

Efficacy analysis of the aprepitant-combined antiemetic prophylaxis for non-round cell soft-tissue sarcoma patients received adriamycin and ifosfamide therapy

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Abstract

Appropriate antiemetic prophylaxis for moderately emetogenic chemotherapy in patients with non-round cell soft-tissue sarcomas (NRC-STs) remains unclear. We retrospectively investigated efficacy and safety of aprepitant-combined antiemetic prophylaxis in patients with NRC-STs receiving adriamycin plus ifosfamide (AI) therapy. Forty NRC-STs patients were enrolled, their median age was 50 years (range 18–74), and 13 (32.5%) were female. Median cycle number of AI therapy was 4. Twenty patients received the doublet antiemetic prophylaxis (5-hydroxytryptamine-3 receptor antagonist and dexamethasone), and 20 received triplet (5-hydroxytryptamine-3 receptor antagonist, dexamethasone, and aprepitant). In the overall period, complete response rate for nausea and emesis in the triplet group was significantly higher than that in the doublet group (70% vs 35%; $P=0.027$). Patients with no-emesis in the overall period were more frequently observed in the triplet group than in the doublet group (90% vs 65%; $P=0.058$). All toxicities other than emesis were almost equivalent in both the groups. These results suggest that a triplet antiemetic prophylaxis may be optimal in the treatment with AI therapy for NRC-STs.

Abbreviations: 5-HT₃ = 5-hydroxytryptamine-3, CYP = cytochrome P450, DEX = dexamethasone, MEC = moderately emetogenic chemotherapy, NK1 = neurokinin 1.

Keywords: antiemetic prophylaxis, aprepitant chemotherapy, soft-tissue sarcoma

1. Introduction

Nausea and vomiting, which are observed in about 80% of patients, are 1 of the most painful problems during chemotherapy for cancers. Appropriate maintenance of these adverse events can achieve better efficacy of chemotherapies and well-preserved quality of life. The introduction of antiemetic drugs, including dopamine receptor antagonists, steroids, and 5-hydroxytryptamine-3 (5-HT₃) receptor antagonists, has been shown to prevent chemotherapy-induced nausea and vomiting (CINV). However, these drugs only possess a modest activity, especially for delayed emesis.^[1–3]

An oral neurokinin 1 (NK1) antagonist, aprepitant, has been reported to prevent not only acute but also delayed CINV in patients receiving highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC).^[4–7] Guidelines for the management of CINV recommend a triplet antiemetic prophylaxis including NK1 antagonists, 5-HT₃ receptor antagonists, and dexamethasone (DEX) for HEC.^[8–10] On the contrary, recommended antiemetic prophylaxis for MEC is a combination of 5-HT₃ receptor antagonists and DEX with or without NK1 antagonists. It is thus unclear whether aprepitant is necessary for all MECs.

Non-round cell soft-tissue sarcomas (NRC-STs) encompass a broad subtype of tumors. The standard therapy for localized NRC-STs is surgical resection. The 5-year survival rate of patients with stage III NRC-STs is still only about 50% because of a high incidence of recurrence and metastasis. A phase III study of adjuvant chemotherapy consisting of anthracycline and ifosfamide compared with surgery alone revealed a significant improvement in the survival of patients with stage III NRC-STs.^[11] These active agents, anthracyclines, which include epirubicin and adriamycin, and also ifosfamide, are classified as moderately emetogenic reagents.^[8,9] Although it has been reported that almost 80% of patients treated with anthracycline plus ifosfamide (AI) had CINV at the any time of the therapeutic periods,^[12,13] no standard antiemetic prophylaxis for AI therapy has yet been established, and especially requisition of NK1 antagonist has not been well proven.

Several studies demonstrated contradictory results about the NK1 antagonists for patients treated with MEC chemotherapy,^[14,15] analyzing each patient population with distinctive background and chemotherapy. Thus, impact of triplet antiemetic

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prophylaxis including NK1 antagonist for AI therapy particularly against NRC-STS still remains unclear. This retrospective study was conducted to investigate the efficacy and safety of a triplet antiemetic prophylaxis for AI therapy for NRC-STS.

2. Patients and methods

2.1. Study design

A retrospective observational study was performed to evaluate the efficacy and safety of antiemetic prophylaxis: 5-HT₃ antagonists and DEX, with or without NK1 antagonist aprepitant, in patients with NRC-STS who received AI therapy. The primary endpoint was antiemetic complete response (CR), defined as no-emetic episodes and no-rescue therapy (defined as treatment with drug to treat nausea or vomiting) in the overall period of the initial cycle. Other endpoints assessed included no emesis; no nausea; no significant nausea defined as grade 0 or 1 nausea; other toxicity. Nausea and vomiting that occurred within 24 hours of the administration of chemotherapy was defined as acute CINV, and nausea and vomiting that occurred after 24 hours was defined as delayed CINV. This study was approved by the local ethics committee of Kyushu University Hospital and was performed according to the Declaration of Helsinki.

2.2. Patients

Patients with the following subtypes of NRC-STS were included: undifferentiated pleomorphic sarcoma, liposarcoma, synovial sarcoma, leiomyosarcoma, fibrosarcoma, malignant peripheral nerve sheath tumor, or unclassified high-grade sarcoma. Other eligibility criteria included: American Joint Committee on Cancer (AJCC) stage III (T2bN0M0) or stage IV; patients who had received at least 1 cycle of AI therapy between January 2007 and January 2014; no history of either chemotherapy or radiotherapy before AI therapy; age between 18 and 75 years; and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 or less. The exclusion criteria were as follows: a serious pre-existing medical condition such as infection, severe heart disease, uncontrolled diabetes mellitus, severe renal dysfunction, brain metastasis, or active double cancer.

2.3. Pretreatment evaluation

The pretreatment evaluation included a complete history, physical examination, performance status assessment, electrocardiogram, chest radiograph, computed tomography (CT) scan or magnetic resonance imaging (MRI), and any other appropriate diagnostic procedure to evaluate the metastatic sites. Laboratory investigations included a complete blood cell count, full chemistry profile, and urinalysis. STS was staged according to the AJCC 6th edition of TNM Classification of Malignant Tumors. The histological grading of the tumors was carried out according to the French Federation of Cancer Center (FNCLCC) Sarcoma Group system.^[16] Toxicities were assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumor (RECIST), version 1.1.^[17]

2.4. Drug administration

Systemic chemotherapy for NRC-STS consisted of intravenous infusion of adriamycin (30 mg/m²/d on days 1 and 2) and ifosfamide (2 g/m²/d on days 1–5) plus mesna (0.4 g/m²

concurrent with ifosfamide, and 0.4 g/m², 4 and 8 hours after ifosfamide infusion). Treatment was repeated every 3 weeks until disease progression or unacceptable toxicity, up to a maximum of 6 cycles. In case of adverse events, doses of the chemotherapeutic agents were reduced or administration was suspended until recovery from the adverse events. Selection of antiemetic prophylaxis (a doublet therapy or a triplet therapy) and modification of each dose was carried out based on the physician's decision. A doublet therapy: a 5-HT₃ receptor antagonist, granisetron (3 mg), and DEX (8–16 mg on day 1, and 8 mg on days 2–5) were given intravenously 30 minutes before the anticancer drugs on days 1 to 5. A triplet therapy: granisetron (3 mg), DEX (12 mg on day 1, and 8 mg on days 2–5), and aprepitant (125 mg on day 1 and 80 mg on days 2–5) were given 30 minutes before administration of the anticancer drugs on days 1 to 5. In our triplet therapy, we employed the same doses of DEX and aprepitant as that given in the previous phase III studies.^[6,7] The prophylactic granulocyte-colony stimulating factor (G-CSF) was used if necessary.

2.5. Statistical methods

The statistical analysis of each result in both antiemetic treatment groups was carried out by using a chi-square test for CR rate, and analyses of nausea and vomiting. Fisher exact test was used for the analyses of adverse events. The statistical significance level was set at $P < 0.05$.

3. Results

3.1. Patient characteristics

Forty eligible patients who were consecutively treated in our hospital were enrolled in this study. Their characteristics are summarized in the Table 1. Thirteen females and 27 males were included. The median age was 50 years, with a range of 18 to 74 years. Twenty-four patients had stage III disease and 16 patients had stage IV disease. There were 12 liposarcomas, 7 synovial sarcomas, 5 leiomyosarcomas, 5 undifferentiated pleomorphic sarcomas, and 11 other subtypes of NRC-STS. Twenty patients received a doublet antiemetic prophylaxis consisting of a 5-HT₃ receptor antagonist and DEX (a doublet therapy), and 20 patients received the doublet therapy plus aprepitant (a triplet therapy). There are no significant differences

Table 1
Patient characteristics.

	Total (N = 40)	Doublet (n = 20)	Triplet (n = 20)	P
Age, y				
Median	50	49	52	0.67
Range	18–74	18–70	18–74	
Sex (male/female)	27/13	17/3	10/10	0.0017*
ECOG-PS (0-1/2)	37/3	18/2	19/1	0.30
Stage (III/IV)	24/16	11/9	13/7	0.35
Histology				
Liposarcoma	12	6	6	
Synovial sarcoma	7	5	2	
Leiomyosarcoma	5	3	2	
UPS	5	2	3	
Others	11	4	7	

UPS = undifferentiated pleomorphic sarcoma.

* Indicates statistically significant differences ($P < 0.05$).

Table 2
Prophylactic antiemetic therapy.

Antiemetic prophylaxis	Doublet (n=20)	Triplet (n=20)
Cycles, median	4	4
Range	1–6	1–6
Mean dose of aprepitant		
Day 1, mg/d	–	125
Days 2–5, mg/d	–	80
Mean dose of granisetron		
Days 1–5, mg/d	3.0±0.0	3.0±0.0
Mean dose of dexamethasone		
Day 1, mg/d	13.0±4.52	12.0±0.0
Days 2–5, mg/d	8.6±1.96	8.0±0.0

in terms of each character between the 2 groups except sex; the doublet group included higher ratio of male patients ($P=0.0017$).

3.2. Chemotherapy and antiemetic prophylaxis

The median number of cycles of AI therapy administered was 4, with a range from 1 to 6 cycles. These AI therapies were terminated because of the completion of scheduled treatment and disease progression in 28 (70%) and 10 (25%) patients, respectively. Two patients discontinued their AI therapy because of toxicities including infection in 1 patient and cellulitis after resection of liposarcoma in 1 patient. The median number of cycles of antiemetic prophylaxis administered was 4 in both groups (Table 2). The mean dose of DEX administered was 13.0±4.52 mg on day 1 and 8.6±1.96 mg on days 2 to 5 in the doublet group, and 12.0±0.0 mg on day 1 and 8.0±0.0 mg on days 2 to 5 in the triplet group.

3.3. Efficacy

The antiemetic CR rate in the triplet group was significantly higher than that in the doublet group in the overall period (70% vs 35%; $P=0.027$) and in the acute phase (70% vs 35%; $P=0.027$). No significant difference of CR rate between the groups was observed in the delayed phase (75% vs 50%; $P=0.102$) (Table 3). Although the difference was not statistically significant, the percentage of patients with no emesis in the triplet group was higher than that in the doublet group in the overall period (90% vs 65%; $P=0.058$) and in the acute phase (90% vs 65%;

Table 3
The rates of complete response, no emesis, and no significant nausea.

Antiemetic prophylaxis	Doublet (n=20)	Triplet (n=20)	P
Complete response, %			
Overall period	35	70	0.027*
Acute phase	35	70	0.027*
Delayed phase	50	75	0.102
No emesis, %			
Overall period	65	90	0.058
Acute phase	65	90	0.058
Delayed phase	90	100	0.14
No significant nausea, %			
Overall period	75	80	0.6
Acute phase	80	80	1.0
Delayed phase	85	95	0.29

* Indicates statistically significant differences ($P<0.05$).

$P=0.058$) (Table 3). In the delayed phase, patients with no emesis were observed in 90% of the doublet group and 100% of the triplet group ($P=0.14$). The percentages of patients with no significant nausea (CTC-AE grade 0 or 1) in the triplet group and the doublet group in the overall period, acute phase, and delayed phase were almost equivalent (80% vs 75%; $P=0.6$, 80% vs 80%; $P=1.0$, 95% vs 85%; $P=0.29$) (Table 3).

3.4. Toxicity

Toxicities in all cycles are summarized in the Table 4. Grade 3 or 4 leucopenia, neutropenia, and anemia were observed in 94%, 100%, and 11% of the patients, respectively. Among the nonhematological toxicities, anorexia and nausea were frequently observed, but they were usually mild. Asthenia was seen in 63%. Although grade 3 hyperglycemia was seen in 1 patient in doublet group, no statistically significant differences between the 2 groups were observed in the occurrence of hyperglycemia and severe infection, which were possibly related to the high dose of DEX. All toxicities other than emesis were equally observed in the 2 groups.

3.5. Factors predicting an antiemetic effect

Univariate analyses were performed to assess correlations between occurrence of emesis and several patient factors. No

Table 4
Adverse events.

Grade (CTCAE v4.0)	Doublet			Triplet			P
	All grades, %	Grade 3	Grade 4	All grades, %	Grade 3	Grade 4	
Leukopenia	18 (90)	3	14	20 (100)	4	16	0.80
Neutropenia	17 (85)	1	15	20 (100)	2	18	0.76
Anemia	16 (80)	2	0	16 (80)	5	0	0.55
Thrombopenia	11 (55)	0	0	14 (70)	0	1	0.91
Malaise	12 (60)	1	0	10 (50)	0	0	0.88
Anorexia	20 (100)	0	0	18 (90)	0	0	0.54
Nausea	17 (85)	0	0	14 (70)	0	0	0.68
Vomiting	7 (35)	0	0	2 (10)	0	0	0.069
Increased AST/ALT	5 (25)	1	0	7 (35)	0	0	0.72
Hyperglycemia	16 (80)	1	0	12 (60)	0	0	0.60
Febrile neutropenia	7 (35)	7	0	11 (55)	11	0	0.48
Infection	1 (5)	1	0	0 (0)	0	0	

ALT=alanine transaminase, AST=aspartate transaminase.

Table 5
Factors predicting antiemetic effects (univariate analysis).

Factor	Odds ratio	P
Age <50	3.0	0.212
Female	3.43	0.014
Stage IV	1.63	0.096
No use of aprepitant	3.0	0.212

use of aprepitant was thought to be a risk factor for emesis (odds ratio [OR] 3.0, $P=0.212$), and also other established risk factors, including age less than 50 years (OR 3.0, $P=0.212$), female sex (OR 3.43, $P=0.014$), and stage IV disease (OR 1.63, $P=0.096$) (Table 5).

4. Discussion

The present study retrospectively examined the efficacy and safety of aprepitant-combined triplet antiemetic prophylaxis (a 5-HT₃ receptor antagonist, DEX, and aprepitant) in patients with NRC-STs treated with AI therapy. AI therapy consists of adriamycin and ifosfamide, which are classified as MEC in terms of CINV. Guidelines for the management of CINV recommend a doublet antiemetic prophylaxis, including 5-HT₃ receptor antagonists and 8 to 16 mg of DEX for MEC based on the results of phase 3 studies.^[8,9] However, insufficient effect of doublet antiemetic prophylaxis leads us to explore more intensive prophylaxis including an additional aprepitant use. A previous randomized clinical trial evaluating antiemetic prophylaxis in MEC demonstrated that an aprepitant-containing triplet therapy for various malignant tumors possessed superior antiemetic efficacy to a doublet therapy without aprepitant, especially in adriamycin plus cyclophosphamide (AC) therapy.^[14] Based on these findings, a triplet therapy has been recommended for antiemetic prophylaxis not only for HEC but also for AC therapy. However, this study did not examine non-AC MEC, such as AI therapy. Additionally, several studies examining NK1 antagonists for non-AC, non-AI MEC have not shown constant results.^[18–22] Since AI therapy is also a combination of an anthracycline and an alkylating reagent, consideration of a triplet therapy for AI could be arisen.

The AC therapy is 1 of the standard chemotherapies for breast cancer, and it is often administered for young females. Several studies have identified emetogenic risk factors, including female sex, younger age less than 50 years, poor PS, alcohol abstinence, and previous CINV.^[23–25] On the contrary, DEX with or without aprepitant therapy was assessed for MEC in nondrinking women younger than 70 years with gynecological malignancies, and no significant differences of overall, acute, and delayed CR rate between the 2 antiemetic therapies was reported.^[15] In the present study, the median age of patients was 50 years, and the proportion of females was 33%, and PS 0 or 1 was in 74% of patients. Even though many patients with low emetogenic risk factors were enrolled in our study, the univariate analysis interestingly suggested that “no use of aprepitant” was a risk factor for emesis, and also the established risk factors. Together, requirement of a triplet therapy for MEC might be variable depending on an individual regimen, disease, and patient background.

Adriamycin plus ifosfamide therapy for NRC-STs patients is generally employed in adjuvant setting and in recurrence or metastatic diseases expecting tumor shrinkage. However,

effectiveness of antiemetic therapy particularly for AI against NRC-STs has not been well determined. CINV was observed in approximately 80% of adult patients with NRC-STs receiving AI therapy even with a standard antiemetic therapy.^[11,12] In the previous study of chemotherapies including adriamycin plus cisplatin, ifosfamide plus etoposide, and AI for bone and soft-tissue sarcoma, effectiveness of the triplet therapy was examined, and AI was administered in 11 courses out of a total of 96 courses of chemotherapy.^[26] Complete response rates of the prophylaxis in an acute, a delayed, and an overall period were 23%, 17%, and 7%, respectively, but specified antiemetic effect of the triplet therapy for AI has not been clarified. In the present study, we also observed that 85% of patients suffered nausea; even prophylaxis by a doublet therapy consisting of 3 mg of granisetron and 8 to 16 mg of DEX (the doublet group) was performed. On the contrary, 70% of patients experienced nausea with the aprepitant-containing triplet therapy (the triplet group). In addition, we observed that the antiemetic CR rate in the triplet group was significantly higher than that in the doublet group. The ratio of patients with no emesis also tended to be higher in the triplet group than that in the doublet group (90% vs 65%). In terms of the delayed phase, triplet therapy only showed a trend of favorable CR rate (75% vs 50%; $P=0.102$), possibly because of the limited number of patients and alteration of the plasma concentration of DEX caused by 5-day schedule of antiemetic therapy. Although the present study retrospectively assessed a small number of patients, these results suggest that the triplet therapy may be an optimal antiemetic prophylaxis for AI. Further prospective study is warranted to evaluate the efficacy and safety of aprepitant-containing antiemetic prophylaxis in AI therapy for NRC-STs.

One of the possible reasons for the enhanced antiemetic effect in the triplet group was the increased plasma concentration of DEX. In a pharmacokinetic study of aprepitant and DEX in Japanese patients with cancer, Nakade et al^[27] found that the clearance of DEX was decreased by as much as 24.7% and 47.5% by co-administration of 40 and 125 mg of aprepitant, respectively. Although we did not measure the plasma concentration of DEX in the present study, we did compare the safety profile of the triplet group to the doublet group. There was no difference in adverse events associated with AI and DEX between the 2 groups, and the incidence of adverse events in this study was similar to that seen in previous clinical trials.^[5,11]

Ifosfamide sometimes induces neurotoxicity, and 1 of the risk factors of neurotoxicity has been reported to be CYP2B6 inhibitor, which could interfere with the metabolism of ifosfamide.^[28] Since aprepitant could inhibit CYP3A4—another metabolizing enzyme for ifosfamide—increasing risk of ifosfamide-induced neurotoxicity has been a concern. A retrospective study suggested a possible risk for ifosfamide-induced neurotoxicity associated with aprepitant use in patients treated with AI,^[29] and a case report of a patient with a malignant peripheral nerve sheath tumor treated with ifosfamide, carboplatin, and etoposide showed an ifosfamide-induced neurotoxicity after the addition of aprepitant.^[30] Since no ifosfamide-induced neurotoxicity appeared in the present study, direct relationship between the neurotoxicity and aprepitant was not suggested. However, potential risk of enhancing ifosfamide-induced neurotoxicity should be carefully considered.

The effectiveness of aprepitant in a secondary antiemetic prophylaxis against CINV of MEC is undetermined. In the present study, 7 patients who failed to respond to the primary prophylaxis in the doublet group were administered aprepitant as

a salvage therapy in the following courses. Among these 7 patients, the aprepitant-containing triplet therapy reduced CINV from grade 2 to grade 0 in 2 patients, and from grade 1 to grade 0 in 3 patients. The CR rate of aprepitant as a salvage therapy was 71%. This observation suggested that the secondary use of aprepitant to 5-HT₃ antagonists and DEX in patients who failed to control the primary antiemetic prophylaxis may enjoy improved control of CINV. Although this observation is suggested from limited number of patients, it is in line with the results of a study by Oechsle et al,^[31] where aprepitant demonstrated a significant antiemetic activity in patients with cisplatin-induced nausea/vomiting that was refractory to prophylaxis with 5-HT₃ antagonists and DEX.

The present study suggested more favorable primary antiemetic activity of an aprepitant-containing triplet therapy than a doublet therapy, especially in patients with NRC-STS receiving AI.

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