GERMINATÍVNE NÁDORY


Germ-cell tumors (GCTs) are highly curable with chemotherapy. Salvage chemotherapy or surgery can cure a proportion of patients, but the ones failing these treatments will die of their disease in the young age. Immune checkpoint pathways are emerging as powerful targetable biomarkers, and a significant preclinical and clinical research is underway to widen our knowledge and expand the treatment possibilities with immune therapy. The concept of immune modulation that was currently adopted in many solid tumors is understudied in GCTs. Herein, we summarize the current knowledge of published literature discussing the immune mechanisms and immune therapy in GCTs.


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

Methods: Two independent cohorts of patients were analysed; 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 (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 International Germ Cell Cancer Collaborative Group criteria in multivariable Cox regression analysis for OS and was validated in an independent cohort. When combining PD-L1 expression on tumour infiltrating lymphocytes (TILs) and SII, we identified three distinctive prognostic groups.

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


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

Materials and methods: GCT survivors (n=155) from the National Cancer Institute of Slovakia completed the Functional Assessment of Cancer Therapy Cognitive Function at a median of 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, whereas the control group included survivors treated with orchietomy only.

Results: Of the total survivors, 138 received treatment beyond orchietomy and 17 controls had orchietomy 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<.05). The burden of chemotherapy plus radiotherapy or radiotherapy versus controls resulted in the impairment in all cognitive functioning domains (all p<.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 guide clinicians' decisions in treatment and follow-up of GCTs.

Implications for practice: In this study, long-term survivors of germ-cell tumors have reported cognitive impairment after curative treatment with radiotherapy and chemotherapy compared with controls who had treatment with orchietomy only. These data provide an argument against the use of adjuvant radiotherapy for stage I seminoma. Unnecessary overtreatment with chemotherapy and additional radiotherapy after chemotherapy should be avoided.

PODPORNÁ LIEČBA


Background: The present review is part of the ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies.
Aims: To review, from an Infectious Diseases perspective, the safety profile of agents targeting CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4 and to suggest preventive recommendations.

Sources: Computer-based MEDLINE searches with MeSH terms pertaining to each agent or therapeutic family.

Content: The risk and spectrum of infections in patients receiving CD22-targeted agents (i.e. inotuzumab ozogamicin) are similar to those observed with anti-CD20 antibodies. Anti-Pneumocystis prophylaxis and monitoring for cytomegalovirus (CMV) infection is recommended for patients receiving CD30-targeted agents (brentuximab vedotin). Due to the scarcity of data, the risk posed by CD33-targeted agents (gemtuzumab ozogamicin) cannot be assessed. Patients receiving CD38-targeted agents (i.e. daratumumab) face an increased risk of varicella-zoster virus (VZV) infection. Therapy with CD40-targeted agents (lucatumumab or dace-tuzumab) is associated with opportunistic infections similar to those observed in hyper-IgM syndrome, and prevention strategies (including anti-Pneumocystis prophylaxis and pre-emptive therapy for CMV infection) are warranted. SLAMF-7 (CD319)-targeted agents (elotuzumab) induce lymphopenia and increase the risk of infection (particularly due to VZV). The impact of CCR4-targeted agents (mogamulizumab) on infection susceptibility is difficult to distinguish from the effect of underlying diseases and concomitant therapies. However, anti-Pneumocystis and anti-herpesvirus prophylaxis and screening for chronic hepatitis B virus (HBV) infection are recommended.

Implications: Specific management strategies should be put in place to reduce the risk and/or the severity of infectious complications associated to the reviewed agents.


Clin Microbiol Infect. 2018 Jun;24 Suppl 2:S71-S82.

Background: The present review is part of the ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies. AIMS: To review, from an Infectious Diseases perspective, the safety profile of agents targeting CD19, CD20 and CD52 and to suggest preventive recommendations.

Sources: Computer-based MEDLINE searches with MeSH terms pertaining to each agent or therapeutic family.

Content: Although CD19-targeted agents (blinatumomab or inebilizumab) are not associated with an increased risk of infection, they may cause IgG hypogammaglobulinaemia and neutropenia. The requirement for prolonged intravenous infusion of blinatumomab may increase the risk of catheter-associated bloodstream infections. Infection remains the most common non-haematological adverse effect of anti-CD20 monoclonal antibodies, including severe respiratory tract infection, hepatitis B virus (HBV) reactivation and varicella-zoster virus infection. Screening for chronic or resolved HBV infection is recommended for patients receiving anti-CD20 monoclonal antibodies. Antiviral prophylaxis should be offered for 12-18 months to hepatitis B surface antigen (HBsAg)-positive and HBsAg-negative/ anti-hepatitis B core antibody (HBc)-positive patients. Anti-Pneumocystis prophylaxis should be considered in patients receiving concomitant chemotherapy, particularly steroids. Alemtuzumab (anti-CD52) increases the risk of infections, in particular among leukaemia and solid organ transplant patients. These populations benefit from anti-Pneumocystis prophylaxis, prevention strategies for cytomegalovirus infection, and screening for HBV, hepatitis C virus and tuberculosis. Antiviral prophylaxis for at least 6-12 months should be provided for HBsAg-positive patients.

Implications: As there are limited clinical data for many of the reviewed agents, special attention must be given to promptly detect and report emerging infectious complications.


Targeted inhibition of the MAPK pathway: emerging salvage option for progressive life-threatening multisystem LCH.


Single-agent vemurafenib leads to a rapid and sustained clinical response in severe multisystem LCH but does not eradicate the disease. Longitudinal assessment of BRAF V600E during treatment shows that clinical remission can occur despite significant amounts of mutated BRAF.

SARKÓMY


Activity and safety of crizotinib in patients with advanced clear-cell sarcoma with MET alterations: European Organization for Research and Treatment of Cancer phase II trial 90101 'CREATE'.


Background: An inflammatory myofibroblastic tumour (IMFT) is a rare mesenchymal neoplasm characterised by anaplastic lymphoma kinase (ALK) gene rearrangements. We assessed the activity and safety of crizotinib, a tyrosine kinase inhibitor, targeting ALK in patients with advanced IMFT either with or without ALK alterations.

Methods: We did a multicentre, biomarker-driven, single-drug, non-randomised, open-label, two-stage phase 2 trial (European Organisation for Research and Treatment of Cancer 90101 CREATE) at 13 study sites (five university hospitals and eight specialty clinics) in eight European countries (Belgium, France, Germany, Italy, Netherlands, Poland, Slovakia, and the UK). Eligible participants were patients aged at least 15 years with a local diagnosis of advanced or metastatic IMFT deemed incurable with surgery, radiotherapy, or systemic therapy; measurable disease; an Eastern Cooperative Oncology Group performance status of 0-2; and adequate haematological, renal, and liver function. Central reference pathology was done for confirmation of the diagnosis, and ALK positivity or negativity was assessed centrally using immunohistochemistry and fluorescence in-situ hybridisation based on archival tumour tissue and defined as ALK immunopositivity or rearrangements in at least 15% of tumour cells. Eligible ALK-positive and ALK-negative patients received oral crizotinib 250 mg twice per day administered on a continuous daily dosing schedule (the duration of each treatment cycle was 21 days) until documented disease progression, unacceptable toxicity, or patient refusal. If at least two of the first 12 eligible and assessable ALK-positive patients achieved a confirmed complete or partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, a maximum of 35 patients were to be enrolled. If at least six ALK-positive patients achieved a confirmed response, the trial would be deemed successful. The primary endpoint was the proportion of patients who achieved an objective response (ie, a complete or partial response) as per RECIST 1.1, with response confirmation assessed by the local investigator every other cycle. Activity and safety endpoints were analysed in the per-protocol population. This trial is registered with ClinicalTrials.gov, number NCT01524926.

Findings: Between Oct 3, 2012, and April 12, 2017, we recruited and treated 20 eligible participants, 19 of whom were assessable for the primary endpoint. Median follow-up was 863 days (IQR 358-1304). Six of 12 ALK-positive patients (50%, 95% CI 211-78.9) and one of seven ALK-negative patients (14%, 0.0-57.9) achieved an objective response. The most common treatment-related adverse events in the 20 participants were nausea (11 [55%]), fatigue (9 [45%]), blurred vision (nine [45%]), vomiting (seven [35%]), and diarrhoea (seven [35%]). Eight serious adverse events occurred in five patients: pneumonia, fever of unknown cause, a heart attack with increased creatinine and possible sepsis, an abdominal abscess with acute renal insufficiency, and a QT prolongation.

Interpretation: With 50% of participants with ALK-positive tumours achieving an objective response, crizotinib met the prespecified criteria for success in this trial. The results presented here support the rationale for inhibiting ALK in patients with IMFT. Crizotinib could be considered as the standard of care for patients with locally advanced or metastatic ALK-positive IMFT who do not qualify for curative surgery.

Funding: The European Organisation for Research and Treatment of Cancer and Pfizer.


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 II trial 90101 ,CREATE.'


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 MET tyrosine kinase inhibitor crizotinib in patients with advanced or metastatic ASPS.

Patients and methods: Eligible patients with reference pathology-confirmed ASPS received oral crizotinib 250 mg bd. 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 end points included duration of response, disease control rate (DCR), progression-free survival (PFS), progression-free rate, 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 assessable. Among 40 MET+ patients, 1 achieved a confirmed partial response (PR) that lasted 215 days and 35 had stable disease (SD) as best response (ORR: 2.5%, 95% CI 0.6% to 80.6%). Further efficacy end points in MET+ cases were DCR: 90.0% (95% CI 76.3% to 97.2%), 1-year PFS rate: 37.5% (95% CI 22.9% to 51.2%) and 1-year OS rate: 97.4% (95% CI 82.8% to 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% to 80.6%) for a DCR of 100% (95% CI 39.8% to 100.0%). The 1-year PFS rate in MET- cases was 50% (95% CI 5.8% to 84.5%) and the 1-year OS rate was 75% (95% CI 12.8% to 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 European Organization for Research and Treatment of Cancer (EORTC) efficacy criteria for soft tissue sarcoma,
our study demonstrated that crizotinib has activity in TFE3 rearranged ASPS MET+ patients. Clinical trial number: EORTC 90101, NCT01524926.

KARCINÓM PĽÚC

Background: The introduction of targeted treatments for subsets of non-small cell lung cancer (NSCLC) has highlighted the importance of accurate molecular diagnosis to determine if an actionable genetic alteration is present. Few data are available for Central and Eastern Europe (CEE) on mutation rates, testing rates, and compliance with testing guidelines.

Methods: A questionnaire about molecular testing and NSCLC management was distributed to relevant specialists in nine CEE countries, and pathologists were asked to provide the results of EGFR and ALK testing over a 1-year period.

Results: A very high proportion of lung cancer cases are confirmed histologically/cytologically (75-100%), and molecular testing of NSCLC samples has been established in all evaluated CEE countries in 2014. Most countries follow national or international guidelines on which patients to test for EGFR mutations and ALK rearrangements. In most centers at that time, testing was undertaken on request of the clinician rather than on the preferred reflex basis. Immunohistochemistry, followed by fluorescent in situ hybridization confirmation of positive cases, has been widely adopted for ALK testing in the region. Limited reimbursement is a significant barrier to molecular testing in the region and a disincentive to reflex testing. Multidisciplinary tumor boards are established in most of the countries and centers, with 75-100% of cases being discussed at a multidisciplinary tumor board at specialized centers.

Conclusions: Molecular testing is established throughout the CEE region, but improved and unbiased reimbursement remains a major challenge for the future. Increasing the number of patients reviewed by multidisciplinary boards outside of major centers and access to targeted therapy based on the result of molecular testing are other major challenges.

MALÍGNE LYMFÓMY


Purpose: While patients with early-stage Hodgkin lymphoma (HL) have an excellent outcome with combined treatment, the radiation therapy (RT) dose and treatment with chemotherapy alone remain questionable. This noninferiority trial evaluates the feasibility of reducing the dose or omitting RT after chemotherapy.

Methods and materials: Patients with untreated supradiaphragmatic HL without risk factors (age ≥ 50 years, 4 to 5 nodal areas involved, mediastinum-thoracic ratio ≥ 0.35, and erythrocyte sedimentation rate ≥ 50 mm in first hour without B symptoms or erythrocyte sedimentation rate ≥ 30 mm in first hour with B symptoms) were eligible for the trial. Patients in complete remission after chemotherapy were randomized to no RT, low-dose RT (20 Gy in 10 fractions), or standard-dose involved-field RT (36 Gy in 18 fractions). The limit of noninferiority was 10% for the difference between 5-year relapse-free survival (RFS) estimates. From September 1998 to May 2004, 783 patients received 6 cycles of epirubicin, bleomycin, vinblastine, and prednisone; 592 achieved complete remission or unconfirmed complete remission, of whom 578 were randomized to receive 36 Gy (n=239), 20 Gy of involved-field RT (n=209), or no RT (n=130).

Results: Randomization to the no-RT arm was prematurely stopped (≥20% rate of unacceptable events: toxicity, treatment modification, early relapse, or death). Results in the 20-Gy arm (3-year RFS, 84.2%) were not inferior to those in the 36-Gy arm (3-year RFS, 88.6%) (difference, 4.4%; 90% confidence interval [CI] -1.2% to 9.9%). A difference of 16.5% (90% CI 8.0%-25.0%) in 5-year RFS estimates was observed between the no-RT arm (69.8%) and the 36-Gy arm (86.3%); the hazard ratio was 2.55 (95% CI 1.44-4.53; P<.001). The 5-year overall survival estimates ranged from 97% to 99%.

Conclusions: In adult patients with early-stage HL without risk factors incomplete remission after epirubicin, bleomycin, vinblastine, and prednisone chemotherapy, the RT dose may be limited to 20 Gy without compromising disease control. Omitting RT in these patients may jeopardize the treatment outcome.


GLOBÁLNA ONKOLÓGIA

Global cancer control: responding to the growing burden, rising costs and inequalities in access
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The cancer burden is rising globally, exerting significant strain on populations and health systems at all income levels. In May 2017, world governments made a commitment to further invest in cancer control as a public...
health priority, passing the World Health Assembly Resolution 70.12 on cancer prevention and control within an integrated approach. In this manuscript, the 2016 European Society for Medical Oncology Leadership Generation Programme participants propose a strategic framework that is in line with the 2017 WHO Cancer Resolution and consistent with the principle of universal health coverage, which ensures access to optimal cancer care for all people because health is a basic human right. The time for action is now to reduce barriers and provide the highest possible quality cancer care to everyone regardless of circumstance, precondition or geographic location. The national actions and the policy recommendations in this paper set forth the vision of its authors for the future of global cancer control at the national level, where the WHO Cancer Resolution must be implemented if we are to reduce the cancer burden, avoid unnecessary suffering and save as many lives as possible.

**ABSTRAKTY A PRÍSPĚVKY ZA ZAHRANIČNÝCH KONFERENCIÍ**

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**Wasat Mansoor Ramucirumab treatment in patients with gastric cancer/gastroesophageal junction adenocarcinoma: Secondary analysis of efficacy and safety results of 4 dosing regimens in the phase II trial I4T-MC-JVDB.**

*J Clin Oncol* 36, 2018 (suppl 4S; abstr 117)

Patrik Palacka, Zuzana Sestakova, Katarina Kalavska, Katarina Rejlekova, Katarina Gasparova, Zuzana Sycova-Mila, Michal Chovanec, Jana Obertova, Daniela Svetlovskova, Michal Mego, Miroslav Chovanec

**Endogenous DNA damage in peripheral blood lymphocytes (PBLs) in patients with metastatic urothelial carcinoma (MUC)**

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**Comparison between radiochemotherapy and other modalities in locally advanced esophageal cancer**