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PRIKAZ SLUČAJA – VAŽNOST MULTIDISCIPLINARNOG TIMA (MDT) U ONKOLOGIJI

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Multidisciplinarnost u onkologiji predstavlja rad više stručnjaka u svrhu postizanja zajedničkog cilja, a to je uspješno liječenje raka. Kod bolesnika u dobi od 46 godina započeta je gastroenterološko/radiološka obrada zbog bolova u trbuhu. Učinjenom obradom prikažu viđen ascites, te paketi uvećanih limfonoda u području burze. Gastroskopski se prikaže neravnija sluznica želuca iz koje se uzmu multiple biospije za PHD, ali se u istima ne nađe tumorskog tkiva. Učinjen endoskopski ultrazvuk kojim se prikažu brojni uvećani limfni čvorovi uz glavu i trup gušterače, te uz trunkus celijakus iz kojih se uzme materijal za citološko/patohistološku dijagnozu. Cito/patološki nalaz odgovara metastatskom adenokarcinomu (tzv. stanice tipa prstena pečatnjaka), ali patolog iz ovog materijala ne može odrediti točnu lokalazaciju tumora. Bolesnik je potom hospitaliziran zbog opstruktivnog ikterusa koji je razriješen implantacijom bilijarne endoproteze. Za vrijeme hospitalizacije učinjen MSCT toraksa kojim se prikažu uvećani medijastinalni i hilarni limfni čvorovi uz sitne nodule po interlobijima obostrano – ddg. limfogeni rasap osnovne bolesti. MSCT trbuha i zdjelice uz aplikaciju gastrografina suspektan infiltrativno stenozirajući proces želuca. Bolesnik je potom prezentiran na MDT za tumore probavnog sustava te se donese odluka o ponavljanju EGD s biopsijom, HER2 testiranje i započimanje liječenja kemoterapijom po protokolu za metastatski karcinom želuca. Opetovanim biopsijama želuca patohistološki se ne nađe tumorskog tkiva. Pregled onkologa otkazan zbog ponovne hospitalizacije zbog pogoršanja bolova u trbuhu, te laboratoerijskih nalaza koji upućuju na akutnu renalnu insuficijenciju. Zbog daljnjeg pogoršanja bubrežne funkcije započeto je liječenje hemodijalizom. Obzirom na akutno renalno zatajenje i planiran kemoterapijski protokol koji sadrži platinski proizvod koji je izrazito nefrotoksičan u dogovoru s nefrologom učinjena je biopsija bubrega (pitanje reverzibilnosti bubrežne funkcije – bolesnik je kroz dulje vrijeme uzimao nekoliko različitih analgetskih pripravaka, te je bila sumnja na tubulointersticijki nefritis).Nalaz patologa KBC Zagreb: u području medule se na više mjesta vide, dijelom intravaskularno smješteni tumorski trombi, građeni od atipičnih epitelnih stanica, dijelom izgleda prstena pečatnjaka. Diferencijalno dijagnostički u obzir dolaze metastaze karcinoma želuca. Kod bolesnika se prati progresija bolova uz rapidno pogoršanje kliničkog stanja zbog čega se i ne uspije započeti specifično onkološko liječenje, te unatoč poduzetim simptomatsko/suportivnim mjerama nastupa smrtni ishod. Ovim prikazom želimo podsjetiti na važnost svake pojedine karike MDT u donošenju točne dijagnoze i odluke za liječenje.

CASE REPORT – THE IMPORTANCE OF MULTIDISCIPLINARY TEAM (MDT) IN ONCOLOGY

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Multidisciplinarity in oncology is the work of several professionals in order to achieve a common goal, which is the successful treatment of cancer. Gastroenterological and radiological diagnostics for abdominal pain was started in patients aged 46 years. The performed treatment shows ascites and packets of enlarged lymph nodes in the area of the omental bursa. Gastroscopically irregular gastric mucosa was described, from which multiple biopsies for PHD were taken, but no tumor tissue was found. Endoscopic ultrasound was performed, which showed numerous enlarged lymph nodes along the head and trunk of the pancreas, and along the celiac trunk, from which material for cytological and pathohistological diagnosis was taken. The cyto / pathological finding corresponded to metastatic adenocarcinoma (so-called signet ring cells), but a pathologist from this material could not determine the exact location of the tumor. The patient was then hospitalized for obstructive jaundice

which was resolved by implantation of a biliary endoprothesis. During hospitalization, a CT scan of the thorax was performed, which showed enlarged mediastinal and hilar lymph nodes with small nodules according to bilateral – differential diagnosis – lymphogenic disintegration of the underlying disease. CT scan of the abdomen and pelvis with the application of gastrografin showed suspected infiltrative stenotic process of the stomach. The patient was then presented on MDT for gastrointestinal tumors and the decision was to repeat EGDS with biopsy, HER2 testing, and initiation of chemotherapy treatment according to the protocol for metastatic gastric cancer. Repeated gastric biopsies did not reveal tumor tissue. Oncologist examination was canceled due to re-hospitalization because of worsening of abdominal pain, and laboratory tests showed acute renal failure. Due to the further deterioration of renal function, hemodialysis treatment was started. As a consequance of acute renal failure and planned chemotherapy protocol containing a platinum product that is highly nephrotoxic, a kidney biopsy was performed (the patient took several different pain killers for a long time, and tubulointerstitial nephritis was suspected). Pathohistological finding of the department of Zagreb University Hospital Center showed tumor thrombi in medulla, partly located intravascularly, consisting of atypical epithelial cells, partly in the appearance of a signet ring. Gastric cancer metastases were considered as differential diagnosis. The progression of pain was monitored in patient with a rapid deterioration of the clinical condition, so unfortunately was not possible to start specific oncological treatment, and despite the symptomatic and supportive care was taken, a fatal outcome occured. With this presentation, we wanted to emphasize the importance of each individual member of MDT in making an accurate diagnosis and treatment decisions.

PRIMJENA NEOADJUVANTNE KEMOTERAPIJE (NAK) U LIJEČENJU MIŠIĆNOINVAZIVNOG RAKA MOKRAĆNOG MJEHURA (MIRMM) – ISKUSTVO JEDNOG CENTRA

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Uvod: Na cisplatini bazirana NAK pokazuje apsolutnu dobrobit od 5% u petogodišnjemu sveukupnom preživljenju kod bolesnika s lokaliziranim MIRMM-om. Poznato je da unatoč ovim rezultatima NAK nije široko prihvaćena. Cilj naše studije je ispitati učinak i toksičnost NAK, te analizirati povezanost između imunohistokemijski (IHK) definiranih biomarkera na kliničke ishode.

Metode: Retrospektivno je evaluirana kohorta bolesnika s lokaliziranim MIRMM-om (cT2-4a, i /ili N+), koji su primili NAK u razdoblju od kolovoza 2017. do kolovoza 2021. Po završetku NAK, prije odluke o radikalnoj cistektomiji (RC), učinjena je radiološka re-evaluacija. Uz standardnu patohistološku analizu tumorskog tkiva, učinjena je IHK analiza koristeći panel protutijela prema Choi konsenzusu (Cancer Cell 2014).

Tablica 1. Kliničke karakteristike ispitanika i liječenja

	Broj	%
Ukupan broj ispitanika	32	
Dob (u godinama), medijan (IKR)	62 (48–73)	
Muškarci	21	65.6
Klinički stadij T:		
T2	13	40.6
T3	11	34.4
T4a	8	25
Klinički stadij N+	18	56.2
Kemoterapijski protokol:		
ddMVAC	25	78.1
GC	6	18.8
nije baziran na cisplatini*	1	3.1
Primili < 4 ciklusa NAK	12	37.5
≥gradus 3 nuspojava povezanih s NAK	8	25
Radikalna cistektomija	22	68.7
Patološki odgovor:		
pCR (ypT0)	6	27%
< ypT2N0	8	36%

Kratice: IKR = interkvartilni raspon, NAK = neoadjuvantna kemoterapija, dd, tj. *dose dense* = protokoli s većom gustoćom doze, MVAC = metotreksat, vinblastin, doksorubicin i cisplatin; GC = gemcitabin i cisplatin, pCR = potpuni patološki odgovor. * karboplatin/gemcitabin

Rezultati: 32 bolesnika su kompletirala NAK, a u trenutku analize u 2 bolesnika NAK je bila u tijeku (Tablica 1). Medijan trajanja NAK iznosio je 7 tjedana (raspon 3–19). U 22 bolesnika (68.7%) učinjena je RC, 2 su odbila RC, 3 su izgubljena iz praćenja, a u 5 bolesnika RC nije učinjena zbog diseminacije bolesti. Između 22

bolesnika koji su primili NAK i podvrgnuti su RC-u, kod 6 bolesnika (27%) zabilježen je potpuni patološki odgovor (pCR), dok je *down-staging* (<ypT2N0) postignut kod 8 bolesnika (36%). Prisustvo pCR-a povezano je s duljim preživljenjem u odnosu na bolesnike kod kojih nije postignut pCR (28 vs 16 mjeseci; HR 6.7, 95%CI 1.4–32.2, p=0.02). Čak 75% bolesnika nije ravilo nuspojave gr. ≥3, a nije zabilježen niti jedan smrtni slučaj povezan s NAK. Nakom medijana praćenja od 12 mjeseci (raspon 2–32), 12 bolesnika (60%) doživjelo je progresiju bolesti. Molekularni profil tumora definiran IHK nije bio ni prognostički ni prediktivno povezan s odgovorom na NAK.

Zaključak: Rezultati studije su potvrdili da je NAK izvediva u našim uvjetima, karakterizirana optimalnim trajanjem i prihvatljivom toksičnošću, a stope pCR prate rezultate iz randomiziranih studija. Potrebno je uložiti veći napor da bismo postigli optimalan vremenski raspon od završetka NAK do RC-a. Prava analiza povezanosti IHK definiranih biomarkera s kliničkim ishodima bit će moguća kad dosegnemo puni uzorak i dulje vrijeme praćenja. Komunikacija između članova multidisciplinarnog tima ključna je za odabir odgovarajućih bolesnika za ovaj modalitet liječenja.

NEOADJUVANT CHEMOTHERAPY (NAC) IN MUSCLE-INVASIVE BLADDER CANCER (MIBC): A RETROSPECTIVE SINGLE INSTITUTION ANALYSIS

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Introduction: Cisplatin-based NAC improves survival in localized MIBC. However, owing to the perception of a modest survival benefit and significant toxicity, the uptake of NAC has been slow. We reported our experience with systematic use of NAC in MIBC, in terms of efficacy, toxicity and pilot biomarker analysis.

Patients and methods: Data were collected retrospectively on patients (pts) with histologically confirmed clinical stage cT2–4a, and/or N+ MIBC who received NAC between August 2017 and August 2021. After NAC pts were re-staged radiologically and then assessed for radical cystectomy (RC). Toxicity was assessed using Common Toxicity Criteria version 4. Tumor specimens were retrospectively immunohistochemically assessed for molecular subtype (basal vs luminal).

Table 1. Patient and treatment-related characteristics

	Number	%
Total number of patients	32	
Mean age at diagnosis (years), range	62 (48–73)	
Male	21	65.6
Clinical T: T2 T3 T4a	 13 11 8	 40.6 34.4 25
Clinical N+	18	56.2
NAC regimen: ddMVAC GC Non-Cisplatin-based*	 25 6 1	 78.1 18.8 3.1
Received < 4 NAC cycles	12	37.5
≥grade 3 NAC-associated toxicity	8	25
Radical cystectomy	22	68.7
Pathological response: pCR (ypT0) < ypT2N0	 6 8	 27% 36%

Abbreviation: NAC = neoadjuvant chemotherapy, dd = dose-dense, MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin, GC = gemcitabine and cisplatin, pCR = *pathological complete response.* * carboplatin/gemcitabine

Results: 32 pts were identified, with two pts still under treatment (Table 1). Median duration of NAC was 7 weeks (range 3–19). Twenty-two pts (68.7%) underwent RC, 2 underwent bladder preservation therapy, and 3 were lost to follow-up (FU). Median time from last NAC cycle to RC was 18 weeks (range 8–74). In 5 pts (15.6%) disease progressed during NAC (3 developed distant metastases, and 2 progression of pelvic lymphadenopathy), and RC was not pursued.

The overall pathological complete response (pCR) was 27% while <ypT2N0 downstaging rate was 36%. ≥grade 3 NAC-associated toxicity was observed in 25% pts, with no treatment-related deaths. At the moment of data analysis, 20 pts were alive, with median FU of 12 months (range 2–32). Distant relapse was the most common recurrence pattern (N=10), and 2 pts had a local relapse. The 2 most frequently used salvage modalities were immunotherapy (N=8), and palliative pelvic radiotherapy (N=2). Pts who experienced pCR to NAC lived

longer compared to pts who did not achieve pCR (28 vs 16 months; HR 6.7, 95%CI 1.4–32.2, p=0.02). Basal and luminal subtyping were neither prognostic nor predictive of response to NAC.

Conclusions: NAC in our center was characterized with optimal duration, and acceptable toxicity. pCR rates were alike in published studies. However, more work is needed to streamline transition from NAC to timely RC. Also, longer FU is needed to assess real correlation of putative molecular subtypes and response to NAC and prognosis of MIBC. Altogether, multidisciplinary care is the key to wider adoption of NAC.

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USPOREDBA UČINKOVITOSTI IMUNOTERAPIJE I TIROZIN KINAZNIH INHIBITORA U DRUGOLINIJSKOM LIJEČENJU BOLESNIKA S UZNAPREDOVALIM RAKOM BUBREGA – ISKUSTVO JEDNOG CENTRA

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Uvod: Nemamo jasnih dokaza uspored/be učinkovitosti nivolumaba (Nivo) i tirozin kinaznih inhibitora (TKI) u drugolinijskom liječenju uznapredovalog raka bubrega (uRB), a nakon prethodnog neuspjeha na TKI rane generacije (sunitinib ili pazopanib). Cilj studije je prikazati naše rezultate i usporediti učinkovitost ove dvije klase lijekova (Nivo i TKI) u drugolinijskom liječenju uRB-a.

Metode: Iz naše prospektivno prikupljane baze podataka, retrospektivno smo analizirali podatke bolesnika s uRB-om koji su započeli drugolinijsko liječenje (Nivo od travnja 2018. do lipnja 2021., ili TKI prije travnja 2018.). Glavne mjere ishoda bili su ukupno preživljenje (OS) i preživljenje bez progresije bolesti (PFS), a sekundarne su stope objektivnog odgovora (ORR) i sigurnost primjene.

Rezultati: U istraživanje je uključeno ukupno 73 bolesnika (Tablica 1) koji su pro-

Tablica 1. Kliničke karakteristike ispitanika

	2. linija Nivo Broj (%)	2. linija TKI Broj (%)	*p*
Dob (u godinama), medijan (IKR)	60 (40–79)	74 (34–81)	0.30
Spol			0.33
M	29 (78.4)	29 (80.6)	
Ž	8 (21.6)	7 (19.4)	
ECOG			0.23
0	25 (67.6)	24 (66.7)	
1	12 (32.4)	10 (27.8)	
≥2	0 (0)	2 (5.5)	
Prethodno nefrektomiran			0.028
Da	30 (81.1)	35 (97.2)	
Ne	7 (18.9)	1 (2.8)	
Broj metastatskih sijela			***0.045***
1	10 (43.3)	17 (47.2)	
2	11 (29.7)	9 (25)	
≥3	16 (27)	10 (27.8)	
IMDC prognostička grupa			***0.027***
Povoljna	3 (8.1)	8 (22.2)	
Srednja	18 (48.7)	23 (63.9)	
Nepovoljna	7 (18.9)	2 (5.6)	
Nedostaje	9 (24.3)	3 (8.3)	
SBRT ili palijativna RT	14 (37.8)	3 (8.3)	0.14
≥ gradus 3 nuspojava	11 (29.7)	13 (36.1)	0.43

Kratice: Nivo = Nivolumab, IKR = interkvartilni raspon, M = muško, Ž = žensko, IMDC = The International Metastatic RCC Database Consortium, SBRT = Stereotactic Body Radiation Therapy (stereotaktična radioterapija), RT = radioterapija.

gredirali na prethodno prvolinijsko liječenje sunitinibom (N=55) ili pazopanibom (N=18). U drugolinijskom liječenju 37 bolesnik je liječen Nivo, a 36 bolesnika TKI-om (22 sorafenib, 14 aksitinib). Medijan praćenja za žive bolesnike iznosio je 36 mjeseci (95%CI 25–41 mjeseci). Medijan trajanja liječenja iznosio je 19 mjeseci u Nivo skupini i 8 mjeseci u TKI skupini (p<0.0001). Dokazano je statistički značajno produljenje PFS-a u Nivo skupini u usporedbi s onima koji su primali TKI (12 vs 5 mjeseci, p<0.001). Dva (5.4%) bolesnika liječena Nivo postigla su potpuni odgovor (CR), dok niti jedan od bolesnika liječenih TKI-om nije imao CR. Uočeno je numerički značajno produljenje OS-a u bolesnika liječenih Nivo (21 vs 13 mjeseci, p=0.08), uz primjetan trend duljeg OS-a kod bolesnika Nivo skupine koji su liječeni i stereotaktičnom radioterapijom (SBRT) u svrhu kontrole oligoprogresije bolesti. U multivarijantnoj analizi jedina varijabla koja je bila značajne za PFS je klasa drugolinijskog lijeka (Nivo vs TKI, p=0.002), dok se za OS, uz klasu drugolinijskog lijeka (Nivo vs TKI, p=0.02), pripadnost IMDC prognostičkoj skupini također pokazala značajnom (p=0.02). Nije zabilježena statistički značajna razlike u pojavnosti nuspojava gradusa ≥3 (TKI 36% vs Nivo 29%, p=0.43). Najčešća nuspojava u Nivo skupini bila je dermatološka toksičnost, a dijareja u TKI skupini.

Zaključak: Naši rezultati učinkovitosti Nivo u drugolinijskom liječenju su usporedivi s rezultatima randomizirane studije CheckMate 025, u kojoj je komparator Nivo bio everolimus. Kod dijela bolesnika primjena Nivo kao drugolinijskog liječenja pokazuje obećavajuće rezultate u smislu dugotrajne kontrole bolesti. Nivo i TKI imaju značajan, ali različit profil toksičnosti s čime svi liječnici trebaju biti upoznati. S obziorom na mali uzorak ispitanika i mogućnost da su dobiveni rezultati posljedica retrospektivne analize i moguće pristrane selekcije ispitanika, naše rezultate treba oprezno tumačiti.

REAL-WORLD COMPARATIVE EFFECTIVENESS OF IMMUNOTHERAPY VS TYROSINE KINASE INHIBITORS (TKI) IN THE SECOND-LINE TREATMENT FOR ADVANCED RENAL-CELL CARCINOMA (ARCC) FOLLOWING FIRST LINE TKI PROGRESSION: SINGLE CENTER EXPERIENCE

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Background: There is limited data on comparison of TKI and nivolumab (Nivo) as second line (2nd L) treatment following first line (1st L) TKI progression for aRCC. The goal of this study was to compare outcomes of these two classes of agents in the 2nd L setting of in aRCC.

Methods: From our prospectively collated database, aRCC patients (pts) who received 2nd L treatment were retrospectively reviewed (Nivo from April 2018 to June 2021 or TKI prior to April 2018). The primary endpoint was progression-free (PFS) and overall survival (OS). The secondary endpoints were overall response rates (ORR) and safety.

Results: We included 73 pts (Table 1) with aRCC who had progression despite 1st L treatment with sunitinib (N=55) or pazopanib (N=18). In 2nd L 37 pts received Nivo, while 36 pts received TKI (sorafenib 22, axitinib 14). Fifty-five pts died. Median follow-up for living pts was 36 months (95%CI 25–41 months). Median treatment duration was 19 months for Nivo and 8 months for TKI (<0.0001). Pts who received 2nd L Nivo had longer PFS compared to pts who received 2nd L TKI (12 vs 5 months, p<0.001). Complete responses (CR) were observed in 2 pts (5.4%) in the Nivo group, and none of the pts in the TKI group experienced CR. There was trend towards longer OS observed in pts treated with 2nd L Nivo (21 vs 13 months, p=0.08). Similarly, trend for longer OS in pts on Nivo who received SBRT for control of oligoprogression was noticed. On multivariate Cox regression analysis, only variable significantly associated with PFS was type of 2nd L treatment (TKI vs Nivo, p=0.002), while for OS significant variables were IMDC risk group (p=0.02), and type of 2nd L treatment (TKI vs Nivo,

p=0.02). Adverse events of any cause of grade 3 or higher occurred in 29.7% of the 37 pts receiving Nivo and in 36.1% of the 36 pts receiving TKI (p=0.45). The most common was dermatologic toxicity in Nivo pts, and diarrhea in TKI pts.

Conclusion: In this real-life analysis Nivo yielded comparable PFS and OS outcomes compared to Checkmate 025 trial where it was randomized against everolimus. In small subset of pts 2nd L Nivo offer chance of long-term disease control. Both Nivo and TKI bear significant but different toxicity profile which practitioners should be aware off. Limitations include small sample size and treatment bias inherent to retrospective nature of this study.

HEMATOM VRATA I MEDIJASTINUMA KAO PRIMARNA PREZENTACIJA KARCINOMA PARATIREOIDNE ŽLIJEZDE

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Uvod: Karcinom paratireoidne žlijezde je vrlo rijedak. Javlja se u manje od 1% slučajeva primarnog hipreparatireoidizma. Oko 90% karcinoma paratireoidne žlijezde je hormonski funkcionalno i povećano izlučuju paratireoidni hormon (PTH). Iz tog razloga većina pacijenata ima izraženu hiperkalcemiju pri postavljanju dijagnoze. Spontano krvarenje iz tumora žlijezde je vrlo rijetko. Takvo krvarenje može biti ozbiljno i potencijalno dovesti do fatalnih komplikacija ukoliko se odgađa operativno liječenje.

Prikaz slučaja: Muškarac od 64 godine je upućen na Kliniku za otorinolaringologiju i kirurgiju glave i vrata iz vanjske ustanove, a radi oticanja i području vrata i promuklosti. Nije imao prethodnu traumu niti kirurški zahvat. Simptomi su se pojavili rano tog dana. Kliničkim pregledom se ustanovi oteklina sluznice hipofarinksa, slabo pomična lijeva strana grkljana, oteklina i crvenilo lijeve strane vrata. CT učinjen u vanjskoj ustanovi opisuje nepravilnu masu veličine 10 x 5,5 x 5,5 cm, a po radiološkim znakovima prvenstveno se radi o hemoragičnom sadržaju. Ta je tvorba komprimirala lijevu zajedničku karotidnu arteriju, jugularnu venu, potiskivala grkljan, dušnik i jednjak prema desno, a pružala se kroz vrat u gornji i stražnji medijastinum sa znakovima medijastinitisa i ezofagitisa. Po dolasku se pacijent osjećao dobro, ali mu se stanje brzo počelo pogoršavati. Počeo se žaliti na osjećaj da ima „tešku glavu“ i tada smo se odlučili na hitan operativni zahvat u općoj anesteziji. Intraoperativno se pronađe tumorska tvorba pored lijevog režnja štitnjače i odstranjena je zajedno s lijevim režnjem štitnjače. Patohistološka dijagnoza pokaže „low grade“ karcinom paratiroidne žlijezde, oko 2 centimetra u promjeru, djelomično raskidan opsežnim krvarenjem. Postoperativni laboratorijski nalazi : TSH3 2.199[mIU/L], FT3 3.55[pmol/L], FT4 12.60[pmol/L], Ca (s) 2.65[mmol/L], iCa++ 1.39[mmol/L], PHOS 0.75[mmol/L], iPTH (pk) > 5000[ng/L]. Ultrazvučni nalaz : hipoehogena tvorba iza gornjeg pola desnog režnja štitnjače veličine 1,8 x 1,6 x 1,1 cm. Pored gore opisane tvorbe nastavljajući se na područje iza stražnje kapsule štitnjače (ekstratiroidno) izdvaja se hipoehogeno područje veličine 3.9x1.9x2.5 cm u kojem se izdvaja hipoanehogeno područje (nodus) veličine 2.4x1.8x2.2 cm. Učinjena citološka punkcija prve tvorbe pokaže tkivo paratireoidne žlijezde, a druge tvorbe koloidnu cistu. Obje tvorbe pokažu PTH > 5000 ng/L. Radi povišenih razina kalcija, ultrazvučnog nalaza i nalaza PTH iz punktata indicira se operativno odstranjenje opisanih masa i desnog režnja štitnjače. PHD pokaže „low grade“ karcinom paratireoidne žlijezde. Po trenutnim saznanjima ne postoji dogovor o načinu liječenja ovog karcinoma. Smatra se da je kirurško liječenje primarno, a o kemoterapiji i radioterapiji nema dovoljno podataka. Radi mogućih recidiva ovog karcinoma pacijent je obavezan na doživotne kontrole.

Zaključak: Kod pacijenta sa disfonijom, slabije pomičnom jednom stranom grkljana, oteklinom u području vrata, a bez prethodne traume ili operativnog zahvata treba se diferencijalno dijagnostički razmišljati i o mogućnosti krvarenja iz adenoma ili karcinoma paratireoidne žlijezde. Također ovo zbivanje se može smatrati kirurškom hitnoćom te se operativni zahvat ne bi smio odgađati.

HEMATOMA OF THE NECK AND MEDIASTINUM AS A PRIMARY PRESENTATION OF PARATHYROID GLAND CANCER

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Introduction: Parathyroid carcinoma is a rare endocrine malignancy. It accounts for <1% of cases of sporadic primary hyperparathyroidism. The majority (90%) of parathyroid carcinomas are hormonally functional and hypersecrete parathyroid hormone (PTH). Thus, most patients exhibit strong symptomatology of hypercalcemia at presentation. Spontaneous haemorrhage of the tumor is rare. Parathyroid extracapsular hemorrhage is a serious, potentially fatal complication of parathyroid gland enlargement due to hyperplasia, adenoma or carcinoma. A delay in surgical procedure can lead to fatal outcome.

Case report: Sixty-four-year old male Caucasian patient was referred to the emergency department due to neck pain, swelling of the neck and dysphonia. He did not report any trauma. The symptoms occurred earlier that day. Clinical examination revealed swelling of the hypopharyngeal mucosa, almost immobile left hemilarynx, edema, eythema and pain of the anterior and left side of the neck. On the computerized tomography scan irregular and heterogenous mass 10 x 5,5 x 5,5 cm was described and according to the image it was primary an accumulation of blood. The mass compromised left common carotid arthery impeling internal jugular vein to the left and larynx, trachea and esophagus to the right, extending to the upper and posterior mediastinum with signs of mediastinitis and esophagitis. Upon admittance the patient's vital signs were stable, however very swiftly his condition started to deteriorate. The patient reported sudden feeling of having a "heavy head" and dyspnea and we performed an emergency neck exploration in general anesthesia. During a neck exploration we found a massive extracapsular haemorrhage on the left side in vincinity of the left thyroid lobe, therefore we performed a left thyroid lobectomy with total excision of the mass. Pathohystologic examination of the mass revealed low grade parathyroid gland carcinoma about 2 centimeters in diameter, ruptured by haemorrhage. Postoperative laboratory tests : TSH3 2.199[mIU/L], FT3 3.55[pmol/L], FT4 12.60[pmol/L], Ca (s) 2.65[mmol/L], iCa++ 1.39[mmol/L], PHOS 0.75[mmol/L], iPTH (pk) > 5000[ng/L]. Ultrasound showed hypoechoic mass behind upper part of the right thyroid lobe, abuot 1.8 x 1.6 x 1.1 cm. Behind that mass there was another hypoechoic mass about 3.9x1.9x2.5 cm and inside of it anechoic zone about 2.4x1.8x2.2 cm. Fine needle aspiration biopsy showed parathyroid gland cells in first mass, and colloid cyst in second mass, both measuring PTH > 5000 ng/L. Due to high serum calcium levels, increased FNAB PTH level and ultrasound examination three months after the first surgery, we decided to perform a second operation, a right thyroid lobectomy and parathyroidectomy. Preoperative examination of the left side did not reveal any enlarged or suspicious masses at that time. PHD was also low grade parathyroid carcinoma. There is no consensus on chemotherapy or radiotherapy in patients with parathyroid carcinoma, however meticulous sugical excision is mandatory. Patient is scheduled for a lifetime follow up.

Conclusion: In patient with compromised airway, massive swelling of the neck and no previous trauma or surgery differential diagnosis should involve possibility of parathyroid gland adenoma or carcinoma with extracapsular haemorrhage.

INDIKACIJE ZA HITNU HOSPITALIZACIJU BOLESNIKA NA KLINIKU ZA ONKOLOGIJU KBC ZAGREB TIJEKOM COVID-19 PANDEMIJE

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Uvod: Zbog pogoršanja epidemiološke situacije u drugom valu pandemije COVID-19 u Klinici za onkologiju KBC Zagreb organiziran je tzv. Akutni odjel namijenjen prijemu bolesnika iz hitne službe. Preduvjet za hospitalizaciju bio je negativan PCR test na SARS-CoV2 virus.

Metode: Učinjena je retrospektivna analiza koja je uključila bolesnike primljene putem hitne službe na Akutni odjel Klinike za onkologiju u razdoblju od 01.12.2020.–15.07.2021. Cilj istraživanja bio je analizirati indikacije za hitnu hospitalizaciju, demografske i kliničke karakteristike bolesnika, trajanje te ishod liječenja.

Rezultati: U promatranom intervalu hospitalizirano je 182 bolesnika, od kojih je 47.3% muškaraca i 52.7% žena, medijana starosti 65 godina. Od toga 12.6% čine bolesnici s lokalnim i lokoregionalno proširenim rakom, a 73.6% bolesnici s uznapredovalim i metastatskim rakom u tijeku aktivnog onkološkog liječenja, dok 13.7% prijema čine palijativni bolesnici. Najzastupljenije sijelo bio je rak dojke 22.5%, zatim slijede urogenitalni 21.9%, probavni tumori 20.3%, te melanomi 8.8%. Najčešći razlog hospitalizacije bile su infekcije 36.3%, od kojih su 13% činile febrilne neutropenije, zatim tromboembolijske komplikacije 10.4%, komplikacije uslijed progresije bolesti (smetnje pasaže, žutica) 8.8% te akutni neurološki deficiti 15.9%, dok su ostali uzroci činili 28.6% prijema. U trenutku hospitalizacije 8.2% bolesnika preboljelo je Covid 19, 6.0% cijepljeno je jednom ili dvije doze cjepiva, a 63.2% bolesnika nije preboljelo niti cijepljeno protiv Covida19. Medijan trajanja hospitalizacije bio je 9 dana. Većina bolesnika, 73.1% otpuštena je kući ili u neku od ustanova za palijativnu skrb, 1.6% u drugu kliniku, dok je 25.3% bolesnika imalo smrtni ishod.

Zaključak: I u uvjetima Covid19 pandemije Klinika za onkologiju nastavila je zbrinjavati onkološke bolesnike nastojeći kroz reorganizaciju postojećih kapaciteta i pojačane epidemiološke mjere zaštititi ih od infekcije SARS-CoV2 virusom. S obzirom da su dio smještajnog kapaciteta konzumirali palijativni pacijenti, do izražaja je došla potreba za unaprijeđenjem palijativne skrbi i osnivanjem dodatnih ustanova za palijativnu skrb.

INDICATIONS FOR URGENT HOSPITAL ADMISSION OF PATIENTS AT THE DEPARTMENT OF ONCOLOGY OF THE UNIVERSITY HOSPITAL CENTRE ZAGREB DURING THE COVID-19 PANDEMIC

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Introduction: Due to the worsening of the epidemiological situation in the second wave of the COVID-19 pandemic, the so-called Acute department (AD) was established at the Department of Oncology of the UHC Zagreb, which was intended for the admission of patients from the Emergency department (ED). A prerequisite for hospitalization was a negative PCR test for the SARS-CoV2 virus.

Methods: A retrospective analysis was performed, which included patients admitted through the ED to the AD in the period from 01.12.2020 to 15.07.2021. The aim of this study was to analyze the indications for emergency hospitalization, demographic and clinical characteristics of patients, duration, and outcome of treatment.

Results: In the observed period, 182 patients were hospitalized, of which 47.2% were men and 52.7% were women. The median age was 65 years. Of these, 12.6% are patients with local and loco-regionally advanced cancer and 73.6% are patients with advanced and metastatic cancer during active oncology treatment, while 13.7% of admissions are palliative patients. The most common site was breast cancer 22.5%, followed by urogenital 21.9%, digestive tumors 20.3% and melanoma 8.8%. The most common reasons for hospitalization were infections 36.3%, of which 13% were febrile neutropenia, thromboembolic complications 10.4%, complications due to disease progression (passage disturbances, jaundice) 8.8% and acute neurological deficits 15.9%, while other causes accounted for 28.6% of admissions. At the time of hospitalization, 8.2% of patients had recovered from Covid 19, 6.0% had been vaccinated with one or two doses of vaccine, and 63.2% of patients had not recovered or been vaccinated against Covid19. The median duration of hospitalization was 9 days. The majority of patients, 73.1% were discharged home or to one of the palliative care facilities, 1.6% to another clinic, while 25.3% died.

Conclusion: Even in the conditions of the Covid19 pandemic, the Department of Oncology continued to care for oncology patients to protect them from SARS-CoV2 infection through the reorganization of existing facilities and enhanced epidemiological measures. Since part of the accommodation capacity was occupied by palliative patients, the need to improve palliative care and establish additional palliative care institutions came to the fore.

NODULARNI HIDRADENOM VJEĐE U ZLOĆUDNOJ TRANSFORMACIJI: PRIKAZ SLUČAJA

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Uvod: Tumor znojne žlijezde vjeđe je tvorba koja se rijetko pojavljuje u kliničkoj praksi. Kliničkim pregledom vidljiv je sporo rastući, asimptomatski čvor, osobito u benignih tumora. Zloćudna transformacija ovih tumora je rijetka.

Prikaz slučaja: U ovom članku želimo izvijestiti o prikazu slučaja nodularnog hidradenoma u zloćudnoj transformaciji u žene kojoj je pri prvom pregledu primijećena nodularna tvorba vjeđe koja je postala ulcerativna pri prijemu u bolnicu radi odstranjivanja tvorbe. Tumor je bio sličan benignom pandanu, ali imao je dodatne značajke poput površinske ulceracije, brojnih mitotičkih figura i infiltrativnog uzorka rasta.

Zaključak: Maligni oblici hidradenoma su rijetki, međutim mogućnost ove varijante treba razmotriti u diferencijalnoj dijagnozi tumora vjeđe.

NODULAR HIDRADENOMA OF THE EYELID IN MALIGNANT TRANSFORMATION: A CASE REPORT

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Introduction: Sweat gland tumor is an unusual lesion of the eyelid. It appears as a non-symptomatic, slow growing nodule, especially in benign variant. Malignant transformation is rare.

Case report: We report a case of nodular hidradenoma in malignant transformation in a female, who presented with a nodular swelling in the eyelid at initial examination that become ulcerative upon admittance to the hospital due to excision of the tumor. The tumor was similar to its benign counterpart but had additional features such as surface ulceration, numerous mitotic figures, and an infiltrative growth pattern.

Conclusion: Malignant forms of hidradenomas are rare, however the possibility of this variant should be considered in the differential diagnosis of eyelid tumors.

PRIKAZ BOLESNIKA S METASTATSKIM MEKOTKIVNIM SARKOMIMA KOD KOJIH JE UČINJENO SVEOBUHVATNO GENSKO PROFILIRANJE – ISKUSTVO KBC-A ZAGREB

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Cilj: Mekotkivni sarkomi (eng. soft tissue sarcoma, STS) heterogena su skupina tumora koji broje više od 80 podtipova. Liječenje predstavlja veliki izazov za mutidisciplinarne timove. Razvojem novih, modernih dijagnostičkih molekulskih metoda, unaprijedilo se liječenje mekotkivnih sarkoma. Sveobuhvatno gensko profiliranje sarkoma daje mogućnost pronalaženje mutacija na koje ponekad možemo djelovati ciljanom terapijom i/ili imunoterapijom (u slučaju visokog Tumor Mutational Burdena-a (TMB) ili Microsatellite instability (MSI-H) statusa). Cilj ovog rada analiza je rezultata dobivenih iz sveobuhvatnog genskog profiliranja sarkoma bolesnika s metastatskom bolesti koji su liječeni u KBC-u Zagreb.

Metode: provedena je analiza 36 bolesnika s metastatskim STS-om kod kojih je u tijeku liječenja na KBC-u Zagreb učinjeno sveobuhvatno gensko profiliranje, Foundation One ® testom. Podaci su dobiveni i analizirani na temelju pretraživanja baza podataka Klinike za onkologiju i Zavoda za patologiju i citologiju KBC-a Zagreb. Prikazat će se bolesnici koji su liječeni na temelju nalaza testiranje te ostale grupe bolesnika kod kojih su pronađene potencijalno targetabilne mutacije, ali bez mogućnosti intervencije (lijekovi nisu dostupni za navedenu indikaciju ili su eksperimentalnog karaktera).

Rezultati: Kod 2 bolesnika, jednog sa solitarnim fibroznim tumorom (SFT) i drugog s malignim tumorom živčanih ovojnica (MPNST) pronađena je fuzija u NTRK genima te je zatraženo i odobreno liječenje inhibitorima NTRK-a, lijekom entrectinib. Kod jednog bolesnika sa sarkomom nejasne histogeneze provedeno je liječenje imatinibom na temelju postojanja amplifikacije KIT gena u analiziranom tumoru.

Zaključak: sveobuhvatno gensko profiliranje omogućava opsežnu analizu gena/mutacijskog statusa kod sarkoma. S aspekta današnje onkologije, broj targetabilnih mutacija je i dalje mali s posljedičnim malim učinkom na promjenu terapijskog plana. Dodatni problem predstavlja uporaba lijekova u indikacijama za koje nisu regi-

strirani (off label) kao i u slučajevima gdje je razina dokaza učinkovitosti niska (na temelju case reporta-a). Svakako su potrebna daljnja istraživanja.

GENOMIC TUMOR PROFILING OF SOFT TISSUE SARCOMAS IN PATIENTS TREATED IN UHC ZAGREB – SINGLE CENTER EXPERIENCE

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Aim: Soft tissue sarcomas (STS) represent heterogenous group of tumors with more than 80 subtypes. Systemic treatment is challenging and multidisciplinary approach is mandatory. Modern techincs in molecular diagnostics improved systemic treatment of STS by defining targetable mutations for targeted therapy or in a case of high tumor mutational burden (TMB) or Microsatellite instability (MSI-H) the potential use of immunotherapy. We ll present our database analyis of genomic tumor profiling in sarcoma specimens of patients treated in our center

Methods: We analyzed results of genomic tumor profiling of 36 pts. with metastatic STS. Testing was performed by using Foudation One ® comprehensive tumor profiling engine to identify clinically relevant alterations and potentially expand patients' treatment options. Results were obtained from clinical databases of Department of oncology and Division of pathology and citology at UHC Zagreb. Only few patients were treated according to FMI results, and majority had mutations without currently available inhibitors or the recommendation was therapy with off label/experimental designation.

Results: After 36 analysis, 2 patients had active NTRK fusion, one with SFT (solitary fibrous tumor) and other with MPNST(malignant peripheral nerve sheath tumor). Therapy with NTRK inhibitor entrectinib was recommended and approved. One patient with sarcoma NOS (non otherwise specified) had c-kit amplification and was treated with imatinib mesilate as a representative of multi tyrosine kinase inhibitor (mutli-TKI).

Conclusion: genomic tumor profiling of STS represents the panel of targetable and non tagetable mutations. From a current oncological perspective, only few targetable mutations in STS are meaningful. Off label and experimentally designated therapies, recommended by genomic profiling are further obstacles in personalized treatment. Further clinical trials are needed.

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Uvod: Klinička slika akutnog obostranog egzoftalmusa je vrlo neobična pojavnost u smislu paraneoplastičnog sindroma. Prikazujemo slučaj pacijenta sa slikom akutnog obostranog egzoftalmusa sa izraženom zastojnom komponentom kao vrlo rijetkim oblikom paraneoplastičnog sindroma povezanog sa karcinomom mokraćnog mjehura.

Prikaz slučaja: Prikazujemo slučaj muškog pacijenta starog 64 godine koji boluje od kronične opstruktivne plućne bolesti i arterijske hipertenzije. Javlja se u hitnu oftalmološku službu radi sve jačeg crvenila očiju unazad 1–2 tjedna. Unatoč primjeni lokalnih oftalmoloških pripravaka stanje očiju se dramatično pogoršava. Na kontrolnom pregledu pacijent je razvio sliku akutnog obostranog egzoftalmusa sa nekrozom spojnice, povišenjem očnom tlaka i dramatičnim padom vidne oštrine uslijed kompresivne optikoneuropatije oba vidna živca. Primje-

njena je hitna kirurška dekompresija orbita te pulsna KS terapija na što se stanje očiju poboljša, no pokazuje ovisnost o steroidima. Obradom pacijenta je isključena bolest štitnjače, bolest vratnih krvnih žila,imunološka bolest te intrakranijska A-V fistula kao najčešći uzroci obostranog egzoftalmusa. Na osnovu laboratorijskih pokazatelja pacijent je upućen urologu te je utvrđen karcinom mokraćnog mjehura. Kirurškom ekscizijom tumora mokraćnog mjehura postigla se konačna stabilizacija stanja pacijentovih očiju.

Zaključak: U diferencijalnu dijagnostiku kliničke slike obostranog egzoftalmusa osim bolesti štitnjače, imunoloških bolesti i intrakranijske A-V fistule, kao najčešćih uzroka, potrebno je uključiti i paraneoplastični sindrom.

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Introduction: The clinical picture of acute bilateral exophthalmos is a very unusual occurrence in terms of paraneoplastic syndrome. We present a case of a patient with an image of acute bilateral exophthalmos with a pronounced congestive component as a very rare form of paraneoplastic syndrome associated with bladder cancer.

Case report: We present a case of a 64-year-old male patient suffering from KOPB and HTA. He reports to the emergency ophthalmological service due to the increasing redness of the eyes in the past 1–2 weeks. Despite the application of local ophthalmic preparations, the condition of the eyes deteriorates dramatically. At follow-up, the patient developed an image of acute bilateral exophthalmos with conjunctival necrosis, increased intraocular pressure, and a dramatic decrease in visual acuity due to compressive optic neuropathy of both optic nerves. Emergency surgical decompression of the orbits and pulse KS therapy were applied, which improved the condition of the eyes, but showed steroid dependence. Treatment of the patient ruled out thyroid disease, cervical vascular disease, immune disease and intracranial A-V fistula as the most common causes of bilateral exophthalmos. Based on laboratory indicators, the patient was referred to a urologist and bladder cancer was diagnosed. Surgical excision of the bladder tumor achieved the final stabilization of the patient's eye condition.

Conclusion: In the differential diagnosis of the clinical picture of bilateral exophthalmos, in addition to thyroid disease, immune diseases and intracranial AV fistula, as the most common causes, it is necessary to include paraneoplastic syndrome.

ISHODI PRVE LINIJE LIJEČENJA METASTATSKOG KOLOREKTALNOG KARCINOMA U KLINIČKOM BOLNIČKOM CENTRU ZAGREB

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Uvod: Metastatski kolorektalni karcinom (mKRK) je neizlječiva bolest u velike većine pacijenata. Sistemska kemoterapija je osnovni oblik liječenja koji može pridonijeti ukupnom preživljenju u ovih pacijenata. Dodatak biološke terapije standardnoj kemoterapiji kao i sekvencijska primjena svih dostupnih kemoterapijskih protokola poboljšala je prognozu bolesti u ovih bolesnika. Medijan OS je sada između 2 do 3 godine.

Materijali i metode: Ova retrospektivna opservacijska studija provedena je u KBC Zagreb. Cilj studije je bio istražiti ishode prve linije liječenja mKRK. Podatci 298 pacijenata su preuzeti iz dostupne medicinske dokumentacije u razdoblju od 1. siječnja 2016. do 1. siječnja 2019 godine. Uključeni su bili bolesnici stariji od 18 godina, s histološki potvrđenom dijagnozom te završenom prvom linijom liječenja do 10 svibnja 2021 godine.Primarni ishod je bio PFS. Pacijenti su dobivali 1. liniju liječenja do radiološke i/ili kliničke progresije bolesti, smrti ili neprihvatljive toksičnosti. Kao procjena odgovora na terapiju se koristila kombinacija kompjuterizirane tomografije i karcinoembrionalnog antigena svakih 6 ciklusa primijenjene terapije.Osim dobi i spola, ostale karakteristike bolesnika koje su bile uključene su bile: ECOG status, RAS status, lijevostrani ili desnostrani tumori te biološki lijek. Coxova regresijska analiza je korištena za utvrđivanje opvezanosti između navedenih varijabli. Preživljenje je procijenjeno uz pomoć Kaplan-Meierove metode a pojedinačne podskupine su uspoređivane koristeći log-rank test. Rezultati su prikazani kao hazardni omjer (HR) sa 95% intervalom pouzdanosti (CI), a statistička značajnost je bila $p< 0.05$.

Rezultati: Osnovne karakteristike bolesnika su dob 64.5 godina, 44% više muškaraca nego žena je bilo uključeno u studiju, a velika većina bolesnika je bila dobrog općeg stanja ECOG 0. Od bolesnika kojima je određen RAS status podjednak broj je imao mutirani RAS gen, kao i divlji tip tumora, a 16.8% bolesnika nije imalo određeno RAS status.Većina bolesnika je primila bevacizumab u prvoj liniji liječenja, zatim slijedi EGFR inhibitori, a 50 bolesnika nije uz kemoterapiju primilo biološki lijek. Ukupni PFS je bio 7.6 mjeseci (95% CI 6.44–8.76) i bio je pozitivno povezan s boljim općim stanjem bolesnika (ECOG status), ljevostranim primarnim tumorima, te dodatkom biološke terapije kemoterapiji. Bolesnici s primarnim lijevostranim tumorima su imali PFS 8.7 mjeseci naspram bolesnika s primarno desnostranim tumorima čiji PFS je bio 5.9 mjeseci. Slično navedenome, ECOG 0 je bio povezan s boljim ishodom u usporedbi s bolesnicima s ECOG statusom ≥1, 8.6 naspram 5.00 mjeseci. Nije nađena statistički značajna razlika između bioloških terapija, iako pacijenti koji nisu dobili biološku terapiju su imali značajno lošije preživljenje. Nije nađena povezanost za dob, spol ili RAS mutacijski status

Zaključak: Rezultati naše studije su usporedivi sa prethodno provedenim studijama te govore u prilog kliničke koristi dodatka monoklonalnih protutijela kemoterapiji za mKRK.

OUTCOMES FOR THE FIRST LINE TREATMENT FOR METASTATIC COLORECTAL CANCER IN THE UHC ZAGREB

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Introduction: Metastatic colorectal cancer (mCRC) is an incurable disease for most of the patients with predominant treatment modality being palliative systemic chemotherapy to improve overall survival (OS). The addition of biological therapy to standard chemotherapy as well as the sequential use of all available treatments have improved prognosis in patients with mCRC with median OS currently reaching 2 to 3 years.

Materials and methods: The objective of this retrospective observational, single-centre study conducted in the UHC Zagreb, was to investigate the outcomes of the first-line treatment for mCRC. Data were retrieved from medical records on 298 patients who began therapy between January 1st, 2016 and January 1st, 2019. All the eligible patients were aged at least 18 years, had histologically confirmed disease, and completed the first-line therapy by May 10th, 2021.

Primary outcome was measured as progression-free survival (PFS). The patients continued the same treatment protocol until radiological and/or clinical disease progression, death, or unacceptable toxicity. Objective evaluation of response to therapy with computed tomography, carcinoembryonic antigen (CEA), was routinely performed every 6 cycles.

Apart from age and sex, other variables were also obtained, including ECOG performance status, primary tumor sidedness, RAS status, and biological agent received. Cox regression analysis was used to examine the

association between variables. Survival was estimated using the Kaplan-Meier method and curves of the specific subgroups were compared using the log-rank test. Results were expressed as hazard ratios (HR) with 95% confidence interval (CI) with statistical significance set at a confidence level of $P<0.05$.

Results: Regarding general characteristics, median age was 64.5 years, 44% more men than women were included in the study, and the majority of patiens were in good general condition (ECOG 0). Of the patients with determined RAS status, a similar number carried the mutation as well as being wild-type, while 16.8% had unknown mutational status. The majority of patients received bevacizumab in the first-line treatment, followed by an EGFR inhibitor, and 50 patients received no biological therapy. Overall PFS was 7.6 months (95% CI 6.44–8.76) and was positively associated with better performance status (ECOG 0), left sided primary cancer, and addition of biological agent to chemotherapy. Patients with left-sided primary cancer had median PFS of 8.7 months compared to 5.9 months for right-sided. Similarly, ECOG 0 was associated with better prognosis compared to ECOG ≥1, 8.6 vs 5.00 months, respectively. There was no statistical difference regarding different biological agents, although patients who received no biological therapy had significantly worse survival. No association was found for age, sex, or RAS mutational status.

Conclusion: Our results are comparable with previously reported studies and support the clinical benefit of adding monoclonal antibodies to standard chemotherapy for mCRC.

UČINKOVITOST T-DM1 NAKON PROGRESIJE NA DVOJNU ANTIHER2 TERAPIJU PERTUZUMABOM I TRASTUZUMABOM

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Uvod: Temeljem rezultata EMILIA studije, ado-trastuzumab emtansine (T-DM1) postao je izbor 2.linije terapije za bolesnice s metastatskim HER2-pozitivnim karcinomom dojke. Otkako su pertuzumab i trastuzumab u kombinaciji s kemoterapijom priznati kao standardna terapija u 1.liniji, postavlja se pitanje je li T-DM1 jednako učinkovit u stvarnom svijetu, uzimajući u obzir ograničene dokaze o njegovoj učinkovitosti nakon uporabe pertuzumaba.

Metode: Cilj ove retrospektivne studije je opisati kliničke karakteristike bolesnika te procjeniti medijan preživljenja bez progresije bolesti (PFS) i medijan ukupnog preživljenja (OS) u HER2-pozitivnih bolesnica koje su dobivale T-DM1 u 2.liniji nakon progresije na dvojnu antiHER2 terapiju. U razdoblju od ožujka 2017. do kolovoza 2021. godine identificirali smo 31 bolesnicu u Kliničkom bolničkom centru Zagreb. Statitička analiza učinjena je pomoću programa IBM SPSS verzija 21.

Rezultati: Medijan starosti bio je 58 godina. Većina bolesnica, 67.8% (N=21) su imale hormonski pozitivnu bolest. 32.2% (N=10) bolesnica su bile inicijalno metastatske, a 67.8% (N=21) je imalo rekurentnu bolest. U skupini bolesnica koje su doživjele povrat bolesti nakon dijagnoze ne-metastatske bolesti, 42.9% su prethodno primile trastuzumab kao (neo)adjuvantnu terapiju. Visceralnu zahvaćenost imalo je 77.4% (N=24) bolesnica. Metastaze na mozgu bile su prisutne kod 22.6% (N=7) bolesnica na početku terapije. Kod zaključenja praćenja podataka, 35.5% (N=21) bolesnica imalo je progresiju bolesti ili smrtni ishod. Medijan PFS-a za ukupnu populaciju bio je 6 mjeseci (95% CI 2.5–10.8). Sveukupno, 15 bolesnica (48.4%) imalo je smrtni ishod kod zaključenja praćenja podataka. Medijan OS-a bio je 17 mjeseci (95% CI 12.0–22.0).

Zaključak: Mi smo uočili kraći medijan PFS-a i OS-a u usporedbi sa studijom EMILIA, ali rezultati naše studije usporedivi su s rezultatima recentno objavljenih retrospektivnih studija (Conte B et al.2020; Michel L et al.2020). Budući da je dvojna antiHER2 terapija pertuzumabom i trastuzumabom relativno novi standard, očekuje se da će nove studije jasno definirati učinkovitost i optimalno sekvenciranje T-DM1 nakon progresije na pertuzumab.

T-DM1 EFFICACY AFTER PROGRESSION ON DUAL ANTIHER2 THERAPY WITH PERTUZUMAB AND TRASTUZUMAB

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Background: Based on results from the EMILIA study, ado-trastuzumab emtansine (T-DM1) has become a second-line option for patients with HER2-positive metastatic breast cancer.

Since pertuzumab and trastuzumab combined with chemotherapy are acknowledged as standard first-line therapy, the question is raised as to whether T-DM1 is equally effective in the real world, considering limited evidence for its efficacy after using pertuzumab.

Methods: This retrospective study aims to describe patient characteristics and evaluate median progression free survival (PFS) and overall survival (OS) time in HER2-positive patients receiving T-DM1 as a second-line option after dual antiHER2 treatment. In a period from March 2017 through August 2021 we identified 31 patients at the University Hospital Centre Zagreb. Statistical analysis was performed with IBM SPSS version 21.

Results: Median age was 58 years. The majority of patients, 67.8% (N=21), had hormone positive disease. 32.2% (N=10) of patients had de novo metastatic disease, and 67.8% (N=21) had recurrent disease. Among the patient who had relapsed after a diagnosis of non-metastatic disease, 42.9% previously received trastuzumab in the (neo)adjuvant setting.

Visceral involvement had 77.4% (N=24) of patients. Brain metastasis was present in 22.6% (N=7) of patients at the baseline. By data cut off, 35.5% (N=21) of patients had progressed or died. The median PFS was 6 months for the total population (95% CI 2.5–10.8). Overall, 15 patients (48.4%) have died at data lock. The median OS was 17 months (95% CI 12.0–22.0).

Conclusion: We observed a shorter median PFS and OS compared to the EMILIA study, but these results are consistent with recent retrospective real-world studies (Conte B et al.2020; Michel L et al.2020). As dual anti-HER2 therapy is the relatively new standard, new studies are expected to clearly define the efficacy and optimal sequencing of T-DM1 after progression on pertuzumab.

AGNOSTIČKI PRISTUP U LIJEČENJU TUMORA GI TRAKTA

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U ovom prikazu slučaja prezentiramo liječenje pacijenta s karcinomom nepoznatog primarnog sijela kojem je izvedena analiza mutacija tumorskog DNA te aplicirana terapija na temelju specifične mutacije i visoke opterećenosti brojem mutacija (TMB). Radi se o pacijentu koji se prezentira s gubitkom apetita, abdominalnim bolovima, općom slabosti i gubitkom tjelesne težine kao glavnim simptomima. Učinjenom dijagnostičkom obradi utvrdi se lezija na jetri s karakteristikama sekundarne lezije, bez da se pronađe primarni tumor. Patohistološki nalaz core biopsije opisane jetrene lezije utvrdi da se radi o karcinomu bez jasnog primarnog sjela tumora. Započinje se liječenje prema kemoterapijskom protokolu s gemcitabinom i karboplatinom no razvije se pancitopenija te se aplikacija drugog ciklusa odgodi uz potrebu za aplikacijom faktora rasta filgrastima. U nastavku se aplicira još jedan ciklus gemcitabina i karboplatine no zbog ponovne pancitopenije liječenje se prevodi na paklitaksel. Zbog teškog podnošenja kemoterapije, razvoja nuspojava i slabog kliničkog odgovora učini se tekuća biopsija i analiza genskih mutacija tumorske DNA putem Foundationone protokola. Utvrdi se mutacija GNAS R201H za

koju je u medicinskoj literaturi opisano povoljno djelovanje MEK inhibitora Trametiniba. Na temelju toga kod našeg pacijenta uvodi se Mekinist u sklopu milosrdnog davanja tvrtke Novartis. Liječenje se uspješno provodi kroz deset mjeseci do razvoja progresije bolesti. Razvila se nuspojava akneiformnog osipa na licu koji se liječi antibiotskom terapijom uz kratki prekid ukidanja lijeka. Nakon progresije bolesti opisane na CT-u ponovi se tekuća biopsija i analiza tumorskog genoma FoundationOne testiranjem te se utvrdi visoko opterećenje brojem mutacija (high tumor mutation burden, TMB). S obzirom na opisan povoljan učinak lijeka atezolizumaba kod tumora s poznatim visokim TMB započinje se liječenje tim imunoterapeutikom. Do pisanja ovog prikaza slučaja terapija atezolizumabom provodi se kroz 7 mjeseci uz praćenje smislenog odgovora.

AGNOSTIC APPROACH IN THE TREATMENT OF GI TRACT TUMOR

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In this case report we present the treatment of a patient with cancer of unknown primary site who underwent analysis of tumor DNA mutations and received therapy based on a specific mutation and a high tumor mutation burden (TMB). The patient presented with loss of appetite, abdominal pain, general weakness, and weight loss as the main symptoms. The performed diagnostic tests revealed a lesion on the liver with the characteristics of a secondary lesion, without finding a primary tumor. The pathohistological finding of the core biopsy of the described liver lesion determines that it is a cancer without a clear primary tumor site. We started the treatment according to the chemotherapy protocol with gemcitabine and carboplatin, but the patient daveloped pancytopenia and the second cycle is delayed with the need for the aplication of filgrastim. Another cycle of gemcitabine and carboplatin is administered, but due to recurrent pancytopenia, treatment is switched to paclitaxel. Due to the sideffects of chemotherapy and poor clinical response, a liquid biopsy and subsequent analysis of gene mutations in tumor DNA is performed via the Foundationone protocol. A mutation in GNAS R201H was identified for which the beneficial effect of the MEK inhibitor Trametinib has been described in the medical literature. Based on this, Mekinist is introduced to our patient as part of Novartis' charitable giving. Treatment is successfully carried out for ten months until the development of disease progression. A side effect of acneiform rash on the face has developed which is treated with antibiotic therapy and a brief discontinuation of the drug. After the progression of the disease described on CT, the liquid biopsy and analysis of the tumor genome by FoundationOne assay are repeated and a high tumor mutation burden (TMB) is determined. Due to the described beneficial effect of atezolizumab in tumors with known high TMB, treatment with this immunotherapeutic is initiated. As this case report is written, atezolizumab has been given for 7 months with a meaningful response to therapy.

UČINAK LIJEČENJA IMUNOTERAPIJOM I SBRT-OM U BOLESNICE S TROSTRUKO NEGATIVNIM KARCINOMOM DOJKE

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Trostruko negativan karcinom dojke predugo vrijeme bio je podtip karcinoma dojke bez novih terapijskih mogućnosti. Zadnjih nekoliko godina i u ovoj indikaciji moguće je uspješno primjeniti imunoterapiju. Ekstrakranijalna SBRT u indikaciji oligometastatskog i oligoprogresivnog karcinoma dojke postiže odličnu lokalnu

kontrolu bolesti.Predkliničke i kliničke studije dokazale su sigurnost primjene i potencijalnu sinergiju imunoterapije u kombinaciji sa SBRT-om.

Pacijentica r.1985 u 5/2019 prima se na Odjel torakalne kirurgije radi recidiva supramamilarnog apscesa lijeve dojke. Gospođa je zdrava, bez kronične terapije, urednih menstralnih ciklusa, zadnje od troje djece rodila je prije 5 godina. Za vrijeme boravka na Odjelu učini se reincizija i biopsija lijeve dojke supramamilarno. Nalaz patologa pokaže da se radi o invazivnom medularnom karcinomu dojke koji je histološkog gradusa III, nuklearnog gradusa III, visokog proliferacijskoga indeksa (Ki67 iznosi oko 80%) ER 0 PR0 HER2 0 Iz dijagnostičke obrade:UZV dojki: BI RADS 2 Mamografija BI RADS 2 MR dojki: U GLK lijeve dojke distorzija parenhima unutar kojeg se izdvajaju dva fokusa postkontastne opacifikacije,promjera 0,9 cm i 1 cm. BI RADS 6 U 07/2019. učinjen op zahvat:ablatio mammae et SLNB axillae sin.PHD: Carcinoma invasivum mammae (NST), gr III, Tm 2x1x2cmm, Ki67 50%,, ER 0, Pr 0, HER2 0 1 od 4 limfna čvora pozitivan. Provedeno adj. liječenje kemoterapijom: ACddT.

12/2019 MSCT TORAKSA pokaže u svim segmentima pluća više nodoznih lezija koje će odgovarati sekudarizmima. Najveća lezija je bazalno lijevo: 6 mm. MSCT ABDOMENA : uredan nalaz

1/2020 PET/CT Fokalna nakupljanja FDG-a u subcentimetarskim nodoznim lezijama oba plućna krila:sekundarni depoziti.

02/2020 učinjena dijagnostička VATS metastazektomija donjeg režnja desnog pluća.PHD: Nalaz odgovara metastatskom tumorskom tkivu karcinoma dojke – subtip trostruko negativan. PDL1 pozitivan

3/2020 početak liječenja nabpaklitakselom i atezolizumabom, bolesnica je još uvijek (09/2021) na istoj terapiji uz kraći prekid zbog hipertireoze gr.3.

10/2020 MSCT TORAKSA: intrapulmonalne nodozne lezije lijevo uz luk aorte danas mjere 7 i 1 mm, ranije 10 i 5 mm.-lezija dorzalno lijevo progresija 15 mm, ranije 10- desno dijafragmalno progresija, 9 mm, ranije 8, ostale lezije su bez promjene oblikom i veličinom, a novih se ne vidi.

12/2020.proveden SBRT na 6 sekundarizama pluća.

02/2021 MSCT toraksa: rezolucija SBRT –om tretiranih lezija parenhima oba pluća, progresija u veličini dva sekundarizma (4mm–8mm, 7–12 mm), ostatak nalaza stacionaran.

03/2021. Provedena SBRT dva sekundarizma u progresiji.

7/2021. MSCT toraksa : regresija SBRT-om tretiranih sekundarizama.

09/2021 MSCT toraksa i abdomena :stacionarna bolest. Bolesnica je odličnog općeg stanja, dobro podnosi liječenje.

SBRT, neinvazivna metoda prema predkliničkim studijama može promijeniti mikrookoliš tumora i učiniti tumor više osjetljivim na PD-1/PD-L1 inhibitore što se može sigurno primjeniti u kliničkoj praksi. Za definiranje najučinkovitijeg protokola liječenja potrebno je pričekati ishode brojnih kliničkih studija koje su u tijeku u indikaciji karcinoma dojke u ovoj kombinaciji liječenja.

EFFECT OF COMBINED TREATMENT WITH IMMUNOTHERAPY AND SBRT IN PATIENT WITH TNBC

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TNBC was long time subtype of breast cancer without novel therapeutic options. In last few years also in this indication it is possible to successfully use immunotherapy. Extracranial SBRT in breast cancer patients with oligometastatic or oligoprogressive disease is well-tolerated with excellent results in local control. Preclinical and clinical trials have proved safety and potential synergistic effect of immunotherapy combined with SBRT.

Patient born in 1985. was admitted in May 2019 on Department of Thoracic Surgery because of recidival supramamilar abscess of left breast. Patient was otherwise healthy, without chronic therapy, with regular men-

strual cycles, last of her three children was born 5 years ago. Incision and biopsy of left breast abscess was performed. Pathologist report revealed invasive medullary breast carcinoma with high histological an nuclear gradus, high proliferation index Ki 67 80% ER 0 PR 0 HER 2 0.Further diagnostics was performed:Breast ultrasound:BI RADS 2 Mammography: BIRADS 2 Breast MRI: in left breast upper outer quadrant visible distorsion of parenchyma, in this area 2 focal postcontrast opacity 0,9 and 1 cm of diameter. BI RADS 6. In June 2019 surgery was performed: left mastectomy and SLNB. Pathological report revealed Ca invasivum mammae l.sin gr.3, ER 0 PR0 HER2 0 Ki 67 50% 1of 4 lymph nodes was positive. Adjuvant chemotherapy ACddT was applied. In December 2019 MSCT of the thorax revealed in all segments of lungs multiple nodal lesions which could be metatases. Biggest lesion on base of left lung : 6mm.January 2020: PET/CT focal uptake of FDG in subcentimetre nodal lesions in both lungs: secondary deposits. February 2020 diagnostic VATS metastasectomy of lower lobe right lung was performed. Pathology report revealed metastatic breast cancer tissue: TNBC, PDL1 positive.In March 2020 treatment with nabpaklitaksel and atezolizumab was applied, patient is still today (September 2021) receiving same treatment with short discontinuation due to hyperthyreosis gr.3 October 2020 MSCT of thorax : pulmonary nodal lesions left near aortic arch 7 and 1 mm, earlier 10 and 5 mm, left dorsal lesion progression 15 mm, earlier 10 mm, right diaphragmatic lesion progression 9 mm, earlier 8 mm, other lesions without changes in shape and length. December 2020 SBRT on 6 secondary lesions of lung was applied. February 2021 Msct of thorax :resolution of lesions treated with SBRT in parenchyma of both lungs, progression 2 not treated secondary lesions ((4mm–8mm, 7–12 mm),other lesion without changes.March 2021 SBRT of two secondary lesions in progression was performed. July 2021 MSCT of thorax and abdomen : regression in size of SBRT treated secondary lesions, otherwise stationary September 2021 MSCT thorax and abdomen – stabile disease. Patient is still ECOG 0, without side effects of treatment.

SBRT, noninvasive method according preclinical trails can change of tumor microenvironment and make tumor more sensitive for PD-1/PD-L1 inhibitors which can be safely used in clinical practice. It is necessary to wait results of many ongoing clinical trials with combined immunotherapy and SBRT in indication of BC to define most efficient protocols of treatment.

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PROCJENA UMORA U OBOLJELIH OD RAKA DOJKE LIJEČENIH NA KLINICI ZA TUMORE PALBOCIKLIBOM I ANTIHORMONSKOM TERAPIJOM PREMA UPITNIKU O ISHODU LIJEČENJA PRIJAVLJENOM OD STRANE BOLESNIK

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Rak dojke je najčešće dijagnosticirani karcinom kod žena i drugi najčešći uzrok smrti od raka kod žena u Hrvatskoj prema podatcima Registra za rak Republike Hrvatske iz 2018. godine. Hormonski receptor (HR) pozitivan, receptor ljudskog epidermalnog faktora rasta 2 (HER-2) negativan rak dojke je imunofenotipski podtip s trenutno najviše dostupnih terapijskih opcija. Unatrag nekoliko godina, zlatni standard u liječenju ovog podtipa raka dojke u uznapredovalom stadiju bolesti, je primjena inhibitora selektivnih ciklin ovisnih kinaza 4/6 (CDK 4/6), kao dodatak antihormonskoj terapiji. To je kombinacija lijekova s dobro poznatim, uglavnom prihvatljivim profilom nuspojava koje se relativno jednostavno mogu zbrinuti. Umor, kao jedan od najučestalijih simptoma kod oboljelih od karcinoma, ima značajan negativan utjecaj na funkcioniranje pacijenata jednako kao i na njihovu kvalitetu života, a u isto vrijeme, umor je često zanemaren i nedovoljno se procjenjuje kao nuspojava.

U ovom istraživanju smo koristili upitnike o ishodu liječenja ispunjene od strane pacijenata (PROs) kao i upitnike o kvaliteti života oboljelih od karcinoma – BR23 Europske organizacije za istraživanje i tretman raka (EORTC-QLQ- BR23) kako bi se procijenila i ispitala učestalost umora i njegov utjecaj na kvalitetu života tijekom specifičnog onkološkog liječenja bolesnica s HR – pozitivnim, HER 2 negativnim diseminiranim rakom dojke liječenih na Klinici za tumore.

Istraživanjem smo obuhvatili podatke 110 bolesnica koje su navele umor kao nuspojavu tijekom liječenja palbociklibom i antihormonskom terapijom u razdoblju od 8/2018 do 12/2020 na Zavodu za internističku onkologiju Klinike za tumore palbociklibom i antihomonskom terapijom. Kao uključni kriterij, bolesnice su trebale provesti barem jedan cjeloviti, četverotjedni, ciklus liječenja uz priložene popunjene upitnike. Za daljnju analizu su bili podobni PROs i EORTC upitnici od ukupno 101 žene, sve postmenopauzalnog hormonskog statusa s medijanom od 67 godina života. Prethodno liječenje uznapredovalog raka dojke provedeno je kod 49% bolesnica i to uglavnom antihormonskom terapijom, što treba uzeti u obzir kada se razmišlja o pretretiranosti bolesnica i posljedično nuspojavama koje utječu na kvalitetu života. U 85 % slučajeva je palbociklibu pridružen fulvestrant, a umor kao nuspojavu ovog sustavnog antineoplastičnog liječenja je prijavilo 83% bolesnica.

U zaključku, ovom analizom iz stvarne kliničke prakse prikazali smo kako je umor u našoj, promatranoj populaciji, česta nuspojava. Također smo ukazali na potrebu za podrobnijem osvrtanju i razumijevanju simptoma na koje se referiraju bolesnici tijekom sustavnog liječenja. Smatramo da je nužno planirati daljnja istraživanja koja bi za cilj imala osvijestiti problem umora kod onkoloških bolesnika kako bi se taj simptom čim ranije prepoznao, a shodno tome i liječio. Umor ima značajan potencijal uzrokovanja akutnog stresa kod onkoloških pacijenata te, iako nije nuspojava koja izravno ugrožava život bolesnika, uistinu je jedan od zahtjevnijih simptoma kako za oboljele tako i za njihove ordinarijuse.

Ključne riječi: HR+ rak dojke, palbociclib, CDK 4/6 inhibitori, umor

ASSESSMENT OF FATIGUE IN CANCER PATIENTS TREATED WITH PALBOCICLIB AND ENDOCRINE THERAPY ACCORDING TO PATIENT-REPORTED OUTCOMES AT THE UNIVERSITY HOSPITAL FOR TUMORS

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Breast cancer is the most common cancer in women and the second cause of mortality from cancer in women in Croatia confer to the last Croatian Registry of cancer. Hormonal receptor (HR) positive and human epidermal growth factor (Her-2) negative breast cancer is the larger therapeutical subtype. For the last few years, the standard of care for this subtype, in the advanced setting, are selective cyclin-dependent kinases 4/6 (CDK 4/6) inhibitors, in addition to endocrine therapy (ET). These agents have acceptable and easily manageable adverse events. Fatigue has a significant negative impact on a patient's functional ability and quality of life as the most prevalent cancer-related symptom but is commonly under-evaluated.

This analysis evaluated patient-reported outcomes (PROs) and the European Organization for Research and Treatment of Cancer Quality of life Questionnaire – BR23 (EORTC-QLQ-BR23) to assess and discuss fatigue and its impact on health-related quality of life in patients with HR-positive, HER 2 negative, metastatic disease treated at University hospital for tumors.

We obtained data from 110 patients with HR-positive HER2- negative breast cancer who were treated at the Division of Medical Oncology with palbociclib and endocrine therapy for division of time from 08/2018 to 12/2020 and who had reported fatigue as an adverse event. Patients had to complete at least one four-week cycle of therapy and fill in the questionnaires. For further analysis were evaluable 101 female patients, postmenopausal, with the median age of 67 years. Previously treatment for advanced breast cancer had 49% of patients, most commonly with endocrine therapy. Predominantly endocrine partner in treatment with palbociclib was fulvestrant, in 85%. As an adverse effect of this specific antineoplastic treatment, 83% of the treated population had reported fatigue.

In conclusion, this analysis of real clinical practice has revealed that fatigue is prevalent in this observed population. Additionally, we indicate the requirement for a better understanding of symptoms experienced by patients on this precise therapy. We consider that is crucial to plan further researches to better identify and objectify fatigue since this symptom is not easy to define. Fatigue has exceptional distress potential, and although not a life-threatening adverse event, this is a challenging symptom for most patients and their physicians.

Keywords: HR+ breast cancer, palbociclib, CDK 4/6 inhibitors, fatigue

PRISUTNOST P53 KAO POTENCIJALNOG MARKERA KAHEKSIJE U UZNAPREDOVALOJ ZLOĆUDNOJ BOLESTI

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Uvod: Bjelančevina p53 ima brojne funkcije uključujući i poticanje apoptoze. Protutijela na 53 povezana su s mutiranim statusom p53. Kaheksija je kompleksno stanje koje nastaje smanjenjem proteinske mase i masnog tkiva, uslijed promjenjenog metabolizma i smanjenog unosa proteina i kalorija, ali i proinflamatornog zbivanja u okviru patofiziologije kronične bolesti. Čak 80% onkoloških bolesnika u uznapredovaloj fazi bolesti ima razvijenu kaheksiju, a u njih 40% to je i uzrok smrti zbog čega kaheksija predstavlja važan prognostički parametar.

Poznato je da su koncentracije TNF-α (tzv. kahetični citokin) povećane u bolesnika s kaheksijom. Istraživanja su pokazala da TNF-α posreduje u inhibiciji miogene diferencijacije kroz p53 PW1 ovisan put. p53 izražen je u matičnim mišićnim stanicama i nedostatak p53 mijenja broj tih stanica.

Cilj: U ovom radu analizirali smo prisutnost protutijela na p53 (p53Abs) u serumu i slini bolesnika s različitim karcinomima. Cilj ovog istraživanja bio je odrediti koncentraciju p53Abs u serumu i slini bolesnika s različitim karcinomima i usporediti je s vrijednostima zdravih ispitanika u serumu i slini. Dobivene rezultate usporedili smo s indeksom tjelesne mase (BMI), dobi, odnosno da li su bolesnici bili kahetični ili nisu temeljem konsenzusa o BMI 19 kg/m2 kao graničnoj vrijednosti.

Materijali i metode: U istraživanje smo uključili 58 bolesnika s različitim karcinomima i 20 zdravih ispitanika. Uzorci za ispitivanje bili su slina i serum bolesnika i zdravih ispitanika. Trinaest bolesnika imalo je kaheksiju, a četrdeset i pet bolesnika nije. Protutijela na p53 u serumu i slini određivali smo ELISA metodom. Cut-off vrijednosti za p53Abs u serumu i slini određene su ROC krivuljom, te je za slinu 7,8 U/ml, a za serum 12,2 U/ml.

Rezultati: Bolesnici su imali povišene koncentracije p53Abs u serumu i slini u odnosu na zdrave ispitanike (serum, p=0.0013; slina, p=0.0001). Koncentracije p53Abs u slini i serumu bile su statistički povezane (p=0,0002). Koncentracije p53Abs u slini bile su više (Median 25,9; 95% CI 19,9 – 43,4) od koncentracija u serumu (13,4; 95% CI 10,8 – 16,6). Analizirali smo i povezanost p53Abs u serumu u kahetičnih i nekahetičnih bolesnika i dobili negativnu statistički značajnu razliku (p=0,0179) te isto tako i negativnu povezanost koncentracije p53Abs i statusa kaheksje u slini istih bolesnika (p=0.013). Statistički negativna povezanost nađena je između koncentracije p53Abs u serumu i BMI (p=0,023), kao i koncentracije p53Abs u slini i BMI (0.019). Nismo dobili statističku povezanost koncentracije p53Abs u serumu i slini bolesnika s dobi bolesnika.

Zaključak: Naši rezultati upućuju na mogućnost određivanja p53Abs u slini bolesnika s karcinomima, kao i moguće povezanosti povećane koncentracije p53Abs i kaheksije. Ovi rezultati ukazuju i na moguće određivanje p53Abs u slini i/ili serumu kao parametra kaheksije, budući da BMI nije uvijek precizna mjera iste.

PRESENCE OF P53 AS A POTENCIAL CAHEXIA MARKER IN ADVANCED MALIGNANT DISEASE

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Introduction: P53 protein has numerous physiological functions including activation of apoptosis. Anti-p53-antibodies are linked with mutational status of p53. Cahexia is a complex condition due to decrease of protein and fat tissue, as a consequence of altered metabolism and decreased protein and calories input, but also because of proinflammatory context in pathophysiology of chronic illness. Almost 80% of oncology patients in advanced phase of disease have fully developed cahexia, and in some 40% it is the direct cause of death. So, cahexia represents important prognostic parameter. It is well known that serum levels of TNF-a (tumor necrosis factor alpha) are increased in patients with cahexia. It has been shown that TNF-alpha mediates process of inhibition of myogenic differentiation through p53 PW1-dependent pathway. P53 is expressed in myocite stem-cells and lack of p53 changes the number ot those cells.

Aim: We analysed the presence of p53 antibodies (p53Abs) in serum as well in salina of patients with different carcinomas. The aim of this research was to assess concentration of p53Abs in serum and salina in patients with different carcinomas and compare it to values in healthy volunteers in serum and salina. The results were analysed with BMI (body mass index), age, and regarding cahexia was present of not on the basis of BMI 19 kg/m2 as cut-off value.

Materials and methods: There were 58 patients with different carcinomas and 20 healthy volunteers analysed in this study. Specimens were salina and serum of patients and healthy volunteers. Thirteen patients had cahexia, and fortyfive didn't have. Antibodies to p53 in serum and salina were analysed with ELISA-assay. Cut-off level for p53Abs in serum and slina were determined by ROC-curve, which was 7,8 U/ml and 12,2 U/ml for salina and serum, respectively.

Results: Patients had increased concentrations of p53Abs in serum and salina compared to control group (healthy ones) (serum, p=0.0013; salina, p=0.0001). Concetrations of p53Abs in salina and serum were statistically confirmed on significant level (p=0,0002). Concentrations of p53Abs were higher in salina (median 25,9; 95% CI 19,9 – 43,4) compared to concentrations in serum (13,4; 95% CI 10,8 – 16,6). We analysed if there is correlation of p53 in serum in cahectic and non-cahectic patients and there was negative statistical correlation (p=0,0179) as well as negative correlation of p53Abs and cahexia-status in salina of same patients (p=0.013). Statisticaly negative correlation was found also between concentration of p53Abs in serum and BMI (p=0,023), as well as concentration of p53Abs in salina and BMI (0.019). We didn't get any significant correlation of p53Abs in serum and salina of patients with their age.

Conclusion: Our results indicate the possibility of assessment of p53Abs in salina of patients with different carcinoma, but also on correlation of increased concentration of p53Abs and cahexia. These results show that assessment of p53Abs in salina and/or serum might represent a cahexia parameter, especially in circumstences of BMI as non-reliable measure of it.

KLINIČKO ISKUSTVO SIGURNOSTI PRIMJENE INHIBITORA KINAZA OVISNIH O CIKLINIMA (CDK4/6) U TERAPIJI HORMONSKI POZITIVNOG HER2 NEGATIVNOG METASTATSKOG RAKA DOJKE: MULTICENTRIČNA, RETROSPEKTIVNA STUDIJA 9 NEKLINIČKIH ONKOLOŠKIH CENTARA U REPUBLICI HRVATSKOJ (RH)

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Uvod: Kombinacija CDK4/6 inhibitora i endokrine terapije (ET) produžuje preživljenje kod bolesnica s metastatskim hormonski ovisnim HER2 negativnim rakom dojke uz prihvatljiv sigurnosni profil. Od kolovoza 2018. godine primjena inhibitora CDK4/6 postala je dio standardnog liječenja hormonski pozitivnog, HER2 negativnog metastatskog raka dojke u RH. Iako je učinkovitost CDK4/6 inhibitora slična uočene su izvjesne razlike u profilu toksičnosti. Namjera ove studije je istražiti i usporediti toksični profil različitih CDK4/6 inhibitora.

Metode: Retrospektivno smo analizirali podatke iz bolničkog informatičkog sustava od 137 bolesnika (134 ženskog i 3 muškog spola) liječenih kombinacijom CDK4/6 inhibitora i ET u devet nekliničkih onkoloških centara: u Županijskoj bolnici Čakovec, te Općim bolnicama u Dubrovniku, Karlovcu, Koprivnici, Puli, Slavonskom Brodu, Šibeniku, Varaždinu i Zadru.

Rezultati: Prosječna dob bolesnika iznosila je 66 godina (36–83 godine), 49% na početku liječenja bilo je starije od 65 godina. 90% su bile postmenopauzalne bolesnice. Na početku liječenja 66% bolesnika je imalo minimalno jedan komorbiditet (1–4). Visceralne metastaze bile su prisutne kod približno 50% bolesnika, samo koštane kod 29%, a druga nevisceralna sijela u 21% slučajeva. Inicijalno metastatskom bolešću prezentiralo se 47 (34%) bolesnika, 82 (60%) bolesnika su prethodno liječena (neo)adjuvantnom ET, a kod 55% (76/137) bolesnika ustanovljena je hormonska rezistencija. CDK4/6 inhibitori primjenjivani su kao 1. linija liječenja kod 91 (67%) bolesnika, u 2. i višim linijama kod 46 (33%) bolesnika. Palbociklib je bio izbor za 78 bolesnika, 48 je liječeno ribociklibom, a 11 abemaciklibom. Najčešći endokrini partner bio je fulvestrant, kod 53% bolesnika. Nakon medijana praćenja od 11 mjeseci (1–37) ukupna hematološka toksičnost zabilježena je kod 75 (55%) bolesnika, a nehematološka kod njih 17 (12%). Neutropenija svih stupnjeva javila se kod 73 (53%), a stupnja 3 ili 4 kod 20 (15%) bolesnika. Porast transaminaza stupnja 3 ili 4 zabilježen je kod 4,4% bolesnika, a proljevi stupnja 1 ili 2 javili su se u približno 50% liječenih abemaciklibom. Kod 6 bolesnika liječenje je prekinuto zbog hepatalne toksičnosti (4 su liječena ribociklibom, 2 abemaciklibom), a kod jednog pacijenta zbog povraćanja (palbociklib).

Zaključak: Ovo retrospektivno kliničko istraživanje pokazalo je sličnu pojavnost neželjenih posljedica liječenja inhibitorima CDK4/6 u usporedbi s prethodnim kliničkim ispitivanjima. Neutropenija stupnja 3 ili 4 zabilježena je kod manjeg broja naših bolesnika nego je prijavljeno u kliničkim studijama. Napominjemo kako je kod

4 bolesnice kojima je prekinuto liječenje jednim CDK4/6 inhibitorom zbog hepatalne toksičnosti nastavljeno liječenje pabociklibom bez ponovljene hepatatoksičnosti. Kombinacija inhibitora CDK4/6 i ET pokazala se u kliničkoj praksi kao sigurna i dobro podnošljiva terapijska opcija. Naše iskustvo sugerira mogućnost nastavka liječenja promijenjenim CDK4/6 inhibitorom.

REAL WORLD SAFETY PROFILE OF CYCLIN DEPENDENT KINASE (CDK4/6) INHIBITORS IN THE TREATMENT OF HORMON RECEPTOR POSITIVE (HR+) HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 NEGATIVE (HER2–) METASTATIC BREAST CANCER (MBC): A MULTICENTRIC RETROSPECTIVE STUDY OF 9 NONCLINICAL ONCOLGY CENTERS IN REPUBLIC OF CROATIA (RC)

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Introduction: Combination of CDK4/6 inhibitors with endocrine therapy (ET) prolongs survival in HR+/ HER2– mBC patients with favourable toxicity profile. Since August 2018 implementation of CDK4/6 inhibitors have become standard of care for patients with HR+/ HER2– mBC in RC. Although, the efficacy of CDK4/6 inhibitors are similar, there are some differences in their toxicity profiles. The purpose of this study is to examinate and compare toxicity of different CDK4/6 inhibitors.

Metods: We have retrospectively evaluated consecutive data from the hospital information system for 137 HR+/ HER2– mBC patients (134 female and 3 male) treated with CDK4/6 inhibitors and ET from August 2018 to August 2020 at County Hospital (CH) Čakovec, General Hospital (GH) Dubrovnik, GH Karlovac, GH Koprivnica, GH Pula, GH Slavonski Brod, GH Šibenik, GH Varaždin and GH Zadar.

Results: Our study included patients with median age of 66 years (36–83 years). Among them 49% patients were > 65 years and 90% were in postmenopausal state. 66% patients had at least one comorbidity (0–4) at the start of the treatment. Visceral disease was observed in approximately 50% patients while bone only metastases were present in around 29% and other non-viceral disease in 21% patients. De novo metastatic disease was present in 47 (34%) patients and 82 (60%) patients had received prior (neo)adjuvant ET, while 55% (76/137) had endocrine resistant disease. CDK4/6 inhibitors were used as a 1st line therapy in 91 (67%) patients and as ≥2nd line of treatment in 46 (33%) patients. Palbociclib was the choice of treatment for 78 patients, while 48 patients received ribociclib and 11 were treated with abemaciclib. The most common ET with CDK4/6 inhibitor was

fulvestrant (53%). After a median follow up of 11 months (1–37) hematologic toxicity of any grade was evaluated in 75 (55%) and non-hematologic toxicity in 17 (12%) patients. Neutopenia of any grade occured in 73 (53%) patients,while serious forms of neutropenia grade 3 or 4 were reported in 20 (15%) patients. An increase in aminotransferase levels grade 3 or 4 occured in 6 (4.4%) patients and diarrhea grade 1 or 2 appeared in approximately 50% patients treated with abemaciclib. Treatment discontinuation due to toxicity happened in 6 patients because of hepatotoxicity (4 ribociclib and 2 abemaciclib) and 1 patient due to vomiting (palbociclib).

Conclusion: This real world data show similar occurence of adverse events during CD4/6 inhibitors treatment, in comparison to previous clinical trials. However, neutropenia grade 3 or 4 occured lower than reported in the clinical trials. It is important to highlight that 4 patients with hepatic toxicity had rechallenge with palbociclib without reappearance of hepatic injury. Combination of CDK4/6 inhibitors and ET is generally well tolerated in routine clinical practice. Our experience suggests the possibility of rechallenge in case of toxicity with a different CDK4/6 inhibitors.

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