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Eur J Cancer, Vol. 27, No. 3, pp. 356–361, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Controlling Emesis Related to Cancer Therapy

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Combinations of dopamine antagonists or high-dose metoclopramide with steroids can provide complete control of chemotherapy-related nausea and vomiting in up to 60–70% of patients undergoing high-dose cisplatin-based chemotherapy. High-dose metoclopramide probably acts as a 5-HT_3 receptor antagonist, but because of its dopamine-receptor antagonism it is the cause of extrapyramidal side-effects. These compounds, and the agents used in combination with them, tend to cause sedation, an undesirable effect in the outpatient setting. Specific 5-HT_3 receptor antagonists (ondansetron, granisetron, tropisetron) give a similar control of chemotherapy related nausea and vomiting, with minimum side-effects. These drugs can cause headaches and constipation and some have been related to transient liver enzyme abnormalities in cancer patients; however, disease and chemotherapy might also be the cause of the enzyme anomalies. Combinations of 5-HT_3 receptor antagonists with steroids may provide a very high degree of protection.
Eur J Cancer, Vol. 27, No. 3, pp. 356–361, 1991.

INTRODUCTION

AFTER THE pioneering efforts of Moertel [1], cancer patients had to wait for a long time before any significant advance could help them with the most feared experience related to cancer chemotherapy, namely nausea and vomiting [2–4].

CLASSIC DRUGS

Corticosteroids

Used in many areas of medicine, sometimes with a rational basis related to their anti-inflammatory effect or in the treatment of specific deficiency states, corticosteroids have also a role in the control of cancer therapy related emesis [5]. Pilot studies of their probable antiemetic effect [6, 7] were rapidly followed by randomised evaluations, and their efficacy as sole antiemetics in patients treated with moderately emetogenic chemotherapy was proven in the early 1980s [8]. Investigators have not yet defined an optimal dose-schedule for the use of these compounds, whose antiemetic mechanism of action remains unknown, although it may be suggested that they act by modifying capillary permeability of the central nervous system [9]. Recent evidence indicates that steroids are efficacious in the animal models used for the study of other antiemetics, and thus support a mechanism unrelated to the general sense of well-being and possible placebo-effect that they may confer [10,11].

Metoclopramide, alizapride and neuroleptics

The most extensively studied agent is metoclopramide, which was proven to prevent high-dose cisplatin related nausea and vomiting [12]. Its use has been subject to several modifications, in logically conducted studies which have successively shown that it can be advantageously combined with steroids and a neuroleptic, to provide antiemetic protection for up to 60–70% of patients treated with high-dose cisplatin based chemotherapy [13].

It is generally accepted that patients younger than 35 years old will frequently experience extrapyramidal side-effects related

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Received and accepted 28 Nov. 1990.
Presented in part at the Second European Winter Oncology Conference (EWOC-2), Méribel, France, January 1991.

to the anti-dopaminergic effects of metoclopramide, although the above-mentioned combination therapy has decreased the severity and incidence of this side-effect. Furthermore, the considerable sedation that patients experience while receiving this drug may be a problem for outpatient treatment, and lower doses of metoclopramide or another agent may be preferred [14]. Alternatives to high-dose metoclopramide are, however, when also used at the most effective high doses, very similar in their side-effect profile, whether they are alizapride (a related benzamide derivative [15]), or a neuroleptic such as droperidol [16] or haloperidol [17]. One of the inconveniences of the use of metoclopramide is the apparent necessity to administer it twice, before and after chemotherapy, or as a continuous infusion after a loading dose (18). Recent data suggest that this may not be the case. Two groups have shown that a single dose of 4 mg/kg is tolerable and possibly [19] or probably [20] equivalent, when used in combination, to a divided dose of two 3 mg/kg administrations 2 hours apart.

Other agents or methods

Phenothiazines (chlorpromazine, thiethylperazine, prochlorperazine) or domperidone have also been evaluated and found to have some activity against moderately emetogenic chemotherapy. There is however no major reason to use these agents, which are not without side-effects, at least as preventative agents of acute chemotherapy induced emesis [21]. Phenothiazines are inexpensive and may have a role in moderately emetogenic chemotherapies, but have not been adequately tested in this setting.

Cannabinoids have been proposed in the past, but although some activity was observed, their side-effect profile has limited their usefulness [21]. Benzodiazepines have been mentioned already, as agents decreasing the side-effects related to metoclopramide; they may also have their own antiemetic efficacy, and their combination with metoclopramide was recently reported as being much more effective than metoclopramide alone [22]. Among many other compounds or methods with some efficacy in controlling cancer treatment related emesis, one may want to mention psychological approaches, like behavioural treatment (23).

SEROTONIN (5-HT_3) RECEPTOR ANTAGONISTS

Among the many effects of serotonin, its mediation of radiation therapy and chemotherapy induced nausea and vomiting is the centre of interest for cancer therapists today. It is presently suggested that although the central nervous system, and in particular the area postrema and the chemoreceptor trigger zone [24] may play a role in mediating cancer treatment induced emesis, a major pathway of this nociceptive response is situated in vagal afferent terminals in the wall of the upper gut, via a specific type of serotonin receptor, the 5-HT_3 receptor [25, 26].

Many 5-HT_3 receptor antagonists have been developed: MDL 72222 [27], tropisetron [2], ICS 205–930 [28], BRL 24924 [29], LY 278584 [30], ondansetron (GR 38032) [31], granisetron (BRL 43694) [32], batonopride [2], BMY 25801-01 [33], zacopride [34], MDL 73147 EF [35], BRL 46470 [36], RG 12915 [37].

The discovery of the antiemetic properties of 5-HT_3 receptor antagonists is related to observations of serotonin antagonism by metoclopramide in rodent gut preparations [38, 39]. These observations, along with the clinical efficacy of high-dose metoclopramide, led to the suggestion that dopamine-receptor antagonism could not explain the antiemetic activity of this drug [40]. BRL 24924 and MDL 72222 were the first two 5-HT_3 receptor antagonists shown to possess antiemetic properties [41, 42].

Batanopride

The first studies with this agent were performed in cancer patients in 1986 [43, 44]. Overall, 35 (67%) of 52 patients undergoing cisplatin-based therapies achieved major antiemetic protection. Side-effects reported in phase I studies included loose stools (possibly cisplatin related) and other minor events. A peculiar side-effect was a slight (> 20%) increase of the QTc from the baseline electrocardiogram (ECG) and the appearance of atrio-ventricular blocks in 2 patients treated at the highest doses.

Ethically discussed placebo-controlled studies indicate good activity: patients with head and neck cancer undergoing cisplatin based chemotherapy (100 mg/m^2) received three doses of 6 mg/kg of batanopride, and 28 out of 33 were completely protected, compared to only 6 of 31 who received placebo ($P < 0.001$) [45, 46]. In patients on non-cisplatin containing chemotherapy, 12 of 15 receiving 1.2 mg/kg of batanopride had no emesis, compared to 5 of 16 under placebo ($P = 0.02$) [47]. In these studies the ECG abnormality was reported in 26 of 85 batanopride patients versus 19 of 88 placebo patients ($P = 0.18$), and had no clinical consequence, while decreases in systolic blood pressure (more than 25 mm Hg) were reported in 27 of 88 batanopride patients versus 14 of 82 placebo patients ($P = 0.04$). These and other data were sufficient ground to stop development of this antiemetic.

Granisetron

Carmichael *et al.* [48] reported that 8 of 14 patients at the highest dose studied (40 μg/kg intravenously) had no nausea or vomiting while undergoing cisplatin-based chemotherapy. Another group confirmed these observations: a single intravenous infusion of ondansetron given one hour prior to cytostatics provided total protection to 6 of 13 non-pretreated patients receiving cisplatin ≥ 50 mg/m^2 [49]. It has now become impossible, for this agent and ondansetron, to cite all published reports, and the choice has been based on an arbitrary decision on the interest of the information.

Addelman *et al.* [50] have shown that this agent has a very long serum half-life, of 9 to 11 hours, with wide interpatient variation, confirming observations by Cassidy *et al.* [51]. Development of granisetron has been along logical steps. To determine if a higher-dose of BRL 43694 in a single-administration could be useful, two dose-finding double-blind multicentre studies were conducted in 296 patients receiving at least 50 mg/m^2 of cisplatin and in 443 patients receiving various moderately emetogenic chemotherapies [52, 53]. The studies compared 40 μg/kg (dose A) to 160 μg/kg (dose B) given intravenously, with the provision that two further 40 mμ/kg doses could be administered within the first 24 hours in refractory patients. Total protection (including "minimal nausea") has been reported in 57% (dose A) and 60% (dose B) of the patients during the first 24 hours on cisplatin, and in 76 (dose A) and 81% (dose B) of the patients receiving less emetogenic chemotherapy. Results over 7 days after initiation of chemotherapy were assessed with the use of a patient questionnaire. Many patients suffered from delayed nausea and vomiting as only 43% of the cisplatin group patients and 41% of the other patients remained asymptomatic.

Having established the activity of a single administration of granisetron, the investigators of these multinational studies next compared the activity of granisetron to other antiemetics. A

"cisplatin patient study" included 234 patients treated with either 40 μg/kg of granisetron or a combination of metoclopramide (3 mg/kg 30 min infusion followed by an eight hour 0.5 mg/kg/h infusion) and dexamethasone (12 mg intravenous). Complete responses (no emesis and allowing "mild nausea") were observed in 70% and 69% of the patients. Once again delayed emesis proved to be a problem, with more than half of the patients experiencing nausea or vomiting in the week after chemotherapy [54]. 228 patients were included in the less emetogenic chemotherapy study, and 70% were protected by granisetron 40 μ/kg compared to 49% of those receiving the combination of chlorpromazine 25 mg (intravenous or intramuscle) and dexamethasone 12 mg intravenously ($P < 0.001$). There was however no difference in control of delayed emesis (44% and 52% failure rates) [55].

Admittedly one tends to be impressed by the results obtained in these studies, which have been confirmed by two double-blind studies conducted by the National Cancer Institute of Canada. They have presented a double-blind study comparing granisetron 80 μg/kg (46% responses) with a combination of metoclopramide 2 mg/kg intravenous every 2 hours 5 times, diphenhydramine and dexamethasone (44% responses), in 149 patients treated with cisplatin at doses above 49 mg/m^2 [56]. They also indicate that control of emesis by granisetron over the first 6 hours is superior to the metoclopramide regimen, with 81% versus 56% responses. These data suggest that multiple doses of granisetron might be superior to a single dose. Repeated dosage might possibly be achieved with the use of oral granisetron, which is also an effective agent in preclinical models [57]. The Canadian group has also reported a double-blind study of granisetron (80 μg/kg) (70% responses) versus dexamethasone and prochlorperazine (34% responses) in patients receiving non-cisplatin based chemotherapies (mainly doxorubicin combinations) [5‹].

The safety of granisetron has been reviewed in 982 patients on granisetron and 233 on comparator regimens by M. Tabona from Beecham [59] who has reported that constipation occurred in 4% and headache in 14% of the patients, compared to 1% and 5% incidences with the comparator. Diarrhoea and somnolence were more frequent in the comparator arms. Extrapyramidal side-effects were observed only in the comparator arms (6% incidence). Animal toxicology data have lead the company to warn investigators that very high doses of the compound given for one year have been found to induce liver tumours in rats.

Ondansetron

A preliminary report appeared in 1987 to indicate total protection by this compound of 14 of 15 patients having experienced emesis with prior chemotherapies. These remarkable results were obtained with an intravenous 4 mg dose followed by 2 oral 4 mg administrations [60]. Side-effects (mainly headache) are limiting at 0.48 mg/kg 3 times every 4 hours [61]. There may be a non-significant trend towards less antiemetic control with higher cumulative doses of the compound [62, 63]. These clinical observations of a probable bell-shaped dose-response curve are in agreement with results observed in the use of 5-HT$_3$ antagonists in psychiatric illnesses [64]. These studies have reported transient elevations of transaminases in 33% of the courses, which may be related to cisplatin, as is frequently observed when either the cumulative or the single dose of cisplatin are 100 mg/m^2 [65]. However, this has not been reported for batanopride in comparable studies conducted by a single group [66]. Smith [67] retains that it is difficult to be certain about the causality between ondansetron and liver enzyme increase. Bryson [68] has reported on the safety profile observed in US trials involving 331 patients, discussing that diarrhoea is less frequent with ondansetron (23 versus 44%), headache more frequent (15 versus 7%) and extrapyramidal side-effects observed in 6% of the patients on metoclopramide, versus none on ondansetron. Pharmacokinetics in patients indicate a serum half-life of 4.5 hours [69].

Ondansetron has been compared to very small doses of oral metoclopramide in patients undergoing single dose 8–10 Gy radiation therapy to the upper abdomen [70]. Patients receiving ondansetron orally, 8 mg three times a day, had no emesis in 73% of the cases (37 patients at risk), compared to 18 of 44 (41%) protection with metoclopramide. A French study has been conducted in double-blind crossover fashion in 97 patients scheduled to receive 80 to 100 mg/m^2 of cisplatin. Complete protection from emesis was observed in 31 of 47 patients starting with ondansetron and 21 of 45 starting with metoclopramide ($P = 0.064$) [71]. Similar results have been observed by a Dutch multicentre group [72]. Bonneterre *et al.* [73] have obtained complete control of vomiting in 86% of the patients undergoing chemotherapy for breast cancer (FAC or FEC) compared to a 42% protection rate in patients treated wtih metoclopramide (60 mg intravenously followed by 20 mg orally every 8 hours). Two other multicentre studies have been reported, using 8 mg ondansetron intravenously or 8 mg ondansetron orally in patients undergoing non-cisplatin based chemotherapy [74, 75]. The use of ondansetron in children, patients who rarely if ever tolerate high-dose metoclopramide, has been documented with encouraging results in non-randomised trials [76, 77]. The ethics of placebo-controlled antiemetic studies are a complex problem but there are two reports of double-blind placebo controlled trials demonstrating the efficacy of ondansetron [78, 79]. Ondansetron has been recently marketed in the UK, France and other countries.

Tropisetron

The first report of clinical activity of this agent described decreased symptoms in a patient suffering from carcinoid syndrome [80]. Antiemetic activity was evaluated in 11 patients, 5 of whom had experienced prior nausea/vomiting. ICS 205–930 was administered as two 10 mg infusions over 15 minutes each, before and after chemotherapy. 31 of 47 courses were without emesis or retching. Headache was observed in 9 courses and sedation (mild) in 7 [81]. This report has been expanded to 25 patients, with decrease of the dose to 5 mg/twice a day [82].

A possible allergic reaction with fever, rash, lymphadenopathy developed in 1 of 5 patients treated for carcinoid syndrome, and reappeared upon drug rechallenge [83]. Very rare allergic reactions have also been reported for ondansetron (68). A dose-ranging trial in 22 patients (up to 48 mg/m^2 intravenous once) has shown no limiting side-effects [84]. Another dose-ranging study of 5 to 20 mg/m^2 indicated that the antiemetic effect would decline after 8 hours [85]. Stamatakis *et al.* [86] have administered doses ranging from 5 to 40 mg to 143 patients receiving cisplatin based chemotherapy (> 50 mg/m^2) and claimed 54% total control of emesis, at any dose-level. The first comparative study reported to date indicates that, in 25 patients receiving high-dose melphalan or cyclophosphamide during autologous bone-marrow transplantation, ICS was clearly superior to alizapride [87]. Tropisetron has antiemetic activity and its side-effect profile is difficult to analyse. It has been reported to induce mainly headache and liver enzyme disturb-

ances and there are single observations of hypotension or allergies.

MDL-73147EF

There are minimal clinical data available for MDL-73147EF. Pharmacology describing its anti-5-HT_3 effect has recently appeared [88]. We have evaluated safety and antiemetic efficacy in a dose ranging study in 32 patients. There were no differences in side-effects or efficacy at doses from 10 to 50 mg intravenously. M. Boyce reported at the Third Perugia International Cancer Conference that in over 200 patients included in parallel dose-ranging studies, less or equal to 2 episodes of emesis were observed in 80% of patients, if one excludes the low 10 mg intravenous dose with headache as a side-effect. MDL 72222 had also been reported to have antiemetic efficacy [88–90]. These data encourage the development of MDL 73147EF, which has a better pharmacodynamic profile and has not been associated with teratogenicity.

Other serotonin antagonists

Zacopride, a substituted benzamide, has been recently re-evaluated and felt to be of moderate interest, confirming prior unpublished data (Ref. 91 and M. Kris, Memorial Sloan-Kettering Cancer Center). Other agents with 5-HT_3 antagonist activity which have or will soon enter in the clinic include ADR-847 [92], LY 277359, and RG 12915.

Control of delayed emesis

We have observed that serotonin antagonists are effective in controlling acute nausea and vomiting, but that there is still a considerable proportion of patients suffering from delayed emesis. Two recent reports confirm the importance of this problem in patients treated with metoclopramide [93, 94]. It seems that a combination of dexamethasone and metoclopramide given for several days after high-dose chemotherapy may be effective in controlling this side-effect in half of the patients.

Anticipatory emesis

Patients suffering from this syndrome tend to have experienced posttreatment nausea and vomiting, are young and often have a history of motion sickness (4). Many techniques, mainly psychological, have been used in this setting, but none is quite satisfactory, as they are difficult to use in a busy clinic due to the time required.

CONCLUSION

Antagonism of the 5-HT_3 receptor is a new means to control some of chemotherapy and radiotherapy induced emesis. Data presently available indicate that these agents are equipotent to the best antiemetic combinations, but have side-effects. Promising early studies have indicated the potential of combining steroids with ondansetron [95, 96]. 102 patients submitted to cisplatin based chemotherapy have been included in a multicentre study. Complete antiemetic protection has been observed in 64% of the patients on 0.15 mg/kg ondansetron intravenously 3 times, 30 min before and 1.5 and 3.5 hours after cisplatin, compared to an impressive 91% in those who received in addition 20 mg dexamethasone intravenously 45 minutes before chemotherapy [97]. A major step towards the control of acute emesis may have been accomplished.

Before this is confirmed it remains difficult to decide which antiemetic to choose, from the classic or the new agents. Although the 5-HT3 antagonists are of promise for children [98] who like young adults tolerate metoclopramide poorly, one must remember that the large majority of cancer patients is more than 40 years old. The indiscriminate use of expensive new agents (ondansetron is marketed at £270 for 30 tablets of 8 mg) may create a major problem. Even if we can obtain a remarkable control rate of acute emesis, presently available data are not encouraging for delayed emesis, and there is little evidence that these new agents are effective in multiple-day chemotherapy related emesis, or over several chemotherapy courses.

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Acknowledgements—Without the secretarial help of Ms. Colette Amez-Droz, and of several companies, it would not have been possible to write this paper. Special thanks go to T. Blackburn, M. Boyce, M. Butcher, R. Dierdorf and J.P. Terrey.