

# Publikujeme v zahraničí

Onkológia (Bratisl.), 2022;17(4):297-300

## GENITOURINÁRNE MALIGNITY

**Lesko P, Chovanec M, Mego M.**

**Biomarkers of disease recurrence in stage I testicular germ cell tumours.**

**Nature Reviews Urology 2022 Aug 26.**

Stage I testicular cancer is a disease restricted to the testicle. After orchiectomy, patients are considered to be without disease; however, the tumour is prone to relapse in ~4-50% of patients. Current predictive markers of relapse, which are tumour size and invasion to rete testis (in seminoma) or lymphovascular invasion (in non-seminoma), have limited clinical utility and are unable to correctly predict relapse in a substantial proportion of patients. Adjuvant therapeutic strategies based on available biomarkers can lead to overtreatment of 50-85% of patients. Discovery and implementation of novel biomarkers into treatment decision making will help to reduce the burden of adjuvant treatments and improve patient selection for adjuvant therapy.

**Hapakova N, Chovanec M, Rejlekova K, Kalavska K, Obertova J, Palacka P, De Angelis V, Svetlovska D, Sycova-Mila Z, Mardiak J, Mego M.**

**Effects of primary granulocyte-colony stimulating factor prophylaxis on the incidence of febrile neutropenia in patients with germ cell tumors.**

**Oncol Lett. 2022 Jul 13;24(3):308.**

Testicular germ cell tumors (GCTs) are the most common solid malignancy in males aged 15-35 years. Febrile neutropenia (FN) is a serious complication of chemotherapy that frequently occurs in patients with GCTs. The present retrospective study aimed to evaluate the effect of primary granulocyte-colony stimulating factor (G-CSF) prophylaxis on the incidence of FN in patients with GCTs. The present study included a review of the medical records of patients diagnosed with GCTs treated with first-line/adjuvant chemotherapy between January

2000 and December 2017 at the National Cancer Institute (Bratislava, Slovakia). In January 2006, a decision was made to administer G-CSF prophylaxis (filgrastim or pegfilgrastim) to patients after every cycle of chemotherapy. The present study included 385 patients, and out of these, 264 patients received primary G-CSF prophylaxis, while 121 patients did not. A total of 71 patients (18.4%) suffered from FN events. In the subgroup that did not receive primary prophylaxis, 42 patients exhibited FN, while only 29 patients with primary prophylaxis suffered from FN (34.7 vs. 11.0%;  $P=0.00000003$ ). According to the subgroup analysis, FN incidence was decreased in all groups that received primary prophylaxis, except for patients with stage I GCT receiving adjuvant chemotherapy, without affecting overall survival. Primary G-CSF prophylaxis was associated with markedly reduced FN incidence in patients treated with first-line chemotherapy for metastatic disease. Therefore, the results of the present study suggested that primary G-CSF prophylaxis should be considered in patients with GCT receiving first-line chemotherapy.

**Palacka P, Janega P, Polakova H, Slopovsky J, De Angelis V, Mego M.**

**Pericardial malignant infiltration as the cause of sudden death of a patient with metastatic urothelial carcinoma treated with atezolizumab.**

**BMC Urol. 2022 Jul 18;22(1):108.**

**Background:** Muscle-infiltrating urothelial carcinoma of the bladder is the most common genitourinary cancer. Immunotherapeutic agents targeting protein-1 programmed death or protein-1 programmed death ligand are currently considered the standard treatment in patients with either inoperable locally advanced or metastatic urothelial carcinoma (MUC) after platinum-based chemotherapy failure.

**Case presentation:** Here we report the case of a Caucasian male patient with metastatic urothelial carcinoma

treated with second-line atezolizumab within a trial who achieved complete response by computed tomography (CT), but suddenly died due to cardiac tamponade resulting from malignant pericardial infiltration. Histopathology confirmed this as the only site of disease progression.

**Conclusions:** Cardiovascular toxicity of atezolizumab was considered within differential diagnoses, however histopathological examination revealed progression of malignancy in the pericardium as the cause of the sudden death. This is the first published case report of a patient treated with second-line atezolizumab in whom the rare disease progression of pericardial infiltration was confirmed. Despite its rarity, the clinicians should always consider the possibility of pericardial metastases.

**Rejlekova K, Kalavska K, Makovnik M, Hapakova N, Chovanec M, De Angelis V, Obertova J, Palacka P, Sycova-Mila Z, Mardiak J, Mego M.**

**Factors Associated With Choriocarcinoma Syndrome Development in Poor-Risk Patients With Germ Cell Tumors.**

**Front Oncol. 2022 Jun 17;12:911879.**

**Background:** Germ cell tumors (GCTs) represent a highly curable cancer. However, a small proportion of poor-risk patients can develop choriocarcinoma syndrome (CS) connected with acute respiratory distress syndrome (ARDS) with a high mortality rate. Our retrospective study aimed to determine the risk factors of poor-risk GCTs susceptible to CS development.

**Patients and methods:** Using a computerized database and a systematic chart review, we identified the records of 532 patients with GCTs treated at the National Cancer Institute from 2000 to 2018. Ninety eligible patients with poor-risk GCTs based on IGCCCG classification were identified. All patients were treated with platinum-based induction chemotherapy. Clinicopathological

variables were collected and analyzed in correlation with CS development.

**Results:** Nine (10%) of 90 patients developed CS in a median of 1 day (1–9 days) after chemotherapy administration. All patients died shortly after the chemotherapy start with a median of 4 days (3–35 days) due to ARDS development. In univariate analysis, metastatic lung involvement  $\geq 50\%$  of lung parenchyma, choriocarcinoma elements in histology specimen, dyspnea, cough, hemoptysis, ECOG PS  $\geq 2$ , weight loss, hemoglobin  $\leq 100$  g/l, and NLR  $\geq 3.3$  at the time of presentation were associated with CS development. In multivariate analysis, ECOG PS  $\geq 2$  and metastatic lung involvement  $\geq 50\%$  were independently associated with CS. All patients with these two characteristics developed CS, compared to 0% with zero or one of these factors ( $p < 0.000001$ ).

**Conclusions:** In our study, we identified factors associated with CS development. These factors might improve the risk stratification of the patients susceptible to CS and improve their outcome.

**Mego M, Svetlovska D, Angelis V D, Kalavska K, Lesko P, Makovnik M, Obertova J, Orszaghova Z, Palacka P, Reckova M, Rejlekova K, Sycova-Mila Z, Mardiak J, Chovanec M.**

**Phase II study of Disulfiram and Cisplatin in Refractory Germ Cell Tumors. The GCT-SK-006 phase II trial. Invest New Drugs. 2022 Oct;40(5):1080–1086.**

**Background:** Multiple relapsed/refractory germ cell tumor (GCT) patients have extremely poor prognosis. Cisplatin resistant testicular GCTs overexpress aldehyde-dehydrogenase (ALDH) isoforms and inhibition of ALDH activity by disulfiram is associated with reconstitution of cisplatin sensitivity in vitro as well as in animal model. This study aimed to determine the efficacy and toxicity of ALDH inhibitor disulfiram in combination with cisplatin in patients with multiple relapsed/refractory GCTs.

**Methods:** Disulfiram was administered at a dose of 400 mg daily until progression or unacceptable toxicity, cisplatin was administered at dose

50 mg/m<sup>2</sup> day 1 and 2, every 3 weeks. Twelve evaluable patients had to be enrolled into the first cohort, and if 0 of 12 patients had treatment response, the study was to be terminated. The results of the first stage of the trial are presented in this report.

**Results:** Twelve patients with multiple relapsed/refractory GCTs were enrolled in the phase II study from May 2019 to September 2021. Median number of treatment cycles was 2 (range 1–6). None of patients achieved objective response to treatment, therefore the study was terminated in first stage. Median progression-free survival was 1.4 months, 95% CI (0.7–1.5 months), and median overall survival was 2.9 months 95% CI (1.5–4.7 months). Disease stabilization for at least 3 months was observed in 2 (16.7%) patients. Treatment was well tolerated, however, 5 (41.7%) of patients experienced grade 3/4 fatigue, 4 (33.3%) thrombocytopenia, 3 (25.0%) anemia, while 2 (16.7%) experienced neutropenia, nausea and infection.

**Conclusions:** This study failed to achieve its primary endpoint and our data suggest limited efficacy of disulfiram in restoring sensitivity to cisplatin in multiple relapsed/refractory GCTs.

Bleve S, Cursano MC, Casadei C, Schepisi G, Menna C, Urbini M, Gianni C, De Padova S, Filograna A, Gallà V, Rosti G, Barone D, **Chovanec M, Mego M**, De Giorgi U.

**Inflammatory Biomarkers for Outcome Prediction in Patients With Metastatic Testicular Cancer.**

**Front Oncol. 2022 Jun 10;12:910087.**

Germ cell tumors are the most common malignant tumors in male young adults. Platinum-based chemotherapy has dramatically improved the outcome of metastatic germ cell tumor patients and overall cure rates now exceed 80%. The choice of medical treatment can be guided by the prognosis estimation which is an important step during the decision-making process. IGCCCG classification plays a pivotal role in the management of advanced disease. However, histological and clinical parameters are the available factors that condition the prognosis, but they

do not reflect the tumor's molecular and pathological features and do not predict who will respond to chemotherapy. After first-line chemotherapy 20%–30% of patients relapse and for these patients, the issue of prognostic factors is far more complex. Validated biomarkers and a molecular selection of patients that reflect the pathogenesis are highly needed. The association between cancer-related systemic inflammation, tumorigenesis, and cancer progression has been demonstrated. In the last years, several studies have shown the prognostic utility of immune-inflammation indexes in different tumor types. This review analyzed the prognostic impact of inflammatory markers retrieved from routine blood draws in GCT patients.

## GASTROINTESTINÁLNE MALIGNITY

**Safcak D, Drazilova S, Gazda J, Andrasina I, Adamcova-Selcanova S, Balazova L, Barila R, Mego M, Rac M, Skladany L, Zigray M, Janicko M, Jarcuska P.**

**Inflammatory Indexes as Prognostic Factors of Survival in Geriatric Patients with Hepatocellular Carcinoma: A Case Control Study of Eight Slovak Centers. J Clin Med. 2022 Jul 19;11(14):4183.**

### Background and aims:

Hepatocellular cancer (HCC) often occurs in geriatric patients. The aim of our study was to compare overall survival and progression-free survival between geriatric patients ( $\geq 75$  years) and patients younger than 75 years and to identify predictive factors of survival in geriatric patients with HCC.

**Material and methods:** We performed a retrospective analysis of patients with HCC diagnosed in Slovakia between 2010–2016. Cases (HCC patients  $\geq 75$  years) were matched to controls (HCC patients  $< 74$  years) based on the propensity score (gender, BCLC stage and the first-line treatment).

**Results:** We included 148 patients (84 men, 57%) with HCC. There were no differences between cases and controls in the baseline characteristics. The overall survival in geriatric patients with HCC was comparable to younger controls ( $p = 0.42$ ). The one-, two-, and three-year overall survival was 42% and

31%, 19% and 12%, and 12% and 9% in geriatric patients and controls, respectively ( $p = 0.2, 0.4, 0.8$ ). Similarly, there was no difference in the one- and two-year progression-free survival: 28% and 18% vs. 10% and 7% in geriatric HCC patients and controls, respectively ( $p = 0.2, 1, -$ ). There was no case-control difference between geriatric HCC patients and younger HCC controls in the overall survival in the subpopulation of patients with no known comorbidities ( $p = 0.5$ ), one and two comorbidities ( $p = 0.49$ ), and three or more comorbidities ( $p = 0.39$ ). Log (CRP), log (NLR), log (PLR), and log (SII) were all associated with the three-year survival in geriatric HCC patients in simple logistic regression analyses. However, this time, only log (NLR) remained associated even after controlling for the age and BCLC confounding (OR 5.32, 95% CI 1.43-28.85).

**Conclusions:** We found no differences in overall survival and progression-free survival between older and younger HCC patients. Parameters of subclinical inflammation predict prognosis in geriatric patients with HCC. A limitation of the study is small number of the treated patients; therefore, further investigation is warranted.

## KARCINÓM PLŮC

**Chowanecova G, Berzinec P, Kosturiakova G, Plank L, Farkasova A, Seke-resova M, Juskanic D, Ondrus D.**

**An EGFR-mutant lung adenocarcinoma that transformed into small-cell lung cancer. A case report.**

**Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2022 Aug 23.**

**Background:** Transformation of EGFR (epidermal growth factor receptor) - mutant non-small cell lung cancer (NSCLC) into small-cell lung cancer (SCLC) is one mechanism of resistance to tyrosine kinase inhibitor (TKI) treatment, seen in approximately 3-10% cases. Such transformed SCLC often retains the original EGFR mutation (EGFRM), which is not otherwise observed in SCLC.

**Case report:** We present a 67 y/o woman with pulmonary adenocarcinoma (AC) and EGFRM deletion on exon 19. After initial treatment with whole brain radiotherapy and 7 months of

TKI afatinib, progression was observed. Liquid biopsy detected deletion on exon 19 and T790M mutation. Chemotherapy carboplatin plus pemetrexed was administered, with no response. Genetics from a rebiopsy of lung revealed deletion on exon 19. After 12 months treatment with TKI osimertinib, a progression in lung and pancreas lesions was detected, docetaxel was used, with followig progression. The lung biopsy revealed SCLC. Significant elevation of serum markers carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) was observed at the time of the SCLC diagnosis. Treatment with carboplatin and etoposide was not effective. The next biopsy found two populations of cells: SCLC and AC. The biopsy from the pancreatic lesion revealed metastasis of SCLC. PCR confirmed EGFRM deletion on exon 19 in the lung SCLC tissue sample. The following treatment lines of topotecan, erlotinib were not effective. The patient survived 36 months from diagnosis, 7 months from detection of SCLC.

**Conclusion:** Screening for transformation of EGFR-mutant NSCLC to SCLC should be considered in resistance to TKI. In the presented case, this rare transformation was confirmed by histopathologic examination and by PCR. EGFRM in the lung SCLC, identical to that found in the original lung AC, was detected. Further, the observed elevation of serum tumor markers NSE and CEA can indicate this infrequent transformation and help to decide on rebiopsy.

Thallinger C, **Berzinec P**, Bicakcic E, Dan A, Fabian G, Gales LN, Kuhar CG, Janzic U, Kahan Z, Mencinger M, Penthedourakis G, Sgouros J, Simetic L, Sirbu D, Vosmik M, Wrona A, Zielinski C.

**Establishment of a virtual transborder tumor board for cancer patients in Central and Southeastern Europe : An initiative of the Central European Cooperative Oncology Group (CECOG). Wien Klin Wochenschr. 2022 Mar 21:1-8.**

**Purpose:** To establish a transborder virtual tumor board (VTB) fostering state-of-the-art management of cancer patients by exchanging knowledge and expertise among oncologists in Central and Southeastern Europe (CEE).

**Methods:** We established and implemented a VTB based on the WebEx platform. This allowed for password-protected and secure upload of patient cases to be presented and discussed among colleagues from various oncology centers scattered throughout CEE in order to arrive at a recommendation for further diagnoses and/or treatment.

**Results:** A total of 73 cases from 16 oncology centers located in 11 CEE countries were uploaded by 22 physicians; 71 were discussed over the course of 17 virtual meetings between June 2018 and May 2019 and 12 different kinds of malignant diseases were discussed with lung cancer (46.6%), melanoma (19.2%) and bladder cancer (13.6%) being the most commonly presented tumor entities. Of the discussed patients, 93.3% had stage IV disease at the time of presentation, 62.6% received chemotherapy or targeted treatment and 67.1% were treated with immune checkpoint inhibitors (ICPIs). The most common causes for presentation and discussion of patient cases were related to the use of ICPIs (80%).

**Conclusion:** When the need for expertise exceeds locally available resources, web-based VTBs provide a feasible way to discuss patient cases and arrive at conclusions regarding diagnoses and/or treatment across large geographic distances. Moreover, VTBs provide an innovative way for proper, state-of-the-art management of patients with malignant diseases in times of social distancing and the resulting need for restricted interaction during the current SARS-CoV-2 (severe acute respiratory syndrome coronavirus type 2) pandemic.

## SUPORTÍVNA LIEČBA

Maertens J, Lodewyck T, Peter Donnelly J, Chantepie S, Robin C, Blijlevens N, Turlure P, Selleslag D, Baron F, Aoun M, Heinz WJ, Bertz H, Ráčil Z, Vandercam B, **Drghona L**, Coiteux V, Llorente CC, Schaefer-Prokop C, Paesmans M, Ameye L, Meert L, Cheung KJ, Hepler DA, Loeffler J, Barnes R, Marchetti O, Verweij P, Lamoth F, Bochud PY, Schwarzingler M, Cordonnier C; Infectious Diseases Group; Acute Leukemia Group of the European Organization for Research and Treatment of Cancer (EORTC).

**Empiric versus pre-emptive antifungal strategy in high-risk neutropenic patients on fluconazole prophylaxis: a randomized trial of the European organization for Research and Treatment of cancer (EORTC 65091).**

**Clin Infect Dis. 2022 Jul 30**

**Background:** Empiric antifungal therapy is considered the standard-of-care for high-risk neutropenic patients with persistent fever. The impact of a pre-emptive, diagnostic-driven approach based on galactomannan (GM) screening and chest CT-scan on demand on survival and on the risk of invasive fungal disease (IFD) during the first weeks of high-risk neutropenia is unknown.

**Methods:** Patients with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and allogeneic hematopoietic cell transplant recipients were randomly assigned to receive caspofungin empirically (Arm A) or pre-emptively (Arm B). All patients received fluconazole 400 mg daily as prophylaxis. The primary endpoint of this non-inferiority study was overall survival (OS) 42 days after randomization.

**Results:** Of 556 patients recruited, 549 were eligible: 275 in Arm A, 274 in Arm B. Eighty percent of the patients had AML or MDS requiring high-dose chemotherapy and 93% of them were in first induction phase. At day 42, the OS was not inferior in Arm B (96.7%; 95% confidence interval (CI), 93.8 - 98.3%)

when compared to Arm A (93.1%; 95% CI, 89.3 - 95.5%). The rates of IFDs at day 84 were not significantly different, 7.7% (95%CI, 4.5-10.8%) in Arm B versus 6.6% (95%CI, 3.6-9.5%) in Arm A, respectively. The rate of patients receiving caspofungin was significantly lower in Arm B (27%) than in Arm A (63%) ( $p < 0.001$ ).

**Conclusions:** The pre-emptive antifungal strategy was safe for high-risk neutropenic patients given fluconazole as prophylaxis, halving the number of patients receiving antifungals without excess mortality or IFDs.

## INÉ

Gvozdičková A, Sumbalova Z, Kucharska J, Rausova Z, Kovalcikova E, Takacsova T, Navas P, Lopez-Lluch G, Mojto V, **Palacka P. Mountain spa rehabilitation improved health of patients with post-COVID-19 syndrome: pilot study**

**Environ Sci Pollut Res Int. 2022 Sep 23. doi: 10.1007/s11356-022-22949-2. Epub ahead of print. PMID: 36151435.**

European Association of Spa Rehabilitation (ESPA) recommends spa rehabilitation for patients with post-COVID-19 syndrome. We tested the hypothesis that a high-altitude environment with clean air and targeted spa rehabilitation (MR - mountain spa rehabilitation) can contribute to the improving platelet mitochondrial bioenergetics, to accelerating patient health

and to the reducing socioeconomic problems. Fifteen healthy volunteers and fourteen patients with post-COVID-19 syndrome were included in the study. All parameters were determined before MR (MR1) and 16-18 days after MR (MR2). Platelet mitochondrial respiration and OXPHOS were evaluated using high resolution respirometry method, coenzyme  $Q_{10}$  level was determined by HPLC, and concentration of thiobarbituric acid reactive substances (TBARS) as a parameter of lipid peroxidation was determined spectrophotometrically. This pilot study showed significant improvement of clinical symptoms, lungs function, and regeneration of reduced CI-linked platelet mitochondrial respiration after MR in patients with post-COVID-19 syndrome. High-altitude environment with spa rehabilitation can be recommended for the acceleration of recovery of patients with post-COVID-19 syndrome.

## ABSTRAKTY Z KONFERENCIÍ

### GENITOURINÁRNE MALIGNITY

**Scepanovic D., Masarykova A., Hurakova A., Zavacka I., Hanicova A., Fekete M. Incidence of biochemical relapse in patients after radical prostatectomy versus radical radiotherapy.**

**28th Meeting of the EAU Section of Urological Research (ESUR22), Innsbruck, Austria, 13-15 October 2022**