičnost onkoloških lijekova. Dok se ne dobiju nedvojbene informacije, potrebno je osvijestiti ovu temu te ograničiti dugotrajno korištenje IPP-ova kao i korištenje van propisanih indikacija. U konačnici, ova tema zahtjeva daljnja opsežna i sveobuhvatna istraživanja.

IMPACT OF GASTRIC BARRIER PROTECTION DRUGS ON EFFECTIVITY AND TOXICITY OF ONCOLOGY DRUGS

JAKŠIĆ P.[1]

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

Introduction: Cancer represents a significant public health problem worldwide, in Croatia as well. According to the Croatian national Cancer registry, in 2019., cancer is a disease of older age, over 65. This is indicative because of comorbidities and potential consequentially polypragmasy. Gastric barrier protection drugs – the main represen-

tatives are proton pump inhibitors (PPI), are one of the most frequently prescribed drugs. According to one prospective study, more than one-quarter of cancer patients use PPI on daily basis and in the long term. (1) There is an emerging number of medicaments used in treating malignancies, not only cytotoxic chemotherapy, but hormonal therapy, biological agents, and immunotherapy. All these agents affect the gastrointestinal tract somehow.

Materials and methods: This paper aims to review currently available knowledge of the effect of acid-suppressive compounds on the effectiveness and toxicity of oncology drugs.

Results: Tumor pH homeostasis varies from that found in normal tissues, and this difference involves a proliferative and progressive advantage for the malignant phenotype. (2) Different preclinical investigations showed that tumor microenvironmental is more acidic than normal tissue, thus impairing the uptake of weakly basic drugs. According to Luciani and colleagues, pretreatment with PPI may improve the therapeutical effectiveness of some antineoplastic drugs, including cisplatin, 5-FU, and vinblastine. (3) Alkalinization is a possible new strategy for overcoming tumor drug resistance to antitumor agents. On the other hand, there are emerging studies that addressed the effect of gastric barrier protection drugs on the lower bioavailability of anticancer drugs, particularly peroral as tyrosine kinase inhibitors (TKIs) or immune checkpoint inhibitors. (4) PPIs interact via the pharmacological and solubility pathways, so drug-drug interactions should be considered as one of the reasons for treatment failure. Several studies apostrophize detrimental effects on PFS due to concomitant use of PPIs and CDK 4/6 inhibitors. (5,6) Suppression of gastric acidity changes the composition of the gut microbiome, inducing a higher risk of enteric infections or impaired absorption of some micronutrients. Ergo, the possible direct impact on the impaired response to immunotherapy. Also, long-term PPI use seems to improve the risk of bone fracture and worsen hypomagnesemia, and iron and vitamin B12 deficiencies.

Conclusion: There are discordant available data about systemic antineoplastic treatment and concomitant use of acid-suppressive compounds. At this point, awareness of this issue is needed, cessation of PPI use after four weeks of treatment, as well beyond the indications. Ultimately, this topic requires further extensive and comprehensive investigations.

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UTJECAJ LIJEKOVA ZA ZAŠTITU ŽELUČANE SLUZNICE NA UČINKOVITOST I TOKSIČNOST ONKOLOŠKIH LIJEKOVA – PRIKAZ SLUČAJA

MLADINOVIĆ M.[1], Kovač Peić A.[1]

[1] Opća bolnica „dr. Josip Benčević" Slavonski Brod
• *Odjel za onkologiju i hematologiju*
martina.mladinovic@hotmail.com

Uvod: Lijekovi za zaštitu želučane sluznice jedni su od najčešće propisivanih lijekova u svijetu. Zbog lake dostupnosti vrlo česta je njihova uporaba kod onkoloških bolesnika. Najčešće se ističu inhibitori protonske pumpe (IPP) za liječenje gastroezofagealnog refluksa i peptičkog ulkusa. IPP imaju dobar sigurnosni profil, dobru podnošljivost i veću inhibiciju kiseline u usporedbi sa starijim lijekovima kao što su antagonisti histaminskih receptora-2 (H2-antagonisti), antikolinergici i sintetski analozi prostaglandina. Inhibiciju želučane i bazne kiseline IPP-ovi ostvaruju kovalentno vezanjem na H+/K+ATP pumpu. Metaboliziraju se u jetri sustavom citokroma P450 putem 2 metabolička puta, no smatra se da metaboliti nemaju farmakološki značaj.

Prikaz slučaja: Prikazujemo slučaj dva bolesnika. Bolesnica u dobi od 60. godina, prije desetak godina liječila ulkus duodenuma. Od lijekova dugo godina uzimala male doze IPP-a. Obradom u 4/2022 dijagnostiran hormonski pozitivan (HR +), humani receptor epidermalnog faktora rasta 2 negativan (HER2 -) invazivni karcinom dojke. Slikovnom obradom verificira se metastatska bolest, metastaze u regionalne limfne čvorove lijeve aksile, vrata, medijastinuma i suspektne metastatske promjene zdjelice. Indicirano liječenje prvom linijom metastatske bolesti za HR+/ HER2 – tumore – selektivnim inhibitorom ciklin-ovisnih kinaza 4 i 6 (CDK4/6 inhibitor) uz inhibitor aromataze u terapijskoj dozi (Ribociklib 600 mg dnevno uz Anastrazol 1 mg dnevno). Prije početka liječenja učinjeni kompletni laboratorijski nalazi i EKG u kojem QTC 460 ms po Frederica, LBBB (anamnestički poznat od ranije). Daljnju primjenu terapije dobro podnosila, biokemijski i slikovnom obradom regresija, redovito kontrolirani laboratorijski nalazi i EKG koji bili uredni prva 3 ciklusa. Potom pojava nelagode u želucu, žgaravica koje nije regrediralo na raniju IPP terapiju, bolesnica se obratila obiteljskom liječniku. Tada od strane obiteljskog liječnika IPP (pantoprazol 20 mg) zamijenjen H2-antagonistom u najnižoj dozi (famotidin 20 mg). Dolaskom na 4. ciklus terapije povremeno manja žgaravica, palpitacije u prsima, vrtoglavica i slabost. U EKG zapisu produžen QTC interval 520 ms po Frederica, hemodinamski stabilna, RR 120/65 mm Hg, p/c 90/min. Naknadno se doznaje, zbog žgaravice pojačala dozu famotidina na 40 mg dnevno. Kontrolni laboratorijski nalazi uredni. Postavljala se pitanje što je uzrok produženja QTC intervala? Ribociklib, raniji pantoprazol, famotidin, famotidin u većoj dozi? Kombinacija lijekova? Elektrolitski disbalans Ca i Mg?

Bolesnik star 74 godine, dijabetičar, hipertoničar, poznat gastritis, kod kojeg je 2017.g učinjena radikalna nefrektomija desnog bubrega zbog karcinoma bubrega. Od lijekova je uzimao: glimepirid, ramipril i pantoprazol. U 12/2020 pojava metastaza u plućima te abdominalnim limfnim čvorovima. Započeto liječenje prvom linijom terapije za metastatsku bolest – pazopanib u terapijskoj dozi 800 mg dnevno. Nakon 3 ciklusa terapije izraženije nuspojave, teško podnošenje, izrazita slabost, mučnina te povišene vrijednosti krvnog tlaka prilikom uzimanja terapije. Radiološkom obradom regresivna dinamika, a u laboratorijskim nalazima prati se porast jetrenih transaminaza. Što je uzrok porasta jetrenih transaminaza i vrijednosti krvnog tlaka? Postavlja se pitanje međusobne interakcije lijekova, oralnih antidijabetika i pazopaniba, pantoprazola i pazopaniba, samo pazopaniba ili pazopaniba i prehrane? Da li je potrebna redukcija pazopaniba?

Zaključak: Farmakokinetička varijabilnost oralnih onkoloških lijekova razlikuje se od parenteralnih lijekova. Kako bi se adekvatno apsorbirali, potrebno je obratiti pozornost na topivost, bioraspoloživost i učinkovitost oralnih lijekova te moguću međusobnu interakciju s drugim lijekovima. S obzirom na današnje spoznaje o međusobnim interakcijama lijekova, postavlja se više pitanja. Znamo li koje lijekove bolesnici dodatno uzimaju? Je li uistinu upotreba inhibitora protonske pumpe, H2-antagonista, antacida opravdana i kada je indicirana? Ukoliko je primjena lijekova za zaštitu sluznice uistinu nužna, potrebno ju je u dogovoru s gastroenterologom provoditi te na pravilan način uzimati lijekove. Imamo li terapijskih opcija i validnih dokaza? Coca cola ili druga gazirana pića?

IMPACT OF GASTRIC BARRIER PROTECTION DRUGS ON EFFECTIVITY AND TOXICITY OF ONCOLOGY DRUGS – CASE REPORT

MLADINOVIĆ M.[1], Kovač Peić A.[1]

[1] General Hospita l „dr. Josip Benčević" Slavonski Brod
• *Department of Oncology and Hemathology*

Introduction: Medicines for protection the gastric mucosa are one of the most prescribed medicines in the world. Due to their easy availability, their use in oncology patients stands out. Proton pump inhibitors (PPIs) are most often used for the treatment of gastroesophageal reflux and peptic ulcer. PPIs have a good safety profile, good tolerability, and greater acid inhibition compared to older drugs such as histamine receptor-2 antagonists (H2-antagonists), anticholinergics, and synthetic prostaglandin analogs. Inhibition of gastric acid and alkalinity is accomplished by PPIs covalently binding to the H+/K+ATP pump. They are metabolized in the liver by the cytochrome P450 system via 2 metabolic pathways, but the metabolites are considered to have no pharmacological significance.

Case report: We present the case of two patients. The patient is 60 years old, treated for a duodenal ulcer ten years ago. She had been taking small doses of PPIs for many years. Treatment in 4/2022 diagnosed hormone-positive (HR +), human epidermal growth factor receptor 2 negative (HER2 -) invasive breast cancer. Metastatic

disease, metastases in the regional lymph nodes of the left axilla, neck, mediastinum and suspected metastatic changes in the pelvis are verified by imaging. Indicated first-line treatment of metastatic disease for HR+/ HER2 – tumors – cyclin-dependent kinase inhibitor 4 and 6 (CDK4/6 inhibitor) with an aromatase inhibitor (Ribociclib 600 mg per day with Anastrasol 1 mg per day). Before the start of the treatment, complete laboratory findings and an ECG were performed, in which the QTC was 460 ms according to Frederic, LBBB (anamnestically known from earlier). She tolerated the further application of the therapy well, biochemically and imaging treatment of regressions, regularly controlled laboratory findings and ECG, which were normal for the first 3 cycles. After the appearance of stomach discomfort, and heartburn that did not regress on the earlier PPI therapy, the patient consulted the family doctor. Then the family doctor replaced the PPI (pantoprazole 20 mg) with H2-antagonist in the lowest dose (famotidine 20 mg). On reaching the 4th cycle of therapy, occasionally minor heartburn, palpitations in the chest, dizziness and weakness. In the ECG recording, the QTC interval was extended to 520 ms according to Frederica, hemodynamically stable, RR 120/65 mmHg, f 90/min. It was subsequently found out that, due to heartburn, she increased the dose of famotidine to 40 mg per day. The control laboratory findings were normal. The questions are: What causes QTC prolongation? Ribociclib, earlier pantoprazole, famotidine, higher dose famotidine? Combination of drugs? Electrolyte imbalance of Ca and Mg?

A 74-year-old patient, diabetic, hypertensive, with known gastritis, underwent a radical nephrectomy of the right kidney in 2017 due to kidney cancer. He was taking glimepiride, ramipril and pantoprazole. In 12/2020, the occurrence of metastases in the lungs and abdominal lymph nodes. First-line treatment for metastatic disease was started – pazopanib at a therapeutic dose of 800 mg per day. After 3 cycles of therapy, more pronounced side effects, difficulty to bear, marked weakness, nausea and elevated blood pressure values when taking the therapy. Radiological treatment shows regressive dynamics, and laboratory findings show an increase in liver transaminases. What is the cause of the increase liver transaminases and blood pressure values? The question arises of drug interactions, oral antidiabetics and pazopanib, pantoprazole and pazopanib, only pazopanib or pazopanib and diet? Is pazopanib reduction necessary?

Conclusion: The pharmacokinetic variability of oral oncology drugs differs from parenteral drugs. For them to be absorbed adequately, it is necessary to pay attention to the solubility, bioavailability and effectiveness of oral drugs and possible mutual interaction with other drugs. Considering today's knowledge of drug interactions, several questions arise: Do we really know what medicines the patients are taking additionally? Is the use of PPIs, H2-antagonists, and antacids really justified and when indicated? If the application of medication to protect the mucous membrane is truly necessary, it should be carried out in consultation with a gastroenterologist and the medication should be taken in the correctly manner. Do we have therapeutic options and valid evidence? Cocacola or other carbonated drinks?

PRIMJENA OPIOIDNIH ANALGETIKA U LIJEČENJU BOLI ONKOLOŠKIH BOLESNIKA

LINARIĆ P.[1]

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*
petralinaric22@gmail.com

U Hrvatskoj je 2019. dijagnosticirano preko 25 000 slučajeva zloćudnih bolesti, a smatra se kako je u 25–50% bolesnika bol prisutna već pri postavljanju dijagnoze te je jedan od najčešćih razloga javljanja liječniku prije verificiranja maligne bolesti. Učestalost i jačina boli ovisi o sijelu i stadiju maligne bolesti. U uznapredovaloj fazi bolesti, čak 75–90% bolesnika trpi bol, a prema dostupnim literaturnim podacima, njih više od 40% ne prima zadovoljavajuću analgetsku terapiju. Bol se u onkoloških bolesnika može pojaviti zbog samog rasta tumora i tumorskih rasadnica, kao posljedica primjene neurotoksične kemoterapije, radioterapije ili kirurškog liječenja, a s obzirom na duže vrijeme trajanja i neotklonjiv uzrok boli, najčešće se radi o kroničnoj boli. Neadekvatno liječena bol može imati značajne fizičke, socijalne, duhovne i emocionalne posljedice te u konačnici negativan učinak na ishod liječenja i kvalitetu života bolesnika, posebice u metastatskom okruženju. Pristup liječenju maligne boli je multidisciplinaran i polimodalan. Iako sustavno onkološko liječenje i radioterapija mogu imati analgetski učinak redukcijom tumorske mase, okosnica liječenja boli je farmakološko liječenje. Unatoč važnosti drugih skupina lijekova u liječenju maligne boli, daleko najveći značaj imaju opioidni analgetici. Opiod je bilo koja tvar koja se veže na opioidne receptore, koji se uglavnom nalaze u središnjem živčanom i probavnom sustavu, posti-

žući analgetski učinak, ali i neželjene učinke poput respiratorne depresije, sedacije, ovisnosti, mučnine, povraćanja, opstipacije i retencije urina. Prema modelu „trostupanjske analgoljestvice", slabi opioidi (tramadol, kodein) koriste se u liječenju srednje jake boli – VAS (vizualno-analogna skala) 6–7, dok su jaki opioidi, s predstavnikom morfinom, zlatni standard u liječenju jake boli (VAS 8–10). Preferira se peroralni unos kod većine bolesnika, zbog jednostavnosti i učinkovitosti, a mogu se primijeniti i transdermalnim, subkutanim ili intravenskim putem u slučaju nemogućnosti peroralnog unosa. Uz praćenje dostupnih algoritama za pristup liječenju, izbora i titracije opioidnih analgetika, rotacije opioidnih lijekova i računanja ekvivalentnih doza, ključno je uvođenje preventivnih mjera, kao i dobro prepoznavanje i zbrinjavanje najčešćih nuspojava liječenja (mučnina, opstipacija i sedacija). Neophodna je edukacija bolesnika i obitelji, radi dobivanja adekvatnih informacija o boli i njenoj terapiji, kako bi bolesnik mogao preuzeti aktivnu ulogu u liječenju. Ključna je psihosocijalna potpora, optimizacija nefarmakoloških metoda liječenja, te kontinuirana i uporna reevaluacija boli i učinka terapije što pridonosi kvaliteti života onkološkog bolesnika.

USE OF OPIOID ANALGETICS IN PAIN MANAGEMENT IN CANCER PATIENTS

LINARIĆ P.[1]

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

In 2019, over 25 000 cases of malignant tumors have been diagnosed in Croatia. Pain is one of the most common reasons patients seek medical care before the diagnosis of malignant disease and it is considered that 25–50% of patients experience pain in the moment of diagnosis. Frequency and intensity of pain depend on cancer site and clinical stage of the disease. At the advanced stage of the disease as many as 75–90% of patients experience pain and, according to available literature data, more than 40% of them do not receive satisfactory analgesic therapy. In cancer patients pain is produced by tumor mass growth and cell proliferation, as well as by neurotoxic chemotherapy, radiation therapy or surgical procedures. Cancer pain is defined as chronic pain considering duration and unremovable cause of symptoms. Inadequate pain management could have significant negative impact on patients' physical, emotional, social and spiritual aspects of life, especially in terms of metastatic disease, as well as negative impact on overall treatment outcome and patients' quality of life. Pain management requires multidisciplinary and polimodal approach. Although chemotherapy and radiotherapy induced tumor mass reduction could alleviate pain, pharmacotherapy is the backbone of pain management. Despite other available pain relief medications, opioid analgesics are most important in cancer pain treatment. Opioid is any substance that binds to opiod receptors, which are mainly located in central nervous and gastrointestinal system, producing the analgesic effect, in addition to side effects including respiratory depression, sedation, addiction, nausea, emesis, opstipation and urine retention. According to WHO three-step analgesic ladder, weak opioids (tramadol, codein) are used in moderate pain management – VAS (visual analogue scale) 6–7, while strong opioids are „the gold standard" for severe pain (VAS 8–10). In most patients, oral intake is preferred because of simplicity and efficacy, but transdermal, subcutaneous and intravenous approach are used in cases where oral intake is not feasible. Following available treatment algorithms is one of the crucial factors for achieving optimal results, along with opioid analgesic choice and titration, opioid rotation and equivalent dose calculation. Implementing preventive measures and early recognition and management of most important side effects (such as nausea, opstipation and sedation) is equally important. Education of patients and familiy members is necessary for obtaining adequate information about pain and its treatment, so the patient could take more active role in pain relief management process. Psychosocial support is essential, as well as introducing non-pharmacological treatment methods, along with continuous and persistent pain and treatment efficacy reevaluation, which overall improves cancer patient's quality of life.

ONKOLOŠKA BOLESNICA S KOMPLEKSNIM BOLNIM SINDROMOM

TOMEK HAMZIĆ D.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
doratomek@icloud.com

Uvod: Onkološki bolesnici često trpe bol. Uzroci mogu biti različiti i zbog toga se i različito prezentiraju i liječe. Često je iznimno teško adekvatno kupirati bol u onkološkog bolesnika. To potvrđuje i činjenica da se u uznapredovalim stadijima bolesti čak i do 90% onkoloških bolesnika žali na neki oblik boli. Ovdje prikazujem slučaj onkološke bolesnice s metastatskim karcinomom dojke koji infiltrira cijelu prsnu stijenku, te uzrokuje teški kompleksni regionalni bolni sindrom koji nismo uspjeli kupirati ni sa više linija analgetika.

Prikaz slučaja: Pedesetogodišnja bolesnica se javila onkologu s već izrazito uznapredovalim i egzulceriranim karcinomom desne dojke. Tada je već imala parezu desne ruke s jakim bolovima, a u terapiji je imala nesteroidni antireumatik i transdermalni opijatni naljepak koji smo povisili do maksimalne doze. Započela je liječenje prvom linijom za metastatsku bolest, na što je i dobro odgovorila. Tijekom liječenja opijatni analgetik je nekoliko puta zamijenjen. Redovito je provođena fizikalna terapija pa je uspjela djelomično vratiti funkciju ruke, no bolove je i dalje imala. Obzirom na neuropatski karakter boli u terapiju je uveden pregabalin do maksimalne doze, bez učinka. Nakon toga je uzimala i gabapentin, također bez učinka. Sada se bolesnica i dalje liječi drugom linijom za metastatski karcinom dojke, uglavnom se žali na stalne bolove koje kratkotrajno može kupirati opijatima.

Zaključak: Bolni sindrom u onkološkog bolesnika je iznimno teško kupirati, pogotovo ako je neuropatskog karaktera. Kada farmakološke metode liječenja nisu dostatne, bilo bi potrebno nefarmakološke i intervencijske metode liječenja boli učiniti dostupnijima za naše bolesnike.

CANCER PATIENT WITH COMPLEX PAIN SYNDROME

TOMEK HAMZIĆ D.[1]

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

Introduction: Cancer patients commonly experience pain. Causes can be different and therefore they are treated differently. It is often extremely difficult to adequately relieve pain in an oncology patient. This confirms the fact that, in advanced stages of the disease, even up to 90% of cancer patients feel pain. Here I will present a patient with metastatic breast cancer and complex regional pain syndrome resistant to multiple lines of analgetic therapy.

Case report: A 50-year-old patient, otherwise healthy, presented to the oncologist with extremely advanced and ulcerated carcinoma of the right breast. She already had paresis of the right hand with severe pain and edema. She was taking NSAID and had a transdermal opiate patch, in maximum doses. She started first-line treatment for metastatic breast cancer, with good response. During treatment, the opiates were changed several times. With regular physical therapy function of her right hand was partially restored, but the pain was persistent. Because of neuropathic pain, pregabalin was prescribed, without effect even in maximum dose. Then gabapentin was prescribed, also without effect. Now the patient is still treated with second-line treatment for metastatic breast cancer, she complains of constant pain that is only temporarily relieved with opiate analgesics.

Conclusion: Pain syndrome in cancer patient is extremely difficult to treat. When pharmacological methods of treatment are not sufficient, it would be necessary to make non-pharmacological and interventional methods of pain treatment more accessible to our patients.

SEKCIJA MEZENHIMALNIH I KOŽNIH MALIGNIH TUMORA / MESENCHIMAL AND SKIN CANCERS SESSION

NAGLASCI IZ KONGRESA AMERIČKOG DRUŠTVA ZA KLINIČKU ONKOLOGIJU (ASCO) I EUROPSKOG DRUŠTVA ZA INTERNISTIČKU ONKOLOGIJU (ESMO) 2022. GODINE ZA SARKOME I MELANOM

HERCEG D.[1,2]

[1] Sveučilište u Zagrebu
• *Stomatološki fakultet*
[2] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
davorinh1@gmail.com

Kod odabira najvažnijih radova s kongresa kriterij može biti utjecaj na sadašnju kliničku praksu, novi dosad nepoznati mehanizam djelovanja ispitivanog lijeka, studija faze tri itd. ili kombinacija navedenih. Ovdje su odabrani radovi, koji su i prema ocjeni organizatora kongresa ASCO 2022. ESMO 2022. izabrani u naglaske kongresa.

Za sarkome su odbrana pet rada: prvi je klinička studija faze III, koja ispituje lijek nirogacestat kod dezmoida s novim mehanizmom na temelju ihibicije *Notch* puta-gama sekretaze; rezultati efikasnosti i toksičnosti omogućit će vjerojatnu skoru registraciju lijeka. U sljedećoj studiji faze III za Ewing sarkom potvrđuje se uloga ifosfamida u drugoj liniji liječenja. Nadopuna otprije poznate neoadjuvantne studije faze III STS 1001: histološki utemeljena kemoterapija u usporedbi sa standardnom kemoterapijom (epirubicina + ifosfamid) potvrđuje prethodne utvrđene prednosti standardne. Prikazuje se i jedna studija faze IB/II, koja ispituje kombinaciju ciljane terapije (lenvatiniba) i kemoterapije (eribulina) kod uznapredovalog liposarkoma i leiomiosarkoma; rezultati su bolji za kombinaciju nego historijski za eribulin. Spominje se i pilot-studija kod uznapredovalog sinovijalnog sarkoma s obećavajućim preliminarnim rezultatima, gdje se koristi inovativna TCR (*T-cell receptor*) adoptivna imunoterapija, koja koristi genetički modificirane autologne limfocite za TCR (T-stanični receptor), koji potom prepoznaje NY-ESO peptid prezentiran na tumoru pomoću HLA klase I molekula.

Za melanom odabrana su tri rada. Prvo su dvije adjuvantne studija, koje proširuju indikaciju liječenja; prva na visokorizični stadij II *(Keynote* 716, koja koristi pembrolizumab)a, druga *Immuned* studija koja širi indikaciju kombinacijske imunoterapije ipilimumab + nivolumab na stadij IV bez znakova bolesti (bolesnici s reseciranim metastazama); obje su studije faze III. Zadnja je studija faze III za uznapredovali melanom i kombinaciju relatrimaba (anti-LAG3 inhibitora) i nivolumaba (anti PD1 inhibitora) i osvježenje podataka nakon medijana praćenja 19.3 mjeseci; rezultati studije uvode jos jednu imunoterapijsku kombinaciju u liječenje uznapredovalog melanoma.

HIGHLITS FROM THE 2022. CONGRESSES OF THE AMERICAN OF CLINICAL ONCOLOGY AND THE EUROPEAN SOCIETY OF MEDICAL ONCOLOGY (ESMO) FOR SARCOMA AND MELANOMA

HERCEG D.[1,2]

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

When selecting the most important papers from the congresses, the criteria can be the impact on current clinical practice, a new hitherto unknown mechanism of action of the tested drug, a phase three study, etc., or a combination of the above. Here are selected posters, which according to the assessment of the organizers of the ASCO 2022 and ESMO 2022 congresses, were chosen as highlights.

Five papers were defended for sarcomas: the first is a phase III clinical study, which examines the drug nirogacestat in desmoid tumor with a new mechanism based on inhibition of the Notch/gamma secretase pathway;

the results of efficacy and toxicity will enable the likely registration of the drug soon. A further phase III study for Ewing sarcoma confirms the role of ifosfamide in second-line treatment. Supplement to the previously known phase III neoadjuvant study STS 1001: histology-tailored chemotherapy compared with standard chemotherapy (epirubicin + ifosfamide) confirms the previously established advantages of standard. One phase IB/II study is also presented, which examines the combination of targeted therapy (lenvatinib) and chemotherapy (eribulin) in advanced liposarcoma and leiomyosarcoma; the results are better for the combination than historically for eribulin. A pilot study in advanced synovial sarcoma with promising preliminary results is also mentioned, where the innovative TCR (T-cell receptor) adoptive immunotherapy is used, which uses genetically modified autologous lymphocytes for the TCR (T-cell receptor), which then recognizes the NY-ESO peptide on theh tumor, presented by a by a HLA class I molecules.

Three papers were selected for melanoma. The first are two adjuvant studies, which expand the treatment indication; the first to high-risk stage II (*Keynote* 716, which uses pembrolizumab), the second *Immuned study* expanding the indication of combination immunotherapy ipilimumab + nivolumab to stage IV with no evidence of disease -NED (patients with resected metastases); both are phase III studies. The latest is a phase III study for advanced melanoma and the combination of relatrimab (anti-LAG3 inhibitor) and nivolumab (anti PD1 inhibitor) and showed updated data after a median follow-up of 19.3 months; the results of the study introduce another immunotherapy combination in the treatment of advanced melanoma.

BOLESNICA SA STADIJEM III MELANOMA

MEĐUGORAC K.[1], Blažičević K.[1], Herceg D.[1], Simetić L.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
kmedjugorac@gmail.com

Uvod: Melanom stadija III odnosi se na bolest kod koje imamo lokoregionalno širenje, odnosno širenje u regionalne limfne čvorove i/ili neposrednu okolinu samog primarnog melanoma (satelitske i in-tranzit metastaze). Ovisno o debljini primarnog tumora, prisutnosti ulceracije te broju zahvaćenih limfnih čvorova govorimo o stadijima IIIA, IIIB, IIIC te IIID. Kod melanoma stadija III postoji visoki rizik za povrat i udaljenu diseminaciju bolesti no pojavom adjuvantnih terapijskih opcija taj rizik je značajno smanjen.

Prikaz slučaja: Prikazati ćemo bolesnicu stadija IIIA, kojoj je u ožujku 2021. učinjena ekscizija kožne promjene na prednjoj stijenci gornjeg dijela abdomena lijevo te je patohistološki nalaz pokazao da se radi o melanomu, pT2a. U lipnju je učinjena reekscizija i sentinel biopsija, te je od ukupno 3 odstranjena limfna čvora u jednom čvoru iz lijeve aksile potvrđena metastaza melanoma, veličine 1,5 mm, bez proboja kapsule. U rujnu 2021. je učinjen PET CT po kojem nije nađeno znakova diseminacije bolesti drugdje u tijelu, pratile su se žarišne lezije u jetri, poznate od ranije (karakteristika hemangioma). Učinjeno je *BRAF* testiranje iz metastaze u limfni čvor u kojem je nađena mutacija u kodonu 600 gena BRAF (V600E/E2/D). Odlukom Multidisciplinarnog tima za melanome, u studenom 2021. započeto je adjuvantno liječenje BRAF+MEK inhibitorima. Bolesnica je do sada 10 mjeseci na terapiji dabrafenibom uz trametinib, a liječenje cijelo vrijeme podnosi bez neželjenih učinaka. Dosadašnjom slikovnom i laboratorijskom reevalucijom bez znakova povrata bolesti i udaljene diseminacije. Sljedeća reevalucija planirana je u studenom 2022., kada je planiran i dovršetak adjuvantnog liječenja.

Zaključak: Pojavom adjuvantnih opcija za liječenje stadija III melanoma značajno su se unaprijedili dugoročni ishodi kod bolesnika uz prihvatljivu toksičnost same terapije. Odluke o primjeni adjuvantne terapije trebale bi se donositi individualiziranim pristupom, putem multidisciplinarnog tima za melanome, a uvažavajući želje svakog bolesnika.

PATIENT WITH STAGE III MELANOMA

MEĐUGORAC K.[1], Blažičević K.[1], Herceg D.[1], Simetić L.[1]

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

Introduction: Melanoma stage III is a type of malignant melanoma which has spread to locoregional lymph nodes and/or surrounding tissue of a primary tumor (satellite and in-transit metastases).

Depending on the tumor thickness, ulceration of the tumor and number of infiltrated lymph nodes, there are four types of melanoma stage III – IIIA, IIIB, IIIC and IIID. In melanoma stage III there is a high risk of relapse or distant dissemination of disease, but, with new adjuvant therapy lines, the risk is significantly reduced.

Case report: We present a female patient with melanoma stage IIIA. In March 2021, an excision of a skin discoloration of the upper part of anterior left abdominal wall was performed, and pathohistological result showed that reexced material is a malignant melanoma, pT2a. Reexcision and sentinel biopsy of three lymph nodes was performed in June 2021, and metastasis of melanoma was found in one of the lymph nodes from left axilla, size 1.5 mm, without breakthrough capsule. PET CT scan was done in September 2021, and there were no signs of distant dissemination.

It showed numerous focal liver lesions, probably hemangiomas, known from before. BRAF testing was also done from the lymph node metastasis, and mutation in codon 600 gene BRAF (V600E/E2/D) was found. In November 2021, patient started therapy with BRAF+MEK inhibitors. Till now, she received the therapy with daBRAFenib and trametinib through 10 months, and she does not have any side effects of applied therapy. So far, imaging and laboratory reevaluation tests did not show signs of relapse or distant dissemination. The next reevaluation is planned for November 2022, when the end of the adjuvant therapy is also planned.

Conclusion: With new adjuvant therapy lines for stage III melanoma, long-term outcomes are significantly improved, with acceptable toxicity of the applied therapy. Decisions about the use of therapy require an individualized approach, and should be disccussed on a Multidisciplinary team, with respect for each patient wishes.

PRIKAZ BOLESNIKA S RETROPERITONEALNIM SARKOMOM

BLAŽIČEVIĆ K.[1], Simetić L.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
kblazice@gmail.com

Uvod: Retroperitonealni sarkomi relativno su rijetki tumori, čine oko 10–15% svih mekotkivnih sarkoma. Najčešći podtipovi su liposarkomi, lejomiosarkomi te nešto rjeđe nediferencirani pleomorfni sarkomi. Imaju lošiju prognozu od mekotkivnih sarkoma udova.

Kompletna kirurška resekcija uz negativne rubove temelj je liječenja retroperitonealnih sarkoma i jedini kurativni modalitet liječenja.

Uz kirurško liječenje, uloga dodatne terapije u vidu kemoterapije i zračenja (bilo kao prijeoperacijski ili poslijeoperacijski) nije jasno definirana.

Prikaz slučaja: Bolesnik u dobi 62 godine obrađen je početkom 2019. godine zbog bolova u desnoj nozi. Učinjenim MSCT-om trbuha verificirana je retroperitonealna tvorba, paravertebralno desno, dužine oko 7.8cm, neodvojiva od zajedničkih ilijačnih žila, ali bez infiltracije istih. Učinjena je biopsija u ožujku 2019., a patohistološki nalaz ukazivao je na slabo diferencirani (pleomorfni) sarkom visokog gradusa (FNCLCC gradus 3). Na multidisciplinarnom timu za sarkome odlučeno je započeti neoadjuvantno liječenje kemoradioterapijom. Od travnja do srpnja 2019. godine provedeno je ukupno 3 ciklusa kemoterapije (AI protokol) te zračenje (50.4Gy u 28 frakcija). Kontrolna radiološka obrada pokazala ja regresivnu dinamiku tumora. Operiran je u rujnu 2019., a patohistološki nalaz ukazivao je na kompletni odgovor na terapiju. Nastavljeno je redovito onkološko praćenje. Zadnja kontrolna obrada u lipnju 2022. godine nije ukazivala na recidiv niti na diseminaciju bolesti.

Zaključak: S obzirom na relativno nisku učestalost retroperitonealnih sarkoma te kompleksnost pristupa i odabira terapijskih modaliteta, dijagnostika i liječenje bi se trebala provoditi u visoko specijaliziranim centrima za sarkomsku problematiku te bi se odluke trebale donositi putem multidisciplinarnih timova.

TREATMENT OF RETROPERITONEAL SARCOMA – A CASE REPORT

BLAŽIČEVIĆ K.[1], Simetić L.[1]

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

Introduction: Retroperitoneal sarcomas are relatively rare tumors, accounting for about 10–15% of all soft tissue sarcomas. The most common subtypes are liposarcomas, leiomyosarcomas and undifferentiated pleomorphic sarcomas. They tend to have worse outcomes than soft tissue sarcomas arising in the extremities. Complete surgical resection with negative margins is the cornerstone of retroperitoneal sarcoma treatment and the only curative treatment modality.In addition to surgical treatment, the role of additional therapy in the form of chemotherapy and radiation therapy (either preoperatively or postoperatively) is not clearly defined.

Case report: A 62-year-old patient was admitted to the hospital at the beginning of 2019 for workup due to right leg pain. MSCT of the abdomen showed a retroperitoneal tumor, about 7.8 cm long, inseparable from the common iliac vessels, but without infiltration. A CT-guided biopsy was performed in March 2019, and the pathohistological findings indicated a poorly differentiated (pleomorphic) high-grade sarcoma (FNCLCC grade 3). Case wes presented within multidisciplinary sarcoma board and it was decided to start neoadjuvant treatment with chemoradiotherapy. From April to July 2019, a total of 3 cycles of chemotherapy (AI protocol) were carried out. Also, radiotherapy was performed during May and June. Reevaluation MSCT after chemoradiotherapy showed regressive dynamics of retroperitoneal tumor. Surgery was performed in September 2019, and the pathohistological findings showed a complete response (no viable tumor cells). Oncological surveillance was continued with regular follow-up visits with imaging. Last reevaluation imaging in June 2022 showed no signs of disease recurrence or dissemination.

Conclusion: Considering relatively low frequency of retroperitoneal sarcomas and the complexity of their treatment, diagnosis and therapeutic modalities should be carried out in highly specialized sarcoma centers and decisions should be made by multidisciplinary sarcoma board.

PRIKAZ BOLESNIKA SA SARKOMOM GLAVE I VRATA

SIMETIĆ L.[1], Jurlina M.[2]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Klinička bolnica Dubrava
• *Klinika za maksilofacijalnu kirurgiju*
luka.doc@gmail.com

Uvod: Liječenje mekotkivnih sarkoma predstavlja veliki izazov. Poznato je više od 100 podtipova mekotkivnih sarkoma (eng. *soft tissue sarcoma* – STS). Liječenje je potrebno provoditi u centrima s velikim iskustvom, koji imaju multidisciplinarne timove sa svim potrebnim specijalistima: patolog, onkolog, kirurg, radiolog, kirurg glave i vrata, specijalisti nuklearne medicine i brojni drugi. Sarkomi glave i vrata izrazito su rijetki entiteti. Predstavljaju dodatni izazov zbog lokacije na kojoj se javljaju, rane simptomatologije, zahtjevne kirurgije i potencijalne mutilacije te blizine centralnog živčanog sustava.

Prikaz slučaja: Prikazat ćemo slučaj mladog bolesnika rođenog 1994. godine sa sarkomom glave i vrata koji je liječen u našoj klinici na KBC-u Zagreb. Bolesnik se prezentirao tumorskom masom u području mastikatorne regije glave i vrata. Učinjena je radiološka obrada i biopsija tvorbe. PHD analizom verificiran je rabdomiosarkom. Nakon biopsije započeto je liječenje neoadjuvantnom kemoterapijom – inicijalno VAI protokol potom VIDE. Nakon kemoterapije učinjena je resekcija primarnog tumora te nekoliko revizijskih i rekonstruktivnih operacija. Postoperativno je provedeno 3D konformalno zračenje primarnog ležišta tumora. Zbog progresije bolesti nakon zračenja nastavljeno je sistemsko liječenje kemoterapijom po temozolamid+ irinotekan protokolu i potom topotekan+ ciklofosfamid. Od studenog 2021.godine bolesnik je u palijativnom zbrinjavanju. Umire u terminalnoj fazi maligne bolesti u veljači 2022. godine.

Zaključak: Liječenja sarkoma glave i vrata predstavlja veliki izazov za kliničare. Potrebno je liječenje provoditi u centrima velikog volumena kojima imaju multidisciplinarne timove specijalizirane u liječenju mekotkivnih sarkoma.

CASE REPORT – PATIENT WITH HEAD AND NECK SARCOMA

SIMETIĆ L.[1], Jurlina M.[2]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
[2] Clinical hospital Dubrava
• *Department of Maxilofacial Surgery*

Introduction: Soft tissue sarcoma treatment is very challenging. Soft tissue sarcoma represent a group of more than 100 subtypes. Treatment should be organized in high volume centers with experienced multidisciplinary teams with pathologist, oncologist, surgeon, radiologist, head and neck surgeon, nuclear medicine specialist and many others. Head and neck STS are very rare entities. Due to localization, early symptoms, difficult surgery and possible mutilation and near brain area they represent one of the hardest localization for multimodality treatment.

Case report: Case report-young patient born in 1994. who was treated in our hospital – UHC Zagreb. He presented with palpable tumor mass in masticatory region of head and neck. CT scan, MRI and biopsy were done in our center. Histopathology showed rhabdomyosarcoma, a subtype of STS. Neoadjuvant chemotherapy started with VAI protocol than continued with VIDE. Extensive operation was performed with two revisions and reconstructions subsequently. Postoperative 3D radiotherapy was apllied to the primary site. Due to early progression we continued systemic treatment with temozolamid+irinotecan and then with topotecan+cyclophosphamide. From November 2021. BSC strategy was recommended. Patient died in February 2022.

Conclusion: The treatment of head and neck STS is very challenging. It is mandatory to organize all steps of multimodality treatment in high volume centers with experienced MDT.

SEKCIJA POTPORNO LIJEČENJE I PALIJATIVNA SKRB / SUPPORTIVE AND PALLIATIVE CARE SESSION

IMUNONUTRICIJA – KLJUČAN SAVEZNIK IMUNOTERAPIJE?

VUČINIĆ D.[1], Dobrila-Dintinjana R.[1]

[1] Klinički bolnički centar Rijeka
• *Klinika za radioterapiju i onkologiju*
damir.vucinic@gmail.com

U eri imunoterapije više nego ikada je jasno kako imunološki sustav igra ključnu ulogu u borbi protiv tumora. Onkološki pacijenti imaju veći rizik od pothranjenosti zbog smanjenog unosa hrane kao i patofizioloških događanja povezanih s bolešću, kao što su povećani mišićni katabolizam i kronična upala, što zajedno pogoršava njihov nutritivni status. Jedan od mehanizama kojim tumor ubrzava svoj rast i teži metastaziranju je imunološki „bijeg“ tumora. Izbjegavanje imunološkog susstava djeluje kroz dva glavna mehanizma. Prvi je moduliranje tumorskog mikrookruženja kojeg predstavljaju stromalne stanice, fibroblasti, masne stanice, vaskularne endotelne stanice, imunološke stanice (tzv. TIL) i makrofagi povezani s tumorom. Imunosupresija izazvana tumorom potiče imunosupresivne stanice da se nakupljaju oko tumora. Proizvodnjom imunosupresivnih čimbenika tumor inaktivira citotoksične CD-8 pozitivne T limfocite. Navedenim događanjima dolazi do predominacije drugih stanica kao što su regulatorne T stanice (Treg stanice), dendritične stanice (DCs), i M2 makrofagi. Drugi mehanizam imunosupresije uključuje pokretanje signalnih puteva odnosno ekspresiju imunosupresivnih molekula ili njihovih receptora, uključujući receptor programirane stanične smrti i njegov ligand (PD-1/PD-L1). Taj sustav može inhibirati aktivaciju efektorskih T limfocita, što u konačnici dovodi do kompletne inhibicije imunološkog odgovora na tumor

Ovaj izazov naveo je autore da analiziraju može li imunonutricija utjecati na imunološki sustav i time pomoći u poboljšanju imunološkog statusa, modulirati stečeni imunološki odgovor, smanjiti toksičnost liječenja i poboljš-

šati rezultate pacijenata. Imunonutricija se može definirati kao modulacija aktivnosti imunološkog sustava i to aktivacijom imunološkog sustava hranjivim tvarima u količinama većim od onih koje se obično susreću u prehrani. Imunonutrijenti koji se spominju u istraživanjima su: omega-3 masne kiseline, glutamin, arginin, β-hidroksi-β-metilbutirat (HMB), aminokiseline razgranatog lanca i nukleotidi.

Važna meta-analiza sugerira da je enteralna imunonutricija (EIN) učinkovito povećala razinu IgA, IgG, IgM, CD4þ, CD3þ, CD4þ/CD8þ omjer i broj NK stanica, poboljšavajući prehrambeni i imunološki status bolesnika s rakom želuca koji su podvrgnuti gastrektomija. Aida i sur. pokazali su da je prehrana s dodatkom arginina i omega-3 masnih kiselina uspješno modulirala diferencijaciju Th1/Th2 i proizvodnju IFN-g potičujući obranu domaćina. HMB je poboljšao imunološki odgovor kod karcinoma gušterače, pojačavajući učinak citotoksične kemoterapije i imunoterapije. HMB-inducirana supresija rasta tumora izazvanog pretilošću mogla bi doprijeniti boljim rezultatima liječenja kemoimunoterapjiom u karcinomu gušterače.

Zaključak: Bolje razumijevanje utjecaja imunonutricije na sudbinu raka ukazati će na nove terapijske mogućnosti. Zaključno, u bliskoj budućnosti mogli bi potencijalno identificirati podskupinu tumora koji bolje reagiraju na imunoterapiju i koristiti imunonutriciju kao ključan saveznik u imunoterapiji.

IMMUNONUTRITION – KEY PARTNER IN IMMUNOTHERAPY?

VUČINIĆ D.[1], Dobrila-Dintinjana R.[1]

[1] University Hospital Centre Rijeka
• *Department of Radiotherapy and Oncology*
damir.vucinic@gmail.com

Immunotherapy has demonstrated that the immune system is crucial in the fight against cancer. Oncological patients have a higher risk of malnutrition because of reduced food intake as well as disease-related pathologies such as increased muscular catabolism and chronic inflammation, which may aggravate their nutritional status. One of the mechanisms by which a neoplasm could grow and metastasize is the tumour immune escape by avoiding recognition and attack from the immune system. The tumour immune escape acts through two main mechanisms. The first is by modulating the tumour microenvironment represented by stromal cells, fibroblasts, fat cells, vascular endothelial cells, immune cells (the so-called TILs) and tumour-associated macrophages. Tumour-induced immunosuppression prompts immunosuppressive cells to accumulate around the tumour and secreted immunosuppressive factors, which inactivate cytolytic CD-8 positive T lymphocytes in order to decrease the immune tolerance of tumour cells, such as regulatory T cells (T reg cells), dendritic cells (DCs), and M2 macrophages. The second mechanism of immunosuppression involves induction of the immunosuppressive molecules or their receptors, including programmed death-ligand 1/programmed death-1 (PDL1/PD-1) which can inhibit the activation of effector T lymphocytes, ultimately leading to tumour immune escape.

This challenge has led researchers to analyze whether the immune influencing capacity of immunonutrition may aid in improving immune status, modulate the acquired immune response, decrease the treatment toxicity and improve patient outcomes. Immunonutrition can be defined as modulation of either the immune system activity or modulation of the consequences of activation of the immune system by nutrients or specific food items fed in amounts above those typically encountered in the diet. Immunonutrients identified and studied are omega-3 fatty acids, glutamine, arginine, β-Hydroxy-β-Methylbutyrate (HMB), branched-chain amino acids, and nucleotides.

An important meta-analysis suggests that enteral immunonutrition (EIN) effectively increased the level of IgA, IgG, IgM, CD4þ, CD3þ, CD4þ/CD8þ ratio, and the count of NK cells, improving the nutritional and immunological status of gastric cancer patients undergoing gastrectomy. Aida et al. demonstrated that immunonutrition with arginine and omega-3 fatty acid supplementation might modulate Th1/Th2 differentiation and IFN-g production inciting host defence against pathogens. HMB enhanced immune surveillance in pancreatic cancer, augmenting both cytotoxic chemotherapy and immunotherapy. HMB-induced suppression of obesity driven tumor growth, and promotion of immune surveillance may provide extend the therapeutic index of both chemotherapies and immunotherapies.

Conclusion: A better understanding of the impact of immune nutrition on cancer destiny may open new therapeutic options. In fact, in the near future, we could potentially identify the subgroup of tumours that are more responsive to immunotherapy and use immunonutrition as an enhancer of the therapies already included in the usual guidelines as chemotherapy or surgery.

THE ROLE OF PALLIATIVE MEDICINE SPECIALIST IN THE ERA OF MULTIDISCIPLINARY APPROACH IN MALIGNANT TREATMENT

KOVAČEVIĆ T.[1,2]

[1] University Of Novi Sad
• *School of Medicine*
[2] Institute for Pulmonary Diseases of Vojvodina
• *Department for Thoracic Oncology*
tomi.kovacevic@mf.uns.ac.rs

Necessity of personalized approach in decision of the treatment modality in person with diagnosed malignancy is unbeatable fact. Development of new onco-specific therapeutic options in a few last decades is increased an taking into account the number of new researches oncology is one of the medical branches in which the progress will be seen in the future. This is undoubtedly benefit for the patients but did we forget to treat the whole person or we treat just the disease?

Holistic approach to ill person is an essence of palliative care. Observing not only physical but also psychosocial and spiritual aspect of one's life should be an imperative in all medical branches, especially in oncology treating the patients diagnosed with unhealable diseases trying to live their life with all their doubts, fears and coping with dying. From all of above conclusion can be that all medical staff involved in the care of patient with malignancy should be able to provide palliative care. Then, is the palliative medicine specialist needed at all and what should be his/her role in multidisciplinary approach in malignant treatment?Common opinion is that palliative care is reserved for end-of-life period when all other therapeutic options are exhausted. Goal of palliative care is to provide the best QoL not only at the EoL but during whole disease trajectory and to be introduced and integrated since the beginning of the disease – since first diagnosis. Providing support to all other specialties synchronously in order to provide the support for patient in specific treatment (surgical, oncological, radiological), and in case of impossibility of applying treatment with curative intent, in the terminal stages of life, helping to the patient and to his family to go through that period with as little suffering as possible, that is, enabling the so-called "good death" is the task of palliative care. After the death, the palliative care specialist stays with the family during the period of bereavement, in order to answer to all remain questions that affect their health. This approach represents the specificity of palliative medicine, and each specific approach requires specific knowledge.Basic "palliative knowledge" is needed (required) for all medical staff and education in this field is mandatory in most European countries as part of the curriculum of basic studies. For the vulnerable patients groups suffering from incurable diseases, it is necessary to apply specific palliative knowledge and skills and integrate it to all other medical specialties. When to apply specialized and when basic skills of palliative care depends on the needs of the patient.

"A patient is not just a set of symptoms but a whole life story" is the quote which, perhaps, describes the necessity of comprehensive care. Palliative care is focused not only on the patient but as well on his family. Thanks to the modern era and new modalities of oncological treatment, life with a malignant disease is much longer compared to just 10 years ago. However, the patient with incurable diagnosis will enter to a period during disease trajectory when it is not possible to apply specific therapeutic options. Unfortunately it often happens that a patient with a malignant disease without the possibility of specific treatment does not have access to specialists who have treated him. Palliative care due to all specificities should be carried out by someone with specialized knowledge, by someone whom patient already know and trust.

Traditionally, palliative care is provided at home by a family doctor or general practitioner. In cases where the patient's complaints are moderate or severe (complex), basic knowledge in the field of palliative care is not enough, and consultation at a "higher level" is necessary. This also applies to the patients in need of palliative care during hospitalization. The importance and role of specific knowledge and skills in palliative care in the era of modern medicine is a necessity in order to provide multidisciplinary approach and provide dignity until death that every person deserves. This multidisciplinary approach should be implemented by professionals who, with their various knowledge and skills, help the patient and their family to live their lives with as little discomfort providing the best possible QoL. The palliative medicine specialist, with his role and approach, can represent a reliable partner to other health workers and associates, as well as confident associate to the patient who will be adequately cared not only for physical but also for all other aspects during the entire duration of the illness, and to patients family as an important companion during the planning of comprehensive care and in preparation for the inevitable.

BEST OF MASCC 2022

KUKEC I.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
ivana.kukec.md@gmail.com

Ovogodišnji MASCC kongres održan je u Torontu, Kanadi od 23–25.6.2022.Prilikom ceremonije otvaranja prof. Maryam Lustberg predsjednica društva podsjetila je na misiju cijelog udruženja a to je poboljšati suportivnu skrb kod oboljelih s rakom od trenutka dijagnoze, kroz fazu liječenja raka, preživljenja raka i skrbi na kraju života. Vizija je da udruženje postane vodeći izvor znanja iz područja onkološkog suportivnog liječenja. Suportivno i palijativno liječenje nije izdvojeno područje koje tek tako treba uključiti, nego je ono dio holističkog pristupa onkološkom bolesniku.

COVID 19 je značajno utjecao na liječenje raka. Pridonijeo je još brojnijim gubicima, ograničio je posjete, uzrokovao izolaciju, smanjio dostupnost skrbi, doveo do prioritizacije i razvoja novih digitalnih načina pružanja skrbi.

Psihologinja Fay Hlubocky govorila je o pojavi i definiciji sindroma izgaranja. Frances Boyle je prezentirala kako se sindrom izgaranja može prevenirati jednostavnim mjerama po preporukama Australske istraživačke grupe. U sekciji o antiemeticima bilo je govora o preporukama za liječenje kemoterapijom uzrokovane mučnine i povraćanja, te dostupnosti antiemetika. Za izdvojiti je multicentrično, randomizirano, dvostruko-slijepo, placebo-kontrolirano istraživanje o upotrebi suplemenata đumbira kod kemoterapijski naivnih pacijenata (103) koji su primali umjereno ili visoko emetogenu terapiju. Rezultati su pokazali da je incidencija, težina osobito odgođene mučnine i povraćanja u korist suplemenata đumbira. Također kvaliteta života, umor i nutritivni status su bili značajno poboljšani uz đumbir.

Zanimljivo je bilo i istraživanje o intermitentnom gladovanju. Kleckner i suradnici su dokazali da intermitentno gladovanje više od 10 sati smanjuje umor u ljudi koji su preživjeli rak. Umor povezan s rakom i/ili liječenjem je ekstremno čest, te može potrajati godinama nakon liječenja raka. Ima negativan učinak na kvalitetu života. U ovoj intervencijskoj studiji sudjelovalo je 39 bolesnika koji su preživjeli rak (6 žena, 35 preboljelo rak dojke). Kroz 14 dana pacijentima je bilo dozvoljeno da jedu od 8–18 sati, vodili su dnevnik spavanja, jela i ispunjavali su upitinik o umoru (FACIT-F). 90.1% pacijent je izdržao navedeni režim hranjenja i gladovanja, a 92.9% ih je završilo studiju. Autori navode poboljšanje statusa umora temeljeno na FACIT-F score ($p>0.001$) nakon 14 dana intermitentnog gladovanja. Što se tiče drugih parametara bolesnici su izguili prosječno 0.5 kg (+/–1.2).

U sekciji o infekcijama i raku za izdvojiti je Kanadsko istraživanje farmaceuta o liječenju febrilne neutropenije. Bolnički farmaceuti su bili uključeni u 93% sluačjeva kao dio multidisciplinarnog bolničkog tima. U 60% slučajeva korišten je specifični protokol za liječenje febrilne neutropenije. Ako postoji lokalni protokol, prvi izbor empirijske antibiotske terapije je bio piperacilin s tazobaktamom, zatim vankomicin, meropenem i ciprofloksacin. U odsustvu specifičnog protokola također je prvi izbor bio piperacilin s tazobaktamom (42%), uz dodatak vankomicina (33%), meropenem i ceftazidim.

Što se tiče terapije boli bilo je nekoliko predavanja o buprenorfinu za bol uzrokovanu rakom. Buprenorfin ima unikatnu strukturu i veže se na različite receptore Mu, Delta, Kappa i ORL-1 (opioid receptor like-1). Zbog navedene unikatne strukture i činjenice da je "low efficacy ili partial" agonist za Mu receptore ima maksimalan učinak uz smanjenje neželjenih djelovanja kao što su respiratorna depresija (ima maksimalan učinak koji se ne može prijeći) i euforija (ima najmanje kognitivnih nuspojava od svih opioida) te time i smanjena mogućnost zlouporabe, manji je broj smrti od predoziranja. Buprenorfin je učinkovit u liječenju boli povezane s rakom, u liječenju neuropatske boli, pokriva širi spektar boli rad djelovanja na različite receptore. Ima manje konstipacije, ne djeluje na Oddijev sfinkter, nema imunosupresivno djelovanje, ne djeluje na endokrini sustav-ne uzrokuje hipogonadizam, ne uzrokuje produženje QTc intervala, siguran je u starijih, kod bubrežnog zatajenja i osoba na dijalizi. Ima blaže simptome sustezanja i manje ovisnosti.

Bilo je brojnih istraživanja o upotrebi digitalnih tehnologija za prijavljivanje i zbrinjavanje nuspojava liječenja. Osobito mi je zanimljiva bila studija provedena putem Facebooka o pozitivnom učinku suksma vyayama yoge kod artralgije uzrokovane aromataznim inhibitorima kod bolesnica s rakom dojke. Radi se o yogi koja opušta zglobove. Provedena je intervencijska studija putem tajne Facebook grupe. Bolesnice su provodile tretmane 4 tjedna i zabilježeno je značajno – 50% poboljšanje.

BEST OF MASCC 2022

KUKEC I.[1]

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

This year's MASCC congress was held in Toronto, Canada from June 23–25, 2022. During the opening ceremony, Prof. Maryam Lustberg, president of the society, reminded of the mission of the entire association, which is to improve supportive carefor cancer patients from the moment of diagnosis, through the phase of cancertreatment, cancer survival and end-of-life care. The vision for the association is to become a leading source of knowledge in the field ofoncological supportive treatment. Supportive and palliative treatment is not a separate area that just needs to be included, but it is part of a holistic approach to the oncology patient.

COVID 19 has had a significant impact on cancer treatment. It contributed to morelosses, limited visits, caused isolation, reduced the availability of care, led to the prioritization and development of new digital ways of providing care. Psychologist Fay Hlubocky spoke about the occurrence and definition of burnout syndrome.

Frances Boyle presented how burnout syndrome can be prevented by simple measures recommended by the Australian Research Group. The section on antiemetics discussed recommendations for the treatment of nauseaand vomiting caused by chemotherapy, and the availability of antiemetics. A noteworthy is multicenter, randomized, double-blind, placebo-controlled study on theuse of ginger supplements in chemotherapy-naïve patients (103) who receivedmoderately or highly emetogenic therapy. The results showed that the incidence, severity of delayed nausea and vomiting wasparticularly in favor of ginger supplements. Also quality of life, fatigue and nutritionalstatus were significantly improved with ginger.

The research on intermittent fasting was also interesting. Kleckner and colleagues haveshown that intermittent fasting for more than 10 hours reduces fatigue in cancersurvivors. Fatigue related to cancer and/or treatment is extremely common, and canpersist for years after cancer treatment. It has a negative effect on the quality of life. 39 cancer survivors participated in this intervention study (6 women, 35 breast cancersurvivors). For 14 days, patients were allowed to eat from 8:00 a.m. to 6:00 p.m., kept asleep diary, ate and filled out a fatigue questionnaire (FACIT-F). 90.1% of the patientsendured the stated feeding and fasting regime, and 92.9% of them completed the study. The authors report an improvement in fatigue status based on the FACIT-F score (p>0.001) after 14 days of intermittent fasting. As for other parameters, the patients lostan average of 0.5 kg (+/–1.2).

In the section on infections and cancer, the Canadian survey of pharmacists on thetreatment of febrile neutropenia is worth highlighting. Hospital pharmacists wereinvolved in 93% of cases as part of a multidisciplinary hospital team. In 60% of cases, aspecific protocol was used for the treatment of febrile neutropenia. If there is a localprotocol, the first choice of empiric antibiotic therapy was piperacillin with tazobactam,followed by vancomycin, meropenem, and ciprofloxacin. In the absence of a specificprotocol, the first choice was also piperacillin with tazobactam (42%), with the additionof vancomycin (33%), meropenem and ceftazidime.

Regarding pain therapy, there were several lectures on buprenorphine for cancer pain. Buprenorphine has a unique structure and binds to different receptors Mu, Delta, Kappaand ORL-1 (opioid receptor like-1). Due to the mentioned unique structure and the fact that it is a "low efficacy or partial"agonist for Mu receptors, it has a maximum effect while reduced unwanted effects suchas respiratory depression (it has a ceiling effect that cannot be exceeded) and euphoria (it has the least cognitive side effects of all opioids), and thus the possibility of abuse isreduced, the number of deaths from overdose is lower. Buprenorphine is effective in the treatment of cancer-related pain, in the treatment ofneuropathic pain, covers a wider spectrum of pain by acting on different receptors. It has less constipation, does not affect the sphincter of Oddi, does not have animmunosuppressive effect, does not affect the endocrine system – does not causehypogonadism, does not cause prolongation of the QTc interval, is safe in the elderly, inpatients with renal failure and people on dialysis. It has milder withdrawal symptomsand less dependence.

There has been a lot of research on the use of digital technologies to report andmanage treatment side effects.I was particularly interested in a study conducted via Facebook on the positive effect of suksma vyayama yoga in arthralgia caused by aromatase inhibitors in breast cancer patients. It is yoga that relaxes the joints. An intervention study was conducted through a secret Facebook group. The patients performed the treatments for 4 weeks and asignificant improvement of 50% was recorded.