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Possible lack of full cross-resistance of 5HT$_3$ antagonists; a pilot study

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Abstract We investigated the potential of cross-over to the serotonin receptor (5HT3) antagonist ondansetron after protection failure with tropisetron. Several cases of complete protection were observed. These limited data suggest that there is an indication for retreatment with a different 5HT3 antagonist after an initial failure to another and also stress the need and relevance for comparative studies between 5HT3 antagonists.

Introduction

With the introduction of selective serotonin receptor (5HT$_3$) antagonists it has become possible to control cisplatin-induced emesis properly in over 70% of patients. After failure with these compounds, treatment with more conventional antiemetics is not effective (de Mulder et al. 1990; Italian Group for Antiemetic Research 1993). In view of the similarity in the mechanism of action and the seemingly comparable efficacy data, few people consider cross-over from one 5HT$_3$ antagonist to another appropriate. Nevertheless the preclinical data do not support this pessimistic approach (Seynaeve et al. 1991). To obtain data for further clinical research, we performed a pilot study on the possible potential of cross-over from one 5HT$_3$ antagonist to another after initial protection failure.

Patients and methods

In the framework of concurrent phase II protocols, cisplatin was administered at a dose of 70–80 mg/m^{-2} week^{-1} for 6 weeks. Patients who were treated with 70 mg/m^2 concurrently received etoposide 50 mg daily. Antiemetic prophylaxis consisted of 5 mg tropisetron i. v. 15 min prior to chemotherapy on day 1 and a once-daily oral dose of 5 mg on days 2–5. The antiemetic response was assessed separately by patient diary cards for days 1 and 2–5 (worst-day analysis). In patients who experienced at least five episodes of vomiting or more than 4 h of nausea per 24 h, this regime was considered to have failed, and they received ondansetron for the corresponding period of the subsequent cycle. The cisplatin dose was not modified. Patients who failed exclusively on days 2–5 still received tropisetron in subsequent courses only on day 1. The ondansetron regimen was a single dose of 8 mg intravenously 30 min before start of chemotherapy on day 1 and 8 mg orally twice daily on days 2–5.

Also, for the ondansetron treatment, the antiemetic efficacy was assessed for days 1–5 separately with patient diary cards, using the same response criteria as mentioned above. For the analysis of cross-over efficacy only complete control (no nausea or vomiting) was considered of clinical benefit.

Results

Of 49 patients treated with tropisetron, 14 crossed-over to ondansetron after protection failure. The patient characteristics are shown in Table 1. The male preponderance is mainly related to the tumor types selected for the phase II studies. Of these 14 patients, 12 were crossed-over for days 2–5 and 2 for day 1, reflecting the decreased activity of 5HT, antagonist for delayed nausea and vomiting. The numbers of cisplatin courses given prior to cross-over due to protection failure were one course (7 patients), two courses (3 patients), three courses (1 patient), and five courses (3 patients). Both patients who received ondansetron for the acute period had a complete response at the subsequent cycle. Of the 12 patients who received ondansetron during the delayed period, 3 experienced a complete response (cycle 2).

Discussion

Previous cross-over studies (de Mulder et al. 1990; Marty et al. 1990) have shown that protection from cisplatin-induced nausea and vomiting with 5HT$_3$ antagonists is possible after

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Table 1 Patient characteristics (*NSCLC*, non-small-cell lung cancer; *ACUP*, adeno carcinoma of unknown primary)

Number of patients	14
Male/female	12/2
Age (years)	
Median	53
Range	30–72
Primary tumor site	
Head and neck	5
Melanoma	3
Mesothelioma	2
Lung (NSCLC)	2
ACUP	1
Testicular cancer	1
Chemotherapy	
Cisplatin 70 mg/m^{-2} week^{-1} + etoposide 50 mg p.o./day	9
Cisplatin 80 mg/m^{-2} week^{-1}	5

the previous failure of more conventional antiemetic treatment, for instance high-dose metoclopramide. The same studies have shown that the opposite is not the case. Metoclopramide is ineffective if $5HT_3$ antagonists are ineffective. Because of the similar mechanism of action, oncologists have refrained from recommending cross-over to another $5HT_3$ antogonist (Seynaeva et al. 1991). However, the presently available $5HT_3$ antagonists are different in their structure their receptor affinity and many other aspects, and data on preclinical cross-resistance are lacking. To obtain data justifying further large-scale studies we performed the present pilot study. These data, although limited, show that complete control with ondansetron can be obtained in patients previously failing with tropisetron. In addition the data also reflect the relative inefficacy of $5HT_3$ antagonists for controlling delayed nausea and vomiting because 12 of 14 patients initially failed to respond to tropisetron during this phase. In the light of this, the 3 cases of complete control achieved with ondansetron are even more interesting. The important question obviously is whether retreatment with the same $5HT_3$ antagonist would also have resulted in complete protection. Data on this topic are markedly lacking. Although in incidental cases retreatment with the same $5HT_3$ antagonist yielded a better result in a subsequent cycle, it would appear highly unlikely that this would transform the outcome from failure (defined as more than five vomiting episodes and/or more than 4 h of nausea) to complete protection. Therefore we feel that our data indicate that there is need for further studies on retreatment with $5HT_3$ antagonists after initial failure. Such studies should investigate, in a randomized trial, the protection rates following retreatment with the same antagonist as well as the protection offered by cross-over to another $5HT_3$ antagonist.

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