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The development of a prediction index for patients at high risk of severe chemotherapy induced nausea and vomiting

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Background: Despite modern antiemetic therapy, 20% to 40% of cancer patients receiving chemotherapy fail to achieve complete control of emesis. Several risk factors for acute and delayed emesis have been identified; these include female gender, daily alcohol intake, chemotherapy emetogenicity and tumour type. We conducted a prospective cohort study to identify risk factors associated with the development of acute and delayed nausea/vomiting in patients receiving chemotherapy. With these data two prediction indices were developed in order to identify a priori patients at high risk for nausea/vomiting.
Materials and methods: Two hundred patients receiving outpatient chemotherapy were asked to complete a questionnaire assessing presence of risk factors prior to their first cycle of chemotherapy. Patients completed diaries tracking their nausea and vomiting using the National Cancer Institute of Canada Common Toxicity Criteria. Outcomes were collected following each cycle of chemotherapy up to 6 cycles. To determine which factors were associated with severe acute and delayed nausea/vomiting, multivariable logistic regression analysis adjusted for clustering was used. Initial variables for model inclusion were based on univariate selection process with an $\alpha = 0.25$. The likelihood ratio test in a backward elimination process was then used to select the final covariates into the model. Based on the regression models, two prediction indices were developed, one for severe acute emesis and one for severe delayed emesis. Risk score categories were calculated along with the area under the receiver operator curve (AUROC).
Results: The 200 cancer patients enrolled completed 864 cycles of chemotherapy. Mean age was 58. The median cycles of chemotherapy completed was 3. Incidence of severe acute nausea/vomiting was 7.2% (62 of 864 chemo cycles). Incidence of severe delayed nausea/vomiting was 9.3% (80 of 864 chemo cycles). On multivariate analysis for acute and delayed emesis, 5 factors were identified for acute (age, comorbidity, chemotherapy, alcohol intake, antiemetics) and 8 for delayed (age, comorbidity, chemotherapy, alcohol, cycle, acute vomiting, antiemetics). Based on these regression models, two prediction indices were developed, one for acute and one for delayed n/v. AUROC was 0.84 (95%CI: 0.78–0.89) and 0.79(95%CI: 0.74–0.88), respectively.

Question	n	r[a]	p-value	Compliance[b]
1. MTS – past 24 hrs	146	0.68	<0.001	80%
2a. MTS – sleeping	145	0.50	<0.001	79%
2b. MTS – swallowing	144	0.66	<0.001	80%
2c. MTS – drinking	144	0.63	<0.001	79%
2d. MTS – eating	141	0.63	<0.001	78%
2e. MTS – talking	144	0.68	<0.001	79%
2f. MTS – entertainment	121	0.36	<0.001	71%
2g. MTS – brushing teeth	134	0.52	<0.001	76%
2h. MTS – kissing	114	0.35	<0.001	67%
2i. MTS – leaving home	106	0.21	0.031	63%
2j. MTS – getting together	115	0.34	<0.001	68%
4. Overall MTS	144	0.57	<0.001	80%
5. Bowel movements	146	−0.01	0.939	80%
8a. DRA – sleeping	107	0.21	0.027	55%
8b. DRA – drinking	107	0.18	0.064	54%
8c. DRA – eating	103	0.20	0.042	52%
8d. DRA – entertainment	90	0.18	0.090	48%
8e. DRA – Taking care of yourself	99	0.32	0.001	51%
8f. DRA – getting together	84	0.21	0.055	45%
8g. DRA – leaving home	72	0.03	0.802	40%
9. Overall discomfort	111	0.01	0.904	56%
10.Overall health	143	−0.32	<0.001	80%

[a]Pearson correlation for OMDQ score and WHO mucositis grade on day 14.
[b]Overall mean compliance for all study days.

Conclusion: To our knowledge, such indices for prediction of high risk emesis are the first in oncology. These tools can be used to identify a priori patients at high risk for n/v and allow optimization of their antiemetic therapy. External validation of the indices is currently ongoing.

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Prevention of anemia by early intervention with once weekly epoetin-alfa during platinum-based chemotherapy

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Background: There is good evidence that epoietin alfa (Eprex®, EPO) is effective in treating moderate to severe anemia during cytotoxic cancer treatment. Further research is required to clarify its role in the treatment of mild anemia and the prevention of anemia in this setting.
Materials and methods: In a randomised, multicentre trial the effects of EPO on hemoglobin (Hb) levels and the need for bloodtransfusions (BT) were assessed in cancer patients started on chemotherapy (CT). Pts with Hb $\leqslant$ 2.1 g/dl and likely to receive CT for at least 12 weeks, were randomised (1:1) to EPO (40.000 U QW) to be started with CT simultaneously (early EPO) or when Hb dropped below 10.1 g/dl. (standard EPO).
Results: A pre-planned interim analysis was performed after 36 pts (18 early EPO vs 18 standard EPO) were enrolled. All pts entered the study before platinum containing CT was started. Data were obtained from the first 12 weeks of therapy. Both treatment groups were comparable for gender, age, performance score and tumor type. Mean Hb at baseline was 11.3 g/dl in both groups. EPO was started at an average Hb value of 11.4 and 9.8 g/dl respectively. Hb values in the early treatment groups increased significantly after week 3, 6 and 10. A global decrease was observed in the standard EPO group after week 2. Changes in Hb values between the 2 treatment groups became significantly different after week 3, 6, 8 and 10. No significant difference was observed in the number of BT's after early vs standard EPO treatment (1 BT in the early treatment group and 3 BT's in the standard treatment group). EPO treatment was well tolerated and no difference in the number of AE's were detected between the groups. Most of the AE's were as expected in a population of cancer patients treated with CT.
Conclusion: EPO treatment for mild anemia upon start of platinum-based CT when Hb becomes $\leqslant$ 12.1 g/dl, increases Hb values and results in significantly higher Hb values as compared to standard EPO therapy initiated when Hb drops below 10.1 g/dl. Maintaining Hb values around 12.1 g/dl may have a positive impact on quality of life according to several literature reports on this topic.

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Fractures negatively impact survival in patients with multiple myeloma or bone metastases from solid tumors

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Background: Patients with malignant bone disease are at high risk of developing multiple skeletal complications, including pathologic fractures, and these skeletal complications contribute to the poor prognosis for these patients. To assess the effect of fractures on survival in patients with multiple myeloma or bone metastases from prostate cancer or lung cancer and other solid tumors, we conducted a retrospective analysis of survival for patients in 3 large, randomized, controlled trials of zoledronic acid based on the occurrence of pathologic fractures on study.
Material and methods: A Cox regression model using fractures as a time-dependent variable was performed in patients with multiple myeloma (N = 513) or bone metastases from prostate cancer (N = 640) or lung cancer and other solid tumors (N = 766) who received 4 mg or 8/4 mg zoledronic acid, pamidronate (multiple myeloma), or placebo (prostate cancer or lung cancer and other solid tumors) every 3 to 4 weeks for up to 21 to 24 months. Treatment was also included in the model. Time to death was defined as the time from randomization to the final visit. Patients were censored at the final visit if death was not observed by end of study. Data from the core and extension phases were included in the analyses and all analyses were performed on the safety-evaluable population.
Results: Patients with multiple myeloma or bone metastases from prostate cancer who did not experience a fracture on study had better survival outcomes compared with patients who did experience a fracture on study. Overall, 43% of multiple myeloma patients experienced a fracture on study, and these patients had a trend of shorter survival with a hazard ratio of 1.304 (95% CI = 0.789, 2.156; P = 0.30) compared with patients who did not experience a fracture on study. In the study of prostate cancer patients, 19%

of the patients experienced a fracture on study with a hazard ratio of 1.455 (95% CI = 0.944, 2.244; P = 0.09), suggesting a negative impact of fractures on survival. In patients with lung cancer, 17% experienced a fracture on study, and the impact on survival appears to be much less compared with other tumor types (hazard ratio = 1.129; 95% CI = 0.767, 1.663; P = 0.54), perhaps due to the very short median overall survival time (approximately 6 months) of these patients.
Conclusions: These exploratory analyses suggest that fractures appear to be associated with shorter survival in patients with multiple myeloma or bone metastases from prostate cancer or lung cancer and other solid tumors.

1266 POSTER

Euthanasia: evaluation of a protocol

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Euthanasia is allowed within the Belgian Law in certain situations. A procedure of euthanasia that could guarantee a serene and effective method of ending a patient's life and that was acceptable for patient, family and health care professional was tested in the "Ziekenhuis Netwerk Middelheim" (ZNA), a 650-bed community hospital in Antwerp, Belgium.
The procedure included all the legal requirements: patients had a terminal disease and were expected to die soon; they were suffering despite optimal palliative care and their situation was considered hopeless; there was a written request stating the reason for euthanasia. An independent physician evaluated the situation and the validity of the request. In case of a positive evaluation, the family doctor was contacted and informed about the wish of the patient. If the patient agreed, the family was informed of the patient's request. The timing of euthanasia was discussed with the patient and if needed with the family and a date and hour was set. The nursing team or the members of the palliative support team were consulted in advance if this time was feasible in relation to availability of staff. The morning of euthanasia, the medication was ordered from the pharmacy so that the material and medication were available at the time of euthanasia. Euthanasia was performed by first administering midazolam 60 mg in 5–10 minutes to induce sleep followed by natriumpenthotal 4000 mg and atracuriumbesilate 50 mg intravenously by bolus injection.
From 25/02/2003 until 01/05/2005, 35 patients died by euthanasia. There were 17 men and 18 women with a median age of 68 years (range 39–90 years). All patients had terminal cancer. In all cases, the family of the patient was present during the administration of the lethal drugs.
All patients died due to euthanasia. Twenty patients fell into a coma and died without any disturbing symptoms. After the injection of midazolam, two patients had non-disturbing rales, eleven patients coughed and one patient developed rales and heavy breathing disturbing for the family. One patient already on high dose of benzodiazepines did not go into a coma after midazolam. After administration of natriumpenthotal he went into a coma and died peacefully.
This procedure assures that euthanasia is effective and is done in a serene atmosphere.

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Dose-response relationship: review of the past to improve the future of chemotherapy

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Background: Chemotherapy can improve survival rates in patients (pts) with solid tumors and hematological malignancies. The administered dose of chemotherapy is crucial to maintain treatment efficacy. The availability of the colony-stimulating factors (G-CSF), such as *filgrastim* and the long-acting *pegfilgrastim* (PGF), can allow the administration of the planned doses by preventing severe myelosuppression and its life-threatening complications. We reviewed data of trials evaluating the impact of the maintenance of the planned dose intensity on outcome in several types of chemosensitive tumors.
Material and methods: The principal databases (PubMed, CancerLit, Medline) have been checked using keywords relative to dose-intensity, CT and myelotoxicity, and considered only for the most representative papers on breast cancer, soft tissue sarcomas, germ cell tumors and malignant lymphomas were considered. All papers have been reviewed focusing on a) if myelotoxicity is an unavoidable adverse event b) if the reduction of dose-intensity is detrimental for the outcome and c) if the use of G-CSF or PGF contributes to the cure of tumors by reducing myelotoxicity and maintaining dose-intensity.
Results: *Breast cancer*: A recent survey on more that 20,000 pts with early-stage breast cancer treated with adjuvant CT showed that 35% of the pts had dose reductions >15%, and 25% had treatment delay > 7 days. Overall 56% of the pts were treated with a relative dose intensity <85%. Moreover several trials have shown that maintaining optimal planned dose is associated with better clinical outcome. In advanced disease a significant relationship between the dose intensities of CT and response rate was observed. A meta-analysis of 8 randomised controlled trials of G-CSF vs placebo found that chemotherapy dose reductions or delay were greater in patients receiving placebo.
Soft Tissue Sarcoma: Studies that used high doses of doxorubicin, epirubicin or ifosfamide in combination, with G-CSF support, resulted in higher response rate (RR) (range 42–67%) and a lower neutropenia rate.
Germ Cell Tumours: All regimens used are characterized by a significant myelotoxicity which often interferes with treatments. The ASCO 2000 recommendations suggest the use of G-CSF after a previous episode of febrile neutropenia, and discourage the reduction of the cytotoxic drugs.
Non-Hodgkin Lymphoma: The prognosis of pts treated with CHOP depends on the relative dose intensity during the first cycle: the five-year survival was 80% in pts treated with >70% of relative dose intensity and 32% in pts having been treated with <70%. The addition of G-CSF to CHOP resulted in a higher delivered dose intensity without affecting the survival outcome.
Conclusions: Myelosuppression is often responsible for dose-intensity reduction. The use of G-CSF, such as PGF, is useful for maintaining the CT dose intensity, and for NHL it is highly recommended.

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Quality of life (QoL) with capecitabine in patients with metastatic colorectal cancer (MCRC)

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Background: The oral fluoropyrimidine capecitabine has superior efficacy and improved safety compared with 5-FU/LV in MCRC and early-stage colon cancer. Consequently, capecitabine is replacing 5-FU/LV as the backbone of MCRC therapy and is now moving into the adjuvant setting. The QoL benefits of oral agents, like capecitabine, over traditional i.v. drugs are becoming increasingly important in MCRC alongside well-established measures of treatment response.
Materials and methods: Patients with MCRC who received oral capecitabine (1250 mg/m^2 twice daily on days 1–14, every 3 weeks) completed EORTC QLQ C-30 (v3.0) and CR-38 questionnaires before cycle 1, at weeks 7 and 13, and at treatment end. Linear models for repeated measures were used to analyse least square mean QoL data over time. Improvement was defined as a $\geqslant$10-point improvement and maintenance as a <10-point improvement/worsening from baseline in domain scores at one or more visits.
Results: Baseline characteristics of 894 evaluable patients were: male/female (50%/50%); median age 60 (20–91) yrs; ECOG performance status 0–1 (81%); Caucasian (81%). Almost half of patients completed QoL questionnaires through to treatment end. In women, significant improvements were observed in global health status ($p = 0.0208$), emotional functioning ($p < 0.0001$), pain ($p < 0.0001$), appetite loss ($p = 0.0403$), future perspective ($p < 0.0001$), micturition problems ($p = 0.0257$), stoma-related problems ($p = 0.0051$), and weight loss ($p < 0.0001$). In men, significant improvements were observed in global health status ($p = 0.0002$), social functioning ($p = 0.0124$), nausea/vomiting ($p = 0.0223$), constipation ($p < 0.0001$), financial problems ($p = 0.0072$), future perspective ($p = 0.0005$), micturition problems ($p = 0.0431$), and weight loss ($p < 0.0001$). Global health status score was improved or maintained in 70% and 71% of women and men, respectively.
Conclusions: Treatment with capecitabine led to improvements or maintenance of QoL in most patients. These data support its increasing use in the first-line and adjuvant settings. The efficacy, safety and convenience benefits of capecitabine as reported previously allow patients with MCRC to maintain a normal lifestyle and have a direct impact on QoL.