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Percentage decrease in Haemoglobin values after chemotherapy and radiation therapy as a predictive response factor to Epoetin beta

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Summary: Erythropoietin receptor agonists (ERA) are effective in the treatment of cancer-related anaemia. Their use improves haemoglobin (Hb) levels, reduces needs for transfusion, and improves quality of life. However, predictive response factors to ERA are insufficiently studied.
Objective: To evaluate the predictive value of response of Epoetin beta, the percentage decrease of Hb due to chemotherapy (CT) and radiation therapy (RT) in patients with lung cancer (LC).
Material and Methods: From May 2004, 23 patients with LC treated with CT and RT, received 30,000 IU per week of Epoetin beta for symptomatic cancer-related anaemia. Thirteen patients received RT-CT (Carbo-Taxol) concomitantly with intentions to cure, 1 patient CT and RT after pneumonectomy and 9 cases underwent diverse regimens of CT for palliative purposes. In all these patients Hb levels were measured at successive points: before oncological treatment (Vo), on initiating treatment with Epoetin beta (V1) and after 4 (V2) and 8 (V3) weeks. Response to treatment was considered as an increase of at least 1 gr/dL in Hb levels after 4 weeks. At the same time, the quality of life of patients was evaluated through questionnaires: Fatigue Symptom Inventory (FSI) and the ECOG scale.
Results: The mean levels of Hb at the successive points of measurement were V0: 12.7 g/dL; V1: 10.4 g/dL; V2: 12.3 g/dL, V3: 13.3 g/dL. The highest value of Hb in V0 and the greatest percentage reduction in Hb after treatment showed significant correlation ($p = 0.028$) after administration of Epoetin beta applying Pearson's test. Patients with concomitant CT-RT showed greater significance ($p < 0.001$). The discriminative point in the response to treatment was 10% in the reduction of Hb levels after CT-RT. Correlation between successive Hb values and scores on FSI and ECOG scales were highly significant. One patient required transfusion. No patient received Epoetin beta in doses of more than 30,000 IU per week.
Conclusions: In this group of patients with lung cancer, Hb levels before CT-RT and percentage decrease in Hb after treatment, are predictive of response o Epoetin beta. The relationship was more evident in the concomitant CT-RT group of patients treated for curative purposes. Variations between values of Hb are closely related to parameters of quality of life.

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Results of a prospective, randomised, placebo-controlled, triple-blind phase III multicenter study on the efficacy of proteolytic enzymes on radiation-induced oral mucositis

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Background: The present study was initiated to investigate the efficacy and safety of a proteolytic enzyme preparation (Wobe-Mugos®E) with regard to a reduction of oral mucositis during radiotherapy for head and neck tumours.
Materials and Methods: The study was designed as a prospective, randomised, multicenter, placebo-controlled, triple-blind phase III study with parallel groups. Sixty-nine patients with carcinomas of the oropharynx or the oral cavity were enrolled between 1996 and 2000 in 5 centers; 54 of these were recruited in Dresden. Of the 69 patients 61 (Dresden: 46) were available for analysis. Radiotherapy protocols comprised conventional fractionation with 1.8−2.0 Gy/fraction, 5x/week to total doses of 60−66 Gy/6−7 weeks, or hyperfractionation with 2×1.2 Gy/day, 5x/week to a total dose of 72 Gy/6−7 weeks. Hyperfractionation was applied in 8/36 (22%) patients in the Wobe-Mugos®E group and in 11/33 (33%) patients in the placebo group. Tumours were mainly located at tonsils (20.5%), floor of the mouth (15.7%), or tongue (margin: 15.7%, base: 12.0%, body: 8.4%), and were well balanced between the groups. All patients received a dose >40 Gy to a significant area of oral mucosa, based on the tumour localisations. The proteolytic enzymes tested (Wobe-Mugos®E) comprised papain 100 mg, trypsin 40 mg, chymotrypsin 40 mg. Primary endpoint for confirmative analysis was the maximum grade of oral mucositis during radiotherapy according to a modified RTOG/EORTC classification. Scoring was done twice per week. Average mucositis scores over weeks 1 to 6 of radiotherapy served as a secondary endpoint.
Results: The enzyme preparation was well tolerated. With regard to maximum mucositis scores during radiotherapy, no statistically significant differences were found between the placebo and the verum group. For the average mucositis scores over weeks 1−6, a significant difference in favour of the placebo arm was found. The latter was based on an earlier onset of mucositis in the group receiving proteolytic enzymes as compared to placebo.
Conclusions: In the present, randomized study, no beneficial effect of treatment with proteolytic enzymes (Wobe-Mugos®E) on radiation-induced oral mucositis was observed. Enzyme treatment resulted in an earlier onset of mucositis.

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A prospective observation study of treatment of chemotherapy-induced anaemia with darbepoetin alfa every 3 weeks: the OASIS (Observational Aranesp® Survey to Investigate the q3w Schedule) study

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Introduction: Darbepoetin alfa (DA) can be administered 500μg every 3 weeks (Q3W) to treat chemotherapy-induced anemia (CIA), allowing synchronisation with Q3W chemotherapy (CTX). This study examines pattern of use of DA Q3W in daily practice in Belgium and Luxembourg, and adherence to erythropoiesis-stimulating agent (ESA) treatment guidelines.
Methods: OASIS was a nationwide, prospective observation study of DA use in 41 oncology centres between April 2005 and January 2006. Adult patients (pts) with non-myeloid malignancies receiving DA for CIA were included. Specific data, described below, were prospectively defined and collected. Pts were followed: begin when DA started, until 1 week after last DA dose, for a maximum of 16 weeks.
Results: 293 pts were included: mean age, 63 yrs (range 25−89); 51% men; mean weight, 68 kg. 263 pts had a solid tumor (NSCLC n = 91; breast cancer n = 64; and SCLC n = 32; others n = 76) and 30 had hematologic malignancies. 57% of pts had platinum (plat)-containing CTX (almost 63% lung cancer pts). 50.9% and 31.1% of pts had baseline Hb of 10−11 g/dL and 9−10 g/dL, respectively. DA was started with the first (21.8%), second (29.4%) and third (24.6%) courses of CTX; median number of administrations was 3. Use of iron supplementation was marginal (8.5% of pts). In an analysis correcting for transfusions (TFN) (disregarding Hb values 28 days after any TFN), the crude hematopoietic response rate was 53.8% in plat-treated pts versus 54.0% in non-plat treated pts. 72% of pts (both plat and non-plat) had Hb $\geqslant$11 g/dL. TFN rate was 26.6%, similar in plat or non-plat treated pts. 63.4% of pts experienced a very good to satisfactory improvement of anemia related symptoms. Most pts (69.6%) were treated in a Q3W CTX schedule (with mostly 6 cycles planned). The DA Q3W interval could be maintained in a 66.7% of pts. The most common reason for not respecting the Q3W DA interval was practical (mainly remain synchronized with CTX). There were no unexpected safety concerns, with only 7 adverse and 3 serious adverse events.
Conclusion: This prospective observation study confirms the phase 3 study efficacy and safety findings of Canon J et al. (2006) in a broader community setting. Adherence to guidelines was good, as ESA therapy was started at a Hb between 9 and 11 g/dL in more than 80% of pts. The synchronisation of Q3W CTX and DA therapy could be maintained in a 76% of pts.

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High dose palonosetron does not alter ECG parameters including QTc interval in healthy subjects: results of a dose-response, double blind, randomized, parallel E14 study of palonosetron vs. moxifloxacin or placebo

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Background: New chemical entities in several drug classes must demonstrate cardiac safety with particular attention to changes in ventricular repolarization assessed by the QTc interval duration (ICH E14). With 5HT3

receptor antagonists (RA), agents used for the prevention of chemotherapy-induced nausea and vomiting (CINV) and surgical procedures, questions about their effects on the QT interval were raised.
Materials and Methods: A clinical study in male and female volunteers was designed in order to evaluate the effect and any dose-response of palonosetron (Aloxi®, Onicit®) on the individually corrected QTc interval (QTcI), and to evaluate its safety and tolerability versus placebo. The active control agent, moxifloxacin, was used as a positive control.
A total of 230 subjects [about 46 per arm] were randomly assigned to placebo, oral moxifloxacin 400 mg, or intravenous (IV) palonosetron at 0.25 mg, 0.75 or 2.25 mg (9 times the approved dose in CINV) in a parallel fashion.
Time-matched analysis of the QTcI interval was the primary endpoint. All ECG intervals (HR, PR, QRS, QT, QTcB, QTcF) and morphology were also analyzed. All adverse events (AEs), reasons for withdrawal, physical examination and vital signs, body temperature and laboratory data were evaluated.
Results: See the table.

Mean change from baseline of QTcI (ms)

	Placebo	Palonosetron			Moxifloxacin
		0.25 mg	0.75 mg	2.25 mg	400 mg
Mean change at Day 1 vs baseline	−4.1	−3.6	−2.9	−1.5	+1.8

For all palonosetron doses mean change from baseline on Day 1 were considered to be not clinically significant. Mean changes form baseline for HR, PR and QRS, as well as QTc duration (using three correction formulae) and morphological changes, were also not clinically significant. All palonosetron dose levels were well tolerated with no serious AEs reported. There was no dose-response effect on AEs such as headache or constipation or on any laboratory parameter.
Conclusion: This validated Thorough ECG E14 study showed that the cardiac profile of palonosetron is the same as placebo. The results demonstrated no ECG or dose-response effects (including QTcI prolongation) of palonosetron, up to a 2.25 mg IV dose, a nine-fold safety margin.

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Management and symptoms' treatment of hospitalized cancer patients(pts) in a general hospital

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Objective: To determine if an accurate evaluation of symptoms makes supportive therapy better monitored improving doctor–patient communication.
Patients and Methods: 181 patients (median age 68 years old), with symptoms due to an advanced cancer, were evaluated and monitored every other day with:
VAS (visual analogue scale): for pain.
ESAS (Edmonton Symptom Assessment Scale): numerical scale ranging from 0−10; a symptom was considered severe if >7.
PAP score (Palliative Prognostic Score): to assess prognosis.
- Group A: life expectancy after 30 d >70%.
- Group B: expectancy after 30 d 30−70%.
- Group C: expectancy after 30 d <30%.

Results: Symptoms, evaluated through ESAS, have shown an improvement in 82% of admissions, no-change in 3%, and a worsening in 15%. Particularly there has been a significant pain's improvement in 59.9%, anorexia's in 58%, dyspnoea's in 49.3%, and asthnenia's improvement in 56.6% of admissions.
Conclusion: A multidimensional evaluation of cancer patients' symptom is crucial to target palliative treatment on patients' real needs and, to this purpose, standardized methods should be regularly used by oncologists working in General Hospital.

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Opioid use patterns, health care utilization and costs in metastatic cancer patients on chronic opioid therapy with constipation compared to patients without constipation

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Objective: 1. To compare opioid use patterns, related side effect rates in opioid-treated metastatic cancer patients with and without constipation. 2. To assess the impact of constipation among opioid users in utilization of health care services and related costs.
Methods: Retrospective insurance claims from the PharMetrics Integrated Outcomes Database were analyzed. Metastatic cancer was defined as ⩾1 ICD-9 code for cancer plus a secondary malignancy code within 6 months of initial cancer diagnosis. An index date was defined as the date of first opioid pharmacy claim between 1/1/99 and 12/31/05. Patients who had ⩾30 days of opioid use and continuous plan coverage for ⩾6 months pre- and ⩾12 months post-index date were included in this analysis. Outcomes were assessed over 12 months post-index date. Constipation was identified using ICD-9 code 564.0 in the follow-up period. Opioid use patterns were compared between opioid initiators with constipation and matched controls without constipation. Two-part semi-logarithmic regression models were used to assess the the impact of constipation on resource utilization and all-cause costs respectively, controlling for covariates.
Results: We identified 2,615 patients with evidence of opioid use, of whom 301 (11.5%) had constipation. Majority of the patients with constipation were female (60%) and ⩾45 years old (76%). Compared to controls, the constipation group had higher rates of concurrent use of ⩾2 opioids (50% vs 41%; $p = 0.018$), opioid switching (63% vs 49%; $p = 0.001$), and related side effects of nausea w/vomiting (41% vs 32%; $p = 0.028$) and urinary retention (9% vs 3%; $p = 0.004$). A higher percentage of patients in the constipation group had use of prescription laxatives (44% vs 15%; $p < 0.001$) and antiemetics (60% vs 50%; $p = 0.014$). Among all opioid users, patients with a constipation diagnosis were more likely to have an inpatient stay (OR: 2.103; $p < 0.001$), emergency care (OR: 2.654; $p < 0.001$), hospice care (OR:2.08; $p = 0.006$) and home health care services (OR = 1.455; $p = 0.003$). Constipation was also found to have a significant impact on outpatient costs ($p < 0.05$), ER costs ($p < 0.001$), inpatient costs ($p < 0.001$) and pharmacy costs ($p < 0.003$).
Conclusions: Opioid-treated metastatic cancer patients with constipation have higher rates of opioid switching, related side effects and are more likely to use hospice and home health care services potentially leading to higher all-cause health care costs than those without constipation.

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Final results of the validation of the PERFORM questionnaire, a new questionnaire to assess the patient perception of cancer-related fatigue

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Background: Fatigue is one of the most debilitating and common symptoms in cancer patients (pts). There are instruments available to measure the intensity, frequency and duration of cancer-related fatigue (CRF) but there are few scales to assess perceptions and beliefs about CRF. The purpose of this study is to validate the recently developed PERFORM Questionnaire (PQ) which attempts to fill this need.
Materials and Methods: An observational and longitudinal multi-centre study was carried out on a sample of cancer pts with CRF. Data were collected at enrollment and 3 months later. The PQ was administered, as well as the Functional Assessment of Cancer Therapy Fatigue Subscale (FACT-F) and Nottingham Health Profile (NHP) health measures, at both visits. Socio-demographic data, key clinical indicators, fatigue intensity (by means of a visual analogue scale) and self-rated stability for patient health status were also collected. Viability, reliability (internal consistency and test-retest) and validity were assessed for the PQ.
Results: A total of 437 pts were included in the study: 60.5% were women; mean age was 59.1 years, mean time since diagnosis was 2.21 years; 33.6% had breast cancer; 54.7% had metastatic disease, mean Karnofsky score was 80.9; and 29.1% had anaemia. Answering the PQ was moderately easy to very easy for 81% of pts and took less than 8 minutes to fill in for 57.3% of the sample. Overall and dimension internal consistencies were high (Cronbach alpha = 0.94, range: 0.80−0.90). Test-retest reliability for overall score (intra-class correlation coefficient = 0.83) and dimension scores (range: 0.76−0.84) were also good in pts without relevant changes in CRF intensity. The PQ had a stronger correlation with FACT ($r = 0.80$) than with NHP ($r = 0.70$), a moderate correlation with fatigue intensity ($r = 0.56$), and a lower correlation with Karnofsky score ($r = 0.30$). Pts with anemia showed a worse overall PQ score than pts without anemia (31.5 vs. 36.3; $p = 0.0006$). The overall PQ score showed good sensitivity to