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Onkológia (Bratisl.), 2014; roč. 9(3): 194–196

KARCINÓM PRSNÍKA

Mego M, Cierna Z, Janega P, Karaba M, Minarik G, Benca J, Sedlackova T, Cingelova S, Gronesova P, Manasova D, Pindak D, Sufliarsky J, Danihel L, Reuben JM**, Mardiak J.** **Matrix metalloproteinase 1 and circulating tumor cells in early breast cancer.**
BMC Cancer, 2014 (In press)

Background: Matrix metalloproteinases (MMPs) are involved in cancer invasion and metastasis. Circulating tumor cells (CTCs) play role in tumor dissemination and are an independent survival predictor in breast cancer (BC) patients. The aim of this study was to assess correlation between CTCs and tumor MMP1 in BC.

Methods: Study included 149 primary BC patients treated by surgery from March 2012 to March 2013. Peripheral blood mononuclear cells (PBMC) were depleted of hematopoietic cells using RosetteSep™ selection kit. RNA extracted from CD45-depleted PBMC was interrogated for expression of EMT (TWIST1, SNAIL1, SLUG, ZEB1) and epithelial (CK19) gene transcripts by qRT-PCR. Patient samples with higher epithelial and/or mesenchymal gene transcripts than those of healthy donors (n=60) were considered as CTC positive. Expression of MMP1 in surgical specimens was evaluated by immunohistochemistry.

Results: CTCs were detected in 24.2% patients. CTCs exhibiting only epithelial markers were present in 8.7% patients, whereas CTCs with epithelial-mesenchymal transition (EMT) markers (CTC_EMT) were observed in 13.4% of patients and CTCs co-expressing both markers were detected in 2.0% patients. Patients with CTC_EMT in peripheral blood had significantly increased expression of MMP1 in tumor cells ($p = 0.02$) and tumor associated stroma ($p = 0.05$) than those of patients without CTC_EMT. In multivariate analysis, CTC_EMT and tumor grade were independently associated with MMP1 expression in cancer cells, while CTC_EMT and Ki67 were independently associated with MMP1 expression in cancer associated stroma.

Conclusion: Our data suggest link between MMP1 and CTCs with EMT phenotype and support role of MMPs and EMT in tumor dissemination.

GASTROINTESTINÁLNE MALIGNITY

Kalinka-Warzocha E, Plazas JG, Mineur L, **Salek T**, Hendlisz A, Decosta L, Vogl, FD, Passalacqua R. **Chemotherapy treatment patterns and neutropenia management in gastric cancer.**
Gastric Cancer, 2014 (In press)

Background: Potentially myelosuppressive doublet and triplet chemotherapy combination regimens are considered the most active treatments in gastric cancer.This multicenter prospective observational study was designed to gain insight into the chemotherapy regimens being used in Europe and to evaluate neutropenia management in patients identified as at high risk for febrile neutropenia (FN).

Methods: Eligible patients had gastric cancer, were scheduled for ≥ 3 cycles of myelosuppressive chemotherapy, and had an investigator-assessed overall FN risk ≥ 20%. Data were collected for up to ten cycles. The primary endpoint was the proportion of patients who received granulocyte colony stimulating factor (G-CSF) primary prophylaxis (defined as G-CSF initiated on days 1-7 of cycle 1). Secondary endpoints included FN incidence, chemotherapy administration, and G-CSF use.

Results: Of 199 patients who met the eligibility criteria and started at least one cycle of chemotherapy, mean age was 63 years, 76% were men, 83 % had an ECOG score of 0 or 1, 54% had metastatic disease, and 24% had received prior chemotherapy. A total of 27 different backbone regimens were given; the most common regimen was modified docetaxel, cisplatin, and 5-fluorouracil (DCF). Despite all patients having been identified as having a ≥ 20% FN risk, only 70 (35%) received G-CSF primary prophylaxis. FN occurred in 14 patients overall (7%). Most FN events occurred in patients who received DCF/modified DCF (9/14 events, 64%).

Conclusion: The results of this study reveal a high use of myelotoxic treatment regimens in gastric cancer in Europe and low adherence to clinical practice guidelines for the use of primary and secondary G-CSF prophylaxis for FN.

SARKÓMY

Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay JY, Kerst JM, **Sufliarsky J**, Whelan J, Hohenberger P, Krarup-Hansen A, Alcindor T, Marreaud S, Litière S, Hermans C, Fisher C, Hogendoorn PC, dei Tos AP, van der Graaf WT; European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. **Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial.**
Lancet Oncol. 2014 Apr; 15(4):415–423.

Backround: Effective targeted treatment is unavailable for most sarcomas and doxorubicin and ifosfamide-which have been used to treat soft-tissue sarcoma for more than 30 years-still have an important role. Whether doxorubicin alone or the combination of doxorubicin and ifosfamide should be used routinely is still controversial. We assessed whether dose intensification of doxorubicin with ifosfamide improves survival of patients with advanced soft-tissue sarcoma compared with doxorubicin alone.

Methods: We did this phase 3 randomised controlled trial (EORTC 62012) at 38 hospitals in ten countries. We included patients with locally advanced, unresectable, or metastatic high-grade soft-tissue sarcoma, age 18-60 years with a WHO performance status of 0 or 1. They were randomly assigned (1:1) by the minimisation method to either doxorubicin (75 mg/m(2) by intravenous bolus on day 1 or 72 h continuous intravenous infusion) or intensified doxorubicin (75 mg/m(2); 25 mg/m(2) per day, days 1-3) plus

ifosfamide (10 g/m(2) over 4 days with mesna and pegfilgrastim) as first-line treatment. Randomisation was stratified by centre, performance status (0 vs 1), age (< 50 vs ≥ 50 years), presence of liver metastases, and histopathological grade (2 vs 3). Patients were treated every 3 weeks till progression or unacceptable toxic effects for up to six cycles. The primary endpoint was overall survival in the intention-to-treat population. The trial is registered with Clinical Trials.gov, number NCT00061984.

Findings: Between April 30, 2003, and May 25, 2010, 228 patients were randomly assigned to receive doxorubicin and 227 to receive doxorubicin and ifosfamide. Median follow-up was 56 months (IQR 31-77) in the doxorubicin only group and 59 months (36-72) in the combination group. There was no significant difference in overall survival between groups (median overall survival 12.8 months [95.5% CI 10.5-14.3] in the doxorubicin group vs 14·3 months [12.5-16.5] in the doxorubicin and ifosfamide group; hazard ratio [HR] 0·83 [95.5% CI 0.67-1.03]; stratified log-rank test p=0.076). Median progression-free survival was significantly higher for the doxorubicin and ifosfamide group (7·4 months [95% CI 6.6-8.3]) than for the doxorubicin group (4·6 months [2.9-5.6]; HR 0.74 [95% CI 0.60-0.90], stratified log-rank test p = 0.003). More patients in the doxorubicin and ifosfamide group than in the doxorubicin group had an overall response (60 [26%] of 227 patients vs 31 [14%] of 228; p< 0.0006). The most common grade 3 and 4 toxic effects-which were all more common with doxorubicin and ifosfamide than with doxorubicin alone-were leucopenia (97 [43%] of 224 patients vs 40 [18%] of 223 patients), neutropenia (93 [42%] vs 83 [37%]), febrile neutropenia (103 (46%) vs 30 [13%]), anaemia (78 [35%] vs 10 [5%]), and thrombocytopenia (75 [33%]) vs one [< 1%]).

Interpretations: Our results do not support the use of intensified doxorubicin and ifosfamide for palliation of advanced soft-tissue sarcoma unless the specific goal is tumour shrinkage. These findings should help individualise the care of patients with this disease.

HEMATOLOGICKÉ MALIGNITY

Kempf W, Kazakov DV, Rütten A, Rupec RA, Talarcik P, **Ballova V,** Kerl K, Dummer R, Lautenschlager S, Zimmermann DR, Tinguely M.

Primary cutaneous follicle center lymphoma with diffuse CD30 expression: A report of 4 cases of a rare variant.

J Am Acad Dermatol. 2014 (In press)

Backround: CD30 is expressed in aggressive and Epstein-Barr virus-associated forms of B-cell non-Hodgkin lymphomas, but is rarely expressed by the majority of tumor cells in primary cutaneous B-cell lymphomas (CBCLs). The expression of CD30 in CBCLs may be at risk for misinterpretation as an unequivocal indicator of a highly aggressive form of the disease.

Objective: We report 4 cases of low malignant primary cutaneous follicle center lymphoma (PCFCL) with diffuse and strong expression of CD30 by the majority of neoplastic cells.

Results: The patients included 3 men and 1 woman with tumors on the scalp (3 patients) and chest wall (1 patient). The histologic examinations revealed a mixed, diffuse, and follicular growth pattern with CD20(+), bcl-6(+), and bcl-2(-) tumor cells. Seventy percent to 90% of the tumor cells expressed CD30. Clonal rearrangement of immunoglobulin heavy chain genes was found in 1 of 4 cases. None of the 3 cases yielded positivity for Epstein-Barr virus RNA.

Limitations: The study is limited by the small number of patients.

Conclusions: This rare variant of CD30(+) PCFCL needs be distinguished from CD30(+) aggressive B-cell lymphomas. CD30 in this variant of CBCLs may serve as a therapeutic target for anti-CD30 antibody-based strategies.

Govi S, Christie D, Messina C, Bruno Ventre M, Gracia Medina EA, Porter D, Radford J, Seog Heo D, Park Y, Martinelli G, Taylor E, Lucraft H, **Ballova V**, Zucca E, Gospodarowicz M, Ferreri AJ; International Extranodal Lymphoma Study Group (I.E.L.S.G.).

The clinical features, management and prognostic effects of pathological fractures in a multicenter series of 373 patients with diffuse large B-cell lymphoma of the bone.

Ann Oncol. 2014 Jan; 25(1):176–181

Backround: Pathological fractures (PFs) occur in 10%-20% of patients with diffuse large B-cell lymphoma (DLBCL) of the bone. The clinical features and the effects of this severe complication on management and prognosis have not been previously analyzed in a large series.

Patients and methods: The effects of PF on management and prognosis were reviewed in an international retrospective series of 373 patients with newly diagnosed bone DLBCL, comparing 78 patients with PF at presentation (group ‚PF-BL') and 295 patients without PF (‚controls').

Results: At a median follow-up of 53 months (range 3-246), PF-BL patients exhibited lower rates of overall response (ORR, 78% versus 85%; p = 0.17), 5-year progression-free survival (PFS, 53 ± 6% versus 61 ± 3%; p = 0.02) and 5-year overall survival (OS, 54 ± 6% versus 68 ± 3%, p = 0.008) than controls. Initial surgical stabilization of the PF did not change therapeutic outcome (5-year OS: 45 ± 9% versus 54 ± 10%; p = 0.20). PF-BL patients referred to irradiation of the fractured bone before chemotherapy exhibited a significantly poorer outcome than patients managed with the inverse sequence (ORR: 52% versus 92%, p = 0.0005; 5-year OS: 22 ± 14% versus 64 ± 9%, p = 0.007). Multivariate analysis confirmed the independent association between PF and worse survival and the negative effect of radiotherapy as initial therapy.

Conclusion: Fracture is an independent, adverse prognostic event in patients with bone DLBCL. Anthracycline-based chemotherapy followed by radiotherapy seems to be the better treatment sequence. Initial fracture stabilization does not seem to improve outcome; it should be used to improve patient's quality of life only if chemotherapy delays can be avoided.

Witzens-Harig M, Foá R, Di Rocco A, van Hazel G, Chamone DF, Rowe JM, Arcaini L, Poddubnaya I, Ho AD, Ivanova V, **Vranovsky A**, Thurley D, Oertel S.

Maintenance with rituximab is safe and not associated with severe or uncommon infections in patients with follicular lymphoma: results from the phase IIIb MAXIMA study.

Ann Hematol. 2014, May 14. (In press)

Previous randomized trials have demonstrated that rituximab maintenance (R-maintenance) can prolong time to progressive disease in patients with follicular lymphoma (FL). The phase IIIb MAXIMA study (NCT00430352) was a large prospective evaluation of R-maintenance in a daily care setting. The primary objective was safety. Secondary objectives included progression-free survival, overall survival, time to next lymphoma treatment, and partial response (PR) to complete response/unconfirmed (CR/CRu) conversion rate. Patients (n = 545) with first-line or relapsed FL who responded to 8 cycles of rituximab-based induction received R-maintenance every 2 months for 2 years. At study entry, 380 patients had CR or CRu, and 165 had PR. The median age was 57.0 years. The most common non-hematologic adverse events (AEs, excluding infusion-related reactions) were cough (9.9% of patients), fatigue (7.5%), nasopharyngitis (7.1%), back pain (6.5%), diarrhea (6.9%), arthralgia (6.0%), headache and hypertension (5.2 %each), and pyrexia (5.1%). The majority of AEs were grade 1 or 2. Grade 3, 4, and 5 infec-

tions occurred in 21 (3.9%), 2 (0.4 %), and 1 (0.2%) patient, respectively. Fifty-one hematologic AEs occurred in 6.6 % (n = 35) of patients. Grade 3/4 prolonged neutropenia and hypogammaglobulinemia occurred in 13 (2.4%) and 5 (0.9%) patients, respectively. All cases of prolonged neutropenia or hypogammaglobulinemia were manageable and resolved. Fast infusion did not alter the safety profile. Efficacy was comparable with results from previous trials. R-maintenance is safe in a daily care setting for patients with first-line or relapsed FL.

ABSTRAKTY A POSTERY ZO ZAHRANIČNÝCH KONFERENCIÍ

KARCINÓM PRSNÍKA

Michal Mego, Dana Cholujova, Paulina Gronesova, Marian Karaba, Gabriel Minarik, Tatiana Sedlackova, Denisa Manasova, Zuzana Cierna, Daniel Pindak, Jozef Sufliarsky, James M. Reuben**, Jozef Mardiak**

Correlation between circulating tumor cells (CTC) and plasma cytokines and angiogenic factors (CAF) in early breast cancer patients.

ASCO 2014 - J Clin Oncol 32, 2014 (suppl; abstr e22038)

GENITOURINÁRNE MALIGNITY

Jozef Mardiak, Igor Jurisica, William Klement, Paulina Gronesova, Vera Miskovska, Jana Obertova, Jan Rajec, Zuzana Sycova-Mila, Vanda Usakova, Katarina Sevcikova, Michal Chovanec, Daniela Svetlovska, Peter Bujdak, Dana Jurkovicova, Stanislav Spanik, Dalibor Ondrus, Michal Mego

MicroRNA profiling of peripheral blood enriched for circulating tumor cells (CTCs) in testicular germ cell tumors (TGCTs).

ASCO 2014 - J Clin Oncol 32, 2014 (suppl; abstr e15530)

Michal Chovanec, Miriam Zatovicova, Dana Cholujova, Paulina Gronesova, Vera Miskovska, Magdalena Vrestiakova, Daniela Svetlovska, Jana Obertova, Bibiana Vertakova-Krakovska, Vanda Usakova, Katarina Sevcikova, Stanislav Spanik, Dalibor Ondrus, Jozef Mardiak, Silvia Pastorekova, Michal Mego

Plasma levels of carbonic anhydrase IX, cytokines, and angiogenic factors in testicular germ cell tumor patients.

ASCO 2014 - J Clin Oncol 32, 2014 (suppl; abstr e15541)

Lance C. Pagliaro, Agnes Laplanche, Aude Flechon, **Jozef Mardiak**, Lionnel Geoffrois, Pierre Kerbrat, Christine Chevreau, Remy Delva, Frederic Rolland, Christine Theodore, Guilhem Roubaud, Gwenaelle Gravis, Jean-Christophe Eymard, Jean-pierre Malhaire, Claude Linassier, Muriel Habibian, Florence Journeau, **Maria Reckova**, Stephane Culine, Karim Fizazi

Validation of a prognostic classification system for mediastinal nonseminomatous germ-cell tumors (MGCT).

ASCO 2014 - J Clin Oncol 32:5s, 2014 (suppl; abstr 4562)

GASTROINTESTINÁLNE MALIGNITY

Michal Mego, Jozef Chovanec, Iveta Andrezalova, Peter Konkolovsky, Milada Mikulova, Maria Reckova, Vera Miskovska, Branislav Bystricky, Lenka Medvecova, Dagmar Mikusova, Adela Lagin, Daniela Svetlovska, Stanislav Spanik, Jozef Mardiak, Vladimir Zajac, Lubos Drgona

Prevention of irinotecan-induced diarrhea by probiotics: Randomized double-blind, placebo-controlled phase III study.

ASCO 2014 - J Clin Oncol 32:5s, 2014 (suppl; abstr 9611)