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Genitourinárne malignity

Chovanec M, Vasilkova L, Setteyova L, Obertova J, Palacka P, Rejlekova K, Sycova-Mila Z, Kalavska K, Svetlovska D, Mladosievicova B, Mardiak J, Mego M.

Long-term sexual functioning in germ--cell tumor survivors

BMC Cancer 2020 Aug 20;20(1):779.

Background: Survivors of germ--cell tumors (GCT) may suffer from long--term adverse consequences. Our study was conducted to assess a long-term sexual functioning in GCT survivors.

Methods: GCT survivors (N = 170) from the National Cancer Institute in Slovakia completed a Sexual Function Questionnaire that was modified from PROMIS Sexual Function and Satisfaction Questionnaire 9-year median follow up (range 5-32) as a primary exploratory aim. Study groups consisted of 17 survivors (10%) who had active surveillance (AS, controls), and 153 (90%) survivors who received treatment beyond orchiectomy (Tx), including cisplatin-based chemotherapy (CT, N = 132; 78%), radiotherapy to the retroperitoneal lymph nodes (RT, N = 12; 7%) or both (CTRT, N = 9; 5%).

Results: In univariate analysis, treatment of any type resulted in difficulty to maintain erection during sexual intercourse compared to patients treated with AS (P = 0.04). Survivors who received CTRT had lower ability to achieve orgasm during sexual activities (P = 0.04) and they reported disappointment with their overall quality of sex life (P = 0.002). The number of attempts to initiate sexual intercourse did not differ. Sexual relationships caused none or mild anxiety and the desire to be sexually active was higher after CTRT (P = 0.05). Multivariable analysis confirmed that orgasmic dysfunction after ≥400 mg/m^2 of cisplatin and issues in maintaining erection after Tx were independent of retroperitoneal lymph-node dissection (P = 0.03 and P = 0.04, respectively). Survivors were disappointed with the quality of sex life and had stronger desire to be sexually active independent of age, (P = 0.01 and P = 0.05, respectively).

Conclusions: This study identified an impairment in sexual function may represent an issue for long-term GCT survivors. Treatment with chemotherapy plus radiotherapy were associated with disappointment and stronger sexual desire, while a higher cumulative dose of cisplatin may be responsible for orgasmic dysfunction.

Schmidtova S, Dorssers LCJ, **Kalavska K, Gercakova K, Miklikova S, Durinikova E, Chovanec M, Matuskova M, Mego M, Kucerova L,** Looijenga LHJ.

In depth investigation of induced cisplatin resistance in a yolk sac tumor cell line: association with upregulation of cancer stem cell markers

Cancer Cell Int. 2020 Aug 3;20:364.

Background: Cisplatin resistance of ovarian yolk sac tumors (oYST) is a clinical challenge due to dismal patient prognosis, even though the disease is extremely rare. We investigated potential association between cisplatin resistance and cancer stem cell (CSC) markers in chemoresistant oYST cells and targeting strategies to overcome resistance in oYST.

Methods: Chemoresistant cells were derived from chemosensitive human oYST cells by cultivation in cisplatin in vitro. Derivative cells were characterized by chemoresistance, functional assays, flow cytometry, gene expression and protein arrays focused on CSC markers. RNAseq, methylation and microRNA profiling were performed. Quail chorioallantoic membranes (CAM) with implanted oYST cells were used to analyze the micro-tumor extent and interconnection with the CAM. Tumorigenicity in vivo was determined on immunodeficient mouse model. Chemoresistant cells were treated by inhibitors intefering with the CSC properties to examine the chemosensitization to cisplatin.

Results: Long-term cisplatin exposure resulted in seven-fold higher IC_{50} value in resistant cells, cross-resistance to oxaliplatin and carboplatin, and increased migratory capacity, invasiveness and tumorigenicity, associated with hypomethylation of differentially methylated genes/promotors. Resistant cells exhibited increased expression of prominin-1 (CD133), ATP binding cassette subfamily G member 2 (ABCG2), aldehyde dehydrogenase 3 isoform A1 (ALDH3A1), correlating with reduced gene and promoter methylation, as well as increased expression of ALDH1A3 and higher overall ALDH enzymatic activity, rendering them cross-resistant to DEAB, disulfiram and napabucasin. Salinomycin and tunicamycin were significantly more toxic to resistant cells. Pretreatment with napabucasin resensitized the cells to cisplatin and reduced their tumorigenicity in vivo.

Conclusions: The novel chemoresistant cells represent unique model of refractory oYST. CSC markers are associated with cisplatin resistance being possible targets in chemorefractory oYST.

Sestakova Z, Kalavska K, Miskovska V, Rejlekova K, Syčova-Mila Z, Palacka P, Obertova J, Hurbanova L, Jurkovicova D, Holickova A, Goffa E, Svetlovska D, Chovanec M, Mardiak J, Mego M, Chovanec M.

Prognostic impact of the DNA damage level in germ cell tumors: a validation study

Mutat Res. 2020 Jun-Jul;854-855:503200

Germ cell tumour (GCT) patients who fail to respond to chemotherapy or who relapse have a poor prognosis. Timely and accurately stratifying such patients could optimise their therapy. We identified endogenous DNA damage levels as a prognostic marker for progression-free (PFS) and overall (OS) survival in chemotherapy-naïve GCT patients. In the present study, we have extended our previous results and reviewed the prognostic power of DNA damage level

in GCTs. Endogenous DNA damage levels were measured with the comet assay. Receiver operator characteristic analysis was applied to determine the optimal cut-off value and to evaluate its prognostic accuracy. PFS and OS were estimated by the Kaplan-Meier method and compared using the log-rank test. Hazard ratio (HR) estimates were calculated by Cox regression analysis. A cut-off value of 6.34 provided the highest sensitivity and specificity, with area under curve values of 0.813 and 0.814 for disease progression and mortality, respectively. A % DNA in tail > 6.34 was significantly associated with shorter PFS (HR = 9.54, 95 % confidence interval [CI]: 3.43-26.55, p < 0.001) and OS (HR = 14.62, 95 % CI: 3.14-67.95, p = 0.001) by univariate analysis. The prognostic value of DNA damage measurement was confirmed by multivariate models (HR = 6.45, 95 % CI: 2.22-18.75, p = 0.001 for PFS and HR = 9.40, 95 % CI: 1.70-52.09, p = 0.010 for OS), when HR was adjusted for relevant clinical categories. The added prognostic value of DNA damage in combination with International Germ Cell Cancer Collaborative Group (IGCCCG) risk groups has been revealed. Endogenous DNA damage is an independent prognosticator for PFS and OS in GCT patients and its clinical use, particularly in combination with IGCCCG risk groups, may help in stratifying these patients.

Borbelyova V, Domonkos E, Chovanec M, Mego M, Celec P.

Transient effects of chemotherapy for testicular cancer on mouse behavior

Sci Rep. 2020 Jun 23;10(1):10224.

The treatment of testicular cancer includes unilateral orchiectomy and chemotherapy and is curative for most patients. However, observational studies revealed an association with depression, anxiety and cognitive impairment. It is unclear whether these side effects are caused by chemotherapy, hemicastration or the disease itself. The aim of our study was to analyse the behavioural effects of hemicastration and chemotherapy in adult male mice. The animals were randomly divided into four groups - control, chemotherapy, hemicastration and hemicastration with chemotherapy. After chemotherapy that included three cycles of bleomycin, etoposide, cisplatin mice underwent a battery of behavioural tests. To assess the long-term effects animals were tested also 3 months after the end of treatment. Chemotherapy led to lower locomotor- and exploratory activity, higher anxiety-like behaviour and worse spatial memory immediately after treatment. These behavioural effects were not present three months later. Hemicastration had no effect on most of the observed outcomes. In conclusion, adverse behavioural effects induced by chemotherapy in mice are transient and disappear later in life. Further studies are needed to elucidate the mechanisms responsible for the observed effects.

Lymfómy

Mosna K, Ladicka M, Drgona L, Vranovska M, Hojsikova I, Tomasova R, Danihel L Jr, Kyselovic J, Babal P.

Ibrutinib treatment of mantle cell lymphoma complicated by progressive multifocal leukoencephalopathy

Int J Clin Pharmacol Ther. 2020 Jun;58(6):343-350.

Objective: Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease of the central nervous system, caused by reactivation of John Cunningham polyomavirus, affecting mainly patients in an immunocompromised state. Recently, drug-associated PML is gaining attention as more cases of PML in connection with the use of various immunomodulatory drugs emerge. Over the last couple of years, sporadic reports have occurred about a possible association between PML and the use of a new immunomodulatory drug, ibrutinib (Imbruvica), primarily indicated for the treatment of various B-cell malignancies.

Case report: Herein, we report a case of a 62-year-old female patient with bilateral mantle cell lymphoma of conjunctiva diagnosed at IVA clinical stage (according to the Ann Arbor staging of lymphomas) of the disease. As a first line of treatment, the patient was given 6 cycles of rituximab-based chemotherapy followed by a complete remission. Seven years later, the patient relapsed, at which point the treatment with ibrutinib was initiated. Three weeks after the initial dosage, the patient started to show signs of progressive neurological symptomatology and died 4 months thereafter due to bilateral bronchopneumonia. Due to unspecific MRI signs and negative PCR results, the diagnosis of PML was confirmed only postmortem.

Conclusion: This case report demonstrates a possible severe adverse effect of the immunomodulatory drug ibrutinib and the importance of a multidisciplinary approach in its diagnosis. Since PML is a rare but highly fatal disease, it is of utmost importance to be aware of the possible connection with the use of this drug to prevent missed or delayed diagnosis, considering that timely therapeutic intervention is crucial for improved prognosis.

Sarkómy

Constantinidou A, Sauve N, Stacchiotti S, Blay JY, Vincenzi B, Grignani G, Rutkowski P, Guida M, Hindi N, Klein A, Thibaud V, **Sufliarsky J**, Desar I, Steeghs N, Litiere S, Gelderblom H, Jones RL.

Evaluation of the use and efficacy of (neo)adjuvant chemotherapy in angiosarcoma: a multicentre study

ESMO Open. 2020 Aug;5(4):e000787.

Introduction: Angiosarcomas constitute approximately 2% to 3% of all soft tissue sarcomas, are characterised by an aggressive clinical behaviour and poor outcome. Optimal management of localised angiosarcomas consists of complete surgical resection with or without radiation. However, due to the infiltrating nature of this disease, complete resection is often not possible. Despite optimal management, the outcome of patients with localised disease remains poor. The role of (neo)adjuvant chemotherapy in angiosarcomas remains undefined. The aim of this study is to document the outcome of patients treated with (neo)adjuvant chemotherapy and assess the feasibility of performing a prospective trial by evaluating the number of patients treated at sarcoma referral centres.

Methods: A retrospective search within participating EORTC (European Organisation for Research and Treatment of Cancer) sites for patients treated with

(neo)adjuvant chemotherapy was made. Patients treated between January 2007 and January 2016 were included.

Results: A total of 15 institutions participated and 86 patients were evaluable, 43 were treated with neoadjuvant, 27 with adjuvant chemotherapy and 16 with both. At the time of analysis, the median follow-up from diagnosis was 4.6 years. Median overall survival (OS) was 4.9 years (2.9 N) and the percentage alive at 4 years was 57.9 (45.5 to 68.4). The median disease-free survival was 1.4 years (0.9 to 1.7) and the percentage disease-free at 4 years was 26.8% (17.9 to 36.5).

Conclusion: The outcome of angiosarcoma patients treated with (neo) adjuvant chemotherapy in this case series compares favourably with previously published data. Due to the aggressive nature of angiosarcoma, a prospective trial of neoadjuvant chemotherapy should be considered.

Karcinóm prsníka

Cortés J, Diéras V, Lorenzen S, Montemurro F, Riera-Knorrenschild J, Thuss-Patience P, Allegrini G, De Laurentiis M, Lohrisch C, **Oravcova E**, Perez-Garcia JM, Ricci F, Sakaeva D, Serpanchy R, **Sufliarsky J**, Vidal M, Irahara N, Wohlfarth C, Aout M, Gelmon K.

Efficacy and safety of trastuzumab emtansine plus capecitabine vs trastuzumab emtansine alone in patients with previously treated ERBB2 (HER2)-positive metastatic breast cancer: a phase 1 and randomized phase 2 trial

JAMA Oncol. 2020 Jun 25;6(8):1-7.

Importance: ERBB2 (HER2)-targeted therapy provides benefits in metastatic breast cancer (mBC) and gastric cancer, but additional treatments are needed to maximize efficacy and quality of life.

Objective: To determine maximum tolerated doses (MTDs) of trastuzumab emtansine (T-DM1) plus capecitabine in patients with previously treated ERBB2-positive mBC and locally advanced/metastatic gastric cancer (LA/mGC) (phase 1) and the efficacy and safety of this combination vs T-DM1 alone in patients with mBC (phase 2).

Design, setting and participants: The MTD in phase 1 was assessed using a 3 + 3 design with capecitabine dose modification. Phase 2 was an open-label, randomized, international multicenter study of patients with mBC treated with T-DM1 plus capecitabine or T-DM1 alone. Eligible patients had previously treated ERBB2-positive mBC or LA/mGC with no prior chemotherapy treatment for advanced disease.

Interventions: Patients in the phase 1 mBC cohort received capecitabine (750 mg/m2, 700 mg/m2, or 650 mg/m2 twice daily, days 1-14 of a 3-week cycle) plus T-DM1 3.6 mg/kg every 3 weeks. Patients with LA/mGC received capecitabine at the mBC phase 1 MTD, de-escalating as needed, plus T-DM1 2.4 mg/kg weekly. In phase 2, patients with mBC were randomized (1:1) to receive capecitabine (at the phase 1 MTD) plus T-DM1 or T-DM1 alone.

Main outcomes and measures: The phase 1 primary objective was to identify the MTD of capecitabine plus T-DM1. The phase 2 primary outcome was investigator-assessed overall response rate (ORR).

Results: In phase 1, the median (range) age was 54.0 (37-71) and 57.5 (53-70) years for patients with mBC and patients with LA/mGC, respectively. The capecitabine MTD was identified as 700 mg/m2 in 11 patients with mBC and 6 patients with LA/mGC evaluable for dose-limiting toxic effects. In phase 2, between October 2014 and April 2016, patients with mBC (median [range] age, 52.0 [28-80] years) were randomized to receive combination therapy (n = 81) or T-DM1 (n = 80). The ORR was 44% (36 of 81 patients) and 36% (29 of 80 patients) in the combination and T-DM1 groups, respectively (difference, 8.2%; 90% CI, -4.5 to 20.9; P = .34; clinical cutoff, May 31, 2017). Adverse events (AEs) were reported in 78 of 82 patients (95%) in the combination group, with 36 (44%) experiencing grade 3-4 AEs, and 69 of 78 patients (88%) in the T-DM1 group, with 32 (41%) experiencing grade 3-4 AEs. No grade 5 AEs were reported.

Conclusions and relevance: Adding capecitabine to T-DM1 did not statistically increase ORR associated with T-DM1 in patients with previously treated ERBB2-positive mBC. The combination group reported more AEs, but with no unexpected toxic effects.

Abstrakty a príspevky z konferencií

Genitourinárne malignity

M. Mego, R. Huddart, J. Voortman, M. Ong, C. Gedye, H. Gurney, A. Fay, A. Bamias, B. Mellado Gonzalez, Y. Loriot, A. Merseburger, D. Castellano Gauna, S. de Ducla, J. Pavlova, S. Fear, C. Sternberg;

Prognostic effect of systemic immune-inflammation index (SII) in 987 patients with advanced/metastatic urinary tract carcinoma (mUTC) treated with atezolizumab in the real-world global SAUL study.

ESMO, 19-21 September, 2020

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

A phase II trial of paclitaxel, ifosfamid and cisplatin in patients with poor-prognosis disseminated non-seminomatous germ cell tumors with unfavorable serum tumor marker decline after first cycle of chemotherapy.

ESMO, 19-21 September, 2020

Daniel Castellano, Craig Gedye, Giuseppe Fornarini, Andre P. Fay, Jens Voortman, **Michal Mego**, Aristotelis Bamias, Jason Francis Lester, Robert A Huddart, Michaela Matouskova, Howard Gurney, Begona Mellado, Michael Ong, Filipa Carneiro, Florian Seseke, Laura Milesi, Shahrokh F. Shariat, Simon Fear, Sabine de Ducla, Cora N. Sternberg.

Atezolizumab (atezo) therapy for locally advanced/metastatic urinary tract carcinoma (mUTC) in patients (pts) with poor performance status (PS): Analysis of the prospective global SAUL study

J Clin Oncol 38: 2020 (suppl; abstr 5035)

Jan Slopovsky, Jarmila Kucharska, Jana Obertova, Michal Mego, Katarina Kalavska, Anna Gvozdjakova, Patrik Palacka

Marker of lipid peroxidation tbars predicts survival in patients with metastaticurothelial carcinoma (MUC)

J Clin Oncol 38: 2020 (suppl; abstr e17023)

Patrik Palacka, Jana Katolicka, Tana Albertova, Katarina Rejlekova, Jana Obertova, Matej Hrncar, Michal Chovanec, Jan Slopovsky, Michal Mego
Systemic immune-inflammation index to predict survival in patients with metastatic urothelial carcinoma treated with second-line vinflunine
J Clin Oncol 38: 2020 (suppl; abstr e17019)

Nikola Hapakova, Michal Chovanec, Katarina Rejlekova, Katarina Kalavska, Jana Obertova, Patrik Palacka, Valentina De Angelis, Zuzana Sycova, Jozef Mardiak, Michal Mego
The effect of primary granulocyte-colony stimulating factor prophylaxis on incidence of febrile neutropenia in patients with testicular germ cell tumors
J Clin Oncol 38: 2020 (suppl; abstr e17056)

Jana Obertova, Patrik Palacka, Dalibor Gallik, Jan Slopovsky, Michal Chovanec, Boris Kollárik, Katarina Rejlekova, Valentina De Angelis, Zuzana Sycova-Mila, Nikola Hapakova, Michal Mego
Systemic immune-inflammation index to predict survival in muscle-infiltrating urothelial carcinoma
J Clin Oncol 38: 2020 (suppl; abstr e17022)

Michal Chovanec, Dominika Galikova, Lucia Vasilkova, Valentina De Angelis, Katarina Rejlekova, Jana Obertova, Zuzana Sycova-Mila, Patrik Palacka, Katarina Kalavska, Daniela Svetlovska, Beata Mladosievicova, Jozef Mardiak, Michal Mego
Effect of long-term peripheral neuropathy induced on cisplatin-based chemotherapy or radiation to the retroperitoneum in testicular germ cell tumor survivors
J Clin Oncol 38: 2020 (suppl; abstr e17062)

Michal Chovanec, Dominika Galikova, Lucia Vasilkova, Valentina De Angelis, Katarina Rejlekova, Jana Obertova, Zuzana Sycova-Mila, Patrik Palacka, Katarina Kalavska, Daniela Svetlovska, Beata Mladosievicova, Jozef Mardiak, Michal Mego
Chemotherapy-induced peripheral neuropathy (CIPN) as a predictor of decreased quality of life and cognitive impairment in testicular germ cell tumor survivors
J Clin Oncol 38: 2020 (suppl; abstr e17063)

Karcinóm pľúc

Danijela Scepanovic, A. Hanicova, M. Kolarcikova–Lukacovicova, M. Dzongov, M. Fekete, M. Pobijakova, A. Masarykova
Prognostic utility of primary tumor and lymph nodes activity by [18F]FDG PET-CT for radiotherapy planning in patients with locally advanced Non Small Lung Cancer International Conference On Frontiers in Lung Cancer, November 16-17, 2020 in Brisbane, Australia

Karcinóm prsníka

Michal Mego, Katarina Kalavska, Marian Karaba, Gabriel Minarik, Juraj Benca, Tatiana Sedlackova, Denisa Manasova, Daniel Pindak, Jozef Mardiak, Peter Celec
Prognostic value of circulating nucleosomes in primary breast cancer
J Clin Oncol 38: 2020 (suppl; abstr e12553)

Karcinóm pažeráka

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Influence of brachytherapy on local control of locally advanced esophageal carcinomas,
ESTRO 2020, 3-7 April 2020, Vienna, Austria