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GENITOURINÁRNE MALIGNITY

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Changes in CoQ_{10}/Lipids Ratio, Oxidative Stress, and Coenzyme Q10 during First-Line Cisplatin-Based Chemotherapy in Patients with Metastatic Urothelial Carcinoma (mUC)

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Oxidative stress plays an important role in cancer pathogenesis, and thiobarbituric acid-reactive substance level (TBARS)-a parameter of lipid peroxidation-has prognostic significance in chemotherapy-naive patients with metastatic urothelial carcinoma (mUC). However, the effect of cisplatin (CDDP)-based chemotherapy on oxidative stress, coenzyme Q10, and antioxidants remains unknown. The objective of this prospective study was to determine possible changes in the CoQ10 (coenzyme Q10)/lipids ratio, antioxidants (α-tocopherol, γ-tocopherol, β-carotene, CoQ10), total antioxidant status (TAS), and TBARS in plasma at baseline and during first-line chemotherapy based on CDDP in mUC subjects. In this prospective study, 63 consecutive patients were enrolled. The median age was 66 years (range 39-84), performance status according to the Eastern Cooperative Oncology Group (ECOG) was 2 in 7 subjects (11.1%), and visceral metastases were present in 31 (49.2%) patients. Plasma antioxidants were determined by HPLC and TAS and TBARS spectrophotometrically. After two courses of chemotherapy, we recorded significant enhancements compared to baseline for total cholesterol (p < 0.0216), very low-density lipoprotein (VLDL) cholesterol (p < 0.002), triacylglycerols (p < 0.0083), α-tocopherol (p < 0.0044), and coenzyme Q10-TOTAL (p < 0.0001). Ratios of CoQ10/total cholesterol, CoQ10/HDL-cholesterol, and CoQ10/LDL-cholesterol increased during chemotherapy vs. baseline (p < 0.0048, p < 0.0101, p < 0.0032, respectively), while plasma TBARS declined (p < 0.0004). The stimulation of antioxidants could be part of the defense mechanism during CDDP treatment. The increased index of CoQ10-TOTAL/lipids could reflect the effect of CDDP protecting lipoproteins from peroxidation.

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Response of the Urothelial Carcinoma Cell Lines to Cisplatin

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Cisplatin (CDDP)-based chemotherapy is the standard of care in patients with muscle-invasive bladder cancer. However, in a large number of cases, the disease becomes resistant or does not respond to CDDP, and thus progresses and disseminates. In such cases, prognosis of patients is very poor. CDDP manifests its cytotoxic effects mainly through DNA damage induction. Hence, response to CDDP is mainly dependent on DNA damage repair and tolerance mechanisms. Herein, we have examined CDDP response in a panel of the urothelial carcinoma cell (UCC) lines. We characterized these cell lines with regard to viability after CDDP treatment, as well as kinetics of induction and repair of CDDP-induced DNA damage. We demonstrate that repair of CDDP-induced DNA lesions correlates, at least to some extent, with CDDP sensitivity. Furthermore, we monitored expression of the key genes involved in selected DNA repair and tolerance mechanisms, nucleotide excision repair, homologous recombination and translesion DNA synthesis, and show that it differs in the UCC lines and positively correlates with CDDP resistance. Our data indicate that CDDP response in the UCC lines is dependent on DNA damage repair and tolerance factors, which may, therefore, represent valuable therapeutic targets in this malignancy.

Schmidtova S, Udvorkova N, Cierna Z, Horak S, **Kalavska K, Chovanec M,** Rojikova L, Vulevova M, **Kucerova L, Mego M.**

Effect of the PARP inhibitor veliparib on germ cell tumor cell lines

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Germ cell tumors (GCTs) usually represent efficiently curable neoplasms due to their chemosensitivity to platinum-based therapeutic regimen. However, some patients develop therapeutic resistance and succumb to their disease. Novel therapeutic approaches are therefore needed for these patients. It has previously been demonstrated that poly (ADP-ribose) polymerase (PARP) expression is upregulated in GCTs compared with normal testis tissue. Therefore, PARP expression was analyzed in GCT cell lines and xenografts and it was examined whether its inhibition by veliparib can reverse cisplatin-resistance. Its expression was analyzed in sensitive and cisplatin-resistant variants (referred to as CisR throughout the manuscript) GCT cell lines and xenografts using quantitative PCR, western blotting and immunohistochemistry. The present study investigated whether the combination of cisplatin with the PARP inhibitor veliparib increased the cytotoxic effect of cisplatin *in vitro* using a luminescent viability assay and an immunodeficient mouse model *in vivo*. PARP expression was observed in all tested cell lines, with the highest expression in embryonal carcinoma (EC) cell lines and xenografts. Low or no expression was detected in the JEG-3 choriocarcinoma cell line pairs and xenografts. The combination of veliparib and cisplatin or carboplatin was examined in the cisplatin-resistant NTERA-2 CisR and NCCIT CisR EC cell lines and synergistic effects

were observed in NTERA-2 CisR cells. However, *in vivo* analysis did not confirm this synergy. The present data indicated PARP expression in GCT cell lines and xenografts. However, veliparib failed to increase the cytotoxicity of platinum-based drugs. Therefore, further research is warranted to effectively inhibit PARP using different PARP inhibitors or other drug combinations.

KARCINÓM PRSNÍKA

Mego M, Vlkova B, Minarik G, Cierna Z, **Karaba M, Benca J,** Sedlackova T, Cholujova D, Gronesova P, **Kalavska K, Pindak D, Mardiak J,** Celec P.

Vitamin D and circulating tumor cells in primary breast cancer

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Background: Circulating tumor cells (CTCs) contribute to the metastatic cascade and represent an independent survival predictor in breast cancer (BC) patients. Vitamin D has pleiotropic effects, and its low concentrations are associated with breast cancer and metastasis. The aim of this study was to assess plasma vitamin D in primary BC patients in relation to CTCs.

Methods: This study included 91 non-metastatic BC patients (stage I-III) and 24 healthy donors. Blood samples for the analyses were drawn at the time of surgery. CTCs were assessed using a quantitative RT-PCR assay for expression of epithelial (CK19) or epithelial-to-mesenchymal transition (EMT) genes (*TWIST1*, *SNAIL1*, *SLUG*, and *ZEB1*). Total 25-OH vitamin D was measured in plasma using ELISA. Plasma cytokines and angiogenic factors were measured by enzyme-linked immunoassay.

Results: CTCs were detected in 30 (33%) patients. Patients with detectable CTCs in peripheral blood had significantly lower vitamin D concentrations in comparison to patients without detectable CTCs ((mean ± SD) 8.50 ± 3.89 μg/L for CTC-positive vs 9.69 ± 3.49 μg/L for CTC-negative patients, p = 0.03). The mean (± SD) vitamin D plasma level was 9.3 ± 3.65 μg/L for breast cancer patients compared to 18.6 ± 6.8 for healthy donors (p < 0.000001). There was no association between plasma vitamin D and other patient/tumor characteristics. Plasma vitamin D levels are inversely correlated with plasma TGF-β1, TGF-β2, IL β, IL-5, and eotaxin (all p < 0.05). Patients with vitamin D above the median had a better overall survival (hazard ratio (HR) = 0.36, 95% CI 0.16-0.80, p = 0.017), and combined analysis showed the best survival for CTC-negative patients with vitamin D levels above the median as compared to patients with opposite characteristics (HR = 0.18, 95% CI 0.05-0.63, p = 0.004).

Conclusions: Low vitamin D could be a consequence and hence a biomarker of a more invasive disease. Alternatively, vitamin D could be associated with survival because of its role in tumor dissemination. Whether its supplementation affects the metastatic cascade should be tested in animal experiments and interventional studies.

SUPORTÍVNA LIEČBA

Royo-Cebrecos C, Laporte-Amargós J, Peña M, Ruiz-Camps I, Puerta-Alcalde P, Abdala E, Oltolini C, Akova M, Montejo M, Mikulska M, Martín-Dávila P, Herrera F, Gasch O, **Drgona L,** Morales HMP, Brunel AS, García E, Isler B, Kern WV, Palacios-Baena ZR, de la Calle GM, Montero MM, Kanj SS, Sipahi OR, Calik S, Márquez-Gómez I, Marin JI, Gomes MZR, Hemmatti P, Araos R, Peghin M, Del Pozo JL, Yáñez L, Tilley R, Manzur A, Novo A, Carratalà J, Gudiol C; IRONIC study group.

Pseudomonas aeruginosa Bloodstream Infections in Patients with Cancer: Differences between Patients with Hematological Malignancies and Solid Tumors

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Objectives: To assess the clinical features and outcomes of *Pseudomonas aeruginosa* bloodstream infection (PA BSI) in neutropenic patients with hematological malignancies (HM) and with solid tumors (ST), and identify the risk factors for 30-day mortality.

Methods: We performed a large multicenter, retrospective cohort study including onco-hematological neutropenic patients with PA BSI conducted across 34 centers in 12 countries (January 2006-May 2018). Episodes occurring in hematologic patients were compared to those developing in patients with ST. Risk factors associated with 30-day mortality were investigated in both groups.

Results: Of 1217 episodes of PA BSI, 917 occurred in patients with HM and 300 in patients with ST. Hematological patients had more commonly profound neutropenia (0.1×10^9 cells/mm) (67% vs. 44.6%; *p* < 0.001), and a high risk Multinational Association for Supportive Care in Cancer (MASCC) index score (32.2% vs. 26.7%; *p* = 0.05). Catheter-infection (10.7% vs. 4.7%; *p* = 0.001), mucositis (2.4% vs. 0.7%; *p* = 0.042), and perianal infection (3.6% vs. 0.3%; *p* = 0.001) predominated as BSI sources in the hematological patients, whereas pneumonia (22.9% vs. 33.7%; *p* < 0.001) and other abdominal sites (2.8% vs. 6.3%; *p* = 0.006) were more common in patients with ST. Hematological patients had more frequent BSI due to multidrug-resistant *P. aeruginosa*(MDRPA) (23.2% vs. 7.7%; *p* < 0.001), and were more likely to receive inadequate initial antibiotic therapy (IEAT) (20.1% vs. 12%; *p* < 0.001). Patients with ST presented more frequently with septic shock (45.8% vs. 30%; *p* < 0.001), and presented worse outcomes, with increased 7-day (38% vs. 24.2%; *p* < 0.001) and 30-day (49% vs. 37.3%; *p* < 0.001) case-fatality rates. Risk factors for 30-day mortality in hematologic patients were high risk MASCC index score, IEAT, pneumonia, infection due to MDRPA, and septic shock. Risk factors for 30-day mortality in patients with ST were high risk MASCC index score, IEAT, persistent BSI, and septic shock. Therapy with granulocyte colony-stimulating factor was associated with survival in both groups.

Conclusions: The clinical features and outcomes of PA BSI in neutropenic cancer patients showed some differences depending on the underlying malignancy. Considering these differences and the risk factors for mortality may be useful to optimize their therapeutic management. Among the risk factors associated with overall mortality, IEAT and the administration of granulocyte colony-stimulating factor were the only modifiable variables.