3021 POSTER

The extent of psychological distress in patients with advanced lung cancer at the end of life

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Background: Psychological distress diminishes quality of life in patients with incurable malignancies. Although it has been stated that psychological distress increases towards death, it could also result from a patient's individual susceptibility. To study this hypothesis, the course of psychological distress in lung cancer patients who participated in the Dutch Bone Metastasis Study (DBMS) was investigated with regard to baseline characteristics.
Material and Methods: From March 1996 to September 1998, 1157 patients with painful bone metastases from solid tumours were randomised between single or multiple fraction radiotherapy in the DBMS. Equal effectiveness of both radiotherapy regimens for painful bone metastasis was assessed.
For this analysis, all patients with lung cancer were selected. At randomisation and during follow-up, patients filled out 13 weekly and thereafter monthly questionnaires. The Rotterdam Symptom Checklist psychological subscale of 7 items was used to assess psychological distress on a 4-point scale ranging from 1 = not at all, to 4 = very much for each item. The minimal sum score is 7 (no distress), the maximum sum score 28. A score $\geqslant$17 is valued as needing further psychological assessment. At randomisation, three risk groups for distress were identified: low risk LR (7−11), intermediate risk IR (12−16), and high risk HR (17−28). Psychological distress was analysed as a function of remaining lifetime in patients who died within the study period. The influence of baseline characteristics age, sex, time since primary diagnosis, performance score and pain score on psychological distress was investigated.
Results: Mean age of the 287 patients (47 female, 240 male) at randomisation was 66 years (SD 9.5), mean time since diagnosis was 9.6 (SD 18.1) months. Mean survival after randomisation was 4.6 months (SD 4.5).
At baseline, 46% was LR, 32% IR and 22% HR. In the HR group, mean psychological distress fluctuated with a considerable increase towards death. Both LR and IR groups showed an increase towards death, but stayed below threshold level.
HR patients had a mean performance score of 60, whereas IR and LR had a score of 70 (ns). Time since diagnosis was shorter in the IR group compared to HR and LR (5.9 vs. 10.8 vs. 13.3 months, p = 0.032).
Conclusion: Towards their death, lung cancer patients with bone metastases showed increasing psychological distress. Interventions should be provided to patients identified as high risk early on in their disease.

3022 POSTER

Neutropenia and hematologic sequelae in patients receiving casopitant-containing antiemetic therapy for cisplatin-based highly emetogenic chemotherapy

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Background: Casopitant, a novel neurokinin (NK)-1 receptor antagonist (RA) in development for prevention of chemotherapy-induced nausea and vomiting (CINV), is a mild to moderate CYP3A inhibitor. Data from 2 randomized double-blind HEC studies were analyzed to assess impact of casopitant coadministration on hematologic parameters.
Methods: Phase III study (n = 802): Patients received placebo, single-dose 150 mg oral (SDO) casopitant, or 3-day 90 mg IV/50 mg oral/50 mg oral casopitant plus standard antiemetic therapy. Phase II study (n = 488): Patients received placebo, 3-day oral casopitant (50, 100, or 150 mg) or aprepitant (125/80/80 mg), or SDO casopitant plus standard therapy. Adverse events (AEs) were reported for all cycles (maximum 4−6). Phase III study included comprehensive laboratory assessments at screening/day (d) 1, d 6 to 10, d 12 to 17 (cycle 1 [C1] only), and at the end of each cycle. The C1 d 12 to d 17 assessment around anticipated neutrophil nadir allowed more comprehensive assessment of hematologic effects than with previous NK-1 RAs.
Results: Integrated AE data from both studies showed no imbalance in incidence of grade 4 (G4) neutropenia with casopitant (any dose, 11%) vs controls (7%). In phase III, rates of G4 neutrophil count toxicities (NCTs) were higher in C1 with casopitant (control 10%; SDO 16%; 3-day IV/oral 17%). This seemed primarily due to increased incidence of G4 NCTs in patients treated with CYP3A-metabolized drugs vinorelbine or etoposide (34% each casopitant arm vs 18% control). Febrile neutropenia AEs were rare (2% all arms) in C1. In phase II, more patients in the combined casopitant arms (27%) who received vinorelbine (but not etoposide) had G4 NCTs vs control subjects (15%). Chemotherapy dose intensity, assessed in phase III, was similar across treatments in all cycles.
Conclusions: Casopitant in combination with cisplatin and certain CYP3A-metabolized chemotherapy led to an increase in G4 neutropenia; however, overall incidence remained within expectations for cisplatin doublets. The neutropenia was not associated with increased sequelae. Blinded treating physicians did not alter their practice of maintaining chemotherapy dose intensity when casopitant was administered.

3023 POSTER

Cardioprotective effect of telmisartan in cancer patients treated with epirubicin

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Background: We previously showed on 31 cancer patients (pts) that early cardiac abnormalities occurred at epirubicin (EPI) doses of 200 mg/m^2 and persisted throughout subsequent EPI doses and even up to 18 months. Early contractility impairment, i.e. Strain rate (SR) reduction was detected by tissue doppler imaging (TDI) associated with high levels of inflammatory/oxidative stress markers. R enin-angiotensin system activation has been suggested to play an important role in the pathogenesis of Anthracycline-induced cardiotoxicity.
Methods: A phase II placebo-controlled study was designed to investigate the possible role of Telmisartan (an antagonist of angiotensine II type I receptor) in preventing both early preclinical and late myocardial damage induced by EPI. The correlation with changes of biochemical/inflammatory markers was also assessed. Planned sample size was 100 pts (50 pts per arm). Inclusion criteria: 18–70 y, histologically confirmed cancer, previously untreated and candidates for an EPI-based regimen; LVEF = 55%; ECOG PS 0−2, no history of cardiac disease and previous mediastinal irradiation. Eligible pts were randomized to receive Telmisartan 40 mg (1 tablet)/day or placebo starting 1 week before EPI until 6 months after the end of EPI administration. TDI as well as inflammatory/oxidative stress markers were assessed at baseline, 24 hours and 7 days at EPI doses of 100, 200, 300, and 400 mg/m^2.
Results: At December 2008 we enrolled 27 pts (M/F: 7/20, mean$\pm$SD age 58$\pm$14 years): 14 Telmisartan and 13 placebo. 15 pts completed EPI treatment (8 Telmisartan and 7 placebo). A significant reduction of SR peak was observed at 200 mg/m^2 of EPI in the placebo arm. *Viceversa* no significant TDI changes occurred in the treatment arm. Proinflammatory cytokines did not change in both arms whilst reactive oxygen species increased significantly in the placebo arm.
Conclusions: The study is in progress.

3024 POSTER

Randomised phase III clinical trial of 5 different arms of treatment for patients with cancer-related anorexia/cachexia syndrome (CACS)

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Background: Cancer-related anorexia/cachexia syndrome (CACS) is a multifactorial syndrome characterized by tissue wasting, loss of body weight, particularly of lean body mass (LBM), metabolic alterations, fatigue, reduced performance status, very often accompanied by anorexia.
Patients and Methods: In April 2005 we started a phase III randomised study to establish the most effective and safest treatment of CACS addressing as primary endpoints: LBM, resting energy expenditure (REE), total daily physical activity, serum IL-6, TNF-a and fatigue. Fatigue has been evaluated by the Multidimensional Fatigue Symptom Inventory − Short Form (MFSI-SF). The sample size was 475 patients (pts). Eligibility criteria: hystologically confirmed tumors of any site; weight loss = 5% in the last 3 months and/or abnormal values of proinflammatory cytokines and oxidative stress parameters predictive of the onset of CACS; life expectancy >4 months, patients treated with either antineoplastic therapy or supportive care. All pts enrolled received as basic oral treatment:

poliphenols + alpha lipoic acid + carbocysteine + Vitamins ACE. Pts were then randomised to one of the following 5 arms: 1) Medroxyprogesterone Acetate (MPA)/Megestrol Acetate (MA); 2) Pharmaco-nutritional support containing EPA; 3) L-carnitine; 4) Thalidomide; 5) MPA/MA + Pharmaco-nutritional support + L-carnitine + Thalidomide. Treatment duration was 4 months. Interim analyses were planned after every 100 randomized pts.
Results. At February 2009, 332 pts were randomized and 290 were evaluable: M/F 170/120, mean age 62 yrs (range 30−84), 96% were stage IV. A first interim analysis on all 125 pts enrolled showed a significant worsening of LBM, REE and fatigue in arm 2 in comparison to the others and it was withdrawn from the study. A second interim analysis after the enrolment of 204 pts showed arm 1 significantly less effective than the others for primary efficacy endpoints: it was withdrawn from the study. Statistical analysis at January 2009 showed in all patients a significant improvement of LBM (by DEXA) and REE and a significant decrease of IL-6 in arm 5. As for fatigue a significant improvement in arm 5 has been observed. As for safety, the treatment was overall well tolerated and the patient compliance was good.
Conclusions. The results so far seem to suggest that the most effective treatment for cancer pts with CACS should be a combination regimen.
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3025 POSTER

Determinants of pain response in patients (pts) with skeletal metastases receiving zoledronic acid (ZOL)

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Background: The prompt and sustained analgesic effect of zoledronic acid (Zometa®) in pts with metastatic bone disease (MBD) is well documented. However, identifying patient specific determinants of individual pain response merits further study to tailor therapy.
Material and Methods: A prospective open-label multi-center trial studied pain response in pts with MBD receiving ZOL. Observation lasted 6 months, with pts evaluated at baseline and receiving 4 mg of ZOL intravenously every 3 or 4 weeks, with reassessments every 6 or 8 weeks, respectively, in a total of 4 visits. A post-hoc linear mixed-effects model analysis explored the predictive value of the following variables on the composite Brief Pain Inventory (BPI): gender, age, tumor type, performance status, mental quality-of-life (QoL) SF-36 questionnaire, analgesics use, prior bisphosphonate (BP) therapy, and baseline BPI score.
Results: In all, 309 pts (124 male, 185 female) could be analyzed out of 313 pts accrued across 46 centers. The median age was 67 years (range 21–89) and pts had breast- (42%), lung- (14%), or prostate cancer (13%), multiple myeloma (10%), or another malignancy (21%). Sixty-seven pts (22%) received prior BP therapy. Age, gender, performance status, and tumor type were not independent determinants of pain. In contrast, mental QoL, baseline pain scores, analgesics use, and prior BP use were significant predictors of pain response (all $p < 0.05$). The mean pain score decreased from 3.50 to 2.70 with 0.035 points per week (ppw) (95% CI 0.024 – 0.046; $p < 0.001$). Above average baseline pain scores and better baseline mental QoL resulted in higher pain reductions of 0.067 ppw (95% CI 0.052 – 0.083; $p < 0.001$) and 0.052 ppw (95% CI 0.036 – 0.068; $p < 0.001$), respectively. Pts requiring more analgesics or with prior BP use had lower decreases in pain scores of 0.021 ppw (95% CI 0.003 – 0.039; $p < 0.001$). Overall, analgesics use decreased non-significantly ($p = 0.09$), but mental QoL improved significantly ($p = 0.02$) while on study. A sensitivity analysis confirmed the results.
Conclusions: Pts with MBD receiving ZOL experience a significant decrease in pain, independent of analgesics use and prior BP treatment. Highest benefits were observed in pts with higher baseline pain scores and lower analgesics use, supporting the early use of ZOL. Intriguingly, these results emphasize the intricate relationship between pain and mental wellbeing.

3026 POSTER

Dutch observational study on anaemia management with epoetin alfa in daily oncology practice – interim analysis results on 1000 patients

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Background: This study is addressing the real-life situation of epoetin alfa (Eprex®) treatment (ET) in chemotherapy-induced anaemia (CIA) in the Netherlands between November 2005 and July 2009.
Material and Methods: Data of the first 1000 patients (pts) enrolled, out of 1928 pts planned, were analysed. Eligible pts were 18 years or older, received ET and chemotherapy (CT) or were about to receive CT within a week as treatment for a solid tumour, Multiple Myeloma and (non-) Hodgkin's Disease. Data on haemoglobin level (Hb), blood transfusions (BTx), CT, ET and treatment-emergent adverse events (TEAE) were collected. Response to ET was defined as either a $\geqslant$1 g/dl Hb rise within first 4 weeks ET or a $\geqslant$2 g/dl Hb rise after baseline or a maintenance of Hb within range 11–13 g/dl after 4 weeks ET onwards until end of study, independent of BTx within 28 days. Continuous data are presented as mean $\pm$ standard deviation.
Results: 47% male and 53% female. Average age is 63.2$\pm$11.0 years. Most pts had lung (47%), breast (15%) and gastro-enterological (10%) tumours. The majority of pts had metastases (58%), received platinum-based CT (65%) and had 3-weekly CT cycles (83%). Last available Hb at CT start was 12.0$\pm$1.6 g/dl. Nearly all pts started with 40.000 IU ET once-weekly (99.6%). Time between start CT and start ET was 38.7$\pm$39.0 days. ET started at an Hb of 10.5$\pm$1.1 g/dl, lasted 12.4$\pm$7.9 weeks and resulted in an Hb-rise of 0.5$\pm$1.6 g/dl after 28 days (28–35 days) ($p < 0.0001$) and 1.3$\pm$2.1 g/dl after 56 days (56–63 days) ($p < 0.0001$), independent of BTx within 28 days. Dose was increased for 87 pts (9%) and 17 pts had a subsequent dose decrease.
More than a quarter of the pts received BTx during ET (27%), of whom 52% received a BTx within the first 4 weeks ET. Response to ET was seen in 63% of pts.
Of all TEAE, investigators assumed 1% to be related to ET. A thrombovascular TEAE (TVE) occurred in 89 pts (9%), was assumed related to ET in 17 pts and lead to an ET stop in 10 pts. During study 110 pts died, the majority (66%) due to disease progression. Four pts died due to a TVE, i.e., cerebrovascular accident (3 pts) and pulmonary embolism (1 patient), all not related to ET.
Conclusion: On basis of these results, in Dutch daily practice ET seems to start according to published American and European guidelines for the treatment of chemotherapy-induced anaemia. In more than 60% of the pts this resulted in a BTx-independent response. No unexpected AE's were reported.

3027 POSTER

Actual or adjusted surface area which shall we choose?

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Background: Calculation of chemotherapeutic drugs doses was standardized to Body Surface Area, with the aim to produce optimum systemic drug level & minimize drug toxicity; it also can be very challenging in obese cancer patients. Obesity represents a condition of excessive adipose tissue with its currently accepted definition is defined as Body Mass Index >30 kg/m^2); it once believed that obese patients who received chemotherapy on their actual body weight would result in increased toxicity, secondary to distribution of lipid soluble drugs into the adipose tissue. By using Adjusted Body Weight it's assumed that cancer patients would receive a dose of a particular cytotoxic drug associated with an acceptable degree of toxicity without reducing its therapeutic effect. The aim of this study is considering the use of adjusted body weight for calculation of chemotherapeutic drugs doses and its impact on the disease free survival in obese female breast cancer patients.
Method: We compared disease free survival between two groups of female breast cancer patients receiving adjuvant chemotherapy, both groups received FEC 100 regimen (Epirubicin 100 mg/m^2, 5-FU 500 mg/m^2, Cyclophosphamide 500 mg/m^2) for 6 cycles in the period between 2000–2008. Group A: (149 patients) received their regimen based on their actual body weight calculation of body surface area [BSA (m^2) = vHt. (cm) $\cdot$ Wt. (kg)/3600]. Group B: (100 patients) received their regimen based on their adjusted body weight (Adjusted Body Weight = Ideal Body weight + 0.4(Actual Body Weight − Ideal Body Weight). Ideal Body Weight