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Genitourinárne malignity

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Prognostic value of teratoma in primary tumor and postchemotherapy retroperitoneal lymph node dissection specimens in patients with metastatic germ cell tumor

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Purpose: Presence of teratoma in patients with metastatic testicular germ cell tumor (GCT) is of unknown prognostic significance. We report survival outcomes of patients with or without teratoma in primary tumor and postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) specimen and assess impact on prognosis.

Patients and methods: Patients with metastatic nonseminomatous GCT (NSGCT) who were evaluated at Indiana University between 1990 and 2016 and had primary testicular tumor specimen from orchiectomy (ORCH) were included. All patients were treated with cisplatin-based combination chemotherapy. The cohort was divided into 2 groups according to presence or absence of teratoma in ORCH specimen. Survival data were correlated with histopathologic findings. Differences in progression-free (PFS) and overall survival (OS) were evaluated using log-rank tests and Cox proportional hazards models to adjust for known adverse prognostic factors.

Results: We identified 1,224 consecutive patients evaluated at Indiana University between 1990 and 2016 who met inclusion criteria. Median age was 27 years (range, 13-71 years); 689 patients had teratoma in ORCH specimen, and 535 did not. With median follow-up of 2.3 years, 5-year PFS was 61.9% (95% CI, 57.1% to 66.2%) for those with teratoma versus 63.1% (95% CI, 58.0% to 67.8%) for those without (P = .66); 5-year OS was 82.2% (95% CI, 77.9% to 85.8%) versus 81.4% (95% CI, 76.5% to 85.3%; P = .91), respectively. A total of 473 patients underwent PC-RPLND; 5-year PFS for patients with pure teratoma in PC-RPLND specimen versus necrosis only was 65.9% versus 79.1% (P = .06), and 5-year OS was 90.3% versus 93.4% (P = .21), respectively.

Conclusion: Presence of teratoma in ORCH and PC-RPLND specimens was not a prognostic factor in this large retrospective study of patients with NSGCT.

Karcinóm prsníka

Miklikova S, Minarik G, Sedlackova T, Plava J, Cihova M, Jurisova S, Kalavska K, Karaba M, Benca J, Smolkova B, Mego M.

Inflammation-based scores increase the prognostic value of circulating tumor cells in primary breast cancer

Cancers (Basel). 2020 May 1;12(5):E1134. doi: 10.3390/cancers12051134.

A correlation between circulating tumor cells (CTCs) and monocytes in metastatic breast cancer (BC), where CTCs and monocyte-to-lymphocyte ratio (MLR) were predictors of overall survival (OS), was recently shown. Herein, we aimed to assess the association between CTCs and the complete blood count (CBC)-derived inflammation-based scores in 284 primary BC patients. CTCs were determined in CD45-depleted peripheral blood mononuclear cells by real time-PCR. This method allowed us to detect a subset of CTCs with an epithelial-to-mesenchymal transition phenotype (CTC EMT), previously associated with inferior outcomes in primary BC. In the present study, CTC EMT positivity (hazard ratio (HR) = 2.4; 95% CI 1.20-4.66, p = 0.013) and elevated neutrophil-to-lymphocyte ratio (NLR) (HR = 2.20; 95% CI 1.07-4.55; p = 0.033) were associated with shorter progression-free survival (PFS) in primary BC patients. Multivariate analysis showed that CTC EMT-positive patients with NLR ≥ 3 had 8.6 times increased risk of disease recurrence (95% CI 2.35-31.48, p = 0.001) compared with CTC EMT-negative patients with NLR < 3. Similarly, disease recurrence was 13.14 times more likely in CTC EMT-positive patients with MLR ≥ 0.34 (95% CI 4.35-39.67, p < 0.001). Given its low methodological and financial demands, the CBC-derived inflammation-based score determination could, after broader validation, significantly improve the prognostication of BC patients.

Mego M, Karaba M, Sedlackova T, Benca J, Repiska G, Krasnicanova L, Macuch J, Sieberova G, Jurisova S, Pindak D, Kalavska K, Mardiak J, Minarik G.

Circulating tumor cells and breast cancer-specific mutations in primary breast cancer

Mol Clin Oncol. 2020 Jun;12(6):565-573.

Circulating tumor cells (CTCs) play a pivotal role in tumor dissemination and progression, and are considered to be a critical part of the metastatic cascade. The aim of the present research article was to examine breast cancer-specific mutations in primary breast cancer (PBC) using targeted resequencing. A total of 78 patients with PBC were enrolled into this translational study. Reverse transcription-quantitative PCR assay for the expression of epithelial markers (*CK19*) or epithelial-to-mesenchymal transition (EMT)-related genes (*TWIST1*, *SNAIL1*, *SLUG* and *ZEB1*) was applied for identification of CTCs prior to surgery. Total DNA was isolated from fresh frozen primary tumors. Sequencing was performed by Agilent SureSelect target enrichment and Illumina paired-end sequencing on the MiSeq platform. The most commonly affected genes were *TP53* (mutated in 21 tumors; 26.9%), followed by *PIK3CA* (mutated in 16 tumors; 20.5%) and *BRCA1/2* (mutated in 7 tumors, *BRCA1* n=2 and *BRCA2* n=5; 9.0%). In our cohort, a significantly higher proportion of patients with epithelial CTCs harbored mutations in the *BRCA1/2* genes in the tumor tissue. There were no mutations in specific genes associated with CTCs with the EMT phenotype. To the best of our knowledge, this study is

the first to report a correlation between the presence of epithelial CTCs in the peripheral blood and mutations of the BRCA1/2 genes in primary tumor tissue.

Plava J, Cihova M, Burikova M, Bohac M, Adamkov M, Drahosova S, Rusnakova D, Pindak D, Karaba M, Simo J, Mego M, Danisovic L, Kucerova L, Miklikova S.
Permanent pro-tumorigenic shift in adipose tissue-derived mesenchymal stromal cells induced by breast malignancy
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During cancer progression, breast tumor cells interact with adjacent adipose tissue, which has been shown to be engaged in cancer aggressiveness. However, the tumor-directed changes in adipose tissue-resident stromal cells affected by the tumor-stroma communication are still poorly understood. The acquired changes might remain in the tissue even after tumor removal and may contribute to tumor relapse. We investigated functional properties (migratory capacity, expression and secretion profile) of mesenchymal stromal cells isolated from healthy (n = 9) and tumor-distant breast adipose tissue (n = 32). Cancer patient-derived mesenchymal stromal cells (MSCs) (MSC-CA) exhibited a significantly disarranged secretion profile and proliferation potential. Co-culture with MDA-MB-231, T47D and JIMT-1, representing different subtypes of breast cancer, was used to analyze the effect of MSCs on proliferation, invasion and tumorigenicity. The MSC-CA enhanced tumorigenicity and altered xenograft composition in immunodeficient mice. Histological analysis revealed collective cell invasion with a specific invasive front of EMT-positive tumor cells as well as invasion of cancer cells to the nerve-surrounding space. This study identifies that adipose tissue-derived mesenchymal stromal cells are primed and permanently altered by tumor presence in breast tissue and have the potential to increase tumor cell invasive ability through the activation of epithelial-to-mesenchymal transition in tumor cells.

Karcinóm pľúc

Cufer T, Ciuleanu TE, **Berzinec P**, Galffy G, Jakopovic M, Jassem J, Jovanovic D, Mihaylova Z, Ostoros G, Thallinger C, Zemanova M, Zielinski C.
Access to novel drugs for non-small cell lung cancer in Central and Southeastern Europe: A Central European Cooperative Oncology Group Analysis
Oncologist. 2020 Mar;25(3):e598-e601. d

Background: Treatment of non-small cell lung cancer (NSCLC) improved substantially in the last decades. Novel targeted and immune-oncologic drugs were introduced into routine treatment. Despite accelerated development and subsequent drug registrations by the European Medicinal Agency (EMA), novel drugs for NSCLC are poorly accessible in Central and Eastern European (CEE) countries.

Material and methods: The Central European Cooperative Oncology Group conducted a survey among experts from 10 CEE countries to provide an overview on the availability of novel drugs for NSCLC and time from registration to reimbursement decision in their countries.

Results: Although first-generation epidermal growth factor receptor tyrosine kinase inhibitors were reimbursed and available in all countries, for other registered therapies-even for ALK inhibitors and checkpoint inhibitors in first-line-there were apparent gaps in availability and/or reimbursement. There was a trend for better availability of drugs with longer time from EMA marketing authorization. Substantial differences in access to novel drugs among CEE countries were observed. In general, the availability of drugs is not in accordance with the Magnitude of Clinical Benefit Scale (MCBS), as defined by the European Society for Medical Oncology (ESMO). Time spans between drug registrations and national decisions on reimbursement vary greatly, from less than 3 months in one country to more than 1 year in the majority of countries.

Conclusion: The access to novel drugs for NSCLC in CEE countries is suboptimal. To enable access to the most effective compounds within the shortest possible time, reimbursement decisions should be faster and ESMO MCBS should be incorporated into decision making.

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.