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Safety and efficacy of a triple antiemetic combination with the NK-1 antagonist aprepitant in highly and moderately emetogenic multiple-day chemotherapy

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ABSTRACT

Aim of the study: In multiple-day chemotherapy (MDC), the combination of a 5-HT_3-antagonist plus dexamethasone is still a standard of care. The role of a NK-1-antagonist remains to be defined.

Patients and methods: Seventy eight cancer patients undergoing multiple-day chemotherapy of high (HEC) or moderate (MEC) emetic risk received granisetron, dexamethasone plus aprepitant during chemotherapy. After the end of chemotherapy, aprepitant plus dexamethasone was given for another 2 days. Primary end-point was complete response (CR) in the overall phase (day 1 until 5 days after the end of chemotherapy).

Results: Thirty eight patients underwent HEC and 40 patients underwent MEC for a median of 3.5 days. CR was seen in 57.9% and 72.5% of patients receiving HEC and MEC, respectively. The tolerability of the aprepitant regimen over 5–7 days was comparable with a 3-day aprepitant regimen.

Conclusions: This is the first report in MDC with a NK-1-antagonist containing antiemetic regimen showing a favourable safety profile with good antiemetic efficacy.

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) are common side-effects of chemotherapy and still a great burden for cancer patients. In single-day chemotherapy, the antiemetic guidelines recommend the triple combination of a 5-HT_3-antagonist plus dexamethasone plus the NK-1-antagonist aprepitant in highly and moderately (AC-based) emetogenic chemotherapies.[1,2] However, this refers exclusively to single-day chemotherapy. In MDC, the use of a 5-HT_3-antagonist plus dexamethasone for acute CINV and dexamethasone alone for delayed CINV is still a standard of care.[2,3] The level of control with this antiemesis prophylaxis in 5-day cisplatin chemotherapy is still suboptimal, achieving acute CR's (no emetic episodes, days 1–5) in the range of 55–58%.[4,5] In order to improve on these results, the addition of a NK-1-antagonist in MDC seems to be the next logical step to enhance the emetic control.

2. Patients and methods

2.1. Design

This non-randomised single institution analysis of the triple combination of aprepitant, granisetron and dexamethasone in MDC was conducted at the university hospital in Halle,

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Germany within a 3-year period. The study was conducted in accordance with the Helsinki declaration and the guidelines on good clinical practice.

2.2. Patients

Patients were considered for this study if they were ⩾18 years and were intended for a MDC (3 or 5 days) of moderate or high emetogenic potential. Post hoc applied exclusion criteria were other antiemetic medication during the study. The concomitant administration of benzodiazepines for insomnia was allowed.

2.3. Treatments and assessments

Oral aprepitant (125 mg) was given 1 h before chemotherapy on day 1, and oral aprepitant (80 mg) was given once daily on each day of the MDC and for two following days. Granisetron (1 mg intravenous (i.v.)) was administered once daily of the MDC. Dexamethasone (8 mg i.v.) was administered once daily of the MDC and orally on the two following days. The choice of rescue medication was left to the discretion of the treating physician and was documented. For efficacy assessment, nausea and vomiting were recorded daily on a special documentary chart. Assessment of toxicity was conducted using the NCI-CTC investigator guide (Version 3.0).

2.4. Statistical analysis

According to the protocol-defined exclusion criteria, a per-protocol efficacy population consisting of all patients who received the whole study drug regimen as indicated and who had efficacy assessment completed was defined for efficacy and safety analyses. The primary end-point for the efficacy was the CR in the overall phase of CINV. The secondary end-points were CR in the acute and delayed phases and the incidence of nausea. CR was defined as no vomiting and no use of rescue medication on chemotherapy days (acute CINV) or on days 1–5 after the end of chemotherapy (delayed CINV). Overall response was defined as CR in the acute and delayed phases. Nausea was classified in yes or no. Kaplan-Meier curves were plotted to analyse the time to first occurrence of emesis. The primary safety hypothesis proposes that the administration of the aprepitant regimen over 5–7 days would be well tolerated.

3. Results

3.1. Patients/chemotherapy

In the study period, 78 patients had received the scheduled aprepitant regimen, matched all criteria of the protocol, and were included in the final analyses. Baseline characteristics are summarised in Table 1. Patients with moderately emetogenic chemotherapies received cytostatics exclusively for 3 days and patients with highly emetogenic chemotherapies for 3 (45%) or 5 (55%) days (mean 4.1). Sixty-six%/85% of patients with highly/moderately emetogenic chemotherapy received a cisplatin/ifosfamide containing regimen, respectively.

3.2. Efficacy

Patients received the aprepitant regimen for a mean of 5.5 days, with a maximum of 7 days. The percentage of patients who achieved a CR in the acute/delayed and overall phases was 65.8%/68.4% and 57.9% for HEC and 72.5%/82.5% and 72.5% for MEC. Regarding single days of the acute phase under HEC, the CR rate decreased from day 1 to day 4 (day 2: 81.6%, day 3: 73.7%) to a minimum of 71.4% (day 4) and improved on day 5 (81%). Under MEC, the CR rate was lowest on day 2 with 82.5% (day 3: 85%). In the delayed phase, CR was lowest on day 1 with 68.4% (day 2: 76.3%, day 3: 84.2%, day 4 89.5%, day 5: 94.7%) and improved day by day in patients receiving HEC

Table 1 – Baseline characteristics.

	Highly emetogenic chemotherapy N = 38	Moderately emetogenic chemotherapy N = 40
Men (%)/women (%)	87/13	75/25
Age: mean (range)	43 (22–71)	38 (18–67)
Cancer type (%)		
Sarcoma	42	33
Germ cell cancer	55	27
Myeloma	–	15
Lymphoma	–	15
Primary unknown (CUP)	3	5
Thymic cancer	–	5
History (%)		
Moderate alcohol consumption	13	8
Chemotherapy-naïve	66	13
Pretreatment anxiety	24	23
Preexisting loss of appetite	13	23
Preexisting nausea	8	0
Brain metastases	11	13
Aprepitant in previous chemotherapy (%)	5	3

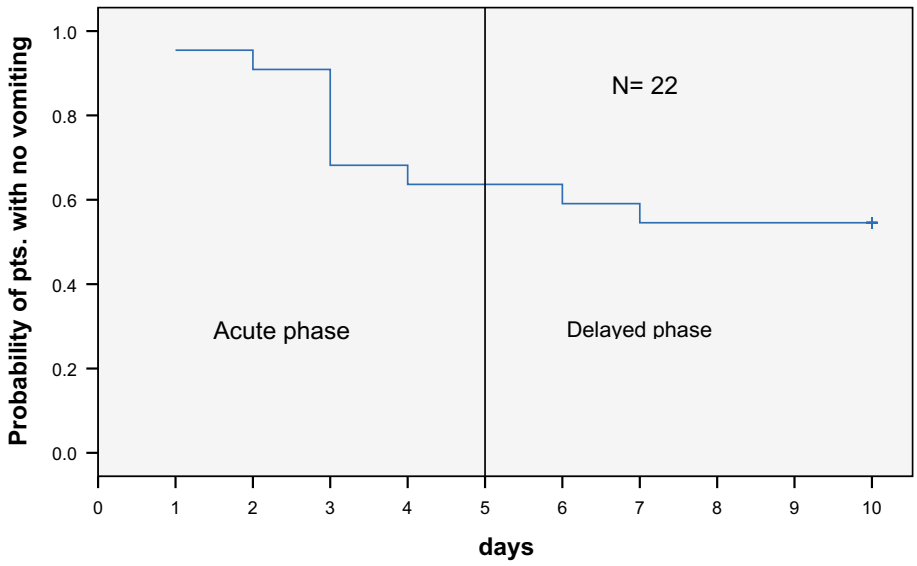

Fig. 1 – Time to the first occurrence of emesis in patients receiving 5-day cisplatin-containing chemotherapy.

and were almost constant on days 1–5 in patients under MEC (day 2 + 3: 87.5%, day 4 + 5: 85%).

With regard to acute/delayed and overall nausea, 21.1%/21.1% and 23.7% of patients receiving HEC and 27.5%/12.5% and 27.5% of patients receiving MEC reported nausea. Preexisting nausea significantly reduced the probability of overall CR ($p < 0.05$). Pretreatment anxiety had also a significant negative impact on the probability of overall CR ($p = 0.001$). Patients with brain metastases were less likely to achieve acute CR ($p = 0.04$).

The Kaplan-Meier plot in Fig. 1 depicts the first onset of vomiting during the 5-day cisplatin-only chemotherapy showing a probability of 54.5% of no vomiting over the whole observational period. During the 3-day moderately emetogenic chemotherapy, the probability of no vomiting over the whole observational time (8 days) was 72.5% (Fig. not shown).

3.3. *Tolerability*

None of the patients discontinued the treatment due to an adverse event. The most common (⩾10%) adverse event, regardless of cause, was neutropenia, thrombocytopenia (both CTC grade 3/4) and loss of appetite (26.9% {18% before start of chemotherapy}). Hiccups occurred in 7.7% of patients. Diarrhoea and constipation grade 3/4 were seen in 4.8%, and 1.1%, respectively. No grade 3/4 headache occurred. Grade 3 hyponatremia and hypokalemia were seen in 2.3% and 1.1%, respectively, whereas no grade 3/4 hyperglycemia occurred. Three of the 56 patients who received ifosfamide developed an ifosfamide psychosis.

4. Discussion

With the standard combination of a 5-HT_3-antagonist plus dexamethasone in 5-day cisplatin, MDC response rates between 55% and 58% can be achieved.[4,5] The role of a NK-1-antagonist in MDC remains to be defined.

In the latest study by Einhorn et al.[6], the combination of palonosetron plus dexamethasone in 41 patients receiving 5-day cisplatin treatment achieved an acute/delayed CR of 34.1% and 61.0%, respectively. Palonosetron (0.25 mg i.v.) was applied on days 1, 3 and 5 and dexamethasone on days 1, 2, 6, 7 and 8. It is assumable that the higher response rates in our study are attributed mainly to the addition of aprepitant on one hand and on the other hand potentially on the addition of dexamethasone on days 3, 4 and 5. The patients in the study by Einhorn had the 'worst' CR rates on days 4 (41.5%) and 5 (56.1%) in comparison to 71.4% (day 4) and 81% (day 5) in our study. To interpret this finding, it must also be considered that days 3–5 have become the most critical days of CINV. This is to be expected because of the potential combination of acute and delayed CINV on these days. Whether the application schedule of palonosetron on days 1, 3 and 5 plays a role in the study by Einhorn, remains a matter of speculation.

Almost no information is available on patients receiving MDC of moderate emetogenic potential, e.g. with ifosfamide. In one study, patients treated with ifosfamide (15 mg/$m^{2)}$ over 5 days received a 5-HT_3-antagonist plus dexamethasone daily during chemotherapy.[7] Complete protection defined as no vomiting or retching was achieved in 95% on day 1, but declined to 43% on the last day of the ifosfamide therapy.

Previous large studies using the 3-day aprepitant regimen showed similar findings in regard to toxicity.[8,9] In our study, no cumulative or unexpected toxicity was seen. 5.4% of patients treated with ifosfamide developed an ifosfamide-induced psychosis. The incidence of ifosfamide-induced psychosis usually ranges from 10% to 30%. Hence, we got no evidence that aprepitant enhances the central nervous toxicity of ifosfamide, as it was reported in a letter of Durand.[10]

5. Conclusions

This is the first report providing evidence for the favourable safety profile showing no cumulative or unexpected toxicity

and good efficacy of the triple antiemetic combination of aprepitant, granisetron and dexamethasone in MDC. Compared to clinical data from the literature, aprepitant could provide additional benefit in preventing CINV during MDC.

Conflict of interest statement

K. Jordan*: consultancies and received honoraria from Roche AG and MSD
I. Kinitz: none declared
W. Voigt: none declared
T. Behlendorf: none declared
H.-H. Wolf: none declared
H.-J. Schmoll: consultancies and received honoraria from Roche AG and MSD

REFERENCES

1. Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J Clin Oncol* 2006;**24**(18):2932–47.
2. Roila F, Hesketh PJ, Herrstedt J. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. *Ann Oncol* 2006;**17**(1):20–8.
3. Jordan K, Schmoll HJ, Aapro MS. Comparative activity of antiemetic drugs. *Crit Rev Oncol Hematol* 2007;**61**(2):162–75.
4. Fox SM, Einhorn LH, Cox E, Powell N, Abdy A. Ondansetron versus ondansetron, dexamethasone, and chlorpromazine in the prevention of nausea and vomiting associated with multiple-day cisplatin chemotherapy. *J Clin Oncol* 1993;**11**(12):2391–5.
5. Weissbach L. Ondansetron. *Lancet* 1991;**338**(8769):753–4.
6. Einhorn LH, Brames MJ, Dreicer R, et al. Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 2007;**15**(11):1293–300.
7. Forni C, Ferrari S, Loro L, et al. Granisetron, tropisetron, and ondansetron in the prevention of acute emesis induced by a combination of cisplatin-Adriamycin and by high-dose ifosfamide delivered in multiple-day continuous infusions. *Support Care Cancer* 2000;**8**(2):131–3.
8. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin – the Aprepitant Protocol 052 study group. *J Clin Oncol* 2003;**21**(22):4112–9.
9. Schmoll HJ, Aapro MS, Poli-Bigelli S, et al. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. *Ann Oncol* 2006;**17**(6):1000–6.
10. Durand JP, Gourmel B, Mir O, Goldwasser F. Antiemetic neurokinin-1 antagonist aprepitant and ifosfamide-induced encephalopathy. *Ann Oncol* 2007;**18**(4):808–9.