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The metastatic cascade is a series of biological processes that enable the movement of tumor cells from the primary site to a distant location and the establishment of a new cancer growth. Circulating tumor cells (CTCs) have a crucial role in tumor dissemination. The role of CTCs in treatment failure and disease progression can be explained by their relation to biological processes, including the epithelial-to-mesenchymal transition and ‘self seeding’, defined as reinfiltration of the primary tumor or established metastasis by more aggressive CTCs. CTCs are a unique and heterogeneous cell population with established prognostic and predictive value in certain clinical situations. The possibility of collecting sequential blood samples for real-time monitoring of systemic therapy efficacy presents new possibilities to evaluate targeted therapies based on the genomic profiling of CTCs and to improve the clinical management of patients by personalized therapy. Interruption of the metastatic cascade via the targeting of CTCs might be a promising therapeutic strategy.

MDR1 (C3435T) polymorphism: relation to the risk of breast cancer and therapeutic outcome

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P-glycoprotein (PGP), the product of the MDR1 gene, is a transmembrane active efflux pump for a variety of carcinogens and cytostatics. It has been suggested that MDR1 polymorphisms contribute to the variability in cancer risk and therapeutic outcome. We examined the relevance of C3435T polymorphism in relation to breast cancer susceptibility, clinical and pathological characteristics of breast carcinoma, the therapeutic response and hematologic toxicities after anthracycline-based chemotherapy. A significant association between allele frequencies and histological type, stage and histological grade was observed (P=0.024, 0.014, 0.006, respectively, chi(2)-test or Fisher’s exact test). We also found significantly higher (P=0.019, chi(2)-test) T allele frequency in breast cancer patients (n=221) than in controls (n=113). A significantly enhanced therapeutic outcome after neoadjuvant therapy (n=38, P=0.021, Fisher’s exact test) and longer time to progression after anthracycline-based chemotherapy (n=102, P=0.049, log-rank test) were observed in CC homozygotes. However, no significant association between hematologic toxicities and C3435T polymorphism was detectable.

18F-FDG PET/CT findings and circulating tumor cell counts in the monitoring of systemic therapies for bone metastases from breast cancer

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Our objective was to compare the predictive significance of (18)F-FDG PET/CT findings and circulating tumor cell (CTC) count in patients with bone metastases from breast cancer treated with standard systemic therapy. METHODS: Breast cancer patients with progressive bone-only metastatic disease without visceral metastases starting a new line of systemic therapy underwent (18)F-FDG PET/CT and had CTC counts determined before and during treatment. Disease status was reassessed by CTC count (> or = 5 vs. < 5 CTC/7.5 mL of blood) and (18)F-FDG PET/CT approximately 2-4 mo after initiation of the new systemic therapy.

RESULTS: CTC counts at follow-up agreed with the (18)F-FDG PET/CT assessment in 43 (78%) of the 55 evaluable patients. Of the 12 patients with discordant CTC and (18)F-FDG PET/CT results, 8 (66%) had > or = 5 CTCs, with no evidence of progressive disease at the time of the (18)F-FDG PET/CT study, whereas 4 (33%) had < 5 CTCs, with evidence of progressive disease by (18)F-FDG PET/CT. (18)F-FDG PET/CT findings and follow-up CTC counts were found to be significantly associated with both progression-free survival (P = 0.02 and P < 0.001, respectively) and overall survival (P = 0.02 and P = 0.01, respectively). In multivariate analysis, the (18)F-FDG PET/CT assessment remained as the only predictive factor for progression-free survival (P < 0.0001), whereas estrogen receptor status was the only predictive factor for overall survival (P = 0.01).

CONCLUSION: (18)F-FDG PET/CT is a useful tool for therapeutic monitoring in patients with bone metastases from breast cancer. Prospective studies are needed to define the role of (18)F-FDG PET/CT and CTC in the setting of response discordance to establish bone-dominant disease as a tumor-response measurable disease.
Concomitant docetaxel plus gemcitabine versus sequential docetaxel followed by gemcitabine in anthracycline-pretreated metastatic or locally recurrent inoperable breast cancer patients: a prospective multicentre trial of the Central European Cooperative Oncology Group (CECOG)  


Docetaxel (D) plus gemcitabine (G) is an active combination in anthracycline pre-treated breast cancer. Impact of sequential administration of these drugs is unclear. This trial aimed to compare concomitant DG with sequential D -> G. Patients were randomised to eight cycles of gemcitabine 1,000 mg/m² on days 1 + 8 plus docetaxel 75 mg/m² on day 8, or 4 cycles of docetaxel 100 mg/m² on day 1, followed by four cycles of gemcitabine 1,250 mg/m² on days 1 + 8, in a 21-day schedule. Time to progression (TTP) was defined as primary endpoint; secondary endpoints were overall response rate (ORR), response duration (RD), overall survival (OS) and toxicity. Due to poor recruitment, the trial was terminated after 100 of a pre-planned 430 patients. Patient characteristics were well balanced. No significant difference was observed in terms of TTP, ORR, RD and OS. Grade 3/4 adverse events encompassed leucopenia (29 vs 68%, P < 0.001), neutropenia (49 vs. 83%, P < 0.001) and febrile neutropenia (4 vs. 9%, n.s.), all favouring D -> G. No difference in efficacy was observed between concomitant and sequential treatment. D -> G produced significantly more episodes of haematological toxicity due to the administration of docetaxel at 100 mg/m² without GCSF support.

Circulating tumor cells and bone metastases as detected by FDG-PET/CT in patients with metastatic breast cancer.  


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BACKGROUND: We evaluated the relationship between the detection and prognostic significance of circulating tumor cells (CTCs) and sites of metastases detected by 2-[fluorine-18] fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) in patients with metastatic breast cancer (MBC).

PATIENTS AND METHODS: From May 2004 to January 2008, 195 patients with relapsed/progressive MBC underwent whole-body FDG-PET/CT and provided blood samples for assessment of CTC count. RESULTS: Higher CTC numbers were detected in patients with bone metastases relative to those with no bone lesions (mean 65.7 versus 3.3, P = 0.0122) and in patients with multiple bone metastases relative to those with one or two bone lesions (mean 77.7 versus 2.6, P < 0.001). CTCs predicted overall survival (OS) in 108 patients with multiple sites of metastases including bone (P = 0.0008) but not in 58 without bone metastases (P = 0.4111) and in 29 with bone involvement only (P = 0.3552). All 15 patients but one with human epidermal growth factor receptor 2 (HER-2) positive tumors who were treated with trastuzumab-based regimens had <5 CTCs at progression. In multivariate analysis, CTCs, but not bone metastases, remained a significant predictor of OS.

CONCLUSION: Presence of extensive bone metastases as detected by FDG-PET/CT is associated with increased CTC numbers in MBC.

GASTROINTESTINAL MALIGNITY

Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOG trial  


Systemic chemotherapy plays the major role in the management of patients with small cell lung cancer. Cisplatin plus etoposide is the most widely used regimen and is considered as standard in patients with limited disease. Cisplatin plus irinotecan improved survival compared to cisplatin plus etoposide in a Japanese trial but failed to do so in two trials in Caucasians. Cisplatin plus topotecan had similar efficacy compared to cisplatin plus etoposide in patients with extensive disease. In the second-line setting, topotecan showed similar efficacy but better tolerability compared to cyclophosphamide, doxorubicin plus vincristine. Oral topotecan was as efficacious as its intravenous formulation and was shown to improve survival compared to best supportive care alone in patients previously treated with chemotherapy. Thus topotecan is considered as the standard second-line chemotherapy in patients with small cell lung cancer.

Therapy of small cell lung cancer with emphasis on oral topotecan  


Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial

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PURPOSE Pazopanib is an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-KIT. This randomized, double-blind, placebo-controlled phase III study evaluated efficacy and safety of pazopanib monotherapy in treatment-naïve and cytokine-pretreated patients with advanced renal cell carcinoma (RCC).

PATIENTS AND METHODS Adult patients with measurable, locally advanced, and/or metastatic RCC were randomly assigned 2:1 to receive oral pazopanib or placebo. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival, tumor response rate (Response Evaluation Criteria in Solid Tumors), and safety. Radiographic assessments of tumors were independently reviewed. Results Of 435 patients enrolled, 233 were treatment naive (54%) and 202 were cytokine pretreated (46%).
PFS was significantly prolonged with pazopanib compared with placebo in the overall study population (median, PFS 9.2 v 4.2 months; hazard ratio [HR], 0.46; 95% CI, 0.34 to 0.62; P < .0001), the treatment-naïve subpopulation (median PFS 11.1 v 2.8 months; HR, 0.40; 95% CI, 0.27 to 0.60; P < .0001), and the cytokine-pretreated subpopulation (median PFS, 7.4 v 4.2 months; HR, 0.54; 95% CI, 0.35 to 0.84; P < .001). The objective response rate was 30% with pazopanib compared with 3% with placebo (P < .001). The median duration of response was longer than 1 year. The most common adverse events were diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting. There was no evidence of clinically important differences in quality of life for pazopanib versus placebo.

CONCLUSION Pazopanib demonstrated significant improvement in PFS and tumor response compared with placebo in treatment-naïve and cytokine-pretreated patients with advanced and/or metastatic RCC.

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BACKGROUND: In metastatic renal cell carcinoma combinations of interferon alfa-2a, interleukin-2, and fluorouracil produce higher response rates and longer progression-free survival than do single agents. We aimed to compare overall survival in patients receiving combination treatment or interferon alfa-2a. METHODS: RE04/30012 was an open-label randomised trial undertaken in 50 centres across eight countries. 1006 treatment-naïve patients diagnosed with advanced metastatic renal cell carcinoma were randomly allocated (1 to 1) by minimisation to receive interferon alfa-2a alone or combination therapy with interferon alfa-2a, interleukin-2, and fluorouracil. Treatment was not masked. The primary endpoint was overall survival. Treatment groups were compared with a non-stratified log-rank test. Analysis was by intention to treat. This study is registered, number ISRCTN 46518965.

FINDINGS: 502 patients were randomly assigned to receive interferon alfa-2a and 504 to receive combined treatment. Median follow-up was 37.2 months (24.8-52.3). Median overall survival was 18.8 months (170-23.2) for patients receiving interferon alfa-2a versus 18.6 months (16.5-20.6) for those receiving combination therapy. Overall survival did not differ between the two groups (hazard ratio 1.05 [95% CI 0.90-1.21], p=0.55; absolute difference 0.3% [-5.1 to 5.6] at 1 year and 2.7% [-8.2 to 2.9] at 3 years). Serious adverse events were reported in 113 (23%) patients receiving interferon alfa-2a and 131 (26%) of those receiving combined treatment. INTERPRETATION: Although combination therapy does not improve overall or progression-free survival compared with interferon alfa-2a alone, immunotherapy might still have a role because it can produce remissions that are of clinically relevant length in some patients. Identification of patients who will benefit from immunotherapy is crucial. FUNDING: UK Medical Research Council.
BCL2/IgH polymerase chain reaction status at the end of induction treatment is not predictive for progression-free survival in relapsed/resistant follicular lymphoma: results of a prospective randomized EORTC 20981 phase III intergroup study


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PURPOSE: The prognostic value of residual BCL2/immunoglobulin heavy chain (BCL2/IgH) -positive cells in peripheral blood (PB) or bone marrow (BM) after induction treatment in follicular lymphoma (FL) is still controversial. In a prospective randomized phase III intergroup trial of 465 patients with relapsed/resistant follicular lymphoma (FL), we showed that addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone induction results in increased overall and complete response rates, and that rituximab maintenance strongly improves median progression-free survival (PFS) as well as overall survival. Here, we studied whether BCL2/IgH major break point levels in PB/BM correlated with response rates/quality for the induction phase and PFS for the maintenance phase. PATIENTS AND METHODS: Samples were obtained before and after induction therapy and at the end of the 2 years maintenance/observation period. BCL2/IgH major break point-positive cells were quantified by genomic quantitative polymerase chain reaction in 792 samples from 238 patients. RESULTS: Pretreatment BCL2/IgH levels had no significant prognostic value for overall response or complete remission rates after induction treatment, but pretreatment positive BM results had an adverse prognostic value for PFS from first randomization (P = .023). Importantly, BCL2/IgH levels at the end of induction treatment had no prognostic value for PFS from second randomization. The highly significant improved PFS by rituximab maintenance was observed in both BCL2/IgH PB/BM-positive and -negative groups.

CONCLUSION: Postinduction BCL2/IgH major break point status in BM/PB is not useful for decisions on subsequent therapy for patients with relapsed/resistant FL.

Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin’s lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study


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PURPOSE: In 2006, we published the results of the European Organisation for Research and Treatment of Cancer phase III trial EORTC 20981 on the role of rituximab in remission induction and maintenance treatment of relapsed/resistant follicular lymphoma (FL). At that time, the median follow-up for the maintenance phase was 33 months. Now, we report the long-term outcome of maintenance treatment, with a median follow-up of 6 years. PATIENTS AND METHODS: Overall, 465 patients were randomly assigned to induction with either six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or rituximab plus CHOP (R-CHOP). Those in complete remission or partial remission after induction (n = 334) were randomly assigned to maintenance treatment with rituximab (375 mg/m² intravenously once every 3 months) or observation. RESULTS: Rituximab maintenance significantly improved progression-free survival (PFS) compared with observation (median, 3.7 years v 1.3 years; P < .001; hazard ratio [HR], 0.55), both after CHOP induction (P < .001; HR, 0.37) and R-CHOP (P = .003; HR, 0.69). The 5-year overall survival (OS) was 74% in the rituximab maintenance arm, and it was 64% in the observation arm (P = .07). After progression, a rituximab-containing salvage therapy was given to 59% of patients treated with CHOP followed by observation, compared with 26% after R-CHOP followed by rituximab maintenance. Rituximab maintenance was associated with a significant increase in grades 3 to 4 infections: 9.7% v 2.4% (P = .01). CONCLUSION: With long-term follow-up, we confirm the superior PFS with rituximab maintenance in relapsed/resistant FL. The improvement of OS did not reach statistical significance, possibly because of the unbalanced use of rituximab in post-protocol salvage treatment.

Identification of carbonic anhydrase I immunodominant epitopes recognized by specific autoantibodies which indicate an improved prognosis in patients with malignancy after autologous stem cell transplantation


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This work employs an epitope mapping of carbonic anhydrase I (CA), isoform I (CA I), for detection of the main immunodominant epitopes. Our interest has arisen from an observed spontaneous tumor regression in patients who developed an aplastic anemia type syndrome after a high-dose therapy with autologous stem cell transplantation and whose sera contained high titer of anti carbonic anhydrase (anti-CA) autoantibodies. There are many indications that the presence of these autoantibodies may provide significant survival benefit for the patients. Western blot analysis confirmed strong immunoreactivity of the patients’ sera with several CA isoforms and the CA I has been selected for our study as a highly abundant and widely distributed isoform. The applied analytical approach consists of specific fragmentation of CA I protein followed by immunospecific isolation of peptides reacting with immunospecific anti-CA I autoantibodies in patients in spontaneous remission. We improved the standard epitope mapping schema by incorporating the benefits of magnetic carriers and biomagnetic separation techniques. Mass spectrometry has been applied for detection and identification of epitopes and the acquired results were verified by bioinformatic tools. The candidate epitopes of CA I protein followed by immunospecific isolation of peptides reacting with polyclonal anti-CA I autoantibodies of patients in spontaneous remission. We improved the standard epitope mapping schema by incorporating the benefits of magnetic carriers and biomagnetic separation techniques.