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The use of cyclin-dependent kinase 4/6 inhibitors in selected patients beyond clinical trials – did we meet selection criteria after approval?

Keywords: CDK-4/6 inhibitor, endocrine sensitivity, endocrine resistance, palbociclib, ribociclib.

Background: No specific subgroup of patients with hormone receptor positive, HER2 negative metastatic breast cancer has been identified to benefit most from the combination of cyclin-dependent kinase (CDK) 4/6 inhibitors and endocrine therapy (ET). In Croatia, CDK-4/6 inhibitors were reimbursed in August 2018. The aim of this review was to analyze patients' characteristics and proportion of endocrine sensitive and resistant subgroup.

Methods: Retrospective review of the medical record database was done. It included patients treated by combination therapy (CDK-4/6 inhibitors and ET) between August 2018 and January 2019 at the University Hospital Center Zagreb. They were divided to endocrine sensitive or naive and endocrine resistant. Comparison of the initial disease presentation, visceral spread and patients' characteristics (menopausal status, age) was done.

Results: Of 44 patients, 36% were endocrine sensitive and 64% endocrine resistant.

Endocrine sensitive subgroup (n=16), median age of 59 years, received CDK-4/6 inhibitor with aromatase inhibitor as the first line therapy (69% were sensitive to prior ET and 31% were initially metastatic). Visceral spread was observed in 50% (50% had liver metastasis).

Endocrine resistant subgroup (n=28), median age of 55 years, received palbociclib in combination with fulvestrant - 25% received combination therapy as first line treatment, 68% as second line and 7% as third line. 57% of patients had visceral spread (93% had liver metastasis).

Conclusion: Our first post approval experiences show more heterogeneous patients' population than studied, but of similar characteristics to the registrational studies Monaleesa-2, Paloma-2 and Paloma-3. Patients' subgroup that will benefit the most is yet to be seen.

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Epidemiological characteristics of breast cancer in the Birac region, Republic of Srpska

Key words: Breast cancer (BC), screening, survival

Background: Review of the basic epidemiological and clinical characteristics of BC in the Birac region, analysis of survival of patients with BC, occurrence and frequency of different relapse localizations, and examination of predictive effects of various factors on the occurrence of fatal outcome and disease relapse.

Methods: Descriptive and analytical statistics, Kaplan-Meyer survival curves, Cox regression analysis.

Results: The analysis involved 129 women. Radical mastectomy was the most common of all surgical interventions. Adjuvant radiotherapy was used in almost half of patients and palliative in 12.4% of patients. Relapses of the disease occurred in 1/3 of patients. Statistically significant differences in the benefit of long-term survival were obtained for lower tumor grade, screening mammography prior to diagnosis, radiotherapy, absence of relapse, and highly statistically significant differences in hormone therapy use, and in relation to lower stage of the disease at the time of diagnosis. As significant variables for the occurrence of

fatal outcome, the grade II and grade III, the time to diagnosis, the use of radiotherapy, hormone therapy and screening, and the recurrence of the relapse disease - time to diagnosis, application and duration of hormone therapy, were distinguished.

Conclusions: There is no organized screening in our country. The most important conclusions are related to the importance of raising the awareness of all members of society in primary and secondary prevention of BC, and as soon as possible the introduction of organized screening as the most important preventive measures for this disease.

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Disease outcome in patients (pts) with HER2-positive (pos) metastatic breast cancer (MBC) treated with trastuzumab (T) and taxanes in Serbia: UMOS real world data study

Key words: metastatic breast cancer, HER2 positive, trastuzumab

Introduction: We analyzed disease outcome in all HER2-pos MBC in Serbia, who started T for MBC between 01/Jan/2010 and 31/Dec/2014.

Patients and methods: This was an observational, multicenter, retrospective cohort study.

Results: Three hundred and fifty six pts, median age of 57.5 yrs (range 27-80), followed for a median of 23.2 mo (range 0.9-82.5); 152 (42.7%) pts were diagnosed in stage 4 BC; among 204 pts initially diagnosed in stage 1-3, 92 (25.8%) pts received (neo)adjuvant T and median treatment-free interval (TFI) was 17.3 mo (95%CI 0.5-63.2). Previous anthracyclines for MBC

received 161 (45.2%) pts and 287 (80.6%) and 69 (19.4%) pts received T as first-line and second-line therapy, respectively. T was combined with docetaxel in 73 (20.5%), 3-weekly paclitaxel in 67 (18.8%) and weekly paclitaxel in 214 (60.1%) pts. Luminal and non-luminal BCs had 199 (55.9%) and 126 (35.4%) pts, respectively. Visceral, brain and bone/soft tissue metastases were found in 189 (53.1%), 14 (3.9%) and 153 (43%) pts, respectively. Overall survival (OS)and progression free survival were as follows [median mo (95%CI)]: 28.5 (25.7-33.5) and 10.8 (9.4-12), respectively. Significantly shorter OS was recorded in pts with TFI ≤ 12 mo compared to pts with TFI >12 mo (Log rank test, $p<0.01$) and pts without previous T (Log rank test, $p<0.001$). Adding of endocrine therapy to T after cessation of taxanes significantly prolonged OS (Log rank test, $p<0.001$).

Conclusion: Real world data showed that patients with HER2-pos MBC pts in Serbia treated with T resembled the data obtained in pivotal clinical trials.

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Takotsubo cardiomyopathy during chemotherapy in patient with metastatic breast cancer - a case report

Key words: breast cancer, chemotherapy, Takotsubo cardiomyopathy

Background: Takotsubo cardiomyopathy (TC) is transient cardiac syndrome that occurs more often in postmenopausal elderly women. It is associated with emotional or physical stress and characterized by a transient hypokinesis of the left ventricular (LV) apex imitating acute coronary syndrome (ACS).

Initial presentation and diagnosis: A 69-year–old female patient presented 5 hours after administration of first cycle of vinorelbine chemotherapy regimen in dose of 25mg/m2 with dyspnea, shortness of breath and cough. Electrocardiography (ECG) showed ST segment elevation in D1, aVL and ST segment depression in D2, D3 and aVF. Levels of cardiac biomarkers and D dimer were in normal range. Patient was sent to cardiologist.

Treatment and follow-up: Patient was admitted at the Cardiology Coronary Unit. Echocardiography showed hypokinesis of the LV apex and distal 2/3 of the LV anterior wall. Ejection fraction (EF) was 55%. The patient underwent emergency cardiac catheterization, which disclosed no substantial epicardial coronary artery stenosis. The patient was treated with antiplatelet therapy, an angiotensin-converting enzyme inhibitor and anticoagulant therapy with symptom improvements. Two weeks later, the ECG showed complete resolution of the ST-segment elevation and no Q-wave formation. Echocardiography revealed improvement of the apical wall motion abnormality and normalization of the EF.

Conclusion: The reported incidence of TC in cancer patients is approximately 10%. Nevertheless, patients under significant stress like uncontrolled malignant disease, ongoing oncology treatment, and those with cardiovascular risk factors complaining of cardiac symptoms should be carefully examined for signs of TC.

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Residual tumor after neoadjuvant chemotherapy for breast cancer: do we know how to treat the changed surrogate subtype

Keywords: breast cancer subtype, neoadjuvant chemotherapy, residual disease

Background: Determination of hormone receptor (HR) and Her2/neu receptor status by immunohistochemistry and fluorescence in situ hybridization (FISH) when indicated is crucial in optimizing breast cancer therapy. The purpose of this study was to evaluate the concordance in breast cancer surrogate subtype between core needle biopsy of primary tumor and residual tumor after neoadjuvant chemotherapy (NACT) and to see if the difference affected therapeutic management.

Methods: We conducted a retrospective review of all breast cancer patients in University Hospital Center Zagreb who received NACT between January 2012 and December 2016. We included only patients who had their primary and residual cancer tested in our institution. Pre and post NACT breast cancer subtype were cross-tabulated to asses change.

Results: We identified 71 patient with residual disease after NACT. Fifty-seven had both IHC and FISH where indicated analysis of primary and residual tumor. Seven (12%) had a change in tumor subtype. HR status changed from positive to negative in two cases, HER 2 status changed from positive to negative in four cases and both HR and HER2 changed from positive to negative status in one patient. In one case there was a conversion from HR negative to positive status. Subtype change led to adjustment in therapy only when the change was from negative to positive status.

Conclusion: Alterations in breast cancer types occur after neoadjuvant chemotherapy. It led to change in treatment only when the conversion was from negative to positive status. There is a need for prospective trial evaluating this problem. We recommend always retesting residual tumor when there is a negative component in primary tumor.

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Breast cancer in men

Key words: breast cancer, men, subtypes

Background: Male breast cancer (MBC) is a relatively rare disease accounting for <1% of all breast cancers (1).

Material and methods: This is a retrospective-prospective study which presents descriptive data related to MBC cases.

Results: From 1991 to 2017, 162 patients were treated at the Institute for Oncology and Radiology of Serbia. Median age at diagnosis was 65 years (range 29-90). Most patients were diagnosed in clinical stage II and III (76,5%). Modified radical mastectomy was performed in 75%. The most common histological type was invasive ductal carcinoma (72,2%), grade 2 in 74%. Most tumours were less than 5 cm in diameter (69,7%). About 36% of patients had negative axillary lymph nodes involvement, 20,4% up to 3 positives, 19,1% more than 3 positive axillary lymph nodes. Most tumours were oestrogen and progesterone

receptor positive (62,3%), one patient had *human epidermal growth factor receptor 2, Her 2* positive breast cancer. Distribution of the subtypes for patients with known receptor status and Ki67≤13% were as follows: Lum A in 22, Lum B in 16, Her 2 like in one patient. Adjuvant chemotherapy was performed in 37,6%, 64,8% had adjuvant hormonetherapy. During period of follow-up (range 1,2- 11 years) 36,4% of patients had relapse of disease (59/162), 56 patients died due to disease progression (34,6%).

Conclusion: Like postmenopausal women majority of the tumours were hormone receptor positive, dominantly Lum A like. Ongoing analysis will compare survival in females with breast cancer matched with known prognostic factors.

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Disease outcome of early breast cancer patients with subsequent pregnancy

Background: The safety of pregnancy after early breast cancer (EBC) treatment is an important issue for large number of young women. We analyzed patients who became pregnant after completion of treatment for EBC.

Methods: This is an observational retrospective-prospective cohort study. Radical surgery was performed in all patients, following adjuvant systemic therapy with or without irradiation.

Results: We identified a group od 32 patients of median age of 31.5 years (range 19-38) at the time of BC diagnosis The majority of patients were diagnosed in clinical stages I/II [29/31 (91%)] and 19/32 (61%) had breast conserving surgery followed by postoperative radiotherapy. Ductal invasive BC was noted in 16/32 (50%), tumour grade 2 in 20/32 (62.5%), luminal BC in 20/32 (62.5%), and HER2 positive BC in 4/32 (12.5%). Majority of patients received adjuvant systemic therapy: 21/32 (66%) chemotherapy, one received adjuvant trastuzumab, and 17/32 (53%) received adjuvant endocrine therapy with a median duration of 2 years (range 2-5). The average time from BC diagnosis to pregnancy was 5.5 years (0.7-10.8); 45 pregnancies were achieved with 42 healthy children born. 11/32 (34%) women initiated breastfeeding. There have been no developmental abnormalities reported in children. After a median follow-up of 11.4 years (4.4 to 40.5), 13/32 (34%) of patients experienced disease relapse, 3/32 (9%) died, two patients from BC and one from lung cancer.

Conclusion: It seemed that pregnancy does not affect survival in EBC patients which is in accordance with literature data.

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Efficacy of trastuzumab-emtansine in heavily pretreated HER2-positive metastatic breast cancer patient

Key words: HER2-positive metastatic breast cancer, T-DM1

A 45 year-old woman was presented to our hospital in June 2014 with tumor in the right breast, clinically staged as T4bN2M0. A breast biopsy reported an invasive ductal carcinoma grade II, HER2-positive, hormone-receptor negative and Ki-67 40%. The initial treatment consisted of 4 cycles of neoadjuvant anthracycline chemotherapy followed by weekly paclitaxel plus trastuzumab for 4 cycles. The patient underwent a radical mastectomy

in September 2014 (non pCR), and she received postoperative radiotherapy and adjuvant trastuzumab for one year.

In December 2015, after only 6 months from the last adjuvant trastuzumab application, abdominal CT scan showed liver metastases. She received 8 cycles of docetaxel plus trastuzumab and continued with trastuzumab until September 2016, when disease progression in liver and lung was verified. Therapy with capecitabine plus lapatinib was introduced and after 8 cycles, progression of liver metastases was confirmed and treatment with navelbine was advised. After only two cycles, disease extensively progressed in lung, mediastinum and liver associated with elevated transaminases grade 2 and performance status 2. The patient received trastuzumab emtansine and after only three cycles of T-DM1, significant clinical and objective improvement was registered: ECOG 0 and CT scan confirmed complete response. Overall, the patient received 17 cycles of T-DM1, when CNS progression occurred with clinical deterioration, and she died three months later.

This is the case reporting rapid, powerful and durable antitumor activity of T-DM1, with a favorable safety profile in the heavily pretreated HER2-positive metastatic BC patient, the finding consistent with reports from real-world experience.

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First-line treatment of the metastatic HER-2 positive breast cancer at the University Hospital Centre (UHC) Zagreb versus Cleopatra study population: Do real world patients reflect clinical study population?

Keywords: breast cancer, dual anti-HER2 blockade, HER2-positive, metastasis, pertuzumab

Background: Dual anti-HER2 blockade with trastuzumab and pertuzumab combined with chemotherapy has become standard of care in the first-line treatment of metastatic HER-2 positive breast cancer after publishing results of Cleopatra trial.

Patients and methods: Retrospective analysis of clinical and pathological characteristics of Cleopatra cohort (n=402) and RL (real life) cohort treated with trastuzumab, pertuzumab and chemotherapy (n=69) at UHC Zagreb was done.

Results: There was no significant difference in median age (55.5yrs vs. 54yrs) and visceral involvement (72.5% vs. 78%). In RL cohort, 7.2% (n=5) patients had brain metastases, while it was one of exclusion criteria in Cleopatra trial. RL patients were more often hormone receptor positive (69.5% vs. 47%) and had more prior exposure to adjuvant trastuzumab than Cleopatra patients (30% vs 12%). The major difference between study groups was lower percentage of *de novo* metastatic disease in RL cohort (26% vs. 54%).

Conclusion: Specificity of our cohort was inclusion of patients with brain metastases and use of endocrine therapy (ET) in combination with dual anti-Her2 blockade after completion of chemotherapy.

At the moment, 62% of RL patients still receive dual anti-HER2 therapy, and the median PFS is yet to be seen. The influence of the previous trastuzumab exposure and combination of ET and dual anti-HER2 blockade on PFS has to be tested.

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The influence of PTEN protein expression on disease outcome in premenopausal hormone receptor-positive early breast cancer patients treated with adjuvant ovarian ablation: long term follow-up

Keywords: early breast cancer, hormone receptors, PTEN

Background: All breast cancer (BC) patients with detectable hormone receptors (HR) expression should be offered endocrine therapy (ET). For premenopausal patients, tamoxifen and/or ovarian suppression (OvS)/ablation (OA) may improve disease outcome. Alteration of phosphatase and tensin homolog (PTEN) signaling pathways could be one of possible mechanisms of resistance to antiestrogen therapy. The aim of this study was to investigate the association of PTEN protein expression with prognostic factors [tumor histology and grade, estrogen receptor (ER) and progesterone receptor (PgR) status, human epidermal growth factor receptor 2 (HER2) status] and disease outcome in premenopausal patients with HR-positive early BCs treated with adjuvant OA.

Methods: We analyzed a group of premenopausal early (stages I/II) HR-pos BC patients who had undergone radical mastectomy followed with adjuvant OA by irradiation only. ER and PgR contents were determined by classical biochemical dextrane-coated charcoal (DCC) method, HER2 status by chromogen *in situ* hybridization (CISH) analysis and PTEN status by immunohistochemistry (IHC).

Results: Sixty-six premenopausal patients included into analysis were followed for a median of 17 years (range 1-29). Compared to PTEN-pos BCs, PTEN-neg BCs were significantly more frequently associated with lobular tumor histology ($p<0.05$) and a higher ER content ($p<0.05$). Patients with PTEN-neg BC had significantly decreased disease-free survival (DFS) and overall survival (OS) ($p<0.01$ for both) compared to patients with PTEN-pos BCs.

Conclusions: It seems PTEN status determined by protein expression may discriminate between subgroups with poor and good prognosis in premenopausal HR-pos BC patients receiving adjuvant OA.

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The role of neoadjuvant chemotherapy in treatment protocol for invasive lobular breast cancer- a case report

Keywords: lobular breast cancer, neoadjuvant chemotherapy, treatment

Invasive lobular breast cancer (ILC) accounts for up to 15 % of all breast cancers and it ranks second among invasive breast cancers. A bulk of evidence suggests that there are significant differences between invasive ductal cancer and other breast cancer forms, in terms of response to treatment. In spite of accumulated evidence, current guidelines don't make the distinction between ILC and other invasive breast cancer forms in terms of recommendation for treatment. Even though there are over 10 histological subtypes, most ILC are hormone receptor- positive and HER2 receptor negative, which makes them amenable to endocrine therapy. On the other hand, neoadjuvant chemotherapy is established standard treatment for patients presenting with locally advanced breast cancer, with its use expanding to less advanced stages of the disease. Historically, ILC are thought to respond relatively poorly to neoadjuvant chemotherapy and response rates are lower than that of invasive ductal cancer (with roughly 30% lower response rates to neoadjuvant therapy for ILC). We present a rare case of a systemically advanced, with complete response to neoadjuvant chemotherapy. A 60-year old female presented with hormonally positive and HER negative ILC in her left breast, with distant metastases present form the onset of the disease (including pleural and peritoneal disease dissemination). Upon administration of neoadjuvant therapy a complete regression of distant metastases was noted, which prompted subsequent mastectomy. We conclude that, even in relatively chemo-resistant breast cancers, such as ILC, neoadjuvant chemotherapy often proves more effective than expected.

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First Line Treatment of HR+/HER- Metastatic Breast Cancer

Keywords: breast cancer, metastatic, chemotherapy, endocrine therapy, progression-free survival

Background: Metastatic breast cancer is an incurable disease with only 25% patients surviving 5 years from diagnosis. Two thirds of these patients have HER2 negative (HER2-), endocrine dependent (HR+) disease where according to guidelines mainstay of treatment is hormonal therapy.

Patients and Methods: This was retrospective observational study conducted in order to assess the first line treatment choice for 141 metastatic HER2-/HR+ breast cancer patients diagnosed during 2014 and 2015 at Oncology Institute of Vojvodina. Potential parameters that had influenced the treatment choice have been assessed. Progression free survival (PFS) for first line treatment was calculated using Kaplan –Meier method.

Results: Patients' median age was 61 (28-85), 122/141 (86,5%) were postmenopausal, 43/141 (30,5%) patients had de novo metastatic disease. 91/141 (64,5%) of the patients were treated with chemotherapy in the first line. These patients were significantly younger, had less comorbidities, had more metastatic sites, visceral disease and were less likely to have bone only metastases in comparison to patients treated with endocrine therapy in the first line. Median PFS for initial chemotherapy was 5 months versus 11 months for initial endocrine therapy $p<0.0001$ HR 0.44 (0.28-0.68), and 7 months when calculated for patients who were

treated with chemotherapy and maintenance endocrine therapy p=0.27 HR 0.81 (0.56-1.18).

Conclusion: According to our data which is in consistency with other real world data, high percentage of patients are treated with first line chemotherapy which is not associated with better outcome.

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Neoadjuvant Dual Anti-HER2 Treatment in Breast Cancer in University Hospital Center Zagreb

Key words: early breast cancer, HER2, neoadjuvant, pertuzumab, trastuzumab

Background: NeoSphere and TRYPHAENA studies proved efficacy of pertuzumab and trastuzumab in combination with chemotherapy in neoadjuvant setting in patients with localized, locally advanced and inflammatory HER2 positive breast cancer. Dual anti-HER2 based protocols have been used in our department since August 2017. The aim of this report is to compare outcomes observed in our patients with the ones reported in the registration studies.

Methods: This is an observational retrospective study that included 43 patients with early HER2 positive breast cancer presenting in our center since August 2017. They have received or are receiving treatment with neoadjuvant pertuzumab and trastuzumab in combination with chemotherapy: anthracycline and taxane (93%, n=40), mono-taxane (5%, n=2) or taxane and platin (2%, n=1). The primary outcome was comparison of pathological complete response (pCR) rate with the data from the registration studies. We also reviewed demographic data, clinicopathological characteristics of tumors, and concordance of magnetic resonance imaging findings after therapy with pathological findings after surgery. It should be mentioned that the number of tumors analyzed was 44, as one patient had bilateral tumors.

Results: So far, out of 43 patients (44 tumors), 29 (67%) have completed the neoadjuvant treatment and surgery was performed, so pCR could be analyzed and it has been obtained in 48% (n=14). Complete remission was correctly described on MRI in only 17% (n=5) patients which grossly underestimates the actual pCR rate.

Conclusion: Our patients had similar outcomes as the patients from the registration studies. These results support the neoadjuvant approach, but they should be reviewed on a larger population.

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Tolerability of bevacizumab in newly diagnosed advanced epithelial ovarian cancer: single institution experience

Key words: advanced epithelial ovarian carcinoma, bevacizumab, toxicity

Background: The aim of our study was to investigate the toxicity profile of bevacizumab used in daily clinical practice among patients with advanced OC.

Patients and Methods: At our Medical Oncology Department, patients with advanced OC (FIGO stage III C and IV) were treated with paclitaxel-carboplatin (TP) chemotherapy regimen plus

bevacizumab. Adverse events (AE) were recorded at each cycle and graded according to CTCAE v.5.0.

Results: Seventy patients were included in the study, median age 56.5 (28-78 age). Patients were well stratified according to ECOG performance status: 33 pts (47.1%) were ECOG 0 and 37 pts (52.86%) were ECOG 1. Majority of the patients were less than 70 years (91.43%) old. Registered toxicity was as follows: 37 pts (52.86%) had hypertension gr 1, 14 pts (20%) had hypertension grade 2 and only 4 pts (5.71%) experienced hypertension grade 3 adequately controlled with antihypertensive therapy. Thromboembolic events were observed in 3 pts (4.26%), two of them confirmed as noncomplicated superficial thrombophlebitis and one was manifested as serious AE, pulmonary thrombosis.

Conclusion: The most frequent AE in our analysis was hypertension, which was easily and successfully managed with appropriate monitoring and antihypertensive therapy.

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Treatment of patients with ovarian cancer at the university hospital for tumors Zagreb

Keywords: FIGO, ovarian cancer, primary cytoreduction, systemic treatment

Background: Ovarian cancer is the 7th most common malignancy in Croatia according to National Cancer Registry 2015. (it accounts for 4% of all cancers in women).

Patients and Methods: In our study we retrospectively analyzed data collected from 57 ovarian cancer patients who were treated with systemic antineoplastic therapy at the Department of Medical Oncology in period from 01/2017 to 01/2019. Included patients' median age was 63 years, they had good performance status (ECOG 0-1) and generally were without heavy comorbidity.

Results: According to FIGO classification, specified by operator gynecologist, most women had stage III disease (40%), while stage IV had 25% patients. For 20 patients (35%), stage of the disease was not specified. Majority of patients, around 75%, had primary cytoreduction and 38% of them had no macroscopic residual disease. In the observed period, 90% of patients postoperatively recieved chemotherapy with paclitaxel and carboplatin and 54% have not recieved bevacizumab in first line therapy. In patient who did recieve bevacizumab, median duration of bevacizumab therapy was seven months.

Conclusion: Decision making in treatment of ovarian cancer involves more than one specialist and individual approach has to be used when defining each patients diagnostic and therapeutic plan.

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Assessment of symptom burden of patients with metastatic NSCLC before the start of immunotherapy - single centre experience

Key words: Edmonton Symptom Assessment System (ESAS), Immunotherapy, Patients reported outcomes (PROs)

Background: Patients with advanced cancer experience high rates of both physical and psychological symptoms. Symptom management guided by patients' self-report of symptoms (PROs) leads to better symptom management, improvement in quaility of life and prolongs overall survival. The Edmonton Symptom Assessment System (ESAS) has been proposed as a screening tool in cancer patients. The objective of this investigation is to assess the symptom burden using ESAS in patients with NSCLC

with PD-L1 expression ≥50% and no driver mutations, that were scheduled to receive first cycle of immunotherapy as part of an expanded access program at the Institute for oncology and radiology of Serbia (IORS).

Patients and methods: ESAS was used to assess symptoms in patients with NSCLC at the time of admission, before immunotherapy. Descriptive statistical methods were used to analyze the collected data.

Results: ESAS records were collected from 10 patients, 5 male and 5 female with the median age of 57. All nine ESAS symptoms were reported as mild (less than 4/10) with mean scores of 2.46, 1.71, 2.80, 2.59, 3.03, 2.02, 1.04, 2.19, 3.06 for pain, nausea, lack of appetite, shortness of breath, fatigue, depression, drowsiness, anxiety and well-being, respectively.

Conclusion: Although high symptom burden is expected in this type of patients, it was not the case in this analyzed group. Even so, ESAS is a useful, easy and not time-consuming screening tool for symptom burden. We are conducting further research to examine the impact of ESAS in the treatment decision-making process.

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Myocarditis in Patient Treated With Immune Checkpoint Inhibitor

Background: Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape for cancer and became a "standard of care" for multiple cancers. Due to the mechanism of action of ICIs, inflammatory reactions against normal tissue were an anticipated side effect of these agents; fortunatly these immune-related adverse events are typically low grade and manageable. But cardiotoxicity has emerged as an uncommon (less than 1%) and potentially life-threatening adverse reaction in patients treated with ICIs.

Case report : A 75-year-old male patient without a history of cardiovascular disease, was admitted for chest pain after recently completing the third cycles of ICI therapy with durvalumab for unresectable stage IIIb NSCLC. Initial ECG scan revealed complete heart block with bradyarrhythmia, NT-proBNP and Tnt levels were elevated at 17000 ng/L and 3500 ng/L, so permanent pacemaker was implanted. He also had coronary angiography, which did not show evidence of obstructive coronary artery disease, echocardiography without ejection fraction abnormalities. Treatment started with high doses of steroids with slow tapering, and careful monitoring. After 9 weeks patient withdrawal steriods due to clinical improvement and no signs of myocarditis.

Conclusion: ICIs hold tremendous promise for extending the lives of patients with cancer. As ICI use increases rapidly in clinical trial and real-world settings, it is critical to undertake efforts to mitigate the risk of uncommon but life-threatening adverse reactions, including myocarditis.

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Tracking resistance to tyrosine kinase inhibitors (TKIs) by *EGFR* mutation testing from liquid biopsy of advanced lung adenocarcinoma patients

Keywords: EGFR, liquid biopsy, lung adenocarcinoma.

Background: In lung adenocarcinoma, *EGFR* gene mutations confer sensitivity to targeted therapy with TKIs and their de-

tection has become a companion diagnostic in Serbia in 2011. Resistance to TKIs eventualy occurs, so mutation testing from liquid biopsy is the method of choice as it is minimally invasive and quickly provides information for additional therapeutic approaches.

Patients and Methods: *EGFR* mutation testing was performed from FFPE tumor samples/glass slides of advanced lung adenocarcinoma patients (stage IIIB/IV, ECOG performance status 0, 1 or 2) by real-time qPCR. Patients with sensitizing *EGFR* mutations were treated with first generation TKIs until progression. *EGFR* mutation testing from liquid biopsy samples (plasma) of patients who progressed on first generation TKIs was introduced in 2016.

Results: In the period from 2011-2018, 4750 analyses were performed, and 11% of *EGFR* mutated samples were detected, which is in good accordance with literature data for the Caucasian population. Since 2016, 104 liquid biopsy samples of Serbian patients who progressed on TKIs were tested, and the T790M mutation was detected in 34 patients (33% of total), which rendered them as candidates for third-line TKIs. Additional 2 patients who tested *EGFR* wt from plasma and were rebiopsied proved to have the T790M mutation as well.

Conclusion: Routine *EGFR* mutation testing from circulating tumor DNA for detecting molecular resistance mechanisms has been successfully implemented in Serbia. Liquid biopsies have also proved invaluable as an alternative sample source for patients with scarce biopsy material or without any at all.

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Clinical efficacy of osimertinib (Osi) in patients (pts) with EGFR mutated lung adenocarcinoma: every-day clinical practice data

Background: Osi has a proven activity in EGFR mutated advanced NSCLC with a good penetration through blood-brain barrier and efficacy in central nervous system (CNS). In this, single-center, retrospective study we analyzed clinical efficacy of Osi in advanced T790M positive NSCLC pts after progression on previous EGFR tyrosine kinase inhibitor (TKI).

Methods: Pts with advanced EGFR T790M positive NSCLC who received Osi following progression on prior EGFR TKI (n=15) from Dec 2015 until March 2018 were analyzed. Pts with clinical suspicion to have CNS metastases (mets) performed CT/MRI before Osi treatment.

Results: 6/15 (40%) pts had CNS mets before Osi treatment, with 5/6 (83%) receiving local CNS treatment with radiotherapy and/or surgery prior Osi initiation. Overall response rate (ORR) in the whole cohort was 87%, with disease control rate (DCR) of 100%, respectively, and median time to progression of 11.9 months. In pts with CNS mets, 83% DCR was observed, with one isolated CNS progression during Osi treatment observed among all analyzed pts; histologically small-cell carcinoma, EGFR exon 19 deletion. Maximum Osi treatment duration in pts with/without CNS mets was 25/28 weeks, respectively. Median duration of treatment at the time of analysis was 54 weeks with 8/15 (53%) of pts still ongoing treatment. 6/15 (40%) of pts received Osi as $\geq 3^{rd}$ line of treatment.

Conclusions: In our real world analysis Osi showed comparable extra- and intra-CNS efficacy to clinical trial results also in heavily pretreated pts.

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Precision medicine in treatment of lung cancer: Case report

Key words: molecular testing, NSCLC, TK inhibitors

Background: Molecular testing to identify non-small-cell lung cancer /NSCLC patients likely to respond to targeted therapy has become a global standard of care.

In our case, we present a female patient, 64 years old, non-smoker. Presented in Jan 2017 with a dry cough and enlarged neck lymph nodes. CT revealed tumor in the upper left lung lobe, 34x24 mm, with micronodules in both lungs and deposits in left adrenal gland (T2aN3M1b). Cervical lymph node was extirpated and histopathology was of lung adenocarcinoma. EGFR wild type. ALK negative. PDL -1 expression was 5 %

Patient was included in clinical trial of paclitaxel/carboplatine + bevacizumab/FKB 238 2017, partial response. Continued maintenance bevacizumab/FKB 238 with stable disease. In August 2018 progression in bones was noted. Bisphosphonates commenced. Due to vertigo MRI of brain was done and revealed 2 small focal changes. Treated with Gamma knife.

Furthermore, FoundationOneCDx (NGS) was done: EGFR E709_T710 >D mutation, with therapeutic implications TKI: Afatinib, Erlotinib, Gefitinib, Osimertinib. Afatinib after 2 months gave very good PR. Due to financial reasons switched to erlotinib. PD. Liquid biopsy: T 790 mutation not found. Afatinib re-commenced with very good PR after 2 months.

Conclusions: Mutations on exon 18 rare, about 4.1%, from which EGFR E709_T710> D is extremely rare. The importance of whole exon testing extremely relevant for targeted therapy for NSCLC.

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A single-centre experience with octreotide in the treatment of patients with gastroenteropancreatic neuroendocrine tumors

Background: Neuroendocrine tumors (NETs) are a heterogenous group of neoplasms whose incidence has increased steadily over the past decades. Octreotide is a somatostatin analogue which has traditionally been used for the relief of symptoms that result from release of peptides and amines (carcinoid syndrome), although a substantial amount of evidence suggest that it has anti-proliferative effects and lengthens time to progression of disease. We've aimed to evaluate the relationship between octreotide use and progression free survival (PFS).

Methods: Medical records of 44 patients with gastroenteropancreatic NETs treated with long acting octreotide in the University Hospital Centre Zagreb were collected and retrospectively analyzed by Kaplan Meier method using the PFS as a primary endpoint.

Results: Median PFS for all patients was estimated at 11 ± 2,6 months (95% CI 5,95-16,05). Median PFS for patients with pancreatic NETs was estimated at 6 ± 0,5 months (95% CI 5,09-6,90), patients with NETs of unknown primary at 9 ± 1,7 months (95% CI 5,68-12,32) and for patients with NETs of small intestine at 30 ± 19,2 months (95% CI 2,57-67,557). Patients with NETs of small intestine had significantly higher PFS than those with pancreatic NETs (p=0.007), however, PFS of patients with NETs of small bowel and NETs of unknown primary did not differ (p=0.18).

Conclusion: Long acting octreotide seems to be an effective treatment option with acceptable tolerability, especially for patients with small intestine NETs.

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Metastatic colorectal cancer treatment modalities and patient characteristics in University Hospital Centre Zagreb

Keywords: Metastatic colorectal cancer; Treatment options; RAS and BRAF testing

Introduction: Colorectal cancer is the most common gastrointestinal cancer in Croatia. According to the National Registry, 25% of patients are diagnosed with stage IV disease. The introduction molecular testing had a significant impact on the choice of systemic therapy.

Methods: Here we report the data on treatment modalities and sequencing, and tumor characteristics in patients treated for metastatic colorectal cancer (mCRC) in the University Hospital Centre Zagreb. This retrospective, observational, single-centre study included 234 patients (142 men, 92 women) who began treatment between January 1st, 2016 and December 31st, 2017. Included patients were aged at least 18 years, had metastatic disease, were in good general condition (ECOG performance status ≤1), and able to receive doublet chemotherapy ± biological agent in the first line. Patients who received monofluoropyrimidines were excluded.

Results: The common age median was 64 years. Seventy-five percent had primary tumor in distal colon and rectum of which 41.2% harboured RAS mutation and 55.4% were wild-type. The RAS mutation in proximal colon primary tumor was present in 47.2%, and in 35.8% no mutation was detected. RAS mutation was not determined in 14 patients. As the first line chemotherapy 66.2% received irinotecan and 33.8% oxaliplatin based chemotherapy. The majority, 193 patients, received biological agent (bevacizumab or anti-EGFR therapy) in this setting. Second line treatment followed after disease progression in 54.3% and patients who maintained adequate performance status were considered for third-line therapy, options being anti-EGFR therapy, trifluridine-tipiracil, or regorafenib.

Conclusion: Our data support a greater understanding of CRC biology and identification of different molecular subtypes leading to improvement in the treatment and overall prognosis.

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Risk factors affecting survival in early colon cancer

Key words: cancer specific survival, early colon cancer, survival

Background: Colon cancer is one of the most common malignancies and one of the most common causes of cancer-related death worldwide. Clinicopathologic staging remains the standard for assessing patient risk and supporting treatment decisions.

Material and Methods: In the 2 years period (2008-2010) we enrolled 273 patients with Duces C and high risk Duces B colon cancer. All of them had undergone curative resection and started

fluorouracil-based adjuvant chemotherapy at the Institute for Oncology and Radiology of Serbia. Patients were prospectively monitored for recurrence of the disease and death from any cause through the adjuvant treatment and in further follow up. Clinicopathological data influencing survival and cancer specific survival was investigated.

Results: In the 60 months of follow up 100 patients developed recurrence of the disease (36.6%). Disease free survival for the whole group was 51.5 months. In the follow up 115 patients died, 86 (31.5%) from primary disease. The survival rate was 77% at 3 years and 63% at 5 years.

The results of univariate analysis suggested tumor perforation at diagnosis, tumor node metastasis, lymphovascular invasion, nodal status, Duces stadium, baseline anemia and leukocytosis, elevated baseline serum CEA and CA19-9 and recurrent disease in the first year of follow up, were negative prognostic factors for overall and cancer specific survival ($p< 0.05$).

Conclusion: In this group of patients, primary clinical and pathological factors largely influence overall survival.

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The impact of bevacizumab plus FOLFOX4 therapy on survival of patients with colorectal liver metastases

Key words: bevacizumab, colorectal cancer, FOLFOX4, hepatectomy, liver metastases

Background: In patients with colorectal liver metastases (CLM) a long term survival might be achieved when preoperative systemic therapy is combined with the liver surgery. The efficacy of aplied regimen is related to liver ressection rates. The purpose of the study was to explore if the efficacy of applied bevacizumab and FOLFOX4 regimen is related to survival of patients with initially unresectable CLM.

Patients and methods: The research included 110 patients with initially unresectable CLM, treated with bevacizumab and FOLFOX4. Response to treatment was assessed every 3 months according to RECIST 1.1. criteria as well as resectability. Patients in which metastases become resectable were operated on, and closely followed up. Overall survival (OS) was estimated using Kaplan Meier method. Comparisson of OS according to hepatectomy and response to therapy was made using log-rank test.

Results: Response rate was 63,88% and resectability was 61,1%. Treatment response was significantly more frequent in patients with hepatectomy (63,63% vs 16,66%, $p<0,001$). One- and three-year survival rate for the whole patient population was 87,3% and 36,1%, respectively; median OS was 23 months [95%CI 19,63-28,26]. One- and three-year survival for patients with hepatectomy was 98,48%, and 54,76%, respectively; median OS was 35 months [95%CI 28,83-41,17]. Three-year survival was significantly better for patients with hepatectomy (HR=3,775 [95%CI 2,150-6,627], $p<0,001$) and patients with objective response to treatment ($p=0,005$).

Conclusion: Bevacizumab and FOLFOX4 is effective regimen resulting in high resectability of molecularly unselected patients with unresectable CLM. Patients with hepatectomy and objective response to treatment have significantly better survival.

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Efficacy of cetuximab as third line treatment in metastatic colorectal cancer

Introduction: Cetuximab is an IgG1 chimeric monoclonal antibody directed against extracellular domain of epidermal growth factor receptor (EGFR). It has antitumor activity in patients without mutations of RAS genes. Its combination with irinotecan is widely accepted in heavily pretreated patients progressed on at least two lines of systemic therapy. It has been reimbursed in by the Serbian Health Insurance Fund from 2009.

Methods: This is a retrospective-prospective study of Cetuximab use in patients with KRAS wild type gen who previously progressed on oxaliplatin and irinotecan-based regimens. Cetuximab was used in combination with irinotecan or as monotherapy, in 14-day cycles, in dose 500mg/m$^{2.}$

Results: 198 patients were treated with cetuximab, after disease progression on at least two lines of systemic treatment. 127 patients were male (64,1%) and 71 female (35,9%), with median age at diagnosis 61 years, range 24 to 81. Median number of cycles of cetuximab was 9, (range 1 to 50). Best response to therapy was partial response in 37 patients (18%), stable disease in 112 patients (56%), and progression in 39 patients (26%). Median progression-free survival (PFS) was 6.8 months (5,65-7.95, CI 95%). There was no statistically significant difference in PFS between men and women, patients with primary colon or rectal tumors, nor depending on localization of metastatic site(s).

Conclusion: In our experience, cetuximab was shown to be a good treatment choice in chemotherapy pretreated patients with wild type RAS genes. It showed a good response rate (18%) with PFS about 6,5 months and was well tolerated. Survival analysis will follow.

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Personalized approach to the treatment of highly aggressive tumors using next generation of sequencing method (NGS)

Key words: Cholangiocellular carcinoma, microsatellite status, molecular profiling, mutation tumor load, next generation sequencing

Introduction: Cholangiocarcinoma is an aggressive malignant tumor of the billiary tract. Aim of this case is to correlate the detected mutations in the tissue sample in relation to the potential therapeutic goals.

Materials and Methods: Immunohistochemistry analysis is performed for CK7, CK8, CK18, CK19, CA19-9, CDX2, PD-L1. After the performed micro-dissection of tumor cells and DNA isolation, molecular profiling is performed using the Foundation One CDx test. In vitro test detects substitutions, insertions, deletions, amplifications and rearrangements in 324 gene, as well as microsatellite instability and tumor mutation burden.

Results: The tumor cells were positive for cytokeratins: CK7, CK8, CK18 and CK19, and negative on markers CA19-9 and CDX2. Low expression of PD-L1 of 1% was identified. NGS of tumor genomic DNA showed the pathogenic mutations in the following genes: amplification of C11orf30 (EMSY) gene, loss of CDKN2A/B homozygous, and the TERT gene promoter mutation. The tumors with pronounced C11orf30 gene amplification are not chemo-sensitive. There are still no drugs that directly affect the TERT gene. The preclinical studies have shown that mutation in the CDKN2A/B gene present in other types of solid tumors may be sensitive to the effects of cytotoxic drugs from

the CDK4/6 inhibitor group. Low level of tumor mutational burden is in value of 4 mutations per mega base. The status of microsatellite instability is stable.

Conclusion: Described molecular profile does not contain a positive prediction marker for the application of a particular cytotoxic or targeted therapy.

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Eleven years of ras testing in colorectal cancer in Serbia: an institutional experience

Keywords: BRAF, colorectal cancer, EGFR-targeted monoclonal antibodies, RAS, real-time PCR

Background: In the era of personalized medicine, treatment options for patients with metastatic colorectal cancer (mCRC) include blocking epidermal growth factor receptor (EGFR) with EGFR-targeted monoclonal antibodies (MAb), cetuximab and panitumumab, in *RAS* wild-type mCRC. Thus, mutation testing of hot-spot codons in exons 2, 3 and 4 of *KRAS* and *NRAS* gene is required. Mutations in *KRAS* and *NRAS* gene occur in 30-50% and less than 5% of mCRC, respectively.

Material and Methods: From April 2008 to March 2019, 3109 mCRC were tested for exon 2; 1786 and 808 of them for exons 2, 3 and 2, 3, 4 *KRAS* mutations, respectively. From January 2017, 765 mCRC were tested for *NRAS* mutations. Formalin-fixed parafin-embedded samples from various centers were referred to Laboratory for molecular genetics. The various diagnostic tests, based on real-time PCR, were used for detection *RAS* hot-spot mutations. For *RAS* testing, the laboratory passed external quality control.

Results: The investigated group comprised of 62.7% men and 37.3% women. The percentage of unsuccessfully analysis was 0.3%. *KRAS* and *NRAS* mutations were identified in 46.6% and 5.2% of CRC, respectively. Among *KRAS* mutated samples 95.0% had mutations in exon 2, 5.6% in exon 3 and 6.7% in exon 4. *RAS* mutations were present in 60.4% of men and 39.6% of women.

Conclusion: Our experience showed that diagnostic real-time PCR based tests are highly sensitive in detection of *RAS* mutations. Implementation of other biomarkers for prognosis and treatment choice in mCRC, such as *BRAF* V600E mutation, is necessary.

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Safety and efficacy of sorafenib in the treatment of advanced hepatocellular carcinoma: a single center experience

Objective: Sorafenib, the standard treatment for patients with advanced hepatocellular carcinoma (HCC) with demonstrated outcome benefits in randomized clinical trials, became available to patients in Serbia in January 2016. With the aim to establish its efficacy and safety in daily clinical practice we present a single-center experience.

Methods: Twenty-eight patients with advanced HCC treated in our center from March 2016 to February 2019 with Sorafenib in daily regime of 400-800 mg/day. OS was the primary endpoint and tumor response was evaluated using the RECIST Criteria. The efficacy and adverse effects of sorafenib were analyzed. The side-effects were summarized, and published data were reviewed.

Results: Twenty patients were male (71%) and 8 female (29%), with median age of 66 years. In TNM classification T3 stage had

12 patients, T4 15 Pts.Twenty two initially had metastatic disease. Performance status was mostly PS 1 in 21 Pts (75%). The median OS was 8.57 months (2.68-14.46, CI95%). A partial response was achieved in two patients and stable disease in 15 patients as best therapeutic response. Eleven patients progressed on first control. Median progression-free survival (PFS) was 3 months (0.04-5.96, CI95%). Diarrhea, hypertension, hand–foot syndrome and fatigue were common adverse effects.

Conclusion: Sorafenib demonstrated good efficacy and acceptable tolerability in treating an advanced HCC patient population. Safety profile in our patients is consistent with profile of sorafenib.

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Renal cell carcinoma with pulmonary and ocular metastases: a case report

Key words: ocular metastases, renal cell carcinoma, sunitinib

Renal cell carcinoma is the third most common urological malignant tumor after prostate and urothelial carcinoma. The prognosis of patients with renal cell carcinoma strongly depends on the time of diagnosis. Early detection of localized disease offers the opportunity of curative e.g. surgical treatment. In case of metastatic renal cell carcinoma, there is usually no curative treatment available. Only for a small number of patients, surgical resection of metastases is reasonable. The use of targeted therapies has significantly improved the outcome of these patients, regarding progression-free survival and overall survival. However, most of the patients achieve partial response or stable disease. The complete response rate is much lower and has been reported to be about 3% during treatment with tyrosine kinase inhibitors, such as sunitinib. The most common site of renal cell carcinoma metastases is usually lungs or bones, but it can also spread to the brain, liver, ovaries and testicles. Metastases of renal cell carcinoma into the eye are unusual and are more likely to infiltrate the choroids, iris and ciliary body, although eyelid, lacrimal sac and orbital metastases have also been reported. Due to high coroidal blood flow, the posterior pole of the oculus is the most common localization of ocular metastases. Here, we report a case of a 51-year old patient who presented with renal cell carcinoma of the left kidney with pulmonary and ocular metastases. The patient initiated therapy with sunitinib and after five months of treatment, the patient achieved radiographic complete response.

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Nivolumab for metastatic renal cell carcinoma: results of the name patient program at the University Hospital Centre Zagreb

Key words: long survivors, metastatic renal cell carcinoma, name patient program, nivolumab, second line

Background: Nivolumab, a fully human programmed death (PD-1) immune checkpoint inhibitor, improves survival and has a more favourable safety profile compared with Everolimus in patients with metastatic renal cell carcinoma (mRCC) according to CheckMate 025 trial.

Materials and methods: Patients with mRCC previously treated with agents targeting the vascular endothelial growth factor pathway (VEGF) received Nivolumab 3mg/kg once every 2 weeks under the name patient program at the University Hospital Centre Zagreb from 2016 to 2019. They were followed up regarding their response time and adverse events.

Results: A total of 30 patients (22 male and 8 female) with mRCC after anti-angiogenic therapy were enrolled with a mean age at diagnosis of 60.2 ± 9.79 years. Most of them were evaluated as having an intermediate risk and most (23/30) received Sunitinib as the first line therapy, following nephrectomy. Seven (23%) patients had survived more than 30 months (31 ± 0.95 months) after the start of Nivolumab therapy. All of them received Sunitinib as the first line therapy and Nivolumab in the second line. The most common adverse event in this group was grade 2 fatigue.

Conclusion: Our analysis has demonstrated an overall long term survival rate of 23% (7/30). The longest observed Nivolumab treatment response time was 35+ months. Further follow up of the long term survival cohort is required to more precisely establish the efficacy and safety of Nivolumab as the second line treatment for mRCC.

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Whether changes in D-dimer values during docetaxel therapy in metastatic castration-resistant prostate cancer can indicate progression of the disease?

Keywords: D-dimer; Hypercoagulability; Prostate cancer

Background: Increased D-dimer value is indirect indicator of hypercoagulability often associated with the progression of malignant disease . The aim of this study was to assess whether D-dimer could be a marker in confirming disease evolution in a metastatic castration-resistant prostate cancer (mCRPC) during chemotherapy, mostly when there is discrepancy in clinical and biochemical course of the disease.

Material and methods:This prospective study included patients with mCRPC treated with systemic chemotherapy at the Institute of Oncology and Radiology of Serbia between January 2011 and October 2013. The PSA and D-dimer values were determined before starting and after four cycles of chemotherapy with docetaxel. Therapeutic response was assessed in both progressive and non-progressive disease.

Results: The present study includes 73 patients of which 62 evaluable. Initially, in 76% patients, the D-dimer was above the cut-off value and in 61% patients the decrease of value after four cycles of chemotherapy was observed. Statistically significant difference was confirmed after docetaxel for the D-dimer values regarding the therapeutic response. High statistical significance was observed in the change of PSA before and after the fourth cycle of chemotherapy compared to the therapeutic response. For change in D-dimer before and after chemotherapy, statistical significance was more pronounced . In monitoring the value of D-dimer in relation to the therapeutic effect, the statistically high significance is maintained.

Conclusion: The association of D-dimer and therapeutic responses in mCRPC, can be significant in patients with discrepancy between clinical and biochemical response. Further research would provide more reliable results.

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F-FDG PET/CT response after pembrolizumab therapy for metastatic melanoma

Immunotherapy has raised the issue of appropriate treatment response evaluation.

Aim: to explore the utility of the ^{18}F-FDG-PET/CT for treatment monitoring in patients with metastatic melanoma receiving pembrolizumab.

Patients and methods: 36 subjects with metastatic melanoma receiving pembrolizumab were enrolled in this prospective study. Fifteen patients had previously received BRAF+MEK inhibitors. A baseline ^{18}F-FDG PET/CT was performed before pembrolizumab administration (PET-0). Three months later, PET/CT was performed to evaluate the therapy response (PET-1). In order to confirm or exclude a progression of metastatic melanoma, PET/CT was performed six months after the baseline (PET-2). The therapy response was assessed at PET-1 and PET-2 according to the PET response criteria for solid tumors (PERCIST) and the immune RECIST (iRECIST).

Results: Four patterns of response to pembrolizumab were observed: 11 patients had a response in baseline lesions, among them 7 had a complete response. Stable disease was recorded in 5 patients. Responses after an initial increase in total tumor burden (pseudoprogression) were notified in 4 patients. In one patient, a reduction in total tumor burden during the appearance of new lesions was observed. Fifteen patients had progressive metabolic disease, and ten patients among them died. Out of 7 (33%) patients with negative FDG PET scans no one progressed within the 6-12 months follow-up period.

Conclusion: Immunotherapy can have delayed response and it can cause temporary increase in tumor size or even appearance of new lesions. This does not mean necessarily progression of the disease. This analysis confirmed that the use of successive PET/CT studies was needed to discriminate a pseudoprogression from a real progression.

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CDK4 gene mutation in Familial Melanoma - single center study

Key words: CDK4, familial melanoma, mutation.

Background: Familial melanoma constitutes 5-12% of all melanoma. Candidate genes for increase familial melanoma risk are *CDKN2A* and *CDK4*. *CDK4* gene, located on 12q14.1, codes for cyclin-dependent kinase, a protein which is a member of Ser/Thr kinases family. Protein kinases participate in cell cycle regulation. Changes in their function cause abnormalities in cell cycle regulation, resulting in neoplastic transformation.

Patients and Methods: Our study included 49 patients - 24 male (48,9%) and 25 (51.1%) female patients from Melanoma outpatient clinic, Military Medical Academy, Belgrade, Serbia who had been surveyed in order to gather information about the existence of melanoma and/or other malignancies within their families. Hotspot mutation in *CDK4* gene (R24H and R24C) were analyzed on 7500 Real Time PCR System (Applied Biosystems, USA) using TaqMan assays (rs104894340 and rs11547328).

Results: All of 49 patients had wild type genotype for rs11547328 (GG) and rs104894340 (TT).

Conclusion: Our results indicate the absence of CDK4 mutations in our patients with melanoma in family. The possible explanation for definite conclusion may be small sample size (previously published studies had much larger sample size).

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Long Range Effect of Immunotherapy in Mucosal Melanoma – Case Report

Keywords: AE, CR, mucosal melanoma, pembrolizumab

Female patient, ECOG PS 1, with no risk factors for mucosal melanoma, with pacemaker implanted and arterial hypertension, presented in 2014 with a nasal cavity tumor. The tumor was removed with histopathological confirmation of mucosal melanoma. In 2015 another operation was performed due to melanoma recurrence.

In December 2016. disease relapsed in both suprarenal glands, retroperitoneal lymph nodes and peritoneum. Tumor was BRAF negative, staged as IV-M1c0, patient had normal laboratory results. Tumor board for melanoma decided to start systemic treatment with pembrolizumab. Effect PR after 4,8 and 12 cycles. Adverse events after 12 cycles fatigue grade 1, dermatological AE (rash, pruritus, vitiligo- grade 1) treated with local and systemic dermatological, treatment with pembrolizumab was continued. After 16, up to 32 cycles, the result was CR and dermatological AE regressed to mild.

Currently she has received 32 cycles with effect of CR with mild dermatological AE (vitiligo, rash grade 1) and no dermatological treatment. Patient is ECOG PS 1, normal laboratory results and excellent life quality along with continuation of pembrolizumab.

Dilemma/Discussion – Best treatment solution without restrictions – *continue Keytruda* OR *treatment interruption* OR *change of therapy*?

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Frequency of familial melanoma in population of Serbia

Keywords: familial melanoma, hereditary disease, pancreatic cancer

Background: Melanoma represents one of the rapidly growing diseases among Caucasoid population. According to the literature, 5-12% of the patients have a genetic predisposition for melanoma and/or pancreatic cancer, and about 45% of these cases are associated with the mutations in high-penetrability genes (CDKN2A, CDK4 and BAP1).

Patients and Methods: From September 2018 to December 2018 564 patients with previously diagnosed melanoma in Melanoma outpatient clinic, Military Medical Academy, Belgrade, Serbia completed questionnaire on occurrence of malign diseases in families. Selected patients were interviewed for family history of disease and demographic characteristics. The criteria of selection were the occurrence of melanoma, pancreatic cancer and non-melanoma skin cancer among first- and second-degree relatives.

Results: 299 of 564 patients (53%) were male and 265 (47%) were female, with average 50 years old at the time of diagnosis. 28 patients (4,96%) had family history of melanoma, 37 patients (6,56%) had family history of melanoma and pancreatic cancer, and 41 patient (7,27%) had family history of melanoma, pancreatic cancer and non-melanoma skin cancer. Sex distribution of familial melanoma is identical in all the defined groups (~50%). Average age of patients diagnosed with sporadic and familial melanoma is of no statistical significance.

Conclusion: Our results confirmed literature founding regarding frequency of familial melanoma. On the other hand, difference in gender and age distribution was not found.

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Coexistence of TERT promoter and BRAF mutations in metastatic melanoma

Keywords: BRAF, melanoma, outcome, prognosis, TERT

Background: Despite of breakthrough in the field of molecular oncology, metastatic melanoma remains difficult to treat. Although 5-year survival rate of 35 - 40% is encouraging, still there is a room for improvement. The most common molecular alteration in metastatic melanoma is mutation in BRAF gene (approximately 60% of melanoma). According to the literature several highly recurrent somatic sequence variations in the promoter region of the telomerase reverse transcriptase (TERT) gene where reported. The aim of this study was to determinate is there a correlation between BRAF and TERT mutational status and clinicopathological features (Breslow thickness, sentinel lymph node metastasis, number of mitotic cells, ulceration)

Patients and Methods*:* We investigated coexistence of TERT and BRAF mutation in 140 patients with metastatic melanoma. All patients were tested for the BRAF V600E mutations using a BRAF Mutation Analysis Kit for Real-Time PCR (Estrogen, USA) while mutation in TERT promoter gene where determined by Sanger sequencing.

Results*:* TERT promoter mutations occurred more frequently in BRAF mutation-positive cases (p=0,001). 31 patient (22,14%) where double wild type (DW), 22 patient harbor only BRAF gene mutation (BM) (15,71%), 31 harbor only TERT gene mutation (TM) (22,14%) while 56 patients where BRAF and TERT mutated (DM) (40%). DM cases were significantly thicker (Breslow, p=0.041) and were more often sentinel lymph node metastatic (p=0.007) than DW melanomas.

Conclusion*:* Coexistence of TERT and BRAF mutations is associated with unfavorable prognostic parameters, suggesting that these molecular alterations could be related with worse outcome and poor prognosis.

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Differences in BRAF mutations status between primary and metastatic melanoma lesions

Keywords: BRAF, metastatic melanoma, primary melanoma, treatment

Background*:* The incidence of melanoma in past few years has tendency to rise. According to the available data, approximately 2% of all individuals born in USA today will develop melanoma. Systemic targeted molecular therapy, with selective BRAF inhibitor, is a standard treatment for patients with BRAF V600 mutation-positive melanoma with unresectable stage III and IV melanoma. Individuals with BRAF negative primary tumors may show BRAF positive metastatic disease and vice versa. It is still unclear are the all metastatic lesions carry the same BRAF

mutation found in the primary tumor and if it is so, in what frequency it occurs. The aim of this study was to investigate this frequency.

Patients and methods: Primary and corresponding metastatic lesions in 30 melanoma patients were tested for the BRAF V600E mutations using a BRAF Mutation Analysis Kit for Real-Time PCR (V600E) (Entrogen, USA).

Results*:* Five patients (16,6%) had different mutation status in their primary and metastatic melanoma. Of these patients, 2 (6,67%) had BRAF positive primary melanomas with BRAF negative metastatic lesions and 3 (10%) patients had BRAF negative melanoma with a BRAF positive metastatic lesion. In summary, difference in BRAF mutation status in primary and metastatic melanoma is not an infrequent event.

Conclusion*:* Our results implies that determination of BRAF mutation of new metastatic tumors in previously negative patients might be useful for proper treatment of patients with BRAF inhibitors therapy.

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Vemurafenib induced toxic epidermal necrolysis - a case report

Keywords: allergic reaction, BRAF inhibitor, dabrafenib vemurafenib switch, toxic epidermal necrolysis.

Vemurafenib is a commonly used selective BRAF inhibitor for uneresectable or advanced melanoma patients with BRAF mutations. It is associated with the risk of developing life-threatening mucocutaneous reaction including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) 4 to 30 days after the onset of drug exposure.

A 50 year-old male patient was treated with vemurafenib for IV stage melanoma. On day 23, the patient presented with fever, malaise and maculopapular rash on the trunk. The rash progressed after two days to the extremities and covered >30% of body surface area. We also observed facial erythema and edema, painful buccal erosions and hemorrhagic crusts of the lips. There was no prior history of an allergies, hypersensitive drug reactions and the patient denied consumption of any other medications. Laboratory investigation included the following: complete blood count, liver and kidney function tests, electrolytes were within normal limits. Blood culture was sterile and serology for hepatitis and HIV infection were negative. Histopathologic examination of the skin demonstrated necrotic keratinocytes in suprabasal layers and moderate dense inflammatory infiltrates in papillary dermis of lymphocytes, neutrophils and eosinophils that support the diagnosis of TEN. Direct immunofluorescence microscopy did not reveal any deposits of immunoglobulin or complement. Vemurafenib was discontinued immediately and initial treatment with methylprednisolone was introduced at a dose of 1 mg/kg/day. Complete remission was achieved and patient after few weeks successfully switch to dabrafenib and trametinib therapy. This case highlights the importance of awareness of the risk of severe cutaneous adverse events associated with target therapy for patients with metastatic melanoma.

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Primary central nervous system lymphoma (PCNSL) - Case report

Key words: primary central nervous system lymphoma, immunochemotherapy, rituximab

Primary central nervous system lymphoma (PCNSL) is an aggressive form of lymphoma (1). PCNSL in is rare and represents 4% of all intracranial neoplasms and 4% to 6% of all extranodal lymphomas (2). Majority of PCNSLs are diffuse large B-cell lymphoma (DLBCL) (3). PCNSL is a diagnostic and therapeutic challenge for clinicians and scientists(4). PCNSLs are potentially curable tumors and are sensitive to chemotherapy and radiotherapy. There is no uniform consensus on the optimal treatment of PCNSL, currently. High-dose methotrexate (HD-MTX) is the backbone of multimodal therapy that includes other chemotherapeutic agents with and without radiation, according to experts. (3)

Forty nine year old patient presents with headaches and unstable walking. MRI scan of the endocranium was performed and a tumor (41x25mm) in the frontal right subcortical region was detected. Surgical extirpation of the tumor was performed and histopathology report showed a diffuse large B cell lymphoma. Postoperative endocranial MRI showed a large encephalic cavity dimension of 35mm with an edema.

Patient was treated in the CSIEA with immunochemotherapy R-MAD, combination of rituximab, high-dose methotrexate, cytarabine, dexamethasone every 3 weeks, with G-CSF support. PET/CT examination has shown a complete remission of disease after six cycles. After the immunochemotherapy, endocranial radiotherapy was performed with TD 40 Gy by July 2016. Complete remission has been maintained for 30 months, and is ongoing.

In conclusion, R-MAD has a good effect on PCNSL patients and is well-tolerated, including elderly patients. Further research is required for optimization of combination based on high-dose MTX (5).

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The use of trabectedin and pazopanib in soft tissue sarcoma: a single center experience

Key words: pazopanib, soft tissue sarcoma, trabectedin

Introduction: Treatment of advanced soft tissue sarcomas (STS) is very challenging. Anthracyclines are the backbone of first-line treatment, while there is no gold standard for the second-line setting or beyond. Several options include treatment with trabectedin, a DNA disruptor which is indicated regardless of the STS histology or pazopanib, a tyrosine-kinase inhibitor used in the treatment of non-adipogenic STS.

Patients and methods: We performed an analysis of progression-free survival (PFS) as a primary endpoint in a cohort of patients with advanced STS who were treated in Clinical Hospital Center Zagreb with pazopanib and trabectedin in the second-line setting or beyond. A total of 39 patients were treated with trabectedin and 51 patients with pazopanib in a period from January 2014. until February 2019.

Results: The mean PFS on trabectedin was 5.95 months, although there was a significant difference in PFS of liposarcoma (13.9 ± 15.27 months) compared to other STS (3.21 ± 2.56 months) (p=0.01). A total of 7 patients have ongoing treatment. The mean PFS of pazopanib was 7.29 months, with 15 patients having ongoing treatment. There was no statistically significant difference in PFS based on pathohistological diagnosis.

Conclusion: The use of trabectedin in the treatment of STS is promising, especially for liposarcoma. On the other side, pazopanib remains an option in the second line treatment for non-adipogenic STS.

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Clear-cell sarcoma responded on pazopanib after triple chemotherapy failure

Introduction: Clear-cell sarcoma (CCS) is a rare soft-tissue sarcoma, mostly reported in young adults, characterized by a translocation t(12;22) (q13;q12) and fusion of EWS (22q12) with ATF1 genes (12q13).

Case presentation: A 28-year old male was diagnosed with sarcoma in December 2015, after surgical excision of a soft tissue tumor mass in right hand. Due to local recurrence, a right-hand disarticulation was performed in March 2016, followed by six cycles of adjuvant chemotherapy with adriamycin/ifosfamide. In July 2017, CT scan revealed lung metastases which were treated with radiosurgery due to patient preferences. In February 2018, a right infraclavicular tumor mass was fully extirpated. In April 2018, a systemic progression was registered on PET/CT, and the patient received four cycles of trabectedin, followed by three cycles of docetaxel and gemcitabine; both regimens with no response. In November 2018, the patient started targeted therapy: pazopanib 800 mg a day, for three months. In February 2019, PET/CT showed significant regression of metastatic disease.

Discussion and conclusion: The data about CCS medical treatment are rare. The largest study until now included 24 patients with various cytostatics and limited responses. Medical literature reported just one CCS case who responded on pazopanib therapy. In PALETTE study, one CCS patient was treated with pazopanib, but there was no data about the therapy response.
We presented a patient with CCS, who showed significant regression of metastatic disease after three failed chemotherapy attempts and this is a second patient with pazopanib therapy response reported in the literature.

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Early evaluation and therapy adjustment in advanced stage Hodgkin lymphoma- the role of PET/CT

Key words: Hodgkin lymphoma, PET-CT, therapy, toxicity

Background: Escalated BEACOPP as a standard of treatment for advanced stage Hodgkin lymphoma has been associated with longer PFS, but also with increased toxicity.

Aim: Our aim was to determine if advanced stage Hodgkin lymphoma patients, who are candidates for escalated BEACOPP can be switched to less toxic treatment if they have good response on interim PET/CT.

Materials and methods: 10 patients with advanced stage of Hodgkin lymphoma (IIB-IVB, according to GHSG), were diagnosed in Institute for radiology and oncology of Serbia in period from 2015 y to 2018y. PET/CT was performed at baseline, after II cycles of escalated BEACOPP (interim PET/CT) and at the end of the treatment.

Results: Median age of patients was 25 years (range, 19-45). The median follow up was 24 months (range, 9-50). All patients received II cycles of escalated BEACOPP and 4 cycles of ABVD. Interim PET/CT was negative (defined as Deauville score ≤ 2) in all patients. PET/CT at the end of treatment revealed CR in all patients. 1 patient (10%) relapsed during follow-up period. Progression free survival and overall survival at 2 years are 90% and 100%, respectively. No major permanent toxicities were registered by now.

Conclusion: In this pilot project, in spite of small number of patients, we showed that escalated BEACOPP followed by ABVD is acceptable option for reducing acute and long term toxicities in young patients. Early PET driven switch to less aggressive regimen can be safely applied. This finding requires further follow up and involvement of more patients.

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Mantle cell lymphoma – clinical case report

Keywords: mantle cell Lymphoma, treatment

71 years old man, presented with enlarged lymph nodes in left axilla and bilateral on neck (September 2010). He had B symptoms: sweating, dry cough.

We made CT scan of thorax and abdomen: enlarged mediastinal, paratracheal, subcarinal, axillary lymph nodes, enlarged epigastric, retroperitoneal, pelvic and inguinal lymph nodes, hepatosplenomegaly and ascites. Histology confirmed mantle cell lymphoma (MCL), stage IVB.E.

First line of chemotherapy R-CHOP started January 2011. Evaluation on July 2011: partial response. We continued with maintenance Rituximab and radiotherapy of the largest residual mass in the abdomen (7,7cm x 3,5cm) till October 2011(TD 30,6Gy). On June 2012: complete response in the abdomen.

December 2014 we had progress of disease. CT scans: enlarged cervical, axillar, mediastinal, retroperitoneal, para hepatic and inguinal lymph nodes, hepatosplenomegaly and lymphomatous involvement of pleura. Cytology of lymph nodes confirmed MCL, CD 20+.

We started second line chemotherapy R-FC. He had persistence of pleural effusion after one cycle. We decided to change chemotherapy for R- Bendamustin. Evaluation with CT scan of thorax and abdomen showed partial response. PET CT January 2016: progression - right neck, retro clavicular and right axilla with symptoms: swelling of the right upper extremity in total.

We started with InBrutinib 560mg January 2016. On Jun 2016: complete response. Patient continued with Ibrutinib (420mg) till October 2016. Patient passed away due to neutropenia and complication in November 2016

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Metastatic Soft Tissue Sarcoma Outcomes – Single Institution Experience

Key words: Connective And Soft Tissue, Neoplasms

Background: In this retrospective observational study, we analysed characteristics and outcomes of patients with metastatic soft tissue sarcoma (mSTS), treated at our institution during the period of 2017 and 2018.

Patients and Methods:18 patients' records from databases of two Institutes were analysed. They were all patients with newly diagnosed mSTS and systemic treatment-naïve.

Results: 18 (54.5%) of all newly diagnosed STS patients (n=33) were initially metastatic, 11 males and 7 females. Liposarcoma accounted for 3 cases, while all other types for less (pleomorphic sarcoma, leiomyosarcoma, epithelioid sarcoma, angiosarcoma and stromal gynecologic sarcoma: n=2, undifferentiated sarcoma, synovial sarcoma, rhabdomyosarcoma, extraosseal Ewing sarcoma, unclassified sarcoma: n=1). The most frequent metatstatic site was lungs (72%). 11 patients (54.5%) received first-line systemic treatment, second and further lines 6, 4 and 2 patients, respectively. Median time-to-progression (TTP) interval with first-line treatment was 4 months, 4 months with second and 3 months.with third-line. Median overall survival (OS) for the 6 treated patients was 6 months and it is still not reached for 5 patients, with their median treatment duration and follow-up of 14 months.

Conclusion: Treatment choice depended on sarcoma type, patient age and co-morbidities, while supportive and palliative approach was reserved for those with poor performance status. This patient group is too small for any general conclusions on the outcomes, and it might be rational to compare these results with the ones from the larger patient group studies.

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Salivary Duct Carcinoma of the parotid gland – case report

Key words : adjuvant treatment, salivary duct carcinoma , trastuzumab

Salivary Duct Carcinoma (SDC) is a rare and agressive malignancy that histologically resembles ductal carcinoma of the breast with both intraductal (or in situ) and invasive component.

Here we present a case of Salivary Duct Carcinoma of parotid gland in 55 year old female. She presented with a swelling behind her right ear. Biopsy was done and pathology report came as adenocarcinoma.

Surgery was performed and total right parotidectomy was done along with selective neck dissection (levels II,III ,VA). Pathology report concluded to G3 (Poorly differentiated) Salivary Duct Carcinoma (micropapillary variant) with lymphovascular and perineural invasion . Three intraparotid lymph nodes were infiltrated with tumor tissue along with cutis , subcutis and muscle . Number of mitosis was 8-10/HPF, Ki 67 positivity 65% and it was not possible to determine resection margins.

Neck lymph nodes: 11 out of 13 were positive for tumor cells with invasion of perinodal tissue and lymphovascular and perineural invasion. IHC was positive for Her 2/neu 3+, EMA , CK (HMW), CEA , AR and GCDFP-15 . IHC was negative for : S100, ER/PR , TTF1 . Adjuvant therapy consisted of concurrent radiation (TD 66 / Gy) and chemotherapy with weekly paclitaxel , carboplatin and trastuzumb (THC) for 6 six weeks followed by THC every three weeks (for 12 weeks) and trastuzumab alone for one year .

Six years after the initial diagnosis patient is still in Follow Up and without evidence of the disease .

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Immunotherapy related side effects: a single center experience

Key words: adverse events, immunotherapy, melanoma

Introduction: Immunotherapy with monoclonal antibodies targeting CTLA-4, PD-1 and PD-LI molecules has become a standard therapy for different solid and haematological malignancies. Immune related adverse events (irAEs) are rare but potentially life treatening complications of immunotherapy that we have to manage on time and properly.

Patients and methods: We performed an analysis of irAEs in patients with advanced melanoma (+ 1 patient with advanced Merkel cell carcinoma) who were treated in University Hospital Center Zagreb with immunotherapy agents: pembrolizumab, nivolumab and avelumab. Combined immunotherapy (pembrolizumab with ipilimumab) was applied in one patient with colitis. A total of 65 patients were treated in a period from February 2017. until February 2019. Different types of irAE were observed: skin toxicities –vitiligo, ocular events –episcleritis, neurological syndromes -bilateral ophtalmoparesis and cranial neuropathies, autoimmune hepatitis, colitis, pneumonitis, sarcoidosis like inflammation of mediastinal lymph nodes and endocrinopathies - diabetes and thyroiditis.

Results: Vitiligo was observed in more than 10 patients. A total of 10 patients had different non-skin toxicities: 3 hepatitis, 1 pneumonitis, 1 colitis, 1 episcleritis, 2 neurological events, 1 thyroiditis and one newly diagnosed diabetes which occurred in patient with pseudoprogression. No fatal irAE occurred.

Conclusion: Immunotherapy related adverse events are unpredictive and heterogenous. A majority of analysed irAE correlate with positive response to immunotherapy. Early treatment with corticosteroids is mandatory.

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Psycho-oncology

Key words: mental health, psycho-oncology, psychological reactions

Psycho-oncology is multidisciplinary specialty concerned with the emotional, social, behavioral, ethical and spiritual aspects of cancer patients and their caregivers. It addresses the two major psychological dimensions of cancer: First, the psychological responses of patients and their caregivers to cancer at all stages of the disease and second the psychological, behavioral and social factors that may influence the disease process.

Cancer is a serious disease which can affect many areas of patients' life. Psychosocial distress should be considered a treatable complication of cancer and its treatment. Receiving a potentially fatal diagnosis, going through treatment protocols, and learning to live with limitations can cause different psychological reactions and feelings in many patients. The most usual are anxiety, depression, denial, anger, fear, sadness, guilt and loneliness. Today, psychosocial distress is considered as 6th vital sign and should be assessed and managed according to available clinical practice guidelines.

Although one in three people with cancer will experience psychosocial distress, the symptoms are too often sidelined. Quality cancer care must integrate psycho-oncology in routine cancer care. Managing mental health needs is a crucial part of the treatment process.

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Body mass index (BMI) as a prognostic factor of overall survival (OS) in locally advanced head and neck (H/N) cancer patients

Keywords: head and neck cancer, malnutrition, overall survival, weight loss

Background: Locally advanced H/N cancer patients represent heterogeneous group of patients with prognostic factors that are not clearly defined. Malnutrition is recognised as a factor of worse outcome in these patients.

Patients and methods: One hundred patients with locally advanced squamous H/H cancer, treated with neoadjuvant Cht and after that RT at the Institute for Oncology and Radiology of Serbia from July 2002 until January 2007 were included in this prospective study. Patients were categorised in 4 groups according to BMI: underweight (BMI<18,5); healthy weight (BMI 18,5-24,9); overweight (BMI 25-29,9); obese (BMI≥30). All patients were treated with chemotherapy and than underwent through follow-up period. Primary endpoint of this study was OS.

Results: Among patients, 23 were underweight, 53 patients were with healthy weight, 18 were overweight and 6 were obese. Clinical response to therapy (CR+PR) was observed in 56 patients, while progression or stabilisation of disease shorter than 6 months was observed in 44 patients. For all patients median OS was 12 months (95%CI, 11 to 13). BMI categories median OS was: 10 months (95%CI, 6 to 13), 12 months (95%CI, 10 to 16), 13.5 months (95%CI, 10 to 16), 16 months (95%CI, 7 to 13) respectively. There was a statistically significant difference in median OS (Log rank, p 0,048) with most prominent difference among underweight and patients with healthy weight (0.012).

Conclusion: In our patients malnutrition is a negative prognostic factor of OS in locally advanced H/N cancer patients treated with chemotherapy.

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Should we use antibiotics in a predominantly oncological hospice care?

Key Words: Antibiotics, Cancer, Hospice care, Survival

Background: A majority of experts in palliative care agree that opioids, anxiolytics, antipsychotics, and anti-muscarinic drugs are essential in the quality care of the dying. However, the use of other drugs such as antibiotics is a controversial issue. Authors such as Oh *et al.* have shown that only around 15% of hospice patients show any kind of positive clinical reaction to antibiotic treatment, while others have shown a longer survival when using antibiotics. We aimed to evaluate the relationship between antibiotic use and survival in hospice patients.

Methods: Our study was a retrospective analysis of 765 patients (91% cancer patients), treated in a hospice from March 2013 to March 2017. The data were collected from the charts and later analyzed using the Kaplan Meier method and Cox proportional hazards.

Results: Antibiotics were used by 195 (26%) patients and were the 8th most prescribed medication in our hospice. Survival analysis showed that patients who used antibiotics had, on average, 9 days longer survival (14 *vs.*5 days, HR 0.56) (p<0.001). The results still favored antibiotics even in a multivariate analysis (HR 0.48).

Conclusion: Infections are present in up to 80% of hospice patients and are responsible for the death of up to 50% of the patients. Although several authors discussed the futility and the lack of clinical response to antibiotics in hospice care, our research shows that using antibiotics, regardless of the type, was associated with statistically and clinically significant longer survival. Hence, we should consider antibiotics as the fifth essential drug in hospice.

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Sentinel lymph node tumor burden and immunophenotype and its correlation with non-sentinel lymph node positivity

Key words: antibodies, immunophenotype, sentinel, tumor burden

Introduction: According the MSLT-II trial overall survival was not improved with complete lymph node dissection (CLND) but regional control of disease was improved.

Goal: goal is to find parameters that could be used for selection of patients that could still benefit from CLND. In this study, sentinel tumor burden and expression of FOXP3, CD4, CD8 and their correlation with non-sentinel lymph node (NSLN) involvement were analyzed.

Methods: SLN biopsy was performed from 2011-2016 in 337 patients. In 63 (19.5%) SLN involvement was diagnosed and in 23/63 (36.5%) further involvement in NSLN was found. In 46 patients SLN tumor burden was evaluated by Rotterdam (maximum diameter of metastasis in SLN), Dewar (localization) criteria and Starz (depth of invasion) classification, as well as expression of FoxP3, CD4 and CD8. These parameters were correlated with the outcome of CLND. Fisher's exact test was done for categorical data, t-test for continuous data, (p<0.05 was considered significant).

Results: NSLN involvement was in correlation with localization of metastasis in SLN (Dewar) and depth of invasion (Starz). Subcapsular localization (p=0.007) and depth of invasion ≥3 um (p=0.08) found more frequently in NSLN negative patients. Intratumoral and peritumoral FoxP3 expression was found in 75% of involved NSLN. The presence of intratumoral CD4 and CD8 lymphocytes was found in 60%, while there was no correlation found for peritumoral CD4 and CD8 expression.

Conclusion: NSLN involvement is more frequent in patients with higher SLN tumor burden. Also, peritumoral and intratumoral expression of FoxP3 and intratumoral CD4 and CD8 expression is more frequently found in involved NSLN.

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Comparison of MASSC and CISNE index for identifying patients with febrile neutropenia and low risk for developing complications – monoinstitutional data

Key words: febrile neutropenia, risk, outcome

Introduction: Treatment of febrile neutropenia is gaining in importance, especially with development of clinical and laboratory parameters contained in MASSC and CISNE index to determine which of the patient will be hospitalized in order to decrease intrahospital infections. MASSC index applies to patients on chemotherapy for hematologic and solid malignancies, while the CISNE is more suitable for patients with solid tumors. Combining these two models provides more opportunities to clinician.

Material and methods: This retrospective cohort included 155 patients with febrile neutropenia who were treated in period from January 2016. until January 2018. in Clinical Centre Kragujevac. They were all treated with cytotoxic therapy in the previous period of 20 days. Primary outcome was the severity of any serious complications during treatment. Hospitalization in intensive care unit and lethal outcome for a period of 30 days from the start of treatment were secondary outcomes.

Results: There were 72 (46,5% of total number of 155) patients with febrile neutropenia with low MASSC risk index for development of febrile neutropenia compared to 20 (12,9%) patients with CISNE index with low risk for development of febrile neutropenia. CINSE index in our clinical practice was more significant in detecting patients in low risk for developing complications than MASSC –p< 0,001.

Conclusion: MASSC and CISNE results have a reasonable prognostic value for patients with low risk febrile neutropenia for developing complications. Risk assessment should be used with clinical assessments for the identification of patients who developed febrile neutropenia and witch of those will be hospitalized.

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SCC in patient with inherited epidermolysis bullosa

Key words: exon 94 (G2413E), Inherited epidermolysis bullosa, squamous cell carcinoma

Epidermolysis bullosa (EB) represents an inherited rare skin disorder (1). The most common and severe complication in these patients is cutaneous squamous cell carcinoma (SCC). Researches show that 90.1% of EB patients develop SCC before the age of 55, and 80% of them die within 5 years (2).

We present two cases. First patient is 46 years old male Caucasian patient with SCC of the left lower leg, treated with tumor excision, skin grafting and left inguinal dissection. In 2007, biopsy was performed and were consistent with dystrophic EB, further confirmed with genetic analysis, that revealed the presence of paternal missense mutation in exon 94 (G2413E) and maternal in exon 3 of the COL7A1 gene coding for collagen VII. The patient was diagnosed with recessive dystrophic EB and aplasia cutis congenita known as Bart syndrome. In 2015 complete excision with a skin graft was done with complete healing. At the last follow-up in November 2018 there were no signs of disease.

The second patient is 45 years old male Caucasian who was diagnosed SCC of the right elbow, at the age of 43. The primary tumor was excised, but during follow-up relapse at primary site and lymphonodopathy occurred, treated with brachial amputation and right axillar dissection. During 21 months of follow-up, patient is without signs of relapse of the disease.

SCC in patients with inherited EB is the most common complication, but with adequate diagnostic and treatment procedures, it is possible to have good control over the disease.

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