Support Care Cancer (2013) 21:2575–2581
DOI 10.1007/s00520-013-1835-2

ORIGINAL ARTICLE

The efficacy of triplet antiemetic therapy with 0.75 mg of palonosetron for chemotherapy-induced nausea and vomiting in lung cancer patients receiving highly emetogenic chemotherapy

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Received: 21 January 2013 / Accepted: 21 April 2013 / Published online: 5 May 2013

Abstract
Background Chemotherapy-induced nausea and vomiting (CINV) are some of the most problematic symptoms for cancer patients. Triplet therapy consisting of a 5HT3 receptor antagonist, aprepitant, and dexamethasone is a guideline-recommended antiemetic prophylaxis for highly emetogenic chemotherapy (HEC). The efficacy and safety of triplet therapy using a 0.75-mg dose of palonosetron have not yet been investigated. We performed a prospective phase II study using triplet antiemetic therapy with 0.75 mg of palonosetron.
Methods Chemotherapy-naïve lung cancer patients scheduled to receive HEC were enrolled. The eligible patients were pretreated with antiemetic therapy consisting of the intravenous administration of 0.75 mg of palonosetron, and 9.9 mg of dexamethasone and the oral administration of 125 mg of aprepitant on day 1, followed by the oral administration of 80 mg of aprepitant on days 2–3 and the oral administration of 8 mg of dexamethasone on days 2–4. The primary endpoint was the complete response rate (the CR rate; no vomiting and no rescue medication) during the overall phase (0–120 h).
Results The efficacy analysis was performed in 63 patients. The CR rates during the overall, acute and delayed phases were 81.0, 96.8, and 81.0 %, respectively. The no nausea and no significant nausea rate during the overall phase were 54.0 and 66.7 %, respectively. The most common adverse event was grade 1 or 2 constipation.

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Conclusions Triplet antiemetic therapy using a 0.75-mg dose of palonosetron shows a promising antiemetic effect in preventing CINV in lung cancer patients receiving HEC.

Keywords CINV · Highly emetogenic chemotherapy · Palonosetron · Aprepitant

Introduction

Chemotherapy-induced nausea and vomiting (CINV) are some of the most problematic symptoms experienced by patients undergoing cancer treatments. Chemotherapeutic agents are classified according to their emetogenicity in the antiemetic guidelines. The guidelines recommend a suitable antiemetic therapy for each emetic risk category [1, 13]. Many medical oncologists agree that there has been remarkable progress with antiemetic therapy for highly emetogenic chemotherapy (HEC). Aprepitant, the first substance P/neurokinin-1 (NK-1) receptor antagonist was approved globally and, as a result, the control of delayed emesis improved [5, 12]. However, the complete response rate (the CR rate) of triplet antiemetic therapy (aprepitant, a first-generation 5-HT3 receptor antagonist [5HT3RA], and dexamethasone) for HEC throughout the entire observation period plateaued at 62.7–72.7 %. These results suggested that approximately one third of the patients treated with HEC experienced some emetic events and that the prevention of CINV in patients receiving HEC needs to be further investigated.

Second-generation 5HT3RA palonosetron was recently approved worldwide. Palonosetron was determined to be more effective than first-generation 5HT3RAs in preventing delayed nausea and vomiting among patients receiving HEC in several phase III studies and a meta-analysis. The 0.75-mg dose of palonosetron was approved in Japan due to the clear dose–response relationship in antiemetic efficacy in two Japanese phase II studies [10, 18], and the efficacy and safety of a 0.75-mg dose of palonosetron with dexamethasone was confirmed in a randomized phase III study in Japan [16]. Triplet antiemetic therapy consisting of a 0.75-mg dose of palonosetron, aprepitant, and dexamethasone is widely used in Japanese clinical practice, although the prospective efficacy data for this triplet antiemetic therapy have not yet been reported.

A 50 mg/m^2 or higher dose of cisplatin is categorized as a highly emetogenic agent [6]. Lung cancer patients are usually treated with cisplatin-based chemotherapy in clinical practice; thus, these patients have had many opportunities to be treated with HEC. The reduction of CINV in highly emetogenic chemotherapy is important for lung cancer patients.

We conducted this prospective phase II study to evaluate the efficacy of the triplet antiemetic therapy consisting of a 0.75-mg dose of palonosetron, a 3-day course of aprepitant, and 4 days of dexamethasone treatment in chemotherapy-naïve lung cancer patients scheduled to receive HEC.

Patients and methods

This study was a prospective, multicenter phase II study conducted in the Niigata Lung Cancer Treatment Group in accordance with the Declaration of Helsinki. This study was registered at the University hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000004865. Written approval was obtained from the Institutional Review Boards. All of the patients provided written informed consent before enrollment. Eleven institutes enrolled patients between Sep 2010 and Jun 2012.

Patient population

This study enrolled chemotherapy-naïve lung cancer patients scheduled to receive HEC. The HEC regimen was defined as doublet chemotherapy containing a 50 mg/m^2 or higher dose of cisplatin, in accordance with the Hesketh classification [6]. The main exclusion criteria were as follows: emesis within 24 h of chemotherapy administration; symptomatic brain metastasis or suspected clinical brain metastasis; concomitant radiotherapy; complications that prohibited dexamethasone use; or known hypersensitivity to palonosetron, aprepitant, or dexamethasone. Eligible patients were treated with the triplet antiemetic therapy, which included the intravenous administration of 0.75 mg of palonosetron, the intravenous administration of 9.9 mg of dexamethasone on day 1, and the oral administration of 125 mg of aprepitant on day 1, followed by 80 mg of aprepitant on days 2 and 3 and 8 mg of dexamethasone on days 2 to 4.

Assessment

The efficacy and safety of the antiemetic therapy were assessed during an observation period that started at the administration of the HEC and lasted up to 120 h. The patients were provided with a daily questionnaire to record any vomiting episodes, nausea ratings, impairment of eating habits, any use of rescue therapy, and the degree of constipation or diarrhea. The patients assessed their nausea with a 100-mm horizontal visual analog scale (VAS). Scores of 5–100 or 25–100 mm in the VAS scale indicated that patients had experienced nonsignificant or significant nausea, respectively.

Objectives

The primary endpoint measured was the proportion of the patients who did not experience vomiting or did not require

rescue medication (CR rate) during any part of the entire observation period (the overall phase). The secondary endpoints were (1) the CR rate during the acute phase (0–24 h) and the late phase (24–120 h); (2) the proportion of the patients who experienced no vomiting episodes and significant nausea without needing rescue medication (complete control rate (CC rate)) during the acute, delayed, and overall phases; (3) the proportion of patients who experienced no nausea, no significant nausea, and no impairment of eating habits during the acute, delayed, and overall phases; and (4) safety. The adverse events associated with the triplet therapy were assessed by the investigators using Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0 criteria.

Statistical analysis

This single-arm phase II study was designed to assess the antiemetic efficacy on the CR rate during the overall phase. The sample size was calculated to be at least 61 patients based on the assumption that the CR rate would be less than or equal to 60 % (null hypothesis), and the alternative hypothesis that the CR rate would be greater than 75 % during the overall phase, with a risk alpha of 5 % and a power of 80 %. Allowing some follow-up losses, the total sample size required was determined to be 65 patients or more. All of the statistical analyses were performed using JMP 9 statistical software for Macintosh (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient characteristics

Seventy-two patients enrolled in the study between Sep 2010 and Jun 2012; five patients were excluded because of protocol violations. The safety analysis included 67 patients. Four patients were excluded from the efficacy analysis because of a lack of efficacy data; thus, the end result efficacy analysis was performed with 63 patients.

The patient characteristics are presented in Table 1. Forty-four of the 67 patients (65.7 %) were male, with a median age of 64 years. All of the patients had performance statuses of 0 to 1. The most common tumor histology was adenocarcinoma (56.7 %), and nine small cell lung cancer patients were included (13.4 %). Most of the patients had advanced or recurrent disease and 22 of the 67 patients (32.8 %) were treated with adjuvant chemotherapy.

All of the patients were treated with a 60 mg/m^2 or greater dose of cisplatin, with a mean cisplatin dose of 76.6 mg/m^2. The concurrent use of emetogenic agents with cisplatin was as follows: pemetrexed (38.8 %), vinorelbine (32.7 %), gemcitabine (9.0 %), irinotecan (7.5 %), etoposide (7.5 %), and docetaxel (4.5 %).

Efficacy results

The primary and secondary endpoints are summarized in Table 2. Fifty-one of the 63 patients achieved CR during the overall phase (81.0, 95 % CI; 69.6–88.8 %); thus, the primary endpoint was met. The CR rates during the acute and delayed phases were 96.8 and 81.0 %, respectively. Almost half of the patients (54.0 %) experienced no nausea during the overall and delayed phase. The proportion of patients who experienced no significant nausea during the overall, acute, and delayed phases was 66.7, 93.8, and 66.7 %, respectively. Over half of the patients suffered from appetite loss due to chemotherapy-induced nausea.

Safety

None of the severe adverse events caused by the antiemetic treatment exceeded grade 3 of the CTCAE criteria. The most common adverse events associated with the antiemetic treatment were constipation (all grades 68.2 % [grade 1 50.0 % and grade 2 18.2 %]) and diarrhea (all grades 21.2 % [grade 1 18.2 % and grade 2 3.0 %]). All of the patients suffering from constipation improved with the use of laxatives such as senna or magnesium oxide, and none of the cases required an enema procedure to reduce symptoms.

Discussion

We performed this prospective phase II study using triplet antiemetic therapy consisting of a 0.75-mg dose of palonosetron, aprepitant, and dexamethasone and were able to demonstrate efficacy in preventing CINV in chemotherapy-naïve lung cancer patients treated with HEC without severe toxicity.

Combination therapy consisting of a 5HT3RA, a NK-1 receptor antagonist, and dexamethasone is currently recommended as a standard antiemetic therapy in patients receiving HEC [1, 13]. The previously reported trials that have used triplet antiemetic therapy for patients receiving HEC are listed in Table 3. The first three trials confirmed that the addition of aprepitant to 5HT3RA and dexamethasone significantly enhanced the efficacy of this combination in preventing acute and delayed emesis for patients receiving HEC [5, 12, 17]. However, the CR rates during the overall phase of these trials ranged from 62.7 to 72.7 %, and approximately half of the enrolled patients experienced nausea or vomiting during the entire observation period. It is important to prevent chemotherapy-induced nausea during

Table 1 Patients' characteristics (n=67)

		Number	Percent (%)
Gender	Male	44	(65.7)
	Female	23	(34.3)
Age, years	Median	64	
	(range)	(36–78)	
Performance status	0	34	(50.7)
	1	33	(49.3)
Histology	Non-small cell lung cancer		
	Adenocarcinoma	38	(56.7)
	Squamous cell carcinoma	16	(23.9)
	Large-cell carcinoma	2	(3.0)
	Not otherwise specified	2	(3.0)
	Small cell lung cancer	9	(13.4)
Stage	IIIa	1	(1.5)
	IIIb	4	(6.0)
	IV	32	(47.8)
	Recurrent	8	(11.9)
	Adjuvant chemotherapy	22	(32.8)
Cisplatin dose	60 mg/m^2	5	(7.5)
	70 mg/m^2	1	(1.5)
	75 mg/m^2	24	(35.8)
	80 mg/m^2	37	(55.2)
	Mean dose, mg/m^2	76.6	
Chemotherapy regimen	Cisplatin/Pemetrexed	26	(38.8)
	Cisplatin/Vinorelbine	22	(32.7)
	Cisplatin/Gemcitabine	6	(9.0)
	Cisplatin/Irinotecan	5	(7.5)
	Cisplatin/Etoposide	5	(7.5)
	Cisplatin/Docetaxel	3	(4.5)

the overall phase because such episodes may impair adequate caloric intake and quality of life [3, 9].

Palonosetron has a higher binding affinity for 5HT3 receptors and a significantly longer half-life than the first-generation 5HT3RAs. The plasma-elimination half-life of palonosetron is reported to be approximately 40 h, which is 4 to 10 times longer than the first-generation 5HT3RAs [19]. In addition, animal data suggest that the cross-talk between the 5HT3 and the NK-1 signaling pathways might initiate a synergistic effect [2, 14]. Thus, triplet antiemetic therapy that uses palonosetron and aprepitant is expected to show a clinically meaningful antiemetic efficacy compared with other 5HT3RA and NK-1 inhibitor combinations; several prospective studies have investigated this hypothesis. These trials investigated palonosetron-containing triplet antiemetic therapies in patients receiving HEC and were reported as two phase II trials and one phase III trial [4, 8, 11]. In these trials, the CR rates during the overall phase ranged from 55.6 to 73 %, results that are similar to other triplet antiemetic therapies. However, these results had some limitations in evaluating the differences between the first-generation 5HT3RA and palonosetron.

As a pilot study, the study by Herrington et al. contained too small a number of patients for an effective evaluation and was therefore inconclusive [4]. The phase III study completed by Navari et al. reported a promising CR rate during the overall phase (73 %). However, 63 % of the patients received a combination of doxorubicin and cyclophosphamide as HEC in this trial [11]. While the combination of doxorubicin and cyclophosphamide is categorized as HEC, the emetogenicity of this regimen is slightly milder than high-dose cisplatin; thus, this result may be overestimated. Longo et al. previously reported a phase II study that investigated the efficacy of triplet antiemetic therapy using a 0.25-mg dose of palonosetron for patients receiving HEC [8]. This previous study observed favorable CR rates during the acute and overall phases (92.8 and 70.3 %, respectively). Likewise, our antiemetic therapy consisting of a 0.75-mg dose of palonosetron achieved favorable CR rates during the acute and overall phases (96.8 and 81.0 %, respectively).

Table 2 Efficacy data of each endpoint during overall, acute, and delayed phase

	Phase	Percent (%)	95 % CI
CR rate	Overall	81.0	69.6–88.8
	Acute	96.8	89.1–99.1
	Delayed	81.0	69.6–88.8
CC rate	Overall	63.5	51.1–74.3
	Acute	92.1	82.7–96.6
	Delayed	63.5	51.1–74.3
No nausea	Overall	54.0	41.8–65.7
	Acute	84.1	73.2–91.1
	Delayed	54.0	41.8–65.7
No significant nausea	Overall	66.7	54.4–77.0
	Acute	93.8	84.8–97.5
	Delayed	66.7	54.4–77.0
No impairment of eating habit	Overall	44.4	32.8–56.7
	Acute	92.0	82.7–96.6
	Delayed	44.4	32.8–56.7

No nausea indicate nausea visual analog scale score <5 mm. No significant nausea indicate nausea visual analog scale score <25 mm

CR complete response, *CC* complete control, *CI* confidence interval, *Overall phase* 0–120 h, *Acute phase* 0–24 h, *Delayed phase* 24–120 h

The meta-analysis revealed no significant difference between 0.25 and 0.75 mg of palonosetron in terms of preventing CINV without aprepitant [7]. However, the triplet antiemetic therapy that utilized a 0.75-mg dose of palonosetron showed an approximate 10 % proportional benefit in the CR rate during the overall phase compared with the triplet antiemetic therapy that utilized a 0.25-mg dose of palonosetron. The reason for this additional effect may be due to the dose–response relationship. Palonosetron exhibits a clear dose–response relationship that correlates with the palonosetron concentration in the plasma [10, 18]. In addition, it was suggested that palonosetron inhibits not only the 5HT3 receptor but also exhibits NK-1/5HT3 cross-talk, a property that was expected to increase the drug's efficacy at preventing delayed CINV [2, 15]. The additional effect in the delayed phase may result from the multiplier effect that occurs due to cross-talk between the 5HT3 receptor and the NK-1 receptor and the dose–response effect of palonosetron. While this result was generated by this small study, we hypothesize the existence of a dose–response relationship between palonosetron and aprepitant use. A multicenter phase III trial has been designed to confirm the superiority of triplet therapy utilizing 0.75 mg of palonosetron compared to 1 mg of granisetron. This phase III study is currently ongoing in Japan (UMIN000004863), and its results will confirm the efficacy of palonosetron combined with aprepitant.

In the current study, the most commonly reported adverse event was constipation. The proportion of the patients who experienced constipation was higher in this study than in other trials (Table 3). The 0.75-mg dose of palonosetron increased the risk of constipation compared to the first-generation 5HT3RA [7]. However, this side effect is not clinically meaningful because all of the constipation symptoms were evaluated as grade 1 or 2 and were easily manageable (almost all of the symptoms were controlled through the administration of oral laxatives). The careful management of constipation should be considered when this antiemetic therapy is used.

There are some limitations that may affect the result of this study. First, the proportion of the female subset was relatively low (34 %) compared with other studies. It has been reported that there is a higher emetic risk in the female population, thus this imbalance might have an influence on our results. In the subset analysis of our study, the CR rate during the overall phase of female and male subsets were

Table 3 The summary of clinical efficacy and adverse events of the triplet antiemetic therapy with 5HT3RA, aprepitant, and dexamethasone in patients treated with cisplatin-based highly emetogenic chemotherapy

Reference	5HT3RA (mg)	Dex (mg) days 1/2/3/4	Number	CR rate			No nausea	No sig. nausea	Adverse events	
				All	Acute	Delay			Constipation	Diarrhea
Hesketh et al. [5]	Ond(32)	12/8/8/8	260	72.7	89.2	75.4	48	73	8.0	NA
Poli-Bigelli et al. [12]	Ond(32)	12/8/8/8	283	62.7	82.8	67.7	49	71	12.4	12.1
Schmoll et al. [17]	Ond(32)	12/8/8/8	244	72	87.7	74.1	NA	73	15.6	12.8
Herrington et al. [4]	Palo(0.25)	12/8/8/8	29	55.6	66.7	63.0	NA	NA	NA	NA
Navari et al. [11]	Palo(0.25)	12/8/8/8	120	73	87	72	38[a]	NA	NA	NA
Longo et al. [8]	Palo(0.25)	20/4/4	222	70.3	92.8	70.3	60[a]	91[a]	39	NA
This study	Palo(0.75)	9.9/8/8/8	64	81.0	96.8	81.0	54.0	66.7	66.7	20.6

[a] The proportion of nausea was evaluated by other tool, such as 0 to 10 VAS scale and four-point Likert scale.

5HT3RA 5-hydroxytriptamine-3 receptor antagonist, *Dex* dexamethasone, *CR* complete response, *sig* significant, *Ond* ondansetron, *Palo* palonosetron, *NA* not available

71.4 and 83.7 %, respectively (p=0.251). The CR rate of the female subset tended to be lower than that of the male, but the difference was not significant. This data indicates that gender did not influence the favorable result of this study. Second, there is the discrepancy between the CR rate (81.0 %) and no significant nausea rate (66.7 %). Usually, the CR rate and no significant nausea rate are similar in the CINV trials (Table 3). This discrepancy implied that some patients suffering significant nausea did not receive the rescue medication, and it might affect the high CR rate of this study. Because the investigators prescribed the rescue medications based on the request of the patient and not the questionnaire of patients, these kinds of biases may have occurred.

In summary, this study suggested that the triplet antiemetic therapy consisting of a 0.75-mg dose of palonosetron, aprepitant, and dexamethasone was the most promising regimen in preventing CINV in chemotherapy-naïve lung cancer patients treated with HEC. However, almost half of the patients experienced nausea and impaired eating habits during the overall phase. Further investigation is needed to control CINV during the delayed phase.

Acknowledgments This study was conducted by the Niigata Lung Cancer Treatment Group. The authors are thankful to the participating institutions and the following collaborating investigators: Koh Sato, Satoshi Hokari, Nao Koshio, Jun Koshio, Kosuke Ichikawa, and Toshiki Furukawa (Niigata University Medical and Dental Hospital); Masachika Hayashi and Hideki Kuriyama (Nagaoka Red Cross Hospital); Junichi Tanaka and Akira Hirata (Niigata Prefectural Shibata Hospital); Katsunori Kawamkami, Takahiro Miyabayashi, and Takashi Ishida (Niigata Prefectural Central Hospital); Junko Baba, Yoshiki Hayashi, Toru Hiura, and Tetsuya Abe (Niigata Cancer Center Hospital); Takeshi Ota and Akira Ishida (Nagaoka Chuo General Hospital); Naoya Matsumoto (Nishi-Niigata Chuo National Hospital); Syotetsu Kawabe and Masaki Terada (Saiseikai Niigata Daini Hospital); Yuka Kimura, Takafumi Tezuka, Kazuhiko Ito, and Hiroki Tsukada (Niigata City General Hospital); Yuichi Shimaoka (Niigata Prefectural Koide Hospital); and Koki Matsuyama (Niigata Prefectural Yoshida Hospital). We would like to thank Kumiko Shirai from the Bioscience Medical Research Center at Niigata University Medical and Dental Hospital for her support in data collection and management.

Conflict of interest None declared.

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