1148

TAXOTERE TOXICITY - PROTECTIVE EFFECTS OF PREMEDICATION

J.Wanders, A.van Oosterom, M.Gore, M.Piccart, I.Wolff, S.Kaplan, M.Roelvink, H.Franklin, S.B.Kaye for EORTC-Early Clinical Trials Group(ECTG) and M.Bayssas for Rhône-Poulenc Rorer.

Taxotere is a new anti-microtubule cytotoxic drug which shows promising results in a broad range of ECTG Phase II study. Within this trial, the toxicities seen include the development of acute hypersensitivity reactions (AHSR), skin and nail toxicity and also peripheral edema which occurs in the majority of patients (pts) who have been treated with 4 or more courses. More than 400 pts are being treated in 9 different tumortypes, 334 pts are now evaluable for toxicity. 87 pts (26%) showed AHSR. 51 of these received premedication (PM) for the next 112 courses (crs) to prevent further AHSR. This PM could be divided in 2 groups: A - PM consisting of corticosteroids (CS), antihistaminics (AH) and H2-antagonists (H2A), B - combinations not containing CS. Fortytwo out of 112 crs showed further AHSR (38%). Subsequent AHSR were usually of a lower severity than preceding AHSR. Group A had 42/105 crs with AHSR (40%), B showed 0/7 AHSR (prior mild reactions). Skintoxicity was seen in a total of 204/334 pts (61%), and this was not lower in the subgroup of pts who had received PM for prior AHSR (39/51, 77%). In pts who did not receive PM for AHSR Edema occurred in a total of 44/75 pts (59%) (mainly after a total of ≥4 crs), and this did seem to occur less frequently in the subgroup of pts who had received PM for prior AHSR (7/29, 24%). **Conclusions:** PM seems to be effective in the prevention of severe AHSR, but a wide variety of combination of CS, AH and H2A has been used and further studies with a strict PM regimen will be conducted within the ECTG-framework to identify the optimal regime. While shortlasting PM does not seem to protect against skin toxicity, there is some apparent protection against the development of edema, and this will be investigated further in prospective studies.

1149

IV GRANISETRON VS IV GRANISETRON PLUS IV DEXAMETHASONE IN THE PROPHYLAXIS OF EMESIS INDUCED BY CYTOTOXIC CHEMOTHERAPY.

Carmichael J (Churchill Hospital, Oxford, UK); Bessell E (Nottingham General Hospital, UK); Hutcheon A (Aberdeen Royal Infirmary, UK).

To determine any additive effect of granisetron and dexamethasone in the prevention of chemotherapy-induced emesis 278 adult male and female patients, receiving moderately emetogenic chemotherapy for the first time, were randomly allocated to receive either IV granisetron 3mg plus IV dexamethasone 8mg or IV granisetron 3mg plus IV placebo dexamethasone prior to chemotherapy. 81.7% of all patients recruited were female, and 91% of all patients consumed less than 10 units of alcohol per week, suggesting a study population with an increased risk of nausea and vomiting. Nausea, vomiting and rescue anti-emetic use were recorded.

In the first 24 hours 85.9% of patients who received granisetron plus dexamethasone were complete responders (complete response = no vomiting, no worse than mild nausea), compared with 75.9% of the patients receiving granisetron alone (p 0.05). There were also statistically significant improvements in complete response over 7 days and in the numbers of patients receiving rescue anti-emetic. There was no significant difference between the groups in the number of adverse experiences reported.

These results show that there is additive benefit with granisetron and dexamethasone in the prevention of cytostatic induced nausea and vomiting.

1150

POSSIBLE LACK OF FULL CROSS-RESISTANCE BETWEEN 5HT3 ANTAGONISTS, A PILOT EXPERIENCE.

Wit de R., Boer de M., Stoter G., Verweij J.. Dept. Medical Oncology, Dr. Daniel den Hoed Kliniek, Rotterdam Cancer Institute, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands.

With the advent of selective $5HT_3$ receptor antagonists, it has become possible to control cisplatin-based chemotherapy induced emesis in over 70% of patients. After failure to these drugs no other antiemetic therapy is considered effective. Although no comparative studies have been published, in current opinion cross-over between these drug is considered not appropriate, due to the similarity of the available $5HT_3$ antagonists and the seemingly comparable efficacy data.

We presently use Tropisetron (T) in preventing chemotherapy-induced nausea and vomiting during 6 cycles of weekly cisplatin (C). C is administered at a dose of 70-80 mg/m², patients (pts) who are treated with 70 mg/m² concurrently receive Etoposide 50 mg daily. T is administered as single 5 mg i.v. dose immediately before C on day 1, followed by a single 5 mg daily oral dose on day 2-5. Response is assessed separately for day 1 and 2-5. Patients failing during day 2-5 but responding on day 1 receive T at subsequent courses only on day 1, until failure. The definition for failure is ≥ 5 vomits (V)/24 hours and/or > 4 hours nausea (N)/ 24 hours. To pilot possible differences in efficacy, pts failing on T receive Ondansetron (O) for the corresponding period at subsequent cycles. O is administered as an 8 mg i.v. dose before C on day 1, and an 8 mg oral dose twice daily on day 2-5. Of 49 patients, 14, median age 53 (30-72) m:f 12:2, were switched to O during the course of chemotherapy. 2 pts who had failed on day 1 had complete protection against N/V (CR) on day 1 with O. Of 12 patients who received O on day 2-5, 3 patients had CR. These limited data suggest that there is an indication for retreatment with a different $5HT_3$ antagonist after an initial failure to another and also stress the need and relevance for comparative studies between $5HT_3$ antagonists.

1151

IMPACT OF ANTIEMETICS IN CANCER TREATMENT: THE EORTC EXPERIENCE

L. Gisle, J. Renard, S. Serbouti, F. Meunier. EORTC Data Center, Brussels, Belgium

Vomiting, is one of the most distressful toxicity of cancer chemotherapy and may prevent an optimal treatment administration.

The EORTC database has been investigated to evaluate the impact of antiemetics, including ondansetron, in cancer treatment. Fifteen phase II & III trials in solid tumors, dealing with emetogenic compounds such as cisplatin, anthracyclin and cyclophosphamide were selected. 1079 eligible patients (pts), registered from 1989 to 1992, have at least 1 treatment cycle documented in terms of treatment (dose & schedule), emesis (WHO grade) and if any, antiemetic (AE) drug given (dose and time of administration). Whenever possible, the 4 first chemotherapy cycles were studied. Pt characteristics are: age (median 57, from 17 to 77), sex (M/F: 495/584), WHO performance status (median: 1), prior chemotherapy (no/yes: 810/269). The tumor type: mainly gynecological (29%), soft tissue sarc. (29%), gastro-intestinal (21%), and the reasons for treatment discontinuation such as excessive toxicity (9%), refusal (6%), lost to follow up (4%), etc... are also studied.

Preliminary results indicate that: 1° - at cycle 1, 76% of the pts receive antiemetics (22% ondansetron, 54% other), given prophylactically in 95% of the pts. (96%. ondansetron, 94% other). 2° - the AE regimen does generally not vary between cycles (same regimen for cy 1 and cy 2: 87%). 3° - the absolute proportion of pts receiving ondansetron has significantly increased from 1989 (6%) to 1992 (34%) : $P < 0.001$, while the absolute proportion of pts receiving other AEs has been decreasing from 1989 (84%) to 1992 (43%) : $P<0.001$. The correlation between the use of AE and particularly ondansetron with all other parameters collected in these pts are currently analysed.

1152

A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF ORG 2766, AN ACTH (4-9) ANALOGUE, FOR THE PREVENTION OF NEUROPATHY INDUCED BY CISPLATIN (P) WITH OR WITHOUT VINCA-ALCALOIDS (VA) COMBINATION CHEMOTHERAPY (CT).

Y. Chraibi[1], A. Fernandez[2], J.P. Drozl[1], G. Said [2], T. Le Chevalier [1], C. Lhomme [1], P. Rougier [1], P. Ruffié [1], C.B. Rocs [3], A. Blum [3], C. Groenhout [3], E. Van Vliet-Daskalopoulou [3]
[1] Institut Gustave-Roussy, Villejuif, France - [2] Hôpital Bicêtre, France - [3] Organon International, Oss, The Netherlands

Neuropathy (N) is a serious consequence of dose dependent toxicity of cisplatin (P) with ± VA combination CT. Org 2766 demonstrated activity to prevent P-induced N. Between 10-1990 and 12-1991 we included 121 patients (pts) in a randomized double-blind, placebo-controlled study of Org 2766, 2 mg s.c., administered before and after every CT course in pts who received P (cumulative dose at least 400 mg/m²) ±VA. One hundred and twelve pts were actually treated, 87 of whom completed the study. Major reasons for discontinuation of CT were intercurrent illness (14 pts), progressive disease (4), protocol violation (4), refusal (3). Pt characteristics were well balanced. Sex male (60), female (52) ; median age 55 (33-75) years ; primary tumor site : lung (30), ovary (22), bladder (16), gastric (14), other (30) ; CT protocol P only (81pts), P+VA (31). Results : paresthesia occured in 23/57 pts and 21/55 pts in the Org 2766 and placebo groups respectively at the end of the CT (p=ns). Comparison of paresthesia-free interval curves by the log-rank test failed to demonstrate a significant difference between the two groups. Results were similar in the P only and P+VA treated groups. Vibration Perception Threshold (VPT) was measured at every other CT course. VPT was increased after 4 courses of CT in both treatment groups irrespective of the CT protocol and other pt or treatment characteristics. There were no side-effects of Org 2766. The response rate to CT was similar in both treatment arms. Conclusion : at the dose of 2 mg administered s.c. before and after every CT course Org 2766 does not demonstrate an activity to prevent P induced N as measured by the main variables VPT and paresthesias. Since some secondary variables, such as vibration sence, showed a trend in favor of Org 2766 further studies of different doses and schedules of Org 2766 in homogenous cancer pt groups are warranted.

1153

THE MANAGEMENT OF EXTRAVASATION OF CYTOSTATICS: CLINICAL RESULTS IN 83 PATIENTS

G.Bertelli, D.Dini, G.Forno, A.Gozza, S.Silvestro, G.Ballella, M.Venturini, R.Rosso, P.Pronzato. National Institute for Cancer Research, Genova, and Ospedale S.Andrea, La Spezia, Italy.

Several commonly used cytostatics may cause severe local toxicity after accidental extravasation (ex.). Antidotes have been studied in animal models but there are few reports of clinical effectiveness. We have employed, immediately after ex., the following antidotes: topical 99.9% dimethylsulfoxide (DMSO) + ice packs in 75 pts for doxorubicin (8 pts), epidoxorubicin (19), mitomycin-C (4), mitoxantrone (10), ifosfamide (8), cisplatin (26) ex.; jaluronidase infiltrations in 6 pts for vinca alkaloids or epipodophillotoxins ex.; and Na thiosulphate infiltrations in 2 pts for dacarbazine ex. The results are extremely encouraging: only one pt in this case series suffered an ulceration, perhaps due to a 'recall phenomenon'.