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KARCINÓM PRSNÍKA

Prognostic Value of EMT-Circulating Tumor Cells in Metastatic Breast Cancer Patients Undergoing High-Dose Chemotherapy with Autologous Hematopoietic Stem Cell Transplantation

Mego M, Gao H, Lee BN, Cohen EN, Tin S, Giordano A, Wu Q, Liu P, Nieto Y, Champlin RE, Hortobagyi GN, Cristofanilli M, Ueno NT, Reuben JM. *J Cancer* 2012; 3: 369–380.

Background: Circulating tumor cells (CTCs) are an independent prognostic factor in metastatic breast cancer (MBC) patients treated by conventional dose chemotherapy. The aim of this study was to determine the role of CTCs and CTCs undergoing epithelial-mesenchymal transition (EMT) in metastatic breast cancer. We used the platform of high-dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplantation (AHSCT) to study the CTCs and CTCs with EMT.

Patients and methods: CTCs were enumerated in 21 MBC patients before apheresis and 1 month after AHSCT. CD34-depleted apheresis products were analyzed for CD326+ epithelial and Aldefluor+ cancer stem cells (CSC) by flow cytometry and were depleted of CD45+ cells and assessed for EMT-inducing transcription factors (EMT-TF) by quantitative RT-PCR.

Results: Patients with ≥ 5 CTCs/7.5 mL of peripheral blood 1 month after AHSCT had shorter progression-free survival (PFS) ($p = 0.02$) and overall survival (OS) ($p = 0.02$). Patients with apheresis products containing high percentages of CD326+ epithelial cells or overexpressing EMT-TF had shorter PFS. In multivariate analysis, low percentage of CD326+ epithelial cells and response to HDCT with AHSCT were associated with longer PFS, whereas lower CTCs after AHSCT were associated with longer OS. High CTCs, 1 month after AHSCT correlated with shorter PFS and OS in MBC patients undergoing HDCT and AHSCT,

while CTCs with EMT and CSCs phenotype in apheresis products are associated with relapse.

Conclusion: Our data suggest that CTC and CTCs with EMT are prognostic in MBC patients undergoing HDCT followed by AHSCT.

Epithelial-Mesenchymal Transition and Stem Cell Markers in Patients with HER2-Positive Metastatic Breast Cancer

Giordano A, Gao H, Anfossi S, Cohen E, **Mego M**, Lee BN, Tin S, De Laurentiis M, Parker CA, Alvarez RH, Valero V, Ueno NT, De Placido S, Mani SA, Esteva FJ, Cristofanilli M, Reuben JM. *Mol Cancer Ther.* 2012, 11: 2526–2534.

Currently, there is extensive information about circulating tumor cells (CTCs) and their prognostic value; however, little is known about other characteristics of these cells. In this prospective study, we assessed the gene transcripts of epithelial-to-mesenchymal transition inducing transcription factors (EMT-TFs) and cancer stem cell features in HER2+ metastatic breast cancer (MBC) patients. Epithelial cells were enriched from peripheral blood mononuclear cells (PBMCs) using antibody-coated anti-CD326 antibody (CD326+) magnetic beads, and the residual CD326- PBMCs were further depleted of leukocytes using anti-CD45 antibody-coated magnetic beads (CD326-CD45-). RNA was extracted from all cell fractions, reverse transcribed to cDNA, and subjected to quantitative reverse transcription-polymerase chain reaction (qRT-PCR) to detect EMT-TFs (TWIST1, SNAIL1, ZEB1, and TG2) as a measure of CTCs undergoing EMT (EMT-CTCs). Additionally, PBMCs were analyzed using multi-parameter flow cytometry for ALDH activity and cancer stem cells (CSCs) that express CD24, CD44, and CD133. Twenty-eight patients were included in this study. At least one EMT-TF mRNA was elevated in the CTCs of 88.2% of patients and in the CD326-CD45- cell fraction of 60.7% of patients. The CD326-CD45- fraction of patients with elevated SNAIL1 and ZEB1 transcripts also had a higher percentage of ALDH+/CD133+

cells in their blood than did patients with normal SNAIL1 and ZEB1 expression ($p = 0.038$). Our data indicate that HER2+ MBC patients have EMT-CTCs. Moreover, an enrichment of cancer stem cells was found in CD326-CD45- cells. Additional studies are needed to determine whether EMT-CTCs and CSCs have prognostic value in HER2+ MBC patients treated with trastuzumab-based therapy.

GENITOURINÁRNE MALIGNITY

Recent patterns in testicular cancer incidence, mortality and survival in the Slovak Republic with reference to international comparisons

Ondrus D, Ondrusova M, Dusek L. *Cancer Invest.* 2012, 30: 545–551.

Incidence of testicular cancer in the Slovak Republic (SR) sharply increased in 1968-2006 (annual change 0.195/100,000, 95% CI = -0.178-0.212, $p < .0001$). Mortality was stabilized in 1968-2006 (-0.005/100,000/year, 95% CI = -0.011-0.001, $p = .148$), however, from 1990, it had a mildly significant decreasing trend. The 5-year relative survival for patients from the cohort 1993-1997 reached 91.7% (95% CI = 87.5-94.7), for the cohort 1998-2002, it was 93.2% (95% CI = 89.5-95.8). The average age of patients with seminomas was 30-41 years (25-75% quantile), for nonseminomas 23-34 years (25-75% quantile).

KARCINÓM PLŮC

Trends in the lung cancer incidence and mortality in the Slovak and Czech Republics in the contexts of an international comparison

Ondrusova M, Muzik J, Hunakova L, **Belohorska B**, Tomek D, **Ondrus D**, Kavcova E. *Clin Transl Oncol.* 2012, 14: 659–666.

INTRODUCTION: Lung cancer represents the most frequent cause of cancer-related deaths in the industrialized countries. The aim of this study was to analyze the lung cancer incidence and

mortality and the possible reasons for any differences discovered in two neighboring Central European countries-the Slovak Republic.

METHODS: We used linear regression model when analyzing incidence and mortality; the trends are presented with corresponding 95% confidence intervals (CI) and p-value with null hypothesis being constant with time.

RESULTS: Statistically significant increase of age-standardized incidence (0.707/100,000/year, 95% CI 0.107-1.307, $p = 0,025$) and mortality (1.339/100,000/year, 95% CI 1.050-1.629, $p < 0.0001$) of the lung cancer was revealed in males in the Slovak Republic (1980-1991). On the contrary, values of both indicators were stabilized in the Czech Republic. Since year 1991-2005 a statistically highly significant decrease of both incidence and mortality values was observed in males, which was greater in the Slovak Republic. Peak of the curve was not reached in women population, while incidence and mortality values have significantly continuous growth in both countries.

CONCLUSIONS: According to the lung cancer incidence and mortality trends in both countries (in correlation with smoking prevalence) we consider the support of efforts to change the attitude towards smoking predominantly in women and younger generation to be the most accurate action to reduce these trends.

GASTROINTESTINÁLNE MALIGNITY

Spectrum of mutations in gastrointestinal stromal tumor patients – a population-based study from Slovakia

Minárik G, Plank L, Lasabová Z, Szemes T, Burjanivová T, Szépe P, Buzalková V, Porubský D, **Sufliarsky J.** APMIS. 2012 Oct 27.

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of gastrointestinal tract and are characterized by presence of mutations in tyrosine kinases cKIT (KIT) and PDGFR α (PDGFRA). Mutations identified are highly heterogeneous, but some mutations are associated with specific clinical features of the tumor. Samples from 278 GIST patients collected during the period 2004-2011 were screened for mutations in exons 9, 11, 13, and 17 of KIT and 12, 14 and 18 of PDGFRA. Results of mutation screening were summarized and tested for possible association with clinical parameters of tumors. Mutations were identified in 83.81% of patients. Most frequent mutations were found in KIT exon 11 reaching frequency

of 62.95%. Other exons contributed to the mutation pool with frequencies 8.27%, 7.55%, 2.52%, 1.44%, 1.08%, and 0.00%, in decreasing order KIT exon 9, PDGFRFA exons 18 and 12, KIT exon 13, PDGFRA exon 14, and KIT exon 17. General linear model analysis showed no effect of any individual analyzed mutation on the phenotypic variables, but we confirmed association between mutations KIT exon 9 p. 503-504_dup2, and PDGFRA exon 18 p. D842V and intestinal and gastric localization of tumors.

HEMATOLOGICKÉ MALIGNITY

Primary Follicular Lymphoma of the GI Tract: An Increasingly Recognized Entity

Jain VK, **Bystricky B**, Wotherspoon AC, Chau I, Cunningham D. J Clin Oncol. 2012 Nov 13.

The GI tract is the most commonly involved extranodal site for non-Hodgkin lymphomas. These tumors form a highly heterogeneous group, with high-grade lymphomas and mucosa-associated lymphoid tissue (MALT) lymphomas being the most common subtypes. FL of the GI tract (GI-FL) is relatively rare, accounting for only 3.6% of GI non-Hodgkin lymphomas. The majority of these cases are diagnosed incidentally. Pathologically, GI-FL is characterized by the presence of centrocytes and centroblasts, with a follicular growth pattern, typical immunophenotype, and the hallmark t(14;18) translocation that results in suppression of apoptosis due to overexpression of the BCL-2 gene. GI-FL usually occurs in the presence of disseminated disease but can rarely be the presenting site of disease (primary GI-FL), as in our patient. While multiple definitions of primary GI-FL exist, the most commonly accepted use of this term describes patients with disease confined to the GI tract (stages IE and IIE). The primary GI-FL has a distinct clinical behavior, with the majority of patients having asymptomatic disease that remains localized to the GI tract.

Micafungin as empirical antifungal therapy in hematological patients: a retrospective, multicenter study in the Czech and Slovak Republics

Racil Z, Toskova M, Kocmanova I, Buresova L, Kouba M, **Drgona L, Masarova L**, Guman T, **Tothova E**, Gabzdilova J, Forsterova K, Haber J, Ziakova B, Bojtarova E, Rolencova M, Timilsina S, Cetkovsky P, Mayer J. Leuk Lymphoma. 2012 Nov 15.

The objective of this retrospective, multicenter study was to evaluate the efficacy and safety of micafungin as empirical antifungal therapy during febrile neutropenia (FN) in 73 hematological patients from six centers in two countries. All patients received 100 mg of micafungin/day. The overall favorable response rate (RR) was 64.8% when the resolution of fever during neutropenia was included in the response criteria and 84.5% when excluded. A significantly lower favorable RR in patients with persistent fever and non-specific pulmonary infiltrates compared to patients with persistent fever only (82.8 vs. 52.4%, respectively; $p = 0.011$) was not found when resolution of fever was not included in the composite endpoint criteria (93.1 vs. 78.6%, respectively; $p = 0.180$). Breakthrough fungal disease developed in 2.7% of patients. Treatment was discontinued in 16.4% of cases. Only one patient (1.4%) discontinued therapy due to an adverse event. Posaconazole prophylaxis improved favorable RR when defervescence was included as composite endpoint criterion ($p = 0.047$), but not when it was excluded ($p = 0.485$). However, neutrophil recovery did not influence favorable RR ($p = 0.803$ and $p = 0.112$, respectively). These data suggest that micafungin is safe and effective as an empirical therapy in patients with FN.

Invasive aspergillosis in patients with hematological malignancies in the Czech and Slovak republics: Fungal InfectioN Database (FIND) analysis, 2005-2009

Racil Z, Weinbergerova B, Kocmanova I, Muzik J, Kouba M, **Drgona L, Masarova L**, Guman T, **Tothova E**, Forsterova K, Haber J, Ziakova B, Bojtarova E, Vydra J, Mudry P, Foralova R, **Sejnova D**, Mallatova N, Kandrnal V, Cetkovsky P, Mayer J. Int J Infect Dis. 2012 Oct 18. pii: S1201-9712.

OBJECTIVES: To evaluate risk factors, diagnostic procedures, and treatment outcomes of invasive aspergillosis (IA) in patients with hematological malignancies.

METHODS: A retrospective analysis of data from proven/probable IA cases that occurred from 2005 to 2009 at 10 hematology centers was performed.

RESULTS: We identified 176 IA cases that mainly occurred in patients with acute leukemias (58.5%), mostly those on induction/re-induction treatments (39.8%). Prolonged neutropenia was the most frequent risk factor for IA (61.4%). The lungs were the most frequently affected site (93.8%) and computed tomography detected abnormalities in all episodes; however, only

53.7% of patients had findings suggestive of IA. Galactomannan (GM) detection in serum or bronchoalveolar lavage fluid (positive in 79.1% and 78.8% of episodes, respectively) played a crucial role in IA diagnosis. Neutrophil count and antifungal prophylaxis did not influence the GM positivity rate, but empirical therapy decreased this rate (in serum). Of the IA cases, 53.2% responded to initial antifungal therapy. The combination of voriconazole and echinocandin, even as initial or salvage therapy, did not perform better than voriconazole monotherapy ($p=0.924$ for initial therapy and $p=0.205$ for salvage therapy). Neutrophil recovery had a significant role in the response to initial (but not salvage) antifungal therapy.

CONCLUSIONS: Our retrospective analysis identified key diagnostic and treatment characteristics, and this understanding could improve the management of hematological malignancy patients with IA.

ABSTRAKTY A POSTERY ZO ZAHRAŇIČNÝCH KONFERENCIÍ

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