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Onkológia (Bratisl.), 2017; roč. 12(6): 452–453

GENITOURINÁRNE MALIGNITY

Loriot Y, Pagliaro L, Fléchon A, **Mardiak J**, Geoffrois L, Kerbrat P, Chevreau C, Delva R, Rolland F, Theodore C, Roubaud G, Gravis G, Eymard JC, Malhaire JP, Linassier C, Habibian M, Martin AL, Journeau F, **Reckova M**, Logothetis C, Laplanche A, Le Teuff G, Culine S, Fizazi K.

Patterns of relapse in poor-prognosis germ-cell tumours in the GETUG 13 trial: Implications for assessment of brain metastases

Eur J Cancer. 2017 Dec;87:140-146.

Background: The GETUG 13 phase III trial tested personalised chemotherapy based on tumour marker decline in patients with poor-prognosis germ-cell tumour (GCT) and demonstrated that a dose-dense regimen improves progression-free survival in patients with an unfavourable decline. We investigated the pattern of relapse for patients included in GETUG 13.

Methods: We conducted an analysis of relapse events in patients from GETUG 13. Baseline procedures before inclusion in the trial comprised a thoraco-abdomino-pelvic computed tomography scan and a magnetic resonance imaging of the brain.

Results: With a median follow-up of 4.1 years (0.3; 8.8 years), a progression event was observed in 109/254 patients (43%). First event consisted in a marker progression only in 47 patients (43%), a radiographic progression only in 35 patients (32%), a mix progression on both markers and imaging in 12 patients (11%) and death in 15 patients (14%). In patients with radiographic progression only, brain was the predominant site (n = 19/35, 54%). Among patients with unfavourable decline who experienced a radiographic progression (as first and subsequent progression event, n = 58), brain was a site of progression in 28 patients (48%): 12/30 (40%) in patients treated with cisplatin, bleomycin and etoposide and 16/28 (57%) in those treated with dose-dense chemotherapy.

Conclusions: Brain metastases develop often, early and frequently as the only site of relapse in the course of poor-prognosis GCT. This raises the question of early detection and optimal treatment of brain metastases in these patients, e.g. by integrating a systematic brain MRI after 2-3 months of chemotherapy.

Chovanec M, Taza F, Kalra M, Hahn N, Nephew KP, Spinella MJ, Albany C.

Incorporating DNA methyltransferase inhibitors (DNMTis) in the treatment of genitourinary malignancies: a systematic review.

Target Oncol. 2017 Dec 11.

Inhibition of DNA methyltransferases (DNMTs) has emerged as a novel treatment strategy in solid tumors. Aberrant hypermethylation in promoters of critical tumor suppressor genes is the basis for the idea that treatment with hypomethylating agents may lead to the restoration of a "normal" epigenome and produce clinically meaningful therapeutic outcomes. The aim of this review article is to summarize the current state of knowledge of DNMT inhibitors in the treatment of genitourinary malignancies. The efficacy of these agents in genitourinary malignancies was reported in a number of studies and suggests a role of induced DNA hypomethylation in overcoming resistance to conventional cytotoxic treatments. The clinical significance of these findings should be further investigated.

Chovanec M, Cierna Z, Miskovska V, Machalekova K, Kalavska K, Rejlekova K, Svetlovska D, Macak D, Spanik S, Kajo K, Babal P, De Giorgi U**, Mego M, Mardiak J.**

Systemic immune-inflammation index in germ-cell tumors

Br J Cancer, 2017 (In press)

Background: We evaluated systemic immune-inflammation index (SII) and its association with patient's outcome in germ-cell tumors (GCTs).

Methods: Two independent cohorts of patients were analyzed; the discovery set (n=171) from a single institution and the validation set (n=181) previously included in a study evaluating PD-L1 in GCTs. The SII was calculated using platelet (P), neutrophil (N) and lymphocyte (L) counts before chemotherapy and correlated with survival using regression analyses and Kaplan-Meier method.

Results: In the discovery cohort, the SII was associated with poor risk clinical features. Patients with low SII had significantly longer progression-free survival (PFS) (HR = 0.22, 95%CI 0.12 – 0.41, P< 0.001) and overall survival (OS) (HR = 0.16, 95%CI 0.08 - 0.32, P< 0.001) compared to high SII. This index was independent of IGCCCG criteria in multivariable cox regression analysis for OS and was validated in an independent cohort. When combining PD-L1 expression on tumor infiltrating lymphocytes (TILs) and SII, we identified three distinctive prognostic groups.

Conclusion: High SII was associated with poor outcome in GCTs. Combination of PD-L1 positive TILs and SII could further refine prognosis in GCTs.

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

Long-term cognitive functioning in testicular germ-cell tumor survivors

The Oncologist, 2017 (In press)

Background: Treatment for cancer may lead to development of cognitive difficulties in cancer survivors. This study aimed to evaluate a long-term cognitive functioning (CogF) in germ-cell tumor (GCT) survivors.

Patients and methods: GCT survivors (*N*=155) from national cancer centre completed the Functional Assessment of Cancer Therapy Cognitive Function (FACT-Cog) at median 10 years of follow up (range 5-32). The study group consisted of survivors receiving a cisplatin-based chemotherapy, radiotherapy to the retroperitoneal lymph nodes or both, while control group included survivors treated with orchiectomy only.

Results: Of survivors, 138 received treatment beyond orchiectomy and 17 controls had orchiec-

tomy alone. Any treatment resulted in significantly greater cognitive difficulties on the overall cognitive function score. Treatment with radiotherapy was associated with cognitive declines in overall cognitive functioning and in subscales for perceived cognitive impairment and cognitive impairment perceived by others (both $P<0.05$). The burden of chemotherapy plus radiotherapy or radiotherapy versus controls resulted in the impairment in all cognitive functioning domains (all $P<0.05$). Overall long-term cognitive impairment was independent of age in the multivariable analysis.

Conclusion: This prospective study shows that GCT survivors suffer from a long-term CogF impairment. These results may help guiding clinicians' decisions in treatment and follow-up of GCTs.

SARKÓMY

Schöffski P, Wozniak A, Kasper B, Aamdal S, Leahy MG, Rutkowski P, Bauer S,Gelderblom H, Italiano A, Lindner LH, Hennig I, Strauss S, Zakotnik B, Anthoney A, Albiges L, Blay JY, Reichardt P, **Sufliarsky J,** van der Graaf WTA, Debiec-Rychter M, Sciot R, Van Cann T, Marréaud S, Raveloarivahy T, Collette S, Stacchiotti S.

Activity and safety of crizotinib in patients with alveolar soft part sarcoma with rearrangement of TFE3. European Organization for Research and Treatment of Cancer (EORTC) phase 2 trial 90101 „CREATE".

Ann Oncol. 2017 Dec 5. doi: 10.1093/annonc/mdx774. [Epub ahead of print]

Background: Alveolar soft part sarcoma(ASPS) is an orphan malignancy associated with a rearrangement of transcription factor E3(TFE3), leading to abnormal MET gene expression. We prospectively assessed the efficacy and safety of the tyrosine kinase inhibitor(TKI) crizotinib in patients with advanced or metastatic ASPS.

Patients and methods: Eligible patients with reference pathology-confirmed ASPS received oral crizotinib 250 mg twice daily. By assessing the presence or absence of a TFE3 rearrangement, patients were attributed to MET+ and MET- sub-cohorts. The primary endpoint was the objective response rate(ORR) according to local investigator. Secondary endpoints included duration of response(DOR), disease control rate(DCR), progression-free survival(PFS), progression-free rate(PFR), overall survival(OS) and safety.

Results: Among 53 consenting patients, all had a centrally confirmed ASPS and 48 were treated. A total of 45 were eligible, treated and evaluable. Among 40 MET+ patients, 1 achieved a confirmed PR that lasted 215 days and 35 had stable disease(SD) as best response(ORR:2.5%, 95%CI:0.6-80.6%). Further efficacy endpoints in MET+ cases were DCR:90.0%(95%CI:76.3-97.2%), 1-year PFS rate: 37.5%(95%CI:22.9-52.1%) and 1-year OS rate:97.4%(95%CI:82.8-99.6%). Among 4 MET- patients, 1 achieved a PR that lasted 801 days and 3 had SD(ORR:25.0%,95%CI:0.6-80.6%) for a DCR of 100% (95%CI:39.8-100.0%). The 1 year PFS rate in MET- cases was 50%(95%CI:5.8-84.5%) and the 1-year OS rate was 75%(95%CI:12.8-96.1%). One patient with unknown MET status due to technical failure achieved SD but stopped treatment due to progression after 17 cycles. The most common crizotinib-related adverse events were nausea(34/48[70.8%]), vomiting (22/48[45.8%]), blurred vision(22/48[45.8%]), diarrhoea(20/48[41.7%]) and fatigue(19/48[39.6%]).

Conclusion: According to EORTC efficacy criteria for soft tissue sarcoma, our study demonstrated that crizotinib has activity in TFE3 rearranged ASPS MET+patients.

Schöffski P, Wozniak A, Escudier B, Rutkowski P, Anthoney A, Bauer S, **Sufliarsky J,** van Herpen C, Lindner LH, Grünwald V, Zakotnik B, Lerut E, Debiec-Rychter M, Marréaud S, Lia M, Raveloarivahy T, Collette S, Albiges L. 14.

Crizotinib achieves long-lasting disease control in advanced papillary renal-cell carcinoma type 1 patients with MET mutations or amplification. EORTC 90101 CREATE trial

Eur J Cancer. 2017 Dec;87:147-163. doi: 10.1016/j.ejca.2017.10.014. Epub 2017 Nov

Purpose: Papillary renal-cell carcinoma type 1 (PRCC1) is associated with MET gene alterations. Our phase II trial prospectively assessed the efficacy and safety of crizotinib in patients with advanced/metastatic PRCC1 with or without MET mutations (MET+ and MET-).

Experimental design: Eligible patients with reference pathology-confirmed PRCC1 received 250 mg oral crizotinib twice daily. Patients were attributed to MET+/MET- sub-cohorts by the sequencing of exons 16-19 of the MET gene in tumour tissue. The primary end-point was objective response rate (ORR). If at least two of the first 12 eligible and evaluable MET+ patients achieved a confirmed partial response (PR) or complete response (CR) (in accordance with the Response Evaluation Criteria in Solid Tumours, version 1.1), a maximum of 35 patients were enrolled. Secondary end-points included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), PFS rate (PFSR), overall survival (OS) and safety.

Results: Forty-one patients provided consent, of whom 23 were eligible, treated and evaluable. In four MET+ patients, two achieved PR and one had stable disease (SD) (ORR 50%; 95% confidence interval [CI]: 6.8-93.2), DOR was 21.8 and 37.3 months, 1-year PFSR: 75.0% (95% CI: 12.8-96.1) and 1-year OS: 75.0% (95% CI: 12.8-96.1). Among 16 MET- patients, one achieved a PR lasting more than 9.9 months and 11 had SD (ORR: 6.3%; 95% CI: 0.2-30.2), 1-year PFSR: 27.3% (95% CI: 8.5-50.4) and 1-year OS: 71.8% (95% CI: 41.1-88.4). Among three patients with unknown MET status (MET?) due to technical failure, one achieved PR lasting more than 6.9 months, and one had SD (ORR 33.3%, 95% CI: 0.8-90.6), 1-year PFSR: 66.7% (95% CI: 5.4-94.5) and 1-year OS: 100%. MET amplification was found post hoc in one MET+ patient (PR, DOR: 37.3 months), and one MET- case who had SD. Common treatment-related adverse events were oedema (47.8%), fatigue (47.8%), nausea (39.1%), diarrhoea (39.1%) and blurred vision (34.8%).

Conclusion: Crizotinib is active and well tolerated in advanced, metastatic PRCC1, achieving objective responses and long-lasting disease control in patients with MET mutations or amplification. Sporadic, durable responses are also seen in MET- and MET? cases, suggesting the presence of other alterations of MET or alternative pathways.

ABSTRAKTY PRÍSPEVKOV ZO ZAHRANIČNÝCH KONFERENCIÍ

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Mego M, Tokar T, Minarik G, Hajduk M, Karaba M, Benca J, Sedlackova T, Repiska G, Krasnicanova L, Macuch J, Sieberova G, Pindak D, Cristofanilli M, Reuben JM, Jurisica I, **Mardiak J.**

Comprehensive analysis of genomic alterations in tumor tissue associated with presence of various subpopulations of circulating tumor cells (CTCs) in primary breast cancer San Antonio Breast Cancer Symposium, December 5-8th, 2017 San Antonio, Texas, USA

GENITOURINÁRNE NÁDORY

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

Poster and oral presentation in Rapid-Fire Abstract Session.

Genitourinary cancers symposium, Feb 7-9th 2018, San Francisco, California, USA