Results of a 7-day aprepitant schedule for the prevention of nausea and vomiting in 5-day cisplatin-based germ cell tumour chemotherapy

Running Head: 7-day aprepitant for 5-day cisplatin

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Abstract

Purpose

To determine the efficacy of adding a 7-day aprepitant schedule to a 5 HT_3 receptor antagonist and dexamethasone for patients with germ cell tumours receiving first-line 5-day cisplatin-based chemotherapy.

Methods

In a single-arm, open-label, multi-center, phase 2 trial, chemo-naive patients received aprepitant 125 mg PO (per oral) day 1 and 80 mg PO days 2 to 7, a $5HT_3$ receptor antagonist days 1 to 5, and dexamethasone 8mg days 1 to 8. The primary endpoint was no emesis (vomiting or dry retching) during days 1 to 7 of cycle 1.

Results

Fifty patients were recruited. For cycle 1, proportions reporting: no emesis on day 1, no emesis on days 1 to 7, no nausea on day 1, and no nausea on days 1 to 7 were 96%, 82%, 71% and 27% respectively. The efficacy was maintained in all cycles with over 80% of patients reporting no emesis on any given day of any given cycle. Emesis was more common on days 4 to 7 (68% episodes) than on days 1 to 3 (32% episodes). Over any 24 hour period, 49% of patients with emesis reported no more than 2 episodes, and 62% of patients with nausea reported intensity as 3 or less on a scale from 0 to 10. There were no unexpected or serious adverse events reported.

Conclusion

Adding 7 days of aprepitant to a $5HT_3$ receptor antagonist and dexamethasone effectively controlled acute and delayed emesis with 5-day cisplatin regimens. Days of nausea were more common than days of vomiting.

Keywords: Aprepitant, dexamethasone, 5hydroxytryptamine$_3$ receptor antagonist, 5 day cisplatin, antiemetic, germ cell tumours

Introduction

The standard curative chemotherapy for metastatic germ cell tumors (GCTs) consists of cisplatin, which is usually administered in combination with bleomycin and etoposide (‘BEP’), etoposide alone (‘EP’), or less commonly in combination with etoposide and ifosfamide (‘VIP’/’VeIP’) [1]. Treatment is repeated for 3 or 4 cycles depending on the prognostic group. The cisplatin is usually split over 5 days, because there is evidence that this regimen reduces toxicity including nausea, vomiting, nephrotoxicity and oto-toxicity, but does not reduce efficacy. However nausea and vomiting remain a significant problem for most patients receiving multiple-day cisplatin based chemotherapy for metastatic germ cell tumours [2].

The patterns of chemotherapy-induced nausea and vomiting (CINV) following cisplatin given on a single day are well studied. Acute emesis occurs in the first 24 hours, followed by a delayed phase of emesis which can last for up to 7 days, and if emesis is experienced in the first cycle, anticipatory emesis can occur in subsequent cycles [3]. The pattern of CINV after cisplatin given over 5 days differs. The reported peak of emesis following 5-day BEP occurs from days 3 to 5, when acute and delayed emesis overlap [4].

The Multinational Association of Supportive Care in Cancer's (MASCC) anti-emetic guidelines for multiple-day cisplatin recommend a $5HT_3$ receptor antagonist and dexamethasone prior to chemotherapy to control acute emesis, and dexamethasone after chemotherapy to control delayed emesis [5]. An Australian and New Zealand Germ Cell Trials Group (ANZGCTG, now part of the Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group) trial of 5-day BEP found that 57% of patients experienced grade 3 or worse nausea and vomiting despite anti-emetic therapy [6]. Therefore new approaches to control of CINV for multiple-day cisplatin are needed to improve the control of delayed emesis and nausea.

Aprepitant (Emend™, MK 0869) is a highly potent and selective antagonist of the human substance P or neurokinin (NK1) receptor [7]. Pivotal phase III trials have shown that the addition of aprepitant to the combination of dexamethasone and a $5HT_3$ antagonist is more effective than the combination alone, for the prevention of nausea and vomiting associated with high dose (>50 mg/m^2), single-day, cisplatin-based chemotherapy and has few adverse effects [8,9]. For single-day cisplatin, complete control of emesis was improved from 65-80% to 80-90% when aprepitant was given at a dose of 125 mg day 1 and 80 mg days 2 and 3 orally with a $5HT_3$ receptor antagonist on day 1 and dexamethasone on days 1 to 4. In the clinical setting, aprepitant appears to be most useful for controlling delayed emesis where $5HT_3$ antagonists are relatively ineffective. There seemed to be no additional benefit from dosing beyond day 3 after a single dose of cisplatin [10]. The doses of dexamethasone are halved when given with aprepitant because it is a CYP3A4 inhibitor and the dexamethasone concentrations are increased twofold [11].

Little data exist for the use of aprepitant with multiple-day cisplatin. This ANZUP Cancer Trials Group study sought to determine whether aprepitant was of value in reducing CINV in patients receiving such regimens. The current study adheres to standard anti-emetic guidelines for multiple-day cisplatin, by giving a $5HT_3$ receptor antagonist and dexamethasone prior to each day of chemotherapy to control acute emesis, and continuing dexamethasone to day 8 to prevent delayed emesis. It used the principles established in regimens using single-day administration of cisplatin of adding aprepitant on each day of cisplatin and for 2 days after (i.e. days 1 to 7).

Participants and Methods

Eligibility

The study population included those over 18 years with pathologically confirmed germ cell tumours (testicular, retroperitoneal, mediastinal or ovarian primary) who were scheduled to receive cisplatin-based chemotherapy on 5 consecutive days (20mg/m^2/ day) i.e. any of BEP (bleomycin, etoposide, cisplatin: Indiana regimen), accelerated BEP (ANZUP phase 2 clinical trial regimen [12]), EP (etoposide, cisplatin), or VIP (etoposide, ifosfamide, cisplatin). Participants were to have a predicted life expectancy ≥ 4 months and an ECOG performance score of 0 to 3; be able to read, understand and complete the patient diary and study procedures; and agree to participate in the study by signing a written consent form.

Patients were excluded if they had received previous chemotherapy, or had received, or were due to receive, abdominal radiotherapy during treatment. Patients with symptomatic brain metastases, infection (e.g., pneumonia) or serious concomitant illnesses, current evidence of alcohol abuse, or who were mentally incapacitated or with a significant emotional or psychiatric disorder were excluded. Patients with known hypersensitivities to aprepitant, $5HT_3$ antagonists, dexamethasone or had previously participated in a study with aprepitant were not eligible for this study. Patients taking CYP3A4 substrates where serious interactions could occur were also excluded.

Ethics

All participants gave written informed consent to participate. The study was approved by the Human Research Ethics Committees of the participating hospitals, based on compliance with the Helsinki Declaration. The study was registered on the ICMJE-compliant Australia New Zealand Clinical Trials Registry (ACTR number ACTRN12608000254392).

Treatment

Patients were treated on an 8-day antiemetic regimen consisting of aprepitant 125 mg PO day 1 and 80 mg PO days 2 to 7, a $5HT_3$ receptor antagonist days 1 to 5, and dexamethasone 8mg days 1 to 8. If patients required rescue medication they could use lorazepam, metoclopramide, haloperidol or prochlorperazine.

Assessment

The assessment of the efficacy of the antiemetic regimen was recorded in patient diaries. An episode of vomiting or dry retching constituted an episode of emesis. Distinct episodes of emesis were, by definition, separated by the absence of emesis for at least one minute. Nausea was assessed using an 11-point rating scale (from 0 = “none” to 10 = “worst I

can imagine") assessing the degree of nausea over the previous 24 hours. Serious unexpected adverse events were recorded. Patients also recorded any use of rescue antiemetics.

The study's primary endpoint was no emesis during days 1 to 7 (i.e. the first 7 x 24 hour periods) of cycle 1 of chemotherapy. Secondary endpoints included no emesis during days 1 to 7 of subsequent cycles, and day 1 of all cycles; no significant nausea, no use of rescue medications, and presence of anticipatory emesis in the 24 hours prior to day 1 of chemotherapy.

Sample size

It was anticipated that a sample size of 50 would provide at least 43 participants with complete data on the primary endpoint. This provided more than 80% power at the 5% significance level to reject the null hypothesis of a no emesis rate $\leq 50\%$ if the true no emesis rate was $\geq 70\%$.

Results

Between May 2009 and December 2010, 50 patients were accrued from 9 Australian sites. There were 48 males and 2 females, all of whom had a good performance status and received chemotherapy regimens containing 5-day cisplatin (BEP, Accelerated BEP or EP) for germ cell tumours. (Table 1)

The $5HT_3$ receptor antagonist used was either intravenous or oral granisetron (32 patients) or tropisetron (18 patients).The adherence with the dosing schedules of the 3 drugs was high over 4 cycles of treatment. Although it was anticipated that dexamethasone (8 mg) over 8 days would be the most problematic, the lowest adherence with that drug was recorded with cycle 1 and was high at 86%. (Table 2)

A total of 164 cycles of chemotherapy were commenced and patient diaries were available for 160. Forty-nine patients commenced 2 cycles, 46 patients commenced 3 cycles, and 19 patients commenced 4 cycles. Four patients recorded emesis within the 24 hours prior to cycle 1, but there was no anticipatory emesis recorded prior to cycles 2 and 4, and only 2 of 44 patients recorded emesis on the day prior to cycle 3.

The control of vomiting with cycle 1 was excellent with 96% of patients reporting no acute emesis on day 1, and 82% (95% confidence interval 68-91%) reporting no emesis during days 1 to 7 of cycle 1 (Table 3). Nausea was not as well

controlled with 71% of patients reporting no acute nausea on day 1, but only 27% reporting no nausea during days 1 to 7 of cycle 1.

The efficacy of the regimen was maintained over 4 cycles of treatment (Table 3). On any given day, over 80% patients recorded no emesis irrespective of whether they were receiving the first or fourth cycle (Figure 1). Although nausea was not as well controlled, the pattern of nausea experienced during a cycle and the percentage of patients with no nausea was similar for all cycles (Figure 1).

Across all cycles, more patients reported emesis days 4-7 (68% of emetic episodes) than on days 1-3 (32% of emetic episodes) of each cycle, however when emesis occurred the number of episodes did not vary by day of the cycle; the mean number of emetic episodes in a 24 hour period ranged from 3.1 to 3.9 for days 1-7.

Over any 24 hour period, 49% of patients with emesis had only 1 or 2 episodes (Figure 2a). In patients who reported nausea, 60% scored its intensity as 3 or less on the scale from 0 to 10 for any 24 hour period (Figure 3b). If rescue medication was required, the choice was metoclopramide (80%), prochlorperazine (9%), lorazepam (6%) and others including cyclizine and domperidone.

There were no unexpected serious adverse events reported that were attributed to adding aprepitant to the $5HT_3$ receptor antagonist and dexamethasone and administering it in this prolonged schedule. The were 8 serious adverse events recorded, 4 infections, 3 pulmonary emboli and 1 gastrointestinal bleeding episode all judged to be unrelated to the antiemetics.

Pre-treatment patient characteristics such as pre-treatment vomiting and serum concentrations of ß-HCG were associated with the percentage of patients recording emesis during days 1 to 7 of cycle 1 (Table 4).

Discussion

The efficacy of triple antiemetic therapy including aprepitant, dexamethasone and a $5HT_3$ antagonist in preventing emesis with single-day chemotherapy regimens of high and moderate emetic potential is well established [8,13]. This study showed that when the triple antiemetic regimen is extended to cover 5 days of cisplatin, including 2 additional days to cover the delayed emesis from the day 5 cisplatin dose, emesis was well controlled. We know that aprepitant has been shown to add efficacy to the $5HT_3$ receptor antagonist and dexamethasone in both the acute and delayed phases of emesis with single-day cisplatin [8,9]. The primary endpoint of this study was emesis, so that the efficacy of the triple antiemetic regimen could be compared between its use with single and multiple day chemotherapy regimens.

The control of emesis in our study was superior to that previously reported for a $5HT_3$ antagonist and dexamethasone given with 5-day cisplatin in the first cycle, but we have further demonstrated that it is maintained over 4 cycles of treatment. Using the previous study as an historical control, Einhorn et al reported 88% no emesis on day 1 as compared to our 96%, dropping to 68% no emesis on day 4 with palonosetron and dexamethasone with a 5-day cisplatin regimen as compared to 82% for days 1 to 7 in our study [15]. Another single arm study using a similar triple antiemetic regimen to ours, in patients receiving 3 or 5 days of chemotherapy and both chemotherapy of moderate or high emetic potential demonstrated the safety of a prolonged antiemetic regimen and showed that it was effective [14]. The efficacy of our triple antiemetic therapy used with 5-day cisplatin regimens is further demonstrated by the observation of very low levels of anticipatory emesis, a learned response, that occurred in subsequent cycles, presumably because of excellent control of emesis in previous cycles. Also, for those who did experience any nausea and emesis, the frequency of emesis and intensity of nausea on any given day was low.

The poorer control of nausea compared to vomiting observed in our study has also been reported with the triple antiemetic regimen when used for single-dose antiemetic regimens with chemotherapy of high or moderate emetic potential. It is suggested that different mechanisms exist for nausea than those identified for vomiting requiring different treatments, or that it is a symptom complex incorporating related symptoms such as heartburn, bloating, and anorexia [16].

The adherence to the antiemetic regimen was good. In particular there was a high adherence to the multiple doses of dexamethasone and no adverse effects were recorded. The antiemetic regimen in general was well tolerated with no serious or unexpected adverse events apparent.

The prognostic factors for post-chemotherapy emesis are similar to those previously recorded and include pre-chemotherapy emesis (Table 4). Previous studies have shown that chronic high alcohol intake is reported to be associated with less emesis in patients receiving cisplatin, particularly for head and neck cancer [17]. The current study has a younger patient population with a shorter duration of cumulative exposure, but a similar outcome.

Another study has explored the use of aprepitant in combination with a $5HT_3$ receptor antagonist and dexamethasone for 5 day cisplatin [18]. However, in this small randomized crossover study, aprepitant (or placebo) was not added until day 3 when it was given as a loading dose of 125 mg then 80 mg from days 4 to 7 and the dexamethasone dose was 20 mg on days 1 and 2, with a further blinded randomization allocating patients to either dexamethasone 4 mg b.i.d. or 8

mg b.i.d. on days 6 and 7 and 4 mg on day 8. The patients were then crossed over. The patients therefore received less aprepitant than in our study and it started later, where it could not improve acute emesis on days 1 and 2. This study reported a 47% complete response with aprepitant versus 19% with placebo after 70 patients had been entered ($p<0.0001$), and 11% had at least 1 episode of vomiting on aprepitant versus 47% on placebo ($p<0.0001$). There was no statistically significant difference between the treatment arms in scores for nausea.

Our study provides proof of principle that triple antiemetic therapy is effective in preventing emesis with 5-day cisplatin regimens; further modifications could explore reducing the dosing of various components of the antiemetic regimen using the current study regimen as the control arm, in order to reduce potential toxicity. One concern is that with prolonged dosing of aprepitant, interactions with the metabolism of cytotoxics may become more likely due to its potential to inhibit CYP enzymes. However, the current study did not demonstrate an increase in unexpected serious adverse events due to chemotherapy. There are also data from studies of casopitant, an NK_1 receptor antagonist now withdrawn due to its toxicity, that larger doses of the NK_1 receptor antagonist given on day 1 may preclude the need for days 2 and 3 dosing [19]. There is also the possibility of intravenous dosing of the NK_1 receptor antagonist using fosaprepitant [20], or use of the novel NK_1 receptor antagonist netupitant.

The question of whether using the longer acting $5HT_3$ receptor antagonist, palonosetron in the regimen would increase efficacy is also worth exploring [15]. Investigating the minimum effective doses of dexamethasone, given the possible toxicities of prolonged dosing, is also a question for future trials, since the optimal dose is unknown.

The strengths of our study include an antiemetic regimen based on prolonging the regimen used with single day chemotherapy, excellent adherence to the regimen by patients, use of a diary for seven days after starting each cycle of chemotherapy, and reporting of data beyond the first cycle of chemotherapy. The major limitation of the study is the lack of a randomized control to prove the superiority of our triple antiemetic regimen.

In summary, results from our phase 2 study support the efficacy, safety, and worthiness for further consideration of using aprepitant on days 1 to 7 in conjunction with dexamethasone and a $5HT_3$ antagonist for patients with germ cell tumours having cisplatin on days 1 to 5.

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Conflict of Interest:

Two of the authors Ian Olver and Martin Stockler applied for and received a grant from Merck Sharp & Dohme (Australia) Pty Limited to partly fund this study but have no other relationship with this company to declare. None of the authors have other conflicts of interest to declare. The authors had full control of the primary data and agree to allow the journal to review that data if requested.

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Figure 1. Percentage of patients with no emesis or no nausea by day and cycle

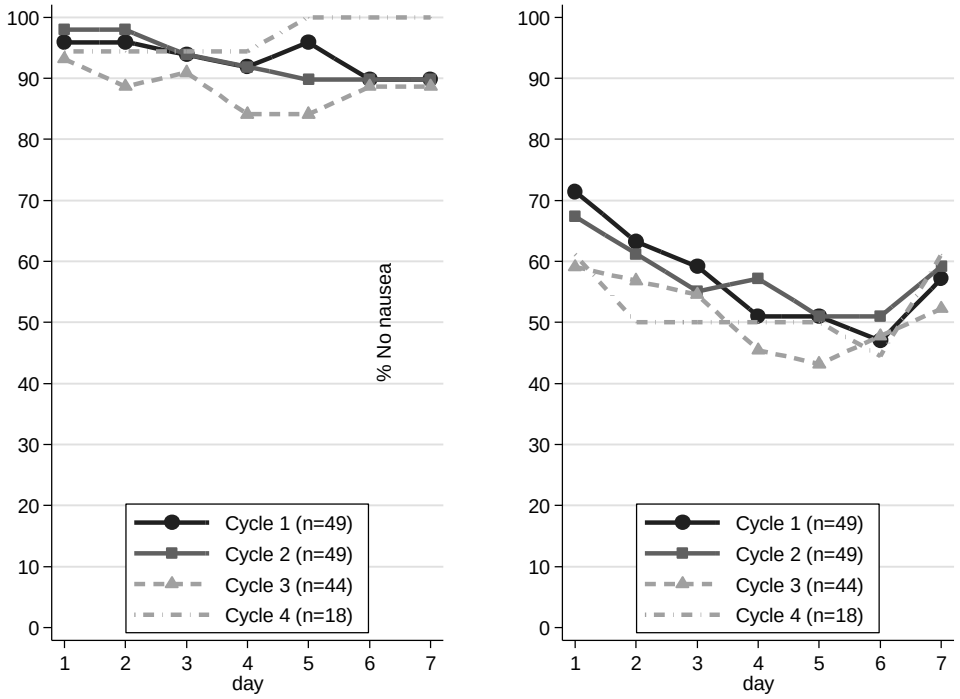

Figure 2. a Number of emetic episodes in 24 hours when emesis occurred on any day of any cycle

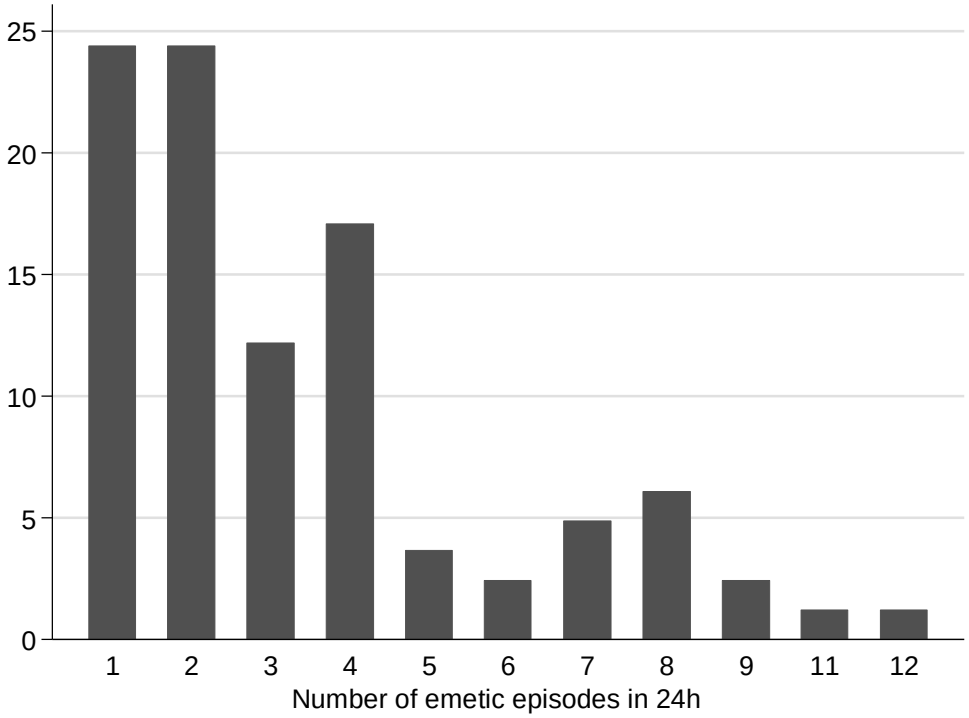

Figure 3. b Intensity of nausea in a 24 hour period when nausea occurred on any day of any cycle

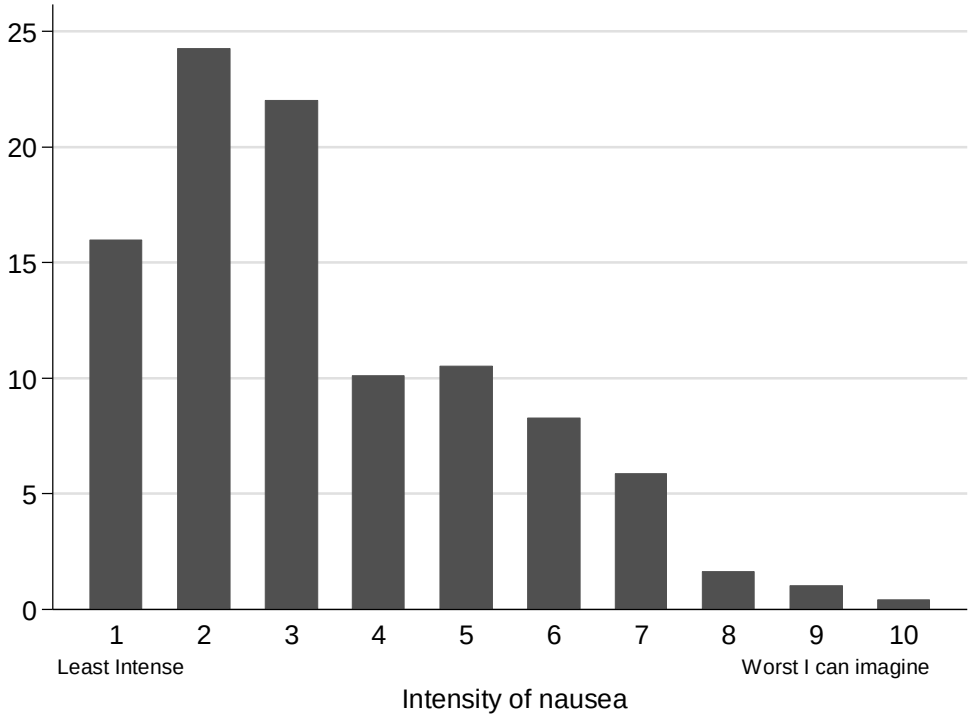

Table 1 Baseline characteristics of the 50 patients enrolled

Characteristic	**Number of patients (%)**
Age (years)	
Median (range)	30 (19-60 years)
≥18 and < 30	24 (48%)
≥ 30 and < 45	18 (36%)
≥ 45	8 (16%)
Sex	
Male	48 (96%)
Female	2 (4%)
ECOG performance status	
0	43 (86%)
1	7 (14%)
N^{o} of alcoholic drinks/week	
Median (range)	1.5 (0-40 drinks)
0	16 (32%)
1-27 (< 4/day)	33 (66%)

28-42 (4-6/day)	1 (2%)
History of motion sickness	
Yes	4 (8%)
No	46 (92%)
Chemotherapy regimen	
BEP	34 (68%)
Accelerated BEP	13 (26%)
EP	3 (6%)
Tumor markers	
AFP	
Median (range) microg/L	7 (1-112885)
< 1000 microg/L	46 (92%)
≥ 1000 and ≤ 10000 microg/L	3 (6%)
> 10000 microg/L	1 (2%)
B-HCG	
Median (range) U/L	6 (1- 989000)
< 5000 U/L	42 (86%)
≥ 5000 and ≤ 50000 U/L	4 (8%)
> 50000 U/L	3 (6%)
LDH	
< 1.5 x ULN	31 (65%)
≥ 1.5 x and ≤ 10 x ULN	16 (33%)
> 10 x ULN	1 (2%)

Table 2 Adherence to antiemetic therapy

Drug	**Cycle**							
	1 (n=50)		2 (n=49)		3 (n=46)		4 (n=19)	
	No	%	No	%	No	%	No	%
Aprepitant	46	92	48	98	43	93	19	100
Dexamethasone	43	86	48	98	40	87	19	100

5 HT_3 Receptor Antagonist	48 96	49 100	46 100	19 100

Table 3 Efficacy of the antiemetic regimen for a cycle

	% Patients			
	Cycle 1		**Cycles 2-3-4**	
	Day 1	**Days 1-7**	**Day 1**	**Days 1-7**
No emesis	96	82	98-93-94	84-80-94
No emesis & no rescue	78	41	82-64-61	55-45-56
No significant nausea (<2/10 VAS)	80	37	76-66-78	43-39-44
No nausea	71	27	67-59-61	41-36-39
No rescue	80	45	84-66-61	57-50-56

Table 4 Outcome by pre-treatment characteristics

	Emesis during days 1 to 7 of cycle 1	
	Yes n=9 (18%)	No n=40 (82%)
Vomited pre-cycle		
No	6 (13%)	39 (87%)
Yes	3 (75%)	1 (25%)
Age		
≥18 and < 30	3 (13%)	21 (88%)
≥ 30 and < 45	3 (18%)	14 (82%)
≥ 45	3 (38%)	5 (63%)
Gender		
Female	0 (0%)	2 (100%)
Male	9 (19%)	38 (81%)

Chemotherapy regimen		
Accelerated BEP	3 (25%)	9 (75%)
BEP	6 (18%)	28 (82%)
EP	0 (0%)	3 (100%)
Extent of alcohol use		
0	4 (27%)	11 (73%)
0.5-27 (< 4/day)	5 (15%)	28 (85%)
28-42 (4-6/day)	0 (0%)	1 (100%)
History of motion sickness		
No	8 (18%)	37 (82%)
Yes	1 (25%)	3 (75%)
Pre-treatment B-HCG level		
< 5000 U/L	6 (15%)	35 (85%)
≥ 5000 and ≤ 50000 U/L	1 (25%)	3 (75%)
> 50000 U/L	2 (67%)	1 (33%)

Author/s:
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