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Onkológia (Bratisl.), 2011; roč. 6 (3): 310–312

KARCINÓM PRSNÍKA

Characterization of metastatic breast cancer patients with nondetectable circulating tumor cells.

Mego M, De Giorgi U, Dawood S, Wang X, Valero V, Andreopoulou E, Handy B, Ueno NT, Reuben JM, Cristofanilli M.

Int J Cancer. 2011 Jul 15; 129(2): 417-23.

Circulating tumor cells (CTC) are an independent prognostic factor in metastatic breast cancer patients (MBC). However, CTC are undetectable in one third of patients. The aim of this study was to assess the prognostic factors in MBC patients without detectable CTC. This retrospective study included 292 MBC patients evaluated between January 2004 and December 2007. CTC were enumerated before patients started a new line of treatment using the CellSearch™. Overall survival (OS) was calculated from the date of CTC measurement and estimated by the Kaplan-Meier product limit method. CTC were not detected in 35.96% patients, whereas 40.75% patients had CTC ≥ 5. Undetectable CTC status was positively correlated with presence of brain metastasis (OR: 6.17, 95%CI = 2.14-17.79; p = 0.001), and inversely correlated with bone metastasis (OR: 0.47; 95%CI = 0.27-0.80; p = 0.01). In multivariate analysis, hormone receptors, number of metastatic sites and lines of therapy were independent prognostic factors for OS in patients without detectable CTC. Patients without detectable CTC before starting of a new line of therapy comprise a heterogeneous group with substantially different prognosis. We showed that some important metastatic disease characteristics are predictive of undetectable CTC status in MBC.

Intrathecal administration of trastuzumab with cytarabine and methotrexate in breast cancer patients with leptomeningeal carcinomatosis.

Mego M, Sycova-Mila Z, Obertova J, Rajec J, Liskova S, Palacka P, Porsok S, Mardiak J.

Breast. 2011, 20: 478-480

HER2-positive status is associated with increased risk of central nervous system (CNS) metastases in breast cancer patients. Leptomeningeal carcinomatosis (LMC) represents a rare but disastrous manifestation of metastatic breast cancer (MBC) with limited treatment options and poor prognosis. Several case reports of iintrathecal (i.t.) trastuzumab in the treatment of LCM were published so far. Usually, i.t. trastuzumab was administered in monotherapy or in combination with metothrexate. Herein, we report for the first time two patients with metastatic breast cancer and leptomeningeal carcinomatosis treated by intrathecal methotrexate (15 mg total dose) and cytarabine (24 mg total dose) with escalating dose of trastuzumab. We observed that up to 100 mg of trastuzumab can be safely administered intratecally with i.t. metothrexate and cytarabine. Both patients achieved good control of leptomeningeal disease for 13.5 and 6 months without significant toxicity. We suggest that i.t. trastuzumab with cytarabine and metothrexate is associated with promising benefit and warrant further investigation.

Primary breast cancer patients with high risk clinicopathologic features have high percentages of bone marrow epithelial cells with ALDH activity and CD44(+) CD24(lo) cancer stem cell phenotype.

Reuben JM, Lee BN, Gao H, Cohen EN, **Mego M**, Giordano A, Wang X, Lodhi A, Krishnamurthy S, Hortobagyi GN, Cristofanilli M, Lucci A, Woodward WA.

Eur J Cancer. 2011 Jul; 47(10): 1527-36.

BACKGROUND: Cancer stem cells (CSCs) are purported to be epithelial tumour cells expressing CD44(+)CD24(lo) that exhibit aldehyde dehydrogenase activity (Aldefluor(+)). We hypothesised that if CSCs are responsible for tumour dissemination, disseminated cells in the bone marrow (BM) would be positive for putative breast CSC markers. Therefore, we assessed the presence of Aldefluor(+) epithelial (CD326(+)CD45(dim)) cells for the presence of the CD44(+)CD24(lo) phenotype in BM of patients with primary breast cancer (PBC). METHODS: BM aspirates were collected at the time of surgery from 66 patients with PBC. Thirty patients received neoadjuvant chemotherapy (NACT) prior to aspiration. BM was analysed for Aldefluor(+) epithelial cells with or without CD44(+)CD24(lo) expression by flow cytometry. BM aspirates from three healthy donors (HD) were subjected to identical processing and analyses and served as controls.

RESULTS: Patients with triple-receptor-negative (TN) tumours had a significantly higher median percentage of CD44(+)CD24(lo) CSC within Aldefluor(+) epithelial cell population than patients with other immunohistochemical subtypes (P=0.018). Patients with TN tumours or with pN2 or higher pathologic nodal status were more likely to have a proportion of CD44(+)CD24(lo) CSC within Aldefluor(+) epithelial cell population above the highest level of HD. Furthermore, patients who received NACT were more likely to have percentages of Aldefluor(+) epithelial cells than the highest level of HD (P=0.004). CONCLUSION: The percentage of CD44(+)CD24(lo) CSC in the BM is higher in PBC patients with high risk tumour features. The selection or enrichment of Aldefluor(+) epithelial cells by NACT may represent an opportunity to target these cells with novel therapies.

Combination therapy of lapatinib and Capecitabine for ErbB2-positive metastatic or locally advanced breast cancer: results from the Lapatinib Expanded Access Program (LEAP) in Central and Eastern Europe.

Greil R, Borštnar S, Petráková K, Marcou Y, Pikiel J, Wojtukiewicz MZ, **Koza I**, Steger GG, Linn M, Das Gupta A, Cwiertka K.

Onkologie. 2011; 34(5): 233-8.

BACKGROUND: The Lapatinib Expanded Access Program (LEAP) was initiated in 45 countries to provide lapatinib in combination with ca-

pecitabine to patients with ErbB2 (HER2)-positive breast cancer already treated with anthracyclines, taxanes and trastuzumab. We report the results from 12 Central and Eastern European countries. PATIENTS AND METHODS: By 30 September 2008, 293 patients were enrolled. Patients were monitored for serious adverse events (SAEs) and for any decrease in left ventricular ejection fraction (LVEF). Overall survival and progression-free survival were also assessed. RESULTS: Mean treatment duration was 30 weeks; 107 patients (36.5%) discontinued therapy during the study, mainly due to disease progression (n = 86; 29.4%). A total of 78 SAEs were reported from 47 patients; the most frequently reported was diarrhoea (13 reports). Treatment had a relatively small effect on LVEF. Decreases were minor (0 to < 20%) in 61% of patients at the end of the study. During the study, 3 patients had decreased LVEF meeting the definition of an SAE; these events all resolved. Median overall and median progression-free survival were 37.6 and 21.1 weeks, respectively. CONCLUSIONS: Heavily pretreated patients with ErbB2-positive locally advanced or metastatic breast cancer may benefit from treatment with lapatinib and capecitabine, with a low risk of cardiac toxicity.

First-line bevacizumab plus taxane-based chemotherapy for locally recurrent or metastatic breast cancer: safety and efficacy in an open-label study in 2,251 patients.

Smith IE, Pierga JY, Biganzoli L, Cortés-Funes H, Thomssen C, Pivot X, Fabi A, Xu B, Stroyakovskiy D, Franke FA, Kaufman B, Mainwaring P, Pienkowski T, De Valk B, Kwong A, González-Trujillo JL, **Kozal I,** Petrakova K, Pereira D, Pritchard KI; ATHENA Study Group.

Ann Oncol. 2011 Mar; 22(3): 595-602.

BACKGROUND: First-line bevacizumab combined with chemotherapy significantly improves efficacy versus chemotherapy alone in human epidermal growth factor receptor 2 (HER2)-negative locally recurrent or metastatic breast cancer (LR/mBC). This large, open-label study further assesses first-line bevacizumab with taxane-based chemotherapy in routine oncology practice. PATIENTS AND METHODS: Patients with HER2-negative LR/mBC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of zero to two and no prior chemotherapy for LR/mBC received bevacizumab 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks plus taxane-based chemotherapy (or other non-anthracycline chemotherapy) until disease progression, unacceptable toxicity or patient withdrawal. The primary end point was safety; time to progression (TtP) was a secondary end point. RESULTS: Median follow-up in 2251 treated patients was 12.7 months. Median age was 53 years and 94% of patients had ECOG PS of zero or one. Bevacizumab was most commonly administered with single-agent paclitaxel (35%), single-agent docetaxel (33%) or taxane-based combination therapy (10%). The most frequent grade ≥3 adverse event (AE) was neutropenia (5.4%). Grade ≥3 AEs previously associated with bevacizumab included hypertension (4.4%), arterial/venous thromboembolism (3.2%), proteinuria (1.7%) and bleeding (1.4%). No new bevacizumab safety signals were observed. Median TtP was 9.5 months (95% confidence interval 9.1-9.9). CONCLUSIONS: The study population in ATHENA was more representative of general oncology practice than populations enrolled into randomised trials, although there may have been some bias towards younger, fitter patients. The safety and efficacy of bevacizumab-taxane therapy in this large study were consistent with results from randomised first-line trials.

KARCINOM PĽÚC

Rapid and Efficient Detection of EGFR Mutations in Problematic Cytologic Specimens by High-Resolution Melting Analysis.

Hlinkova K, Babál P, **Berzinec P**, Majer I, Ilencikova D.

Mol Diagn Ther. 2011 Feb 1; 15(1): 21-9.

Background and Objective: Chemotherapy for advanced non-small-cell lung cancer (NSCLC) remains marginally effective, with a 5-year overall survival rate of approximately 5%. Recently, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib was approved in Slovakia for the treatment of metastatic NSCLC. Gefitinib is a selective EGFR inhibitor that binds to the adenosine triphosphate binding pocket of the kinase domain and blocks downstream signaling pathways. Mutations of the EGFR gene, particularly an in-frame 15 bp deletion (delE746_A750) in exon 19 and the L858R mutation in exon 21, correlate with enhanced clinical responsiveness to EGFR tyrosine kinase inhibitors. However, the detection of these mutations and thereby prediction of the therapy outcome is sometimes unreliable due to the low sensitivity of direct sequencing if the proportion of tumor cells in the tissue is less than 25%. Therefore we decided to test the applicability of other methods, particularly high-resolution melting analysis (HRMA), for detection of these mutations in clinical samples. Methods: We analyzed 53 archival cytologic specimens for the presence of EGFR mutations, using the HRMA method. Results were verified by direct sequencing. For samples containing less than 25% tumor cells, we used mutant-enriched PCR before sequencing. We also performed a titration assay to establish the lower limit of the proportion of tumor cells for detection of EGFR mutations. Results: EGFR mutations were detected in 13 cases (24%). In-frame deletions in exon 19 were detected in eight cases (15%) and the L858R mutation in exon 21 was detected in five cases (9%). The positive results of the HRMA were confirmed by direct sequencing only in five of 13 cases. In the remaining eight positive samples, HRMA results were confirmed by sequencing analysis after mutant-DNA enrichment. The titration assay established that the lower limit for detection of EGFR mutations by HMRA was 1% tumor cells in the clinical sample. Conclusion: Our results indicated that HRMA in combination with mutant-enriched PCR represents a sensitive method for detection of EGFR mutations from cytologic specimens. When properly executed, this protocol allows identification of EGFR mutations in specimens containing a minimal percentage of tumor cells.

Cancer epidemiology in Central, South and Eastern European countries.

Vrdoljak E, Wojtukiewicz MZ, Pienkowski T, Bodoky G, **Berzinec P**, Finek J, Todorovic V, Borojevic N, Croitoru A.

Croat Med J. 2011 Aug 15; 52(4): 478-87.

Aim. To collect cancer epidemiology data in South Eastern European countries as a basis for potential comparison of their performance in cancer care. Methods. The South Eastern European Research Oncology Group (SEEROG) collected and analyzed epidemiological data on incidence and mortality that reflect cancer management in 8 countries - Croatia, Czech Republic, Hungary, Romania, Poland, Slovakia, and Serbia and Montenegro in the last 20-40 years. Results. The most common cancer type in men in all countries was lung cancer, followed by colorectal and prostate cancer, with the exception of the Czech Republic, where prostate cancer and colorectal cancer were more common. The most frequent cancer in women was breast cancer followed by colorectal cancer, with the exceptions of Romania and Central Serbia where cervical cancer was the second most common. Cancer mortality data from the last 20-40 years revealed two different patterns in men. In Romania and in Serbia and Montenegro, there was a trend toward an increase, while in the other countries mortality was declining, after increasing for a number of years. In women, a steady decline was observed over many years in the Czech Republic, Hungary, and Slovakia, while in the other countries it remained unchanged.

Conclusions. There are striking variations in the risk of different cancers by geographic area. Most of the international variation is due to exposure to known or suspected risk factors which provides a clear challenge to prevention. There are some differences in incidence and mortality that cannot be explained by exposure to known risk factors or treatment availabilities.

GENITOURINÁRNE MALIGNITY

Can a cure be achieved with taxane-based chemotherapy plus surgery in patients with primary mediastinal non-seminomatous germ cell tumors and progression or relapse despite first-line chemotherapy?

Miskovska V, Levy A, Massard CC, Gross-Goupil M, Bossi A, Fizazi K.

Onkologie. 2010; 33(3): 119-20.

Primary mediastinal non-seminomatous germ cell tumors (NSCGTs) have a poor prognosis in the International Germ Cell Cancer Collaborative Group (IGCCCG)classification. There is no clear standard of treatment at relapse. Between 1995 and 2005, 13 patients experienced progression or relapse, and 1 patient was cured with a taxane-based chemotherapy plus surgical resection at our institution.

Trends in prostate cancer incidence and mortality before and after the introduction of PSA testing in the Slovak and Czech Republics.

Ondrusova M, **Ondrus D**, Karabinos J, Muzik J, Kliment J, Gulis G.

Tumori. 2011 Mar-Apr; 97(2): 149-55

Aims and background. As two neighboring countries in central Europe with national cancer registries, the Slovak (SR) and Czech Republics (CR) are countries with a medium global rate in the occurrence of prostate cancer. This paper analyzes the incidence of prostate cancer and mortality before and after the introduction of PSA testing in the two Republics and the possible reasons for any differences discovered and compares the results with selected regions and countries of the world. Study design and results. In the Slovak Republic, prostate cancer incidence (age-adjusted to the world standard population) has risen from 14.6/100,000 in 1968 (95% CI, ±1.5772) to 36.2/100,000 in 2005 (95% CI, ±2.0678). The estimated annual increase in the incidence during the period 1968-1991 (before nationwide PSA testing) was 0.421; from 1991 (when nationwide PSA testing began) to up to 2003 it was 0.941. Mortality rates grew from 7.3/100,000 in 1968 to 14.9/100,000 in 2005. In spite of the geographic proximity of the two countries, the increase in incidence occurred faster in the Czech than in the Slovak Republic, from 15.8/100,000 in 1977 (95% CI, ±0.9748) to 59.5/100,000 in 2005 (95% CI, ±1.7187). The estimated annual increase in incidence in the Czech Republic for the period of 1977-1991 was 0.581. From 1991 (when national PSA testing began) until 2003, it was 1.981. In the period before 1991, mortality rose more sharply in the Czech than in the Slovak Republic, whereas after the introduction of PSA testing mortality stabilized more quickly in the Czech than in the Slovak Republic. In the Slovak Republic, a significant reduction in mortality was observed after 2002 and has continued to the present and probably is not affected only by the results connected with the increase in PSA testing. Conclusions. The difference in the incidence and mortality of prostate cancer in the Slovak and the Czech Republics results from a difference in the intensity of PSA testing as well as from the introduction of complex, more effective treatment in advanced clinical stages.

Tubulocystic renal carcinoma: a clinical perspective.

Hora M, Urge T, Eret V, Stránský P, Klečka J, Kreuzberg B, Ferda J, Hyršl L, Breza J, Holečková P, **Mego M**, Michal M, Petersson F, Hes O.

World J Urol. 2011 Jun; 29(3): 349-54.

INTRODUCTION: Tubulocystic renal carcinoma (TCRC) is a recently described neoplastic entity. To date, clinicopathological features on less than hundred cases of these rare tumours have been characterized exclusively in the pathological literature. Herein, we present five additional cases emphasizing clinical aspects on these rare renal neoplasms. MATERIAL AND METHOD: Cases diagnosed as TCRC were retrieved and reviewed from the routine and consultation files of the Pilsen tumour registry comprising over 20,000 cases of renal tumours.

RESULTS: All patients were men, mean age 56 years (range 29-70). Features on computed tomography (CT) were in two cases Bosniak III, one IV and two were solid tumours. In four patients, nephrectomy was performed, and one patient underwent resection. At the time of surgery, two patients had metastases. In one case, both primary tumour and metastases were active on FDG positron emission tomography (PET)/CT. Both patients with metastatic disease were treated with sunitinib with partial response. One patient died 26 months postoperatively and the other patient is alive 5 months after surgery. Three patients with localized tumours are without evidence of disease 31, 28 and 7 months after surgery. In one case, the resected tumour was histologically combined with a papillary renal cell carcinoma (PRCC). CONCLUSION: TCRC occurs predominantly in men with a wide age range. TCRC frequently displays a cystic component which may render a radiological classification of Bosniak III or IV. FDG PET/CT is helpful in the detection of metastases. TCRC has definitive malignant potential. Our findings support a possible relationship to PRCC. The tyrosine kinase inhibitor sunitinib may be used a therapeutical agent with partial response and temporary effect.

GASTROINTESTINÁLNE MALIGNITY

Optimal therapeutic strategies for resectable oesophageal or oesophagogastric junction cancer.

Bystricky B, Okines AF, Cunningham D.

Drugs. 2011, 71: 541-555.

Oesophageal cancer is the eighth most common cancer diagnosed worldwide, with almost half a million new cases diagnosed each year. Despite improvements in surgical and radiotherapy techniques and refinements of chemotherapeutic regimens, long-term survival, even from localized oesophageal cancer, remains poor. Surgical resection alone remains the standard approach for very early stage disease (stage I), but whilst surgery remains fundamental to the treatment of stage II-III resectable adenocarcinoma, multimodality therapy with chemotherapy or chemoradiation (CRT) is internationally accepted as the standard of care. Data from two large, randomized phase III trials support the use of perioperative combination chemotherapy in lower oesophageal and oesophagogastric junction adenocarcinomas, but the contribution of the adjuvant therapy is uncertain. There are conflicting data from randomized studies of a purely neoadjuvant approach; however, recent meta-analyses have demonstrated that chemotherapy or CRT given prior to radical surgery improves survival in patients with adenocarcinoma of the oesophagus. Neoadjuvant CRT but not chemotherapy alone is also beneficial for patients with squamous cell carcinoma. Definitive CRT has emerged as a useful option for the treatment of resectable squamous cell carcinoma of the oesophagus, avoiding potential surgical morbidity and mortality for most patients, with salvage surgery reserved for those with persistent disease. In this review, we focus on the pharmacotherapy of resectable oesophageal and oesophagogastric junction cancers and how clinical trials and meta-analyses inform current clinical practice.