Original article

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Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type

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Background: We conducted two parallel phase II trials in chemonaïve and previously treated patients with metastatic nasopharyngeal carcinoma (NPC) to evaluate the tumour response, progression-free and overall survival, and toxicity of gemcitabine.

Patients and methods: Gemcitabine 1250 mg/m^2 was given on days 1 and 8 of a 21-day cycle. Patients with an Eastern Cooperative Oncology Group performance status <2, adequate renal, hepatic and bone marrow function, and radiologically measurable NPC were eligible.

Results: Twenty-five chemonaïve and 27 previously treated patients were enrolled. The overall response rate was 28% [95% confidence interval (CI) 14% to 48%] for the chemonaïve and 48% (95% CI 31% to 66%) for previously treated patients. Toxicities greater than or equal to grade 3 occurred in 15 (60%) chemonaïve and 13 (48%) previously treated patients. Neutropenia was uncommon in chemonaïve patients, but occurred in 37% of previously treated patients. The median time to progression was 3.6 months (range 0.9–7.9) for chemonaïve and 5.1 months (0.9–13.1) for previously treated patients. Median overall survival time was 7.2 months (1.4–15.6) and 10.5 months (2.4–15.0) for chemonaïve and previously treated patients, respectively.

Conclusions: Gemcitabine has moderate activity in NPC with minimal toxicity, and is also an effective salvage agent for patients who have failed or progressed after treatment with other agents.

Key words: gemcitabine, metastatic nasopharyngeal carcinoma

Introduction

Nasopharyngeal carcinoma (NPC) differs from squamous-cell head and neck cancer. Most notable are its unusual geographical distribution and a greater tendency for systemic dissemination [1, 2]. NPC is endemic in Singapore, ranking among the top 10 cancers in both genders [3] and accounting for approximately 60% of all head and neck cancers. At least 60% of patients with NPC present with locally advanced disease, while 5% to 8% present with distant metastases at diagnosis [4, 5]. With radical radiotherapy as the sole treatment modality, 30–60% of the patients with stages III and IV disease will relapse systemically within 5 years of diagnosis.

The high response rate to chemotherapy of NPC is well documented [6–14]. Platinum-based regimens, which are often used in the palliative setting, have demonstrated reproducibly high activity. The combination of cisplatin and 5-fluorouracil (5-FU) developed by Wayne State University is well established as an effective regimen for squamous-cell head and neck cancer [15]. This combination was also found to have high activity in NPC [6, 7]. Interestingly, there were two studies that reported long-term disease-free survivors in patients treated with more aggressive platinum-containing regimens [11, 12]. To date, however, there have been no randomised studies comparing the different platinum-containing regimens in NPC. Due to the high activity and the relatively low myelotoxicity and good tolerability, the combination of cisplatin and 5-FU has remained a standard regimen in metastatic NPC in our centre.

Few studies, however, have examined the activity of the newer chemotherapeutic agents or regimens specifically in NPC. This is partly because NPC is uncommon in the Western world, where much of the cancer research activity occurs. In 1994, we reported that paclitaxel when used as a single agent at 175 mg/m^2 infused over 3 h has a partial response rate of 22% with no complete responses seen [8]. When combined with carboplatin at an area under the curve of 6 mg·min/ml, the response rate improved to 75% with only one complete response seen [9]. Yeo et al. [10] reported a slightly lower

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response rate of 59% with the same combination, but with a lower dose of paclitaxel at 135 mg/m^2 infused over 3 h. The durability of the responses and the median survival with this combination do not appear to be improved when compared with our historical data with 5-FU and cisplatin in combination.

Gemcitabine, a novel nucleoside anti-metabolite, has gained worldwide interest in the oncology community for, among other reasons, its broad spectrum of activity against various solid tumours including head and neck, non-small-cell lung, ovarian and pancreatic cancers [16, 17], its ease of administration and its favourable toxicity profile. The last feature is especially attractive for use in the palliative setting. Gemcitabine's novel mechanism of action, compared with the other known active agents, makes it worthwhile to study this agent in NPC and to incorporate it into new combination regimens if it proves to be active.

We, therefore, conducted two parallel trials of gemcitabine in metastatic NPC to determine the efficacy and tolerability of gemcitabine as first-line therapy in chemonaïve patients and as salvage treatment in patients who have failed or progressed after treatment with other chemotherapeutic agents.

Patients and methods

Eligibility criteria

Patients eligible for the study were required to have histologically confirmed undifferentiated carcinoma arising from the nasopharynx. They had to have bidimensionally measurable disease based on radiological and/or clinical examination. The measurable lesion(s) of interest must not have been within any prior radiotherapy fields. Patients had to be between 18 and 75 years old, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) <2. Additional eligibility criteria included adequate bone marrow reserve (white blood cell count >3000/mm^3 and platelets >100 000/mm^3), adequate renal function (serum creatinine level <141 μmol/l) and hepatic function (alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase concentrations <2 times the upper limit of normal and bilirubin level <24 μmol/l). Written informed consent was obtained from each patient prior to enrolment and the protocol was approved by the Ethics Committee of the Institution and the Medical Clinical Research Committee of the Ministry of Health in Singapore. Patients were excluded from the study if they exhibited other malignant disease and unstable serious coexisting medical condition(s).

Treatment schedule

All patients were administered with a maximum of six cycles of gemcitabine at a dose of 1250 mg/m^2 over 30 min on days 1 and 8 of a 21-day cycle. Gemcitabine therapy was discontinued if there was disease progression or unmanageable toxicity.

Gemcitabine was reduced to 75% of the calculated dose for thrombocytopenia (a platelet count between 75 000 and 100 000/mm^2) and granulocytopenia (a granulocyte count between 1000 and 1500/mm^2). If the platelet and granulocyte counts were <75 000 and 1000/mm^2, respectively, treatment was withheld for that particular dose until the next scheduled dose was due. If haematological recovery did not occur at the next scheduled dose, the patient did not continue in the study.

Baseline and treatment evaluations

Pre-treatment evaluation included a medical history, clinical examination, a complete blood cell count and chemistry assessment and urinalysis. Computed tomography scans of the relevant region(s) were obtained for all patients at baseline and repeated every two cycles to assess tumour response. Standard World Health Organisation (WHO) criteria were used in the evaluation of tumour response. Time to progression was computed from the time of enrolment to the first documentation of disease progression. Similarly, survival time was calculated from the time of enrolment to the time of death or, in the case of continuing survival or lost to follow-up, the date of last contact.

Best response, which was recorded from the start of treatment until disease progression or up to a maximum of six cycles of gemcitabine, was used in the assessment of objective tumour response. The overall response rate was thus expressed as the proportion of patients demonstrating a complete or partial response based on all patients recruited. Those patients in whom the response could not be assessed were regarded as treatment failures.

Toxicity observed during treatment was graded according to WHO toxicity criteria [18] after each cycle of chemotherapy was completed. Safety and tolerability were assessed by physical examination, observation and questioning of patients regarding adverse events, and monitoring of haematology and clinical chemistry. Patients were followed up monthly for 6 months and every 2 months thereafter.

Statistical design and evaluations

Patients who were chemonaïve and those who had prior chemotherapy were registered in two parallel trials using a common protocol through the Clinical Trials and Epidemiology Research Unit of the National Medical Research Council in Singapore. The sample size was estimated separately for each trial, assuming a one-sided test size of 5% and a power of 80%.

A total of 25 chemonaïve patients were to be enrolled in the first trial (trial 1), which assumed an overall response rate (complete plus partial) of 30% and no further interest in gemcitabine if the response was as low as 10%. Using the Simon minimax design [19], 15 patients were to be recruited in stage 1, requiring at least two responses before proceeding to recruit an additional 10 patients in stage 2. Efficacy was demonstrated if six or more responses were observed from the total of 25 patients.

A total of 27 patients who had previous chemotherapy were to be enrolled in the second trial (trial 2), which assumed an overall response rate of 20% and no further interest in gemcitabine if the response was as low as 5%. Using the Simon minimax design, 13 patients were to be recruited in stage 1, requiring at least one response before proceeding to recruit an additional 14 patients in stage 2. Efficacy was demonstrated if four or more responses were observed from the total of 27 patients.

The 95% confidence interval (CI) for the response rate was calculated using the formula described by Newcombe and Altman [20]. The 95% CIs for the survival estimates were calculated using Greenwood's formula. Progression-free and overall survival probabilities were estimated using the Kaplan–Meier method [21].

The trial data were collected on printed forms, and subsequently entered into CLINTRIAL [22], specialised software for managing longitudinal trial data. This program facilitates interactive entry and data correction, and maintains consistent and accurate trial data. All statistical

analyses were generated using SPSS for Windows Version 8.0 [23] and performed on an intention-to-treat basis.

Results

A total of 52 patients were enrolled in the two trials between January and November 1999; 25 chemonaïve patients (15 in stage 1 and 10 in stage 2) were enrolled in trial 1 and 27 prior chemotherapy patients (13 in stage 1 and 14 in stage 2) were enrolled in trial 2.

Patient characteristics

Patient characteristics for trials 1 and 2 are presented in Table 1. In trial 1, the median age of the 25 chemonaïve

Table 1. Patient demographic and clinical characteristics

	Trial 1 (*n* = 25)	Trial 2 (*n* = 27)
Median age (range), years	47 (29–75)	46 (35–67)
Male/female, *n* (%)	18 (72.0)/7 (28.0)	24 (88.9)/3 (11.1)
Race, *n* (%)		
Chinese	24 (96.0)	24 (88.9)
Malay	1 (4.0)	2 (7.4)
Indian	0	1 (3.7)
ECOG performance status, *n* (%)		
0	5 (20.0)	14 (51.9)
1	11 (44.0)	11 (40.7)
2	9 (36.0)	2 (7.4)
Locoregional disease status, *n* (%)		
Yes	15 (60.0)	13 (48.1)
No	10 (40.0)	14 (51.9)
Previous RT, *n* (%)		
Yes	19 (76.0)	22 (81.5)
No	6 (24.0)	5 (18.5)
Site of metastasis, *n* (%)		
Bone only	2 (8.0)	0
Liver only	1 (4.0)	4 (14.8)
Lung only	2 (8.0)	3 (11.1)
Distant lymph node only	0	4 (14.8)
Multiple sites	20 (80.0)	16 (59.3)
Bone, liver	2 (8.0)	5 (18.5)
Bone, lung	2 (8.0)	1 (3.7)
Liver, lung	1 (4.0)	0
Liver, lymph node	1 (4.0)	0
Lung, lymph node	2 (8.0)	3 (11.1)
Skin, lymph node	1 (4.0)	0
Others	11 (44.0)[a]	7 (25.9)[b]
Previous chemotherapy, *n* (%)		
5-fluorouracil (5-FU) + cisplatin (PF)	–[c]	16 (59.2)
Cisplatin alone	–	1 (3.7)
Oral 5-FU + eniluracil	–	2 (7.4)
Paclitaxel + carboplatin (TC)	–	2 (7.4)
PF followed by TC	–	3 (11.1)
Oral 5-FU+ eniluracil followed by TC	–	3 (11.1)

[a]Includes seven cases with three sites involving bone, liver or lung; and four cases with four sites involving bone, liver or lung.
[b]Includes four cases with three sites involving bone, liver or lung; and three cases with four sites involving bone, liver or lung.
[c]Chemonaïve patients.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy.

patients was 47 years, with a range of 29 to 75 years. There was a prevalence of males (72%) and Chinese (96%). The majority (64%) of patients had a baseline ECOG PS of 0 or 1. At the time of enrolment, 15 (60%) patients had locoregional disease; nine (60%) of these had previous radiotherapy. Twenty (80%) patients had multiple sites of metastasis at the time of recruitment: 15 (60%) had liver metastasis, 17 (68%) lung metastasis and 15 (60%) bone metastasis. Two (8%), two (8%) and one (4%) patient(s) had single metastatic sites in the bone, lung and liver, respectively.

In trial 2, the median age of the 27 previously treated patients was 46 years (range 35–67 years). Eighty-nine per cent were male; the proportion of patients of Chinese ethnicity was the same. Most patients had a baseline ECOG PS of 0 (52%) or 1 (41%). Thirteen patients (48%) had locoregionally active disease, of whom eight (62%) had previous radiotherapy. At the time of enrolment, 16 (59%) patients had multiple sites of metastasis: 16 (59%) had liver, 11 (41%) lung and 12 (44%) bone metastasis. Four (15%) patients had metastasis to the liver only and three (11%) in the lung only. There were also four (15%) patients who had metastasis to the distant lymph nodes only.

Previous chemotherapeutic agents administered included 5-FU, cisplatin, paclitaxel and carboplatin. The majority (78%) of patients had received one previous combination regimen; six patients (23%) were treated with two different combination regimens before accrual. The progression-free interval between starting accrual on this trial and the last prior chemotherapy dose was <3 months in seven (26%) patients and >3 months in 20 (74%) patients, with a median of 8 months (range 1–27).

Treatment compliance

In trial 1, treatment was discontinued for 11 chemonaïve patients because of disease progression. Of the 11 patients, one completed only the first cycle, four completed two cycles, one completed three cycles and five completed four cycles of chemotherapy. In addition, the dose was reduced per protocol because of low neutrophil counts for two patients; one subsequent gemcitabine dose was also omitted in one of these patients because of grade 3 neutropenia. Three patients refused further treatment after cycles 2, 3 and 5, respectively. Another patient did not feel well enough to receive the last dose of gemcitabine in cycle 6.

In trial 2, treatment was discontinued for seven patients who had prior chemotherapy (one after cycle 1, two after cycle 2, three after cycle 4 and one after cycle 5) due to disease progression. Additionally, gemcitabine doses were reduced per protocol in three patients because of low neutrophil counts and one gemcitabine dose was omitted in four patients due to grade 3 neutropenia. One patient defaulted treatment after the first cycle, and an additional patient refused treatment at cycle 6.

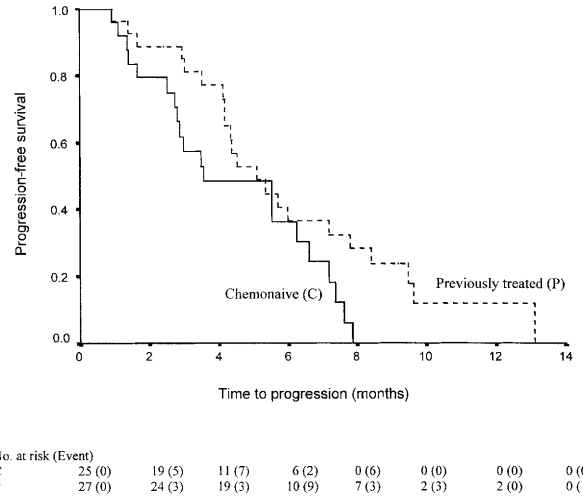
Tumour response

Tumour response for both trials is presented in Table 2. Of the 15 chemonaïve patients recruited in stage 1 of trial 1, four were not evaluable for tumour response (two refused further treatment and two died from pulmonary embolism and pneumonia, respectively, after cycle 2). Tumour evaluation for these two patients was not possible because the pulmonary embolism and pneumonia, which were deemed non-treatment-related, occurred soon after the second cycle. Of the 11

Table 2. Response to treatment

Response	Stage 1 *n* (%)	Stage 2 *n* (%)	Total *n* (%)	ORR (95% CI)
Trial 1				
Complete	0	1 (10.0)	1 (4.0)	—
Partial	3 (20.0)	3 (30.0)	6 (24.0)	—
Stable	5 (33.3)	2 (20.0)	7 (28.0)	—
Progression	3 (20.0)	4 (40.0)	7 (28.0)	—
Not evaluable	4 (26.7)	0	4 (16.0)	—
Total	15	10	25	28.0% (14.3–47.6%)
Trial 2				
Complete	1 (7.7)	0	1 (3.7)	—
Partial	6 (46.2)	6 (42.9)	12 (44.4)	—
Stable	4 (30.8)	4 (28.6)	8 (29.6)	—
Progression	1 (7.7)	2 (14.3)	3 (11.1)	—
Not evaluable	1 (7.7)	2 (14.3)	3 (11.1)	—
Total	13	14	27	48.1% (30.7–66.0%)

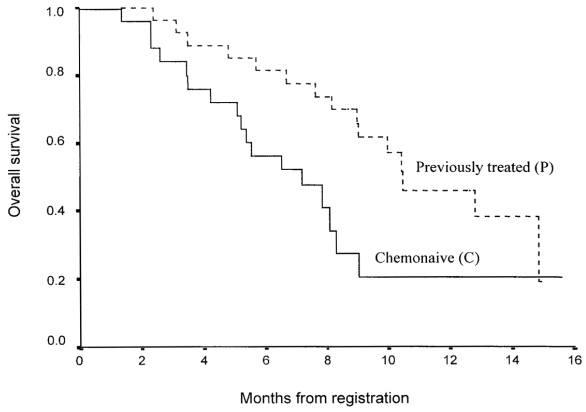
Abbreviation: ORR, overall response rate (complete + partial).



No. at risk (Event)

C	25 (0)	19 (5)	11 (7)	6 (2)	0 (6)	0 (0)	0 (0)	0 (0)
P	27 (0)	24 (3)	19 (3)	10 (9)	7 (3)	2 (3)	2 (0)	0 (1)

Figure 1. Progression-free survival distribution of chemonaïve and previously treated patients.



No. at risk (Death)

C	25 (0)	24 (1)	19 (5)	14 (5)	6 (3)	1 (3)	1 (0)	1 (0)	0 (0)
P	27 (0)	27 (0)	24 (3)	22 (2)	19 (2)	13 (4)	8 (2)	3 (1)	0 (1)

Figure 2. Overall survival distribution of chemonaïve and previously treated patients.

patients who were evaluable for tumour response, a complete response was not observed, while three patients achieved partial response.

The recruitment of an additional 10 patients as indicated by the study design was thus initiated in stage 2, with four additional patients achieving a response (one complete, three partial). The overall response rate to gemcitabine in trial 1 was, therefore, 28% (95% CI 14% to 48%). A total (in stages 1 and 2) of seven patients each had stable disease or progressed.

Of the 13 previously treated patients recruited in stage 1 of trial 2, seven achieved a response (one complete, six partial) and one patient was not evaluable. The latter patient defaulted soon after the first cycle and did not return for the follow-up measurement, thus no tumour response data were available for this patient. The responses observed among the 12 assessable patients led to a subsequent recruitment of 14 additional patients in stage 2. Two of the 14 patients were not evaluable. One of these patients had a 25% reduction of measurable sites after cycle 2, but died shortly after cycle 3 before confirmation of a partial response; he was admitted to the hospital for massive nasal bleeding that led to cardiac arrest and anoxic encephalopathy. The other patient had achieved more than a 50% reduction of measurable sites, but died after cycle 3 before confirmation of a partial response. We were unable to determine the cause of death for each of these patients and whether the deaths were treatment-related. Of the 12 assessable patients, an additional six partial responses were observed. Thus, the overall response rate to gemcitabine among the 27 evaluable patients was 48% (95% CI 31% to 66%). A total (in stages 1 and 2) of eight patients attained stable disease and three progressed. Three of seven patients who began gemcitabine treatment within 3 months of their previous chemotherapy regimens had response with salvage gemcitabine: one patient achieved complete response, one had a partial response and one showed more than a 50% reduction of measurable sites after the second course of gemcitabine, but died shortly after the third course of gemcitabine. The cause of death was unknown.

Time to progression

At a median follow-up time of 9.7 months in trial 1, disease had progressed in 20 (80%) chemonaïve patients, with a median time to progression of 3.6 months (range 0.9–7.9). The rate of progression at 6 months was 36% (95% CI 15% to 58%). In trial 2, with a median follow-up time of 12.6 months, disease had progressed in 22 (81%) previously treated patients, with a median time to progression of 5.1 months (range 0.9–13.1). At 6 months, the progression rate was 41% (95% CI 21% to 60%). Figure 1 presents the Kaplan–Meier curves of progression-free survival for trials 1 and 2.

Survival

A total of 17 deaths have been reported in trial 1: 13 due to disease progression, three due to pneumonia and one due to pulmonary embolism. The median follow-up time for the eight patients who are alive was 7.7 months (range 7.2–15.6), although all eight patients have progressed. The median overall survival time was 7.2 months (range 1.4–15.6) and the 1-year survival rate was 20% (95% CI 1% to 40%).

A total of 15 deaths have been reported in trial 2: 13 due to disease progression, one from massive nasal bleeding and another from an unknown cause. The median follow-up time for the 12 patients who are alive was 11.4 months (range 6.4–15.0). Disease progression has been documented in all but two of these patients, both of whom had a partial response. The median overall survival time was 10.5 months (range 2.4–15.0) and the 1-year survival probability was 46% (95% CI 25% to 67%). The Kaplan–Meier curves of overall survival are presented in Figure 2.

Toxicity

Toxicities reported for both trials are presented in Table 3. No treatment-related deaths were reported in either trial. In general, gemcitabine was well tolerated and the main toxicities were mainly haematological. In trial 1, a total of 102 cycles of gemcitabine were administered to all 25 chemonaïve patients. Fifteen (60%) patients had either grade 3 or 4 toxicity. Of these only two patients had grade 4 toxicities, one with anaemia and the other with grade 4 infection. The most common toxicity was that of anaemia accounting for 14 episodes in nine patients. Neutropenia was uncommon in this group, with only one case (grade 3) reported.

In trial 2, the 27 patients with prior chemotherapy received a total of 135 cycles of gemcitabine. Grade 3 or 4 toxicity was observed in 13 (48%) patients, of whom one each had grade 4 anaemia, elevated serum alkaline phosphatase and thrombocytopenia. In contrast to the chemonaïve patients in trial 1, neutropenia (grade 3 only) was the most common toxicity in trial 2, with 15 episodes occurring in 10 patients.

Five patients (two in trial 1 and three in trial 2) had dose reductions due to a low neutrophil count and five patients (one in trial 1 and four in trial 2) had dose omissions due to grade 3 or 4 neutropenia. The actual mean dose per week for gemcitabine was 1245.8 mg/m^2 (for the six cycles) for chemonaïve patients and 1230.6 mg/m^2 for previously treated patients.

Discussion

The high response of NPC to chemotherapy is well established, with response rates of approximately 17% to 39% for single-agent chemotherapy [24] and 60% to 70% for combination chemotherapy in chemonaïve patients [6–14]. In our analysis of the prognostic determinants of more than 200 patients with metastatic NPC, chemotherapy administration was shown to have a favourable impact on the survival outcome of these patients [25].

The combination of cisplatin and 5-FU is very active and has been used as a standard regimen for NPC in our centre to date [6, 7]. The response duration, however, is invariably short, averaging approximately 7 months in most studies. Paclitaxel was found to be active in NPC, with single-agent activity of approximately 20% [8]. The combination of paclitaxel and carboplatin appeared to have activity equivalent (approximately 60% to 70%) to that of the platinum and 5-FU combination, although there was no improvement in the response duration [9, 10].

In conclusion, gemcitabine has moderately high single-agent activity in NPC of the undifferentiated type. It is effective as both a first-line and a salvage treatment as indicated by the response rates of 28% and 48%, respectively, observed in our study. In addition, it appears to be relatively non-cross-resistant with other active agents. This is supported by the responses observed in three of seven patients who had progressed within 3 months of receiving treatment with a platinum-based regimen. While it appears that patients who had prior treatment seemed to respond better to gemcitabine, this can probably be explained by patient selection. The patients who had prior chemotherapy had better PSs and lower disease bulk, as evidenced by the fewer sites of distant metastases, at accrual. Gemcitabine is well tolerated, with a low incidence of haematological and non-haematological toxicity (Table 3). Patients who had prior chemotherapy appeared predisposed to gemcitabine-induced neutropenia, but the incidence of sepsis or fever was similar for the two groups.

Combining gemcitabine with other agents would be the next logical step in enhancing its chemotherapeutic effectiveness against NPC. The inclusion of gemcitabine in a triplet combination is an attractive option. The use of triplet combinations has shown improved results in terms of response rate and survival in other solid tumours, particularly lung cancer [26–28]. On the basis of these results, we have designed a study to investigate the triplet combination of gemcitabine, paclitaxel and carboplatin in metastatic NPC.

Table 3. Distribution of World Health Organisation grades 3 and 4 toxicity

Toxicities	Trial 1				Trial 2			
	grade 3		grade 4		grade 3		grade 4	
	patient (n = 25)	cycle (n = 102)	patient (n = 25)	cycle (n = 102)	patient (n = 27)	cycle (n = 135)	patient (n = 27)	cycle (n = 135)
Anaemia	8 (32.0%)	13 (12.7%)	1 (4.0%)	1 (1.0%)	4 (14.8%)	7 (5.2%)	1 (3.7%)	2 (1.5%)
Alkaline phosphatase	4 (16.0%)	4 (3.9%)	0	0	2 (7.4%)	6 (4.4%)	1 (3.7%)	1 (0.7%)
Neutropenia	1 (4.0%)	1 (1.0%)	0	0	10 (37.0%)	15 (11.1%)	0	0
Leukopenia	1 (4.0%)	1 (1.0%)	0	0	5 (18.5%)	6 (4.4%)	0	0
Thrombocytopenia	2 (8.0%)	3 (2.9%)	0	0	0	0	1 (3.7%)	1 (0.7%)
Infection	1 (4.0%)	1 (1.0%)	1 (4.0%)	1 (1.0%)	0	0	0	0
Neurotoxicity	2 (8.0%)	3 (2.9%)	0	0	0	0	0	0
Other[a]	1 (4.0%)	1 (1.0%)	0	0	1 (3.7%)	1 (0.7%)	0	0

[a]Includes nausea and vomiting in trial 1 and transaminitis in trial 2.

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