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KARCINÓM PRSNÍKA

Mego M, Cholujova D, Minarik G, Sedlackova T, Gronesova P, Karaba M, Benca J, Cingelova S, Cierna Z, Manasova D, Pindak D, Sufliarsky J, Cristofanilli M, Reuben JM, **Mardiak J.**

CXCR4-SDF-1 interaction potentially mediates trafficking of circulating tumor cells in primary breast cancer.

BMC Cancer 2016 (In press)

Background: Cytokines are involved in cancer invasion and metastasis. Circulating tumor cells (CTCs) play key role in tumor dissemination and are an independent survival predictor in breast cancer patients. The aim of this study was to assess correlation between CTCs and plasma cytokines in primary breast cancer (PBC) patients.

Methods: This study included 147 chemotherapy naïve PBC patients. Peripheral blood mononuclear cells (PBMC) were depleted of hematopoetic cells using RossetteSepTM negative 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. The concentrations of 51 plasma cytokines were measured using multiplex bead arrays.

Results: CTCs were detected in 25.2% patients. CTCs exhibiting only epithelial markers (CTC_EP) and only EMT markers (CTC_EMT) were present evenly in 11.6% patients, while CTCs co-expressing both markers were detected in 2.0% patients. Patients with presence of CTC_EP in peripheral blood had significantly elevated levels of plasma IFN-α2, IL-3, MCP-3, β-NGF, SCF, SCGF-β, TNF-β and SDF-1 compared to patients without CTC_EP. CTC_EP exhibited overexpression of SDF-1 receptor and CXCR4, but not other corresponding cytokine receptor, and in multivariate analysis SDF-1 was independently associated with CTC_EP. There was an inverse correlation between CTC_EMT and plasma cytokines CTACK, β-NGF and TRAIL, while presence of either subtype of CTCs was associated with increased level of TGF-β2.

Conclusion: Using cytokine profiling, we identified cytokines associated with CTCs subpopulations in peripheral blood of PBC. Our data suggest that CXCR4-SDF-1 axis is involved in mobilization and trafficking of epithelial CTCs.

GYNEKOLOGICKÉ MALIGNITY

Pujade-Lauraine E, Selle F, Weber B, Ray-Coquard IL, Vergote I, **Sufliarsky J**, Del Campo JM, Lortholary A, Lesoin A, Follana P, Freyer G, Pardo B, Vidal L, Tholander B, Gladieff L, Sassi M, Garin-Chesa P, Nazabadioko S, Marzin K, Pilz K, Joly F.

Volasertib Versus Chemotherapy in Platinum-Resistant or –Refractory Ovarian Cancer: A Randomized Phase II Groupe des Investigateurs Nationaux pour l'Etude des Cancers de l'Ovaire Study.

J Clin Oncol. 2016 Jan 11.

Purpose: Volasertib is a potent and selective cell-cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting Polo-like kinase. This phase II trial evaluated volasertib or single-agent chemotherapy in patients with platinum-resistant or -refractory ovarian cancer who experienced failure after treatment with two or three therapy lines.

Patients and methods: Patients were randomly assigned to receive either volasertib 300 mg by intravenous infusion every 3 weeks or an investigator's choice of single-agent, nonplatinum, cytotoxic chemotherapy. The primary end point was 24-week disease control rate. Secondary end points included best overall response, progression-free survival (PFS), safety, quality of life, and exploratory biomarker analyses.

Results: Of the 109 patients receiving treatment, 54 received volasertib and 55 received chemotherapy; demographics were well balanced. The 24-week disease control rates for volasertib and chemotherapy were 30.6% (95% CI, 18.0% to 43.2%) and 43.1% (95% CI, 29.6% to 56.7%), respectively, with partial responses in seven (13.0%) and eight (14.5%) patients, respectively. Median PFS was 13.1 weeks and 20.6 weeks for volasertib and chemotherapy (hazard ratio, 1.01; 95% CI, 0.66 to 1.53). Six patients (11%) receiving volasertib achieved PFS for more than 1 year, whereas no patient receiving chemotherapy achieved PFS greater than 1 year. No relationship between the expression of the biomarkers tested and their response was determined. Patients treated with volasertib experienced more grade 3 and 4 drug-related hematologic adverse events (AEs) and fewer nonhematologic AEs than did patients receiving chemotherapy. Discontinuation resulting from AEs occurred in seven (13.0%) and 15 (27.3%) patients in the volasertib and chemotherapy arms, respectively. Both arms showed similar effects on quality of life.

Conclusion: Single-agent volasertib showed antitumor activity in patients with ovarian cancer. AEs in patients receiving volasertib were mainly hematologic and manageable.

du Bois A, Kristensen G, Ray-Coquard I, Reuss A, Pignata S, Colombo N, Denison U, Vergote I, Del Campo JM, Ottevanger P, Heubner M, **Minarik T**, Sevin E, de Gregorio N, Bidziński M, Pfisterer J, Malander S, Hilpert F, Mirza MR, Scambia G, Meier W, Nicoletto MO, Bjørge L, Lortholary A, Sailer MO, Merger M, Harter P; AGO Study Group led Gynecologic Cancer Intergroup (GCIG)/ European Network of Gynaecologic Oncology Trials Groups (ENGOT) Intergroup Consortium.

Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial.

Lancet Oncol. 2016 Jan;17(1):78-89.

Background: Angiogenesis is a target in the treatment of ovarian cancer. Nintedanib, an oral triple angiokinase inhibitor of VEGF receptor, platelet-derived growth factor receptor, and

fibroblast growth factor receptor, has shown activity in phase 2 trials in this setting. We investigated thecombination of nintedanib with standard carboplatin and paclitaxel chemotherapy in patients with newly diagnosed advanced ovarian cancer.

Methods: In this double-blind phase 3 trial, chemotherapy-naive patients (aged 18 years or older) with International Federation of Gynecology and Obstetrics (FIGO) IIB-IV ovarian cancer and upfront debulking surgery were stratified by postoperative resection status, FIGO stage, and planned carboplatin dose. Patients were randomly assigned (2:1) via an interactive voice or web-based response system to receive six cycles of carboplatin (AUC 5 mg/mL per min or 6 mg/mL per min) and paclitaxel (175 mg/m(2)) in addition to either 200 mg of nintedanib (nintedanib group) or placebo (placebo group) twice daily on days 2-21 of every 3-week cycle for up to 120 weeks. Patients, investigators, and independent radiological reviewers were masked to treatment allocation. The primary endpoint was investigator-assessed progression-free survival analysed in the intention-to--treat population. This trial is registered with ClinicalTrials.gov, number NCT01015118.

Findings: Between Dec 9, 2009, and July 27, 2011, 1503 patients were screened and 1366 randomly assigned by nine study groups in 22 countries: 911 to the nintedanib group and 455 to the placebo group. 486 (53%) of 911 patients in the nintedanib group experienced disease progression or death compared with 266 (58%) of 455 in the placebo group. Median progression-free survival was significantly longer in the nintedanib group than in the placebo group (17·2 months [95% CI 16·6-19·9] vs 16·6 months [13·9-19·1]; hazard ratio 0·84 [95% CI 0·72-0·98]; p = 0·024). The most common adverse events were gastrointestinal (diarrhoea: nintedanib group 191 [21%] of 902 grade 3 and three [<1%] grade 4 vs placebo group nine [2%] of 450 grade 3 only) and haematological (neutropenia: nintedanib group 180 [20%] grade 3 and 200 (22%) grade 4 vs placebo group 90 [20%] grade 3 and 72 [16%] grade 4; thrombocytopenia: 105 [12%] and 55 [6%] vs 21 [5%] and eight [2%]; anaemia: 108 [12%] and 13 [1%] vs 26 [6%] and five [1%]). Serious adverse events were reported in 376 (42%) of 902 patients in the nintedanib group and 155 (34%) of 450 in the placebo group. 29 (3%) of 902 patients in the nintedanib group experienced serious adverse events associated with death compared with 16 (4%) of 450 in the placebo group, including 12 (1%) in the nintedanib group and six (1%) in the placebo group with a malignant neoplasm progression classified as an adverse event by the investigator. Drug-related adverse events leading to death occurred in three patients in the nintedanib group (one without diagnosis of cause; one due to non-drug-related sepsis associated with drug--related diarrhoea and renal failure; and one due to peritonitis) and in one patient in the placebo group (cause unknown).

Interpretation: Nintedanib in combination with carboplatin and paclitaxel is an active first-line treatment that significantly increases progression-free survival for women with advanced ovarian cancer, but is associated with more gastrointestinal adverse events. Future studies should focus on improving patient selection and optimisation of tolerability.

Funding: Boehringer Ingelheim.

NÁDORY HLAVY A KRKU

Lakota J, Gocarova K, Spanik S

Treatment of metastatic head and neck cancer with mesenchymal stem cells combined with prodrug gene therapy.

Exp Oncol. 2015 Dec;37(4):298.

This is a clinical observation of a patient treated for metastatic head and neck cancer with mesenchymal stem cells mediated prodrug gene therapy. The cells were applied intravenously. We did not observe any therapeutic effect. However, a temporal bicytopenia was observed.

KARCINÓM PĽÚC

Jeremić B, Casas F, **Dubinsky P**, Gomez-Caamano A, Čihorić N, Videtic G.

Surgery for Stage IIIA Non-Small-cell Lung Cancer: Lack of Predictive and Prognostic Factors Identifying Any Subgroup of Patients Benefiting From It.

Clin Lung Cancer. 2015 Nov 11. pii: S1525-7304(15)00265-X

Although a trimodality regimen for patients with stage IIIA/pN2 non-small-cell lung cancer (NSCLC) has been variably used owing to limited evidence for its benefits, it remains unknown whether any patient subgroup actually receives benefit from such an approach. To explore this question, the published data were reviewed from 1990 to 2015 to identify the possible predictors and prognosticators in this setting. Overall survival was the endpoint of our study. Of 27 identified studies, none had studied the predictors of improved outcomes with trimodality treatment. Of the potential patient- and tumor-related prognosticators, age, gender, and histologic type were the most frequently formally explored. However, none of the 3 was found to influence overall survival. The most prominent finding of the present review was the substantial lack of data supporting a trimodality treatment approach in any patient subgroup. As demonstrated in completed prospective randomized studies, the use of surgery for stage IIIA NSCLC should be limited to well-defined clinical trials.