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KARCINÓM PRSNÍKA

Smolkova B, Cierna Z, Kalavska K, Miklikova S, Plava J, Minarik G, Sedlackova T, Cholujova D, Gronesova P, Cihova M, Majerova K, Karaba M, Benca J, Pindak D, Mardiak J, Mego M.

Increased Stromal Infiltrating Lymphocytes Are Associated with the Risk of Disease Progression in Mesenchymal Circulating Tumor Cell-Positive Primary Breast Cancer Patients

Int J Mol Sci. 2020 Dec 12;21(24):9460.

Circulating tumor cells (CTCs) and the immune infiltration of tumors are closely related to clinical outcomes. This study aimed to verify the influence of stromal lymphocyte infiltration and the immune context of tumor microenvironment on the hematogenous spread and prognosis of 282 chemotherapy naïve primary BC patients. To detect the presence of mesenchymal CTCs, RNA extracted from CD45-depleted peripheral blood was interrogated for the expression of mesenchymal gene transcripts. Tumor-infiltrating lymphocytes (TILs) were detected in the stromal areas by immunohistochemistry, using CD3, CD8, and CD45RO antibodies. The concentrations of 51 plasma cytokines were measured by multiplex bead arrays. TILs infiltration in mesenchymal CTC-positive patients significantly decreased their progression-free survival (HR = 4.88, 95% CI 2.30-10.37, p < 0.001 for CD3high; HR = 6.17, 95% CI 2.75-13.80, p < 0.001 for CD8high; HR = 6.93, 95% CI 2.86-16.81, p < 0.001 for CD45ROhigh). Moreover, the combination of elevated plasma concentrations of transforming growth factor beta-3 (cut-off 662 pg/mL), decreased monocyte chemotactic protein-3 (cut-off 52.5 pg/mL) and interleukin-15 (cut-off 17.1 pg/mL) significantly increased the risk of disease recurrence (HR = 4.838, 95% CI 2.048-11.427, p < 0.001). Our results suggest a strong impact of the immune tumor microenvironment on BC progression, especially through influencing the dissemination and survival of more aggressive, mesenchymal CTC subtypes.

Kalavska K, Cierna Z, Karaba M, Minarik G, Benca J, Sedlackova T, Kolekova D, Mrvova I, Pindak D, Mardiak J, Mego M.

Prognostic role of matrix metalloproteinase 9 in early breast cancer

Oncol Lett. 2021 Feb;21(2):78.

MMP9 is involved in extracellular matrix degradation during various physiological and pathological conditions, including tumorigenesis. The present study aimed to assess the prognostic role of intratumoral MMP9 and to determine its association with circulating tumor cells (CTCs) in patients with early breast cancer. A total of 318 patients with primary breast cancer (PBC) were enrolled into the present study. Specimens were subjected to immunohistochemistry analysis, using the MMP9 monoclonal antibody. MMP9 expression was scored using a weighted histoscore (WH). The results demonstrated that the mean WH ± SEM for MMP9 expression was significantly higher in breast tumor cells compared with tumor associated stromas (132.0±5.2 vs. 50.8±3.7; P<0.00001). Furthermore, a positive association was observed between MMP9 expression, the hormone positive status and proliferation index of analysed breast cancer tumour cells. Notably, the prognostic role of MMP9 was not observed in tumor cells [hazard ratio (HR) =0.96; 95% confidence interval (CI), 0.58-1.59; P=0.864] or tumor associated stroma (HR=1.29; 95% CI, 0.60-2.78; P=0.547). Subgroup analysis demonstrated that patients that were HR negative or triple negative, with low MMP9 expression in tumor cells and stroma had a significantly improved disease-free survival than patients with high MMP9 expression. Taken together, the results of the present study demonstrated that high MMP9 expression in PBC was associated with favorable tumor characteristics. However, the prognostic value of MMP9 was limited to only the HR negative and CTC epithelial-to-mesenchymal transition positive subgroups. Thus, analyzing MMP9 tumor expression may help identify patients with increased risk of disease recurrence in these subgroups.

Cierna Z, Smolkova B, Cholujova D, Gronesova P, Miklikova S, Cihova M, Plava J, Mego M.

Decreased levels of circulating cytokines VEGF, TNF-β and IL-15 indicate PD-L1 overexpression in tumours of primary breast cancer patients

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Programmed death ligand 1 (PD-L1) overexpression has been associated with poor clinical outcomes in several human cancers whose increased malignant behaviour might be related to PD-L1 mediated systemic immunological tolerance. This study aims to verify if circulating cytokines may serve as a proxy for non-invasive identification of sensitive prognostic biomarkers reflecting tumour and its microenvironment. Immunohistochemistry was used to measure PD-L1 expression in tumour tissue sections of 148 chemonaïve breast cancer (BC) patients. The panel of 51 cytokines was analysed using multiplex bead arrays. High PD-L1 expression in tumours was associated with shorter progression-free survival (HR 3.25; 95% CI 1.39-7.61; P = 0.006) and low circulating levels of three multifunctional molecules; VEGF, TNF-β and IL-15 (P = 0.001). In multivariate analysis, patients with low VEGF had 4.6-fold increased risk of PD-L1 overexpression (P = 0.008), present in 76.5% of patients with all these three cytokines below the median (vs. 35.6% among the others; P = 0.002). The area under the curve value of 0.722 (95% CI 0.59-0.85; P = 0.004) shows that this combination of cytokines has a moderate ability to discriminate between PD-L1 high vs. PD-L1 low patients. Plasma cytokines, therefore, could serve as potential non-invasive biomarkers for the identification of high-risk BC cases.

GENITOURINÁRNE MALIGNITY

Makovnik M, Rejlekova K, Uhrin I, Mego M, Chovanec M.

Intricacies of Radiographic Assessment in Testicular Germ Cell Tumors

Front Oncol. 2021 Jan 5;10:587523.

Testicular germ cell tumors (GCTs) are malignancies with a unique biology, pathology, clinical appearance, and excellent outcomes. A correct radiographic assessment of GCTs is extremely important for the clinical management in several typical scenarios. Advancements in the field of diagnostic medicine bring an increasing

number of sophisticated imaging methods to increase the performance of imaging studies. The conventional computed tomography (CT) remains the mainstay of diagnostic imaging in the management of GCTs. While certain improvements in the sensitivity and specificity are suggested with magnetic resonance (MR) imaging with lymphotrophic nanoparticles in evaluating retroperitoneal lymph nodes during the staging procedure, further exploration in larger prospective studies is needed. A common diagnostic dilemma is assessing the post-chemotherapy residual disease in GCTs. Several studies have consistently shown advantages in the utility of positron emission tomography (PET) scanning in post-chemotherapy residual retroperitoneal lymph nodes in patients with seminoma, but not with non-seminoma. Recommendations suggest that seminoma patients with a residual disease in the retroperitoneum larger than 3 cm should be subjected for PET scanning with 18-fluorodeoxyglucose. Relatively high sensitivity, specificity and a negative predictive value (80–95%) may guide clinical decision to spare these patients of high morbidity of an unnecessary surgery. However, a positive predictive value of around 50% renders PET scanning difficult to interpret in the case of positive finding. These patients often require extremely difficult surgical procedures with the high risk of post-operative morbidity. Therefore, seminoma patients with PET positive residual masses larger than 3 cm still remain a serious challenge in the decision making of nuclear medicine specialist, oncologists, and urologic surgeons. In this article, we aim to summarize data on controversial dilemmas in staging procedures, active surveillance, and post-chemotherapy assessment of GCTs based on the available published literature.

HEMATOLOGICKÉ MALIGNITY

Ciernikova S, Kasperova B, Drgona L, Smolkova B, Stevurkova V, Mego M.

Targeting the gut microbiome: An emerging trend in hematopoietic stem cell transplantation

Blood Rev. 2020 Dec 26:100790.

Mounting evidence has demonstrated the critical role of the gut microbiome in different cancer treatment modalities showing intensive crosstalk between microbiota and the host immune system. In cancer patients receiving hematopoietic stem cell transplantation (HSCT), conditioning regimens including chemotherapy, radiotherapy, and immunosuppressive therapy, as well as antimicrobial prophylaxis, result in intestinal barrier disruption and massive changes in microbiota composition. According to clinical studies, a drastic loss of microbial diversity during HSCT is associated with enhanced pro-inflammatory immune response and an increased risk of transplant-related complications such as graft-versus-host disease (GvHD) and mortality. In this review, we outline the current understanding of the role of microbiota diversity in the patient response to cancer therapies and highlight the impact of changes in the gut microbiome on clinical outcomes in post-HSCT patients. Moreover, the therapeutic implications of microbiota modulation by probiotics, prebiotics, and fecal microbiota transplantation (FMT) in hematologic cancer patients receiving HSCT are discussed.