66 POSTER

Serum immunoreactive thrombopoietin levels in patients and response to ICE-chemotherapy-induced thrombocytopenia

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Purpose: The glycoprotein hormone thrombopoietin (TPO) is the primary and specific regulator of platelet production. The aim of our studie was to determine serum TPO concentration in normal subjects and during chemotherapy-induced thrombocytopenia. Additionally, we studied the serum concentration of two other megakaryocyte stimulatory cytokines, IL-6 and IL-11 during this period.

Methods: A quantitative sandwich ELISA-technique was employed for measurement of TPO in sera from 37 healthy subjects, 29 untreated tumor patients, and in sera from 6 patients up to 17 days after ICE administration. For L-6 and IL-II commercial ELISA were used.

Results: Normal subjectes: platelets 248/nl, TPO 287 pg/ml, Tumor patients: significantly increased to 436 pg/ml, platelets to 310/nl. After ICE platelets decreased to 67/nl during nadir on day 13 and recovered to 112/nl until day 17 This was inversely correlated to the raised serum TPO concentrations of 1050 pg/ml on day 13 and 832 pg/ml on day 17. No correlations between IL-6 and IL-11 and changes of TPO concentrations or platelets were observed.

Conclusion: We have elaborated a TPO-specific ELISA to determine the serum TPO concentration. Untreated tumor patients exhibited eleveted serum TPO and increased platelets counts. The serum TPO was inversely correlated to platelet counts, maximum TPO on day 13 after onset of chemotherapy, coincided with platelets nadir. Based on the time course of the changes in platelet counts and the concentration of TPO after chemotherapy, we wish to propose that treatment with recombinant human TPO approximately 4 days before expected platelet nadir could prevent life-threating bleedings and the need for platelet transfusion.

67 POSTER

Control of acute cisplatin-induced nausea and emesis using a once daily oral treatment regimen of ondansetron plus dexamethasone

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For patients receiving highly emetogenic chemotherapy intravenous (iv) ondansetron (OND) and iv dexamethasone (DEX) is currently recommended for the acute emesis period (0–24 hr). However, tablets may be a useful alternative particularly in an outpatient setting. The purpose of this multicentre, randomised, double-blind, double-dummy, parallel group study was to determine whether oral (po) OND 24 mg given as a single dose (od) plus po DEX 12 mg od is as effective and well tolerated as iv OND 8 mg plus iv DEX 20 mg in acute cisplatin-induced nausea and emesis.

A total of 528 (intent-to-treat population) patients were recruited into the study, 262 in the po group and 266 in the iv group. In the po group, 90% of patients had complete or major control of emesis (0–2 emetic episodes) compared to 89% in the iv group The percentage of patients experiencing none or mild nausea was 85% in both treatment groups of the study and both treatments were well tolerated. In conclusion, there was no significant difference between either once daily oral dosing with OND 24 mg plus DEX 12 mg or iv OND 8 mg plus DEX 20 mg in the control of acute cisplatin induced nausea and emesis.

68 POSTER

Recombinant human granulocyte colony-stimulating factor (G-SCF) in patients receiving chemotherapy for gynecologic cancer

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Purpose: To investigate the value of filgrastim (Granulokine, Roche) on duration of neutropenia, use and duration of antibiotics, duration of hospitalization, incidence and duration of neutropenic fever, incidence of demonstrated infection and mucositis, we evaluated 287 patients with gynecologic cancer.

Methods: Patients received filgrastin, 5 mg/Kgr s.c. daily (n = 197) or placebo (n = 90) on days 4–17 of the 21-day treatment cycle. Filgrastim was withdrawn if the post-nadic neutrophil count was $>10 \times 10^9$/lt (12th day). Patients' ages ranged from 33 to 70 years, with median age 56 years.

Results: At least one episode of neutropenic fever occurred in 43 out of 90 (47.77%) placebo treated patients compared with only 36 out of 197 (18.27%) filgrastim treated patients ($x^2 = 18.9$, $p < 0.0001$). Median duration of neutropenia (absolute neutrophil count $< 1.0X10^9$/lt in filgrastim treated patients was 2.96 ± 2.33 days, compared with 7.76 ± 4.4 in the placebo group ($t = 6.56$, $p < 0.0001$), and median duration of fever was shorter in filgrastim group (4.27 ± 3.92 vs 10.35 ± 8.42 $t = 6.4$, $p < 0.001$). At least one course of intravenous antibiotics in cases of neutropenic fever was administered to 46.66% and 18.27% of placebo and filgrastim treated patients respectively ($x^2 = 15.36$, $p < 0.0001$). Moreover the duration of antibiotics administration was shorter in filgrastim group (6.08 ± 9.41 vs 13.26 ± 9.59, $t = 6.05$, $p < 0.001$). The duration of hospitalization was significantly less in filgrastim group (7.00 ± 5.40 vs 14.19 ± 9.52, $t = 6.05$, $p < 0.001$) and there were also fewer confirmed infection in this group (3.55% vs 20%, $x^2 = 19.04$, $p < 0.0001$). Over all cycles the percentage of patients who developed mucositis was reduced from 36.66% in the placebo group to 4.56% in the filgrastim arm ($x^2 = 35.62$, $p < 0.00001$). Adverse effects were similar between groups, except for the incidence of musculoskeletal pain, which was greater in the filgrastim treated group (15.22%).

Conclusions: These results indicate that filgrastim is well tolerated and effective in reducing the morbidity associated with chemotherapy-induced neutropenia in women with gynecologic cancer.

69 POSTER

Drug utilization for prevention of chemotherapy (CT)-induced emesis

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Purpose: The combination of a 5-HT_3 antagonist with a corticosteroid is the most efficacious treatment for acute emesis induced by both highly and moderately emetogenic CT. However no data exist on antiemetic utilization in daily practice by oncologists. A prospective drug utilization study at 33 Italian oncological centers was carried out.

Methods: In June 1996, for two consecutive weeks, all adult patients (pts) starting any CT were blindly monitored for antiemetic prescription. Excluded from the study were pts with acute leukemia and pts receiving high-dose CT or radiotherapy.

Results: 1220 pts were evaluated. Of these, 140 received cisplatin (CDDP), 742 moderately emetogenic CT (MEC) (carboplatin, epirubicin, doxorubicin, cyclophosphamide and mitoxantrone) and 338 low emetogenic CT (LEC) (i.e., vincristine, vinblastine, etoposide, etc.). Rates of utilization of different antiemetic drugs were:

Treatment regimen	CDDP (%)	MEC (%)	LEC (%)
5-HT_3 antagonists alone	22.8	46.0	37.0
5-HT_3 antagonists + steroids	76.4	42.3	10.6
Steroids alone	0	2.8	8.9
Antidopaminergics alone	0	4.3	28.1
Other	0.8	3.1	4.5
No antiemetic treatment	0	1.5	10.9

Prophylaxis for delayed emesis was prescribed overall in 30.9% of pts (52.9% receiving CDDP, 33.6% MEC and 15.7% LEC).

Conclusion: The study showed that both undertreatment and overtreatment occurred in many pts with respect to the evidence provided by clinical trials

70 POSTER

Amelioration doxorubicin efficacy through reduction of anthracycline toxicity by calcium gluconate

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The study was undertaken to investigate the influence of modulator of calcium dependent ion pump by calcium gluconate (CaG) on the biological effects of doxorubicin (DOX). In acute toxicological experiments we have

shown that the survival time of DOX-treated mice receiving CaG was nearly 2.5-fold longer as compared to no CaG. LD_{100} DOX injected with CaG was about LD_{50} as compared to no CaG. The manifistation of DOX intestinal toxicity were lower after the DOX+CaG injection. In chronic experiments CaG caused a two-fold increase in mean survival time of DOX-treated mice and maximum total DOX dose. It was shown also that CaG does not influence on specific therapeutic activity of DOX in tumor-bearing animals. In experiments on the MOPS-406 plasmocytoma-bearing mice we have shown that therapeutic effect of small doses of DOX with CaG was the same as DOX alone. The antitoxic effect of CaG was clearly evident when toxic DOX doses were injected. All DOX-treated mice died earlier than the control tumor-bearing animals. In contrast there were no early deaths in DOX+CaG group and significantly higher DOX efficacy was achieved. Besides, there were cured animals in groups receiving high doses of DOX with CaG· 20 or 40% of mice with 15 or 20 mg/kg DOX+CaG respectively. Comparable results were obtained on hemoblastosis La-bearing mice. We conclude that CaG is perspective modifier which can be used in cancer patients and can increase the efficacy of anticancer DOX therapy by decreasing drug toxicity. Supported: the Russian Foundation for Basic Researches (Grant N 48796).

71 POSTER

Clinical evaluation of azasetron tablets in prevention of cisplatin-induced acute emesis – Multicenter double blind test with ondansetron tablets as control

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Purpose: To evaluate the effectiveness, safety and usefulness of azasetron tablets (Group A) in prevention of cisplatin-induced acute emesis, a double blind test was conducted with ondansetron tablets (Group O) as control.

Materials and Methods: Subjects were inpatients with malignancy receiving cisplatin (≥50 mg/m^2) alone or in combination chemotherapy with cisplatin. Tablets were orally administered before start of cisplatin. Antiemetic efficacy and adverse effects of antiemetic drugs were evaluated. Antiemetic efficacy were evaluated according to the degree of nausea and the number of vomiting episodes.

Results: 245 patients were entered, of whom 232 patients (121 in Group A, 111 in Group O) were accepted for analysis of effectiveness and usefulness, and 245 patients for analysis of safety. The rate of efficacy on acute emesis was 78% (94/121) in Group A and 73% (81/111) in Group O. The equivalence in effectiveness between ondansetron and azasetron tablets was verified. The rate of safety was 94% (120/127) in Group A and 88% (104/118) in Group O (p = 0.074). Adverse reactions were observed in 3 patients in Group A (headache, fever) and in 7 patients in Group O (headache, dull headache, diarrhea, fever and defective colulour vision) with the incidence being 2% and 6%, respectively. The rate of usefulness was 78% (94/121) in Group A and 72% (80/111) in Group O (p = 0.067). Group A was slightly better than Group O about the rate of safety and usefulness, with no significant difference between the two groups.

Conclusion: Group A were as effective as Group O, and slightly better than Group O in safety and usefulness, with no significant differences between two groups. We therefore consider that azasetron tablets is a useful drug in prevention of cisplatin-induce emesis.

72 POSTER

Effect of the perioperative selective bowel decontamination in abdominothoracal resections of the esophagus

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Purpose: The study was designed to evaluate the efficiency of the perioperative selective decontamination of the bowel in patients with abdominothoracal resections of a carcinoma of the cardia or the esophagus.

Method: 73 patients were included in a prospective randomized study. Loss of body weight </> 10% and carcinomas of the esophagus/cardia were stratified. The treatment group (n = 28) orally received 80 mg Gentamycin, 100 mg Polymyxin B and 200 mg Amphotericin B four-times a day starting 4 days prior to surgery. Postoperatively, the drugs were applied by a gastrointestinal tube.

Results are shown in the table.

	Treatment group (n = 28)	Control group (n = 45)
Artificial respiration	3.6 ± 5.0 days*	5.3 ± 9.5 days*
Stay in the ICU	9.1 ± 7.1 days*	11 6 ± 13.7 days*
Hospitalization	33.1 ± 16.1 days*	40.4 ± 27.3 days*
Pneumonia	36%	40%
Sepsis	11%	13%
Mortality	3 6%	8.9%

*[med ± SD]

Conclusion: No statistically significant differences were observed between both groups. The analysis of the postoperative course, however, shows that patients with a delayed postoperative weaning may profit from a perioperative selective bowel decontamination. This therapy should be focussed on this high risk patients.

73 POSTER

Risk factors and reversibility of neurotoxicity induced by high-dose paclitaxel

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Peripheral neuropathy (PN) is the main side effect with repetitive cycles of paclitaxel at standard doses. High-dose paclitaxel (HDP) with peripheral blood stem cell (PBSC) rescue is a novel treatment of patients (pts) with advanced cancer. No systematic evaluation of the neurotoxicity of HDP is available. Neurotoxicity of HDP was evaluated during a Phase I trial of HDP (500–800 mg/m^2 by 24-hour infusion, on day 1) followed by high-dose cyclophosphamide, thiotepa and carboplatin (Antman et al, J Clin Oncol, 1992, 10, 102) + PBSC rescue. Eighteen pts with metastatic cancer were treated with escalating doses of HDP (500 mg/m2, 3 pts; 600 mg/m2, 3 pts; 650 mg/m2, 3 pts; 700 mg/m2, 6 pts; 800 mg/m2, 3 pts) plus CTCb and evaluated before, during and after treatment with neurological examination (Neuropathy Symptom Score (NDS) and NCI common toxicity criteria (NCI-CTC), nerve conduction study (NCS) and evaluation of autonomic function. Four pts had been previously treated with neurotoxic chemotherapy (NC) (cisplatin, 3 pts; vinorelbine, 1 pt; paclitaxel, 1 pt). Pts with prior PN (grade, 2, NCI-CTC) were excluded. All pts had distal paresthesias and 5 had distal motor symptoms. None had vegetative symptoms and 2 had abnormalities on vegetative evaluation. Symptoms started 2.9 ± 0.3 days after HDP, worsened for 9 ± 0.8 days and improved by day 15.2 ± 0.4. Nerve conduction studies showed axonal neuropathy predominantly in the legs. Dose escalation correlated with duration of symptoms and delayed improvement (p = 0.013, Spearman). Previous NC but not dose escalation, was associated with more severe PN (p = 0.005, M-W). PN resolved within 2–4 months. PN induced by HDP is reversible and not dose limiting. Increasing dose is associated with more prolonged PN but not with severity. Neurotoxicity of HDP is moderate except in pts with prior NC.

74 PUBLICATION

Protective action of EHF electromagnetic irradiation on cisplatin-suppressed functional activity of immune system cells

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The question addressed in this study was how low-intensity non-ionizing electromagnetic irradiation (EMI) of extremely high frequency (EHF) range would modulate suppressive action of anticancer drug cisplatin (DDP) on specific activities of immune system cells, in particular, rosette-forming activity of T-lymphocytes (RFA) and phagocytic activity of neutrophils (PCA). G-protein inhibitor pertussis toxin (PT) was used to evaluate the role of cell signaling systems in the effects of DDP and EMI. Mice blood cells were exposed in vitro to DDP, PT and EMI, and assayed for functional responses as described in (A. Luik et al., Exp. Oncol., 1994, v. 16, p. 71–75).

DDP and PT inhibited RFA by 35 and 25%, respectively. Their joint effect was multiplicative (decrease by 55%), suggesting G-protein-independent route of DDP action. EMI did not affect normal or PT-suppressed RFA but completely reversed the effects of DDP, applied either alone or with PT.

Individual effects of DDP, EMI and PT on PCA were similar to their effects on RFA. However, joint effect of DDP and PT on RFA was synergistic rather than multiplicative (decrease by 75%). EMI did not reverse PT effect, activated by 20% PCA suppressed by DDP, and activated by 100% PCA suppressed by DDP+PT.