Publikujeme v zahraničí

Onkológia (Bratisl.), 2018;13(5):382-383

GENITOURINÁRNE MALIGNITY

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

βcatenin is a marker of poor clinical characteristics and suppressed immune infiltration in testicular germ cell tumors

BMC Cancer. 2018 Nov 3;18(1):1062

Background: WNT/βcatenin (WNTβ) pathway is activated in early stages of embryonic development. We aimed to evaluate the significance of βcatenin in germ cell tumors (GCTs) and explore associations with the inflamed environment.

Methods: Surgical specimens from 247 patients were analyzed. βcatenin expression was detected in the tumor tissue by immunohistochemistry and correlated with clinical characteristics, outcome, PD-L1 expression and systemic immune-inflammation index (SII). The Ingenuity Pathway Analysis (IPA) was used to investigate the immune-cell related effects of βcatenin and PD-L1 encoding genes.

Results: βcatenin was expressed in 86.2% of GCTs. The expression in seminomas was significantly lower compared to all subtypes of non-seminoma (all P< 0.0001). A high expression (weighted histoscore >150) was associated with primary mediastinal non-seminoma (P = 0.035), intermediate/poor risk disease (P = 0.033) and high tumor markers (P = 0.035). We observed a positive correlation with the PD-L1 in tumor and an inverse correlation with the SII. IPA uncovered relationships of CTNNB (βcatenin) and CD274 (PD-L1) genes and their effects on differentiation, proliferation and activation of lymphocyte subtypes.

Conclusion: Herein, we showed that βcatenin is associated with male adult GCT characteristics as well as suppressed immune environment.

Mego M , van Agthoven T, **Gronesova P, Chovanec M, Miskovska V, Mardiak J**, Looijenga LHJ.

Clinical utility of plasma miR-371a-3p in germ cell tumors

Journal of Cellular and Molecular Medicine, 2018 (In press)

Background: Germ cell tumors predominantly of the testis ((T)GCTs) are remarkably chemotherapy sensitive solid malignancies. However, a small proportion of patients fail to be cured with cisplatin-based combination chemotherapy. miR-371a-3p is a new specific liquid biopsy molecular biomarker for (T)GCTs, however, data related to its clinical utility is limited. The aim of this study was to evaluate clinical utility of plasma miR-371a-3p level in (T)GCT patients starting systemic chemotherapy.

Methods: This translational study included TGCT patients with available plasma before 1st cycle (N = 180) and 2nd cycle (N = 101) of systemic first line chemotherapy, treated between July 2010 and May 2017. Plasma miR-371a-3p levels were measured using the ampTSmiR test and evaluated using the 2-ΔΔCT method, compared to disease characteristics and patients' outcome.

Results: Pretreatment plasma miR-371a-3p levels were significantly associated with number of metastatic sites, presence of lung, retroperitoneal and mediastinal lymph node metastases, S – stage, IGCCCG risk group and response to therapy. Patients with a negative pretreatment plasma level had significantly better progression-free survival (PFS) and overall survival (OS) compared to patients being positive for miR-371a-3p (hazard ratio [HR] = 0.26, 95% CI 0.09 – 0.71, P = 0.02 for PFS and HR = 0.21, 95% CI 0.07 – 0.67, P = 0.03 for OS, respectively). Patients with a negative miR-371a-3p measurement in both samples had a significantly superior PFS (HR = 0.10, 95% CI 0.01 – 21.49, P = 0.02) and OS (HR = 0.08, 95% CI 0.01 – 27.81, P = 0.008) compared to patients with miR-371a-3p positive in both samples.

Conclusion: This study demonstrates clinical value of plasma miR-371a-3p level in chemotherapy naïve (T)GCT patients starting first line of chemotherapy to predict prognosis. Moreover, plasma miR-371a-3p was associated with several clinically relevant disease characteristics.

Kalavska K, Kucerova L, Schmidtova S, Toro L, Kozovska Z, Plank L, Chovanec M, Palacka P, Pindak D, Macak D, Mardiak J and Mego M.

Lymphoma transformation of tumor infiltrating lymphocytes observed in testicular patient-derived xenograft models

Oncology reports 40: 3593-3602, 2018

Testicular germ cell tumors (TGCTs) are highly sensitive to cisplatin-based chemotherapy. Nevertheless, there are metastatic tumors that do not completely respond to front-line chemotherapy. For these tumors, surgical resection of residual masses is necessary to achieve long-term disease control. Resected tissues represent valuable clinical material, which may be used for the engraftment into immunocompromised mice to produce patient-derived xenografts (PDXs). They typically maintain similarities to the parental tumors and therefore serve as more realistic preclinical models. Moreover, a correlation between PDX treatment outcomes and clinical response to chemotherapy has been previously described. The aim of the present study was to establish and characterize TGCT patient-derived xenografts. These originated from retroperitoneal lymph node metastases infiltrated with TGCTs following previous cisplatin-based chemotherapy, in order to analyze novel treatment options for cisplatin-resistant testicular tumors. We generated two testicular patient-derived xenograft models in SCID beige male mice. Immunohistochemical analyses demonstrated that histological characteristics of the primary tumor were not

retained, and transformation into lymphoma, and eventually plasmocytoma, was observed. A potential explanation for the lymphoma transformation observed in PDXs may include tumor-infiltrating lymphocytes (TILs) in xenografted samples of patients, which are transformed following engraftment into immunodeficient recipient mice. Based on these data, we indicated that lymphomagenesis prevention and terminal differentiation represent new challenges in the establishment of PDX models derived from patients with germ cell tumors.

GYNEKOLOGICKÉ MALIGNITY

Kalavska K, Minarik T, Vlkova B, Manasova D, Kubickova M, Jurik A, Mardiak J, Sufliarsky J, Celec P, Mego M.

Prognostic value of various subtypes of extracellular DNA in ovarian cancer patients

J Ovarian Res. 2018 Sep 22;11(1):85.

Background: Patients with ovarian cancer represent a heterogeneous population with a variable prognosis and response to chemotherapy. Plasma DNA has been shown to have a prognostic value in different types of cancer including ovarian carcinoma. Whether total circulating DNA, which can be assessed much easier without knowing the tumor-specific mutations, has similar informative value is currently unknown. The aim of this study was to evaluate the prognostic value of extracellular DNA in advanced ovarian cancer.

Methods: This prospective study included 67 patients (pts) with ovarian cancer treated with 1st line paclitaxel and carboplatin (25 pts) and paclitaxel, carboplatin and bevacizumab (42 pts). Thirty-five patients had optimal surgical debulking before chemotherapy. Extracellular DNA was quantified using real time PCR before administration of chemotherapy (67 pts) and after 6 cycles of chemotherapy (44 pts).

Results: Total extracellular DNA (ecDNA), as well as extracellular DNA of nuclear (nDNA) and mitochondrial origin (mtDNA) significantly ($p < 0.05$) decreased after 6 cycles of chemotherapy (by 54%, 63% and 52%, respectively. Patients with stage I disease had significantly lower mtDNA compared to patients with stage II-IV (8604 vs. 16, 984 ge/mL, $p = 0.03$). Patients with lower baseline nDNA had superior progression-free (HR = 0.35 (0.14-0.86)) and overall survival (HR = 0.18 (0.04-0.77). The prognostic value of nDNA was confirmed independent of tumor stage and confirmed in multivariate analysis.

Conclusion: Our data suggest that ecDNA of both, nuclear and mitochondrial origin could be added to prognostic markers in ovarian cancer. Analysis of ecDNA does not require the knowledge of tumor-specific mutations in contrast to the quantification of tumor-derived ecDNA. Study of the dynamics and cell type-specific source of the ecDNA could shed light on its biology in cancer and might help to direct the treatment of ovarian cancer.

Ryska A, **Berzinec P,** Brcic L, Cufer T, Dziadziuszko R, Gottfried M, Kovalszky I, Olszewski W, Oz B, **Plank L,** Timar J.

NSCLC molecular testing in Central and Eastern European countries

BMC Cancer. 2018 Mar 9;18(1):269

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.

Conclusion: 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.