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SARKÓMY

Schöffski P, **Kubickova M**, Wozniak A, Blay JY, Strauss SJ, Stacchiotti S, Switaj T, Bücklein V, Leahy MG, Italiano A, Isambert N, Debiec-Rychter M, Sciot R, Lee CJ, Speetjens FM, Nzokirantevye A, Neven A, Kasper B.

Long-term efficacy update of crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumour from EORTC trial 90101 CREATE

Eur J Cancer. 2021 Oct;156:12-23. doi: 10.1016/j.ejca.2021.07.016. Epub 2021 Aug 13. PMID: 34392187.

Purpose: European Organisation for Research and Treatment of Cancer (EORTC) 90101 (CREATE) was a prospective, multicentric, non-randomised, open-label phase II basket trial to assess the efficacy and safety of crizotinib in patients with different types of cancers, including advanced inflammatory myofibroblastic tumour (IMT) with or without anaplastic lymphoma kinase (ALK) rearrangements. Here, we report updated results with long-term follow-up.

Patients/methods: After central reference pathology, eligible ALK-positive and ALK-negative patients with advanced/metastatic IMT deemed incurable with surgery, radiotherapy or systemic therapy received oral crizotinib 250 mg twice daily. The ALK status was assessed centrally using immunohistochemistry and fluorescence in situ hybridisation. The primary end-point was the proportion of patients who achieved an objective response (i.e. complete or partial response). If ≥ 6 ALK-positive patients achieved a confirmed response, the trial would be deemed successful.

Results: At data cut-off on 28th January 2021, we performed the final analysis of this trial. Of the 20 eligible and treated patients (19 of whom were evaluable for efficacy), with a median follow-up of 50 months, five were still on crizotinib treatment (4/12 ALK-positive and 1/8 ALK-negative patients). The updated objective response rate (ORR) was 66.7% (95% confidence interval [CI] 34.9-90.1%) in ALK-positive patients and 14.3% (95% CI 0.0-57.9%) in ALK-negative patients. In the ALK-positive and ALK-negative patients, the median progression-free survival was 18.0 months (95% CI 4.0-NE) and 14.3 months (95% CI 1.2-31.1), respectively; 3-year overall survival rates were 83.3% (95% CI 48.2-95.6) and 34.3% (95% CI 4.8-68.5). Safety results were consistent with previously reported data.

Conclusion: These updated results confirm previous findings that crizotinib is effective, with durable responses, in patients with locally advanced or metastatic ALK-positive IMT. With further follow-up after the original primary analysis, the ORR increased, as patients derived long-term benefit and some responses converted from stable disease to partial responses.

MALÍGNY MELANÓM

Palacka P, Slopovsky J, Makovnik M, Kajo K, Obertova J, Mego M.

A case report of a patient with inoperable primary diffuse leptomeningeal melanomatosis treated with whole-brain radiotherapy and pembrolizumab.

Medicine (Baltimore). 2022 Jan 21;101(3):e28613.

Rationale: Primary diffuse leptomeningeal melanomatosis (PDLM) is a rare disease that affects melanocytes in the leptomeninges. There is very limited data on the efficacy of immunotherapy in this setting. Patient concerns: A patient (23 years old) was diagnosed with PDLM. Histologically, atypical melanocytic cells were also observed.

Diagnosis: Immunohistochemistry showed positivity for S100 protein, NKiC3, and vimentin, and negativity for Melan-A and HMB-45, with a proliferation index of 30%. Extracranial disease was excluded using dermatological and other examinations, including positron emission tomography/computed tomography with 18F-fluorodeoxyglucose.

Interventions: The patient was treated with whole-brain radiotherapy (10 fractions to a total dose of 30 Gy) concomitantly with pembrolizumab and then continued with immunotherapy until disease progression with a maximum effect of partial remission on magnetic resonance imaging scans.

Outcomes: Progression-free survival was 6.0 months and overall survival 6.5 months. Lessons: This is one of the few case reports of an adult patient with this rare malignancy being treated with a programmed death-1 inhibitor with partial response. Immunotherapy in metastatic PDLM may be a reasonable therapeutic option.

GENITOURINÁRNE MALIGNITY

Palacka P, Gvozdjakova A, Rausova Z, Kucharska J, **Slopovsky J, Obertova J,** Furka D, Furka S, Singh KK, Sumbalova Z.

Platelet Mitochondrial Bioenergetics Reprogramming in Patients with Urothelial Carcinoma

Int J Mol Sci. 2021 Dec 30;23(1):388.

Mitochondrial bioenergetics reprogramming is an essential response of cells to stress. Platelets, an accessible source of mitochondria, have a crucial role in cancer development; however, the platelet mitochondrial function has not been studied in urothelial carcinoma (UC) patients. A total of 15 patients with UC and 15 healthy controls were included in the study. Parameters of platelet mitochondrial respiration were evaluated using the high-resolution respirometry method, and the selected antioxidant levels were determined by HPLC. In addition, oxidative stress was evaluated by the thiobarbituric acid reactive substances (TBARS) concentration in plasma. We demonstrated deficient platelet mitochondrial respiratory chain functions, oxidative phosphorylation (OXPHOS), and electron transfer (ET) capacity with complex I (CI)-linked substrates, and reduced the endogenous platelet coenzyme Q10 (CoQ10) concentration in UC patients. The activity of citrate synthase was decreased in UC patients vs. controls (p = 0.0191). γ-to-

copherol, α-tocopherol in platelets, and β-carotene in plasma were significantly lower in UC patients (p = 0.0019; p = 0.02; p = 0.0387, respectively), whereas the plasma concentration of TBARS was increased (p = 0.0022) vs. controls. The changes in platelet mitochondrial bioenergetics are consistent with cell metabolism reprogramming in UC patients. We suppose that increased oxidative stress, decreased OXPHOS, and a reduced platelet endogenous CoQ10 level can contribute to the reprogramming of platelet mitochondrial OXPHOS toward the activation of glycolysis. The impaired mitochondrial function can contribute to increased oxidative stress by triggering the reverse electron transport from the CoQ10 cycle (Q-junction) to CI.

Hires M, Jane E**, Kalavska K, Chovanec M, Mego M,** Kasak P, Bertok T, Tkac J.
Glycan signatures for the identification of cisplatin-resistant testicular cancer cell lines: Specific glycoprofiling of human chorionic gonadotropin (hCG)
Cancer Med. 2022 Feb;11(4):968-982.

Background: Testicular cancer (TC) is the most frequent type of cancer among young men aged between 15 and 34 years. TC is treated using cisplatin, but 3%-5% of TC patients fail to respond to cisplatin, with a very bad to fatal prognosis. Accordingly, it is most important to quickly and readily identify those TC patients who are resistant to cisplatin treatment.

Methods: This study seeks to investigate changes in the glycosylation associated with cisplatin resistance to TC cell lines.

Results: A specific glycoprofiling of human chorionic gonadotropin (hCG) was analysed in three TC cell lines and one cell line of female origin. A typical calibration curve for hCG glycoprofiling showed a dynamic range up to 50 ng/ml, with a limit of detection of 0.3 ng/ml and assay reproducibility represented by relative standard deviation of 3.0%. Changes in the glycan signatures on hCG were analysed in cisplatin-sensitive cell lines and in their cisplatin-resistant sub-lines using an enzyme-linked lectin assay (ELLA) protocol. An immobilised antibody was applied to a selective capture of hCG from a cytoplasmic fraction of cell lysates with final incubation using a lectin from a panel of 17 lectins.

Conclusion: The results suggest that one particular lectin Dolichos biflorus agglutinin (DBA) can selectively discriminate sensitive TC cell lines from resistant TC cell lines. Moreover, there are additional lectins which can provide useful information about the strength of cisplatin resistance.

MIKROBIÓM

Sevcikova A, Izoldova N, Stevurkova V, Kasperova B, Chovanec M, Ciernikova S, Mego M.
The impact of the microbiome on resistance to cancer treatment with chemotherapeutic agents and immunotherapy
Int J Mol Sci. 2022 Jan 1;23(1):488.

Understanding the mechanisms of resistance to therapy in human cancer cells has become a multifaceted limiting factor to achieving optimal cures in cancer patients. Besides genetic and epigenetic alterations, enhanced DNA damage repair activity, deregulation of cell death, overexpression of transmembrane transporters, and complex interactions within the tumor microenvironment, other mechanisms of cancer treatment resistance have been recently proposed. In this review, we will summarize the preclinical and clinical studies highlighting the critical role of the microbiome in the efficacy of cancer treatment, concerning mainly chemotherapy and immunotherapy with immune checkpoint inhibitors. In addition to involvement in drug metabolism and immune surveillance, the production of microbiota-derived metabolites might represent the link between gut/intratumoral bacteria and response to anticancer therapies. Importantly, an emerging trend of using microbiota modulation by probiotics and fecal microbiota transplantation (FMT) to overcome cancer treatment resistance will be also discussed.

INFEKCIE V ONKOLÓGII

Busca A, Salmanton-García J, Corradini P, Marchesi F, Cabirta A, Di Blasi R, Dulery R, Lamure S, Farina F, Weinbergerova B, Batinic J, Nordlander A, Lopez-Garcia A**, Drgona L,** Espigado I, Falces-Romero I, Garcia-Sanz R, Garcia-Vidal C, Guidetti A, Khanna N, Kulesekararaj A, Maertens J, Hoenigl M, Klimko N, Koehler P, Pagliuca A, Passamonti F, Cornely O, Pagano L.
COVID-19 and CAR-T cells: current challenges and future directions-a report from the EPICOVIDEHA survey by EHA-IDWP
Blood Adv. 2021 Nov 8:bloodadvances.2021005616.

Patients receiving chimeric antigen receptor T cells (CAR-T cells) therapy may be particularly susceptible to coronavirus disease 2019 (COVID-19) because of several factors including the immunosuppression associated to the underlying disease and delayed cytopenias. Regrettably, data on outcomes of CAR-T recipients with COVID-19 are extremely scarce. The aim of this study was to investigate the characteristics and outcomes of COVID-19 in patients treated with CAR-T therapy. The European Hematology Association - Scientific Working Group Infection in Hematology endorsed a survey to collect and analyze data from patients developing COVID-19 after CAR-T therapy. Overall, 459 patients treated with CAR-T cells were reported from 18 European centers. The prevalence of COVID-19 cases was 4.8%. Median time from CAR-T therapy and COVID-19 diagnosis was 169 days. Severe infection occurred in 66.7% of patients and 43.3% of the subjects required admission to ICU. The COVID-19 mortality was 33%. In multivariable analysis, the disease status at the time of COVID-19 trended marginally towards adverse outcome (P=0.075). In conclusion, we documented a high fatality rate for CAR-T patients with COVID-19, supporting the need to design successful interventions to mitigate the risk of infection in this vulnerable group of patients.

Stemler J, **Drgona L.**
EHA endorsement of the global guideline for the diagnosis and management of rare yeast infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology and American Society for Microbiology
Hemasphere. 2021 Sep 30;5(10):e644