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KARCINÓM PRSNÍKA

Mego M, Giordano A, De Giorgi U, Masuda H, Hsu L, Giuliano M, Fouad TM, Dawood S,Ueno NT, Valero V, Andreopoulou E, Alvarez RH, Woodward WA, Hortobagyi GN,Cristofanilli M, Reuben JM.

Circulating tumor cells in newly diagnosed inflammatory breast cancer.

Breast Cancer Res. 2015 Jan 9;17(1):2.

Introduction: Circulating tumor cells (CTCs) are an independent prognostic factor for progression-free survival (PFS) and overall survival (OS) in patients with metastatic breast cancer. Inflammatory breast cancer (IBC) is one of the most aggressive forms of breast cancer. The prognostic value of a CTC count in newly diagnosed IBC has not been established. The aim of this study was to assess the prognostic value of a baseline CTC count in patients with newly diagnosed IBC.

Methods: This retrospective study included 147 patients with newly diagnosed IBC (77 with locally advanced and 70 with metastatic IBC) treated with neoadjuvant therapy or first-line chemotherapy during the period from January 2004 through December 2012 at The University of Texas MD Anderson Cancer Center. CTCs were detected and enumerated using the Cell Search system before patients were started with chemotherapy.

Results: The proportion of patients with 1 CTC was lower among patients with stage III than among patients with metastatic IBC (54.5% versus 84.3%; P=0.0002); the proportion of patients with 5 CTCs was also lower for stage III than for metastatic IBC (19.5% versus 47.1%; P=0.0004). Patients with <5 CTCs had significantly better progression-free survival (PFS) (hazard ratio [HR]=0.60; P=0.02) and overall survival (HR=0.59; P=0.03) than patients with 5 CTCs. Among patients with stage III IBC, there was non-significant difference in PFS (HR=0.66; 95% confidence ratio (CI), 0.31 to 1.39; P=0.29) and OS (HR=0.54; 95% CI, 0.24 to 1.26; P=0.48) in patients with no CTCs compared to patients with 1 CTCs. In multivariate analysis, CTC was prognostic for PFS and OS independently from clinical stage.

Conclusions: CTCs can be detected in a large proportion of patients with newly diagnosed IBC and are a strong predictor of worse prognosis in patients with newly diagnosed IBC.

Mego M

Emerging role of circulating tumor cells in cancer management. (Editorial)

Indian J Med Paediatr Oncol. 2014 Oct;35(4):237-8.

Circulating tumor cells (CTCs) play a crucial role in metastatic cascade, tumor dissemination and progression. CTCs represent a unique biomarker and are different from any of existing cancer biomarkers, as they represent a sampling of a patient's tumor. Prognostic value of CTCs was demonstrated in numerous clinical trials in primary and metastatic breast cancer patients. Several trials are ongoing aimed to demonstrate clinical utility of CTCs detection and profiling to facilitate rational treatment decisions for breast cancer patients.

SARKÓMY

Joensuu H, Rutkowski P, Nishida T, Steigen SE, Brabec P, **Plank L**, Nilsson B, Braconi C, Bordoni A, Magnusson MK, **Sufliarsky J**, Federico M, Jonasson JG, Hostein I, Bringuier PP, Emile JF.

KIT and PDGFRA Mutations and the Risk of GI Stromal Tumor Recurrence.

J Clin Oncol. 2015 Feb 20;33(6):634-642.

Purpose: Mutated KIT and platelet-derived growth factor alpha gene (PDGFRA) drive GI stromal tumor (GIST) oncogenesis, but th clinical significance of their single mutations is known incompletely.

Patients and methods: We identified 11 population-based series of patients with GIST through a literature search and pooled individual data from 3,067 patients treated with macroscopically complete tumor excision. Mutation analysis was done from 1,505 tumors. We analyzed associations between KIT and PDGFRA mutations and recurrence-free survival (RFS) in the subsets in which patients were treated with surgery alone.

Results: We identified 301 different single mutations in KIT and 33 in PDGFRA. Patients with PDGFRA mutations had more favorable RFS than those with KIT mutations (hazard ratio, 0.34; P=.004). Only one of the 35 GISTs with KIT exon 11 duplication mutations recurred. Patients with deletions of only one codon of KIT exon 11 had better RFS than those with another deletion type, and some KIT exon 11 substitution mutations (Trp557Arg, Val559Ala, and Leu576Pro) were also associated with favorable RFS. Patients with an identical mutation had greatly variable outcomes depending on the standard prognostic factors, notably, mitotic count. Commonly used risk stratification schemes tended to overestimate the risk for recurrence in subgroups with prognostically favorable mutations.

Conclusion: GISTs with an identical KIT or PDGFRA mutation may have widely varying risks for recurrence. Most of the patients with PDGFRA mutations and hose with KIT exon 11 duplication mutation or deletion of one codon have favorable RFS with surgery alone and are usually not candidates for adjuvant therapy.

GENITOURINÁRNE MALIGNITY

Vrdoljak E, Géczi L, **Mardiak J**, Ciuleanu TE, Leyman S, Zhang K, **Sajben P**, Torday L.

Central and Eastern European Experience with Sunitinib in Metastatic Renal Cell Carcinoma: A Sub-analysis of the Global Expanded-Access Trial.

Pathol Oncol Res. 2015 Jan 4. [Epub ahead of print]

A global, open-label, expanded-access trial (EAT) provided sunitinib treatment on a compassionate-use basis to patients with metastatic renal cell carcinoma (mRCC) between 2005 and 2011. This retrospective analysis examines outcomes in patients from Central and East European (CEE) countries participating in the global EAT. Sunitinib (starting dose 50 mg orally once daily, with dose reduction for toxicity) was administered in repeated 6-week cycles (4 weeks on and 2 weeks off) until occurrence of disease progression or unacceptable to-

xicity. Tumor assessments were guided by Response Evaluation Criteria in Solid Tumors (RECIST) criteria but were performed according to local standards of care. In total, 401 CEE patients received sunitinib (median treatment duration 9.6 months), of whom 378 were evaluable for tumor response. The most frequent grade ≥3 toxicities were fatigue (7.5%), hypertension (7.0%), thrombocytopenia (6.5%), diarrhea (4.2%), nausea and hand-foot syndrome (both 3.7%) and neutropenia (3.0 %). Median overall survival was 30.7 months (95% CI 23.3, – months). Overall survival tended to be longer in cytokine-naïve than cytokine-experienced patients (median 60.8 vs. 27.5 months; P=0.1324). Among patients with evaluable tumors, 4.0% achieved a complete and 14.6% a partial response [objective response rate (ORR) 18.5% (95% CI 14.7, 22.8%)]. Median progression-free survival was 11.6 months (95% CI 10.3, 12.8 months). Sunitinib demonstrates safety and effectiveness in real-world mRCC patients in CEE countries. Expanded-access program patients showed a lower tumor response rate but similar survival outcomes to patients in the pivotal Phase III clinical trial of sunitinib in mRCC.

Fizazi K, Pagliaro L, Laplanche A, Fléchon A, **Mardiak J**, Geoffrois L, Kerbrat P, Chevreau C, Delva R, Rolland F, Theodore C, Roubaud G, Gravis G, Eymard JC, Malhaire JP, Linassier C, Habibian M, Martin AL, Journeau F, **Reckova M**, Logothetis C, Culine S.

Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): a phase 3, multicentre, randomised trial.

Lancet Oncol. 2014 Dec;15(13):1442-50.

Background: Poor prognosis germ-cell tumours are only cured in about half of patients. We aimed to assess whether treatment intensification based on an early tumour marker decline will improve progression-free survival for patients with germ-cell tumours.

Methods: In this phase 3, multicentre, randomised trial, patients were enrolled from France (20 centres), USA (one centre), and Slovakia (one centre). Patients were eligible if they were older than 16 years, had evidence of testicular, retroperitoneal, or mediastinal non-seminomatous germ cell tumours based on histological findings or clinical evidence and highly elevated serum human chorionic gonadotropin or alfa-fetoprotein concentrations that matched International Germ Cell Cancer Consensus Group poor prognosis criteria. After one cycle of BEP (intravenous cisplatin [20 mg/m(2) per day for 5 days], etoposide [100 mg/m(2) per day for 5 days], and intramuscular or intravenous bleomycin [30 mg per day on days 1, 8, and 15]), patients' human chorionic gonadotropin and alfa-fetoprotein concentrations were measured at day 18-21. Patients with a favourable decline in human chorionic gonadotropin and alfa-fetoprotein continued BEP (Fav-BEP group) for 3 additonal cycles, whereas patients with an unfavourable decline were randomly assigned (1:1) to receive either BEP (Unfav-BEP group) or a dose-dense regimen (Unfav-dose-dense group), consisting of intravenous paclitaxel (175 mg/m(2) over 3 h on day 1) before BEP plus intravenous oxaliplatin (130 mg/m(2) over 3 h on day 10; two cycles), followed by intravenous cisplatin (100 mg/m(2) over 2 h on day 1), intravenous ifosfamide (2 g/m(2) over 3 h on days 10, 12, and 14), plus mesna (500 mg/m(2) at 0, 3, 7 and 11 h), and bleomycin (25 units per day, by continuous infusion for 5 days on days 10-14; two cycles), with granulocyte-colony stimulating factor (lenograstim) support. Centrally blocked computer-generated randomisation stratified by centre was used. The primary endpoint was progression-free survival and the efficacy analysis was done in the intention-to-treat population. The planned trial accrual was completed in May, 2012, and follow-up is ongoing. This study is registered with ClinicalTrials.gov, number NCT00104676.

Findings: Between Nov 28, 2003, and May 16, 2012, 263 patients were enrolled and 254 were available for tumour marker assessment. Of these 51 (20%) had a favourable marker assessment, and 203 (80%) had an unfavourable tumour marker decline; 105 were randomly assigned to the Unfav-dose-dense group and 98 to the Unfav-BEP group. 3-year progression-free survival was 59% (95% CI 49-68) in the Unfav-dose-dense group versus 48% (38-59) in the Unfav-BEP group (HR 0.66, 95% CI 0.44-1.00, P=0.05). 3-year progression-free survival was 70% (95% CI 57-81) in the Fav-BEP group (HR 0.66, 95% CI 0.49-0.88, P=0.01 for progression-free survival compared with the Unfav-BEP group). More grade 3-4 neurotoxic events (seven [7%] vs one [1%]) and haematotoxic events occurred in the Unfav-dose-dense group compared with in the Unfav-BEP group; there was no difference in grade 1-2 febrile neutropenia (18 [17%] vs 18 [18%]) or toxic deaths (one [1%] in both groups). Salvage high-dose chemotherapy plus a stem-cell transplant was required in six (6%) patients in the Unfav-dose-dense group and 16 (16%) in the Unfav-BEP group.

Interpretation: Personalised treatment with chemotherapy intensification reduces the risk of progression or death in patients with poor prognosis germ-cell tumours and an unfavourable tumour marker decline.

Jäger D, Ma JH, **Mardiak J**, Ye DW, Korbenfeld E, **Zemanova M**, Ahn H, Guo J, Leonhartsberger N, Stauch K, Böckenhoff A, Yu J, Escudier B.

Sorafenib Treatment of Advanced Renal Cell Carcinoma Patients in Daily Practice: The Large International PREDICT Study.

Clin Genitourin Cancer. 2014 Aug 23.

Background: Patients with advanced renal cell carcinoma in routine clinical practice can differ considerably from those in phase III studies.

Patients and methods: Predict (Patient characteristics in REnal cell carcinoma and Daily practICe Treatment with sorafenib) was a prospective, noninterventional study of open-label sorafenib for the treatment of advanced RCC conducted in 18 countries. Patient characteristics, therapy duration, tumor status, and tolerability were assessed at baseline and during routine follow-up.

Results: Overall, 2599 patients were evaluable for safety and 2311 for efficacy. The diverse population included patients with brain metastases (5%), non-clear-cell histologies (17%), high Memorial Sloan-Kettering Cancer Center risk score (11%), poor Eastern Cooperative Oncology Group performance status (PS ≥ 2, 29%), and patients with no previous nephrectomy (16%) or no previous systemic therapy (37%). The median duration of sorafenib therapy was 7.3 months and was similar in clinically relevant subgroups (eg, patients with PS 2, brain metastases, or concomitant hypertension or diabetes [range, 6.7-7.0 months]). The median duration of therapy was shorter for patients with PS 3 or non-clear-cell histologies (4.6 and 4.8 months, respectively). The most common drug-related adverse events were hand-foot skin reaction (20%), diarrhea (17%), and rash (8%).

Conclusion: Sorafenib was generally well tolerated and provided clinical benefit in a large, diverse population of patients with advanced RCC treated in routine clinical practice.

Oldenburg J, Aparicio J, Beyer J, Cohn-Cedermark G, Cullen M, Gilligan T, De Giorgi U, De Santis M, de Wit R, Fosså SD, Germà-Lluch JR, Gillessen S, Haugnes HS, Honecker F, Horwich A, Lorch A, **Ondrus D**, Rosti G, Stephenson AJ, Tandstad T; On behalf of: SWENOTECA (Swedish Norwegian Testicular Cancer group), the Italian Germ Cell Cancer Group (IGG), Spanish Germ Cell Cancer Group (SGCCG).

Personalizing, not patronizing: the case for patient autonomy by unbiased presentation of management options in stage I testicular cancer.

Ann Oncol. 2014 Nov 6. pii: mdu514. [Epub ahead of print]

Testicular cancer (TC) is the most common neoplasm in males aged 15-40 years. The majority of patients have no evidence of metastases at diagnosis and thus have clinical stage I (CSI) disease

[Oldenburg J, Fossa SD, Nuver J et al. Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24(Suppl 6): vi125--vi132; de Wit R, Fizazi K. Controversies in the management of clinical stage I testis cancer. J Clin Oncol 2006; 24: 5482-5492.]. Management of CSI TC is controversial and options include surveillance and active treatment. Different forms of adjuvant therapy exist, including either one or two cycles of carboplatin chemotherapy or radiotherapy for seminoma and either one or two cycles of cisplatin-based chemotherapy or retroperitoneal lymph node dissection for non-seminoma. Long-term disease-specific survival is 99% with any of these approaches, including surveillance. While surveillance allows most patients to avoid additional treatment, adjuvant therapy markedly lowers the relapse rate. Weighing the net benefits of surveillance against those of adjuvant treatment depends on prioritizing competing aims such as avoiding unnecessary treatment, avoiding more burdensome treatment with salvage chemotherapy and minimizing the anxiety, stress and life disruption associated with relapse. Unbiased information about the advantages and disadvantages of surveillance and adjuvant treatment is a prerequisite for informed consent by the patient. In a clinical scenario like CSI TC, where different disease-management options produce indistinguishable long-term survival rates, patient values, priorities and preferences should be taken into account. In this review, we provide an overview about risk factors for relapse, potential benefits and harms of adjuvant chemotherapy and active surveillance and a rationale for involving patients in individualized decision making about their treatment rather than adopting a uniform recommendation for all.

PREDNÁŠKY A POSTERY ZO ZAHRANIČNÝCH KONFERENCIÍ

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Mego M, Gao H, Cohen EN, Anfossi S, Giordano A, Sanda T, Fouad TM, Woodward WA, Alvarez RH, Valero V, Ueno NT, Hortobagyi GN, Cristofanilli M, Reuben JM.

Circulating tumor cells (CTC) are associated with defects in innate and adaptive immunity in inflammatory breast cancer (IBC) patients.

San Antonio Breast Cancer Symposium, December 9-13, 2014, Cancer Research, Vol. 74, No. 24, Suppl. (2014), s. P4-01-04

KARCINÓM PĽÚC

Berzinec P, Kasan P, Plank L, Andrasina I, Godal R, Mazal J, Cipkova A, Denkova L, Chowaniecova G, Kuliskova I.

Crizotinib in metastatic ALK-positive lung cancer – results from clinical practice in Slovakia.

XIV Central European Lung Cancer Conference, 29.11. 02.12.2014, Transl Lung Cancer Res 2014;3(5):AB027.

Masarykova A, Scepanovic D, Povinec P, Bires P, Pobijakova M.

Use of 18 FDG PET/CT in the radiotherapy planning of lung cancer – our updated experiences.

XIV Central European Lung Cancer Conference, 29.11. - 02.12.2014, Vienna, Austria (poster)