Clinical Efficacy of Aprepitant in Patients with Gynecological Cancer after Chemotherapy Using Paclitaxel and Carboplatin

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Abstract. *Aim: This study aimed to evaluate the efficacy of aprepitant, a neurokinin (NK)1 receptor antagonist, on chemotherapy-induced nausea and vomiting (CINV). Patients and Methods: A randomized, open-labeled, parallel-design study was undertaken in gynecologic-cancer (GC) patients at the Fukuoka University Hospital. Twenty-three patients were divided into without (group A) or with aprepitant (Group B) in the first cycle of paclitaxel and carboplatin (TC) therapy. From the second cycle onwards, all patients used aprepitant. Statistical significance was assessed using McNemar and Chi-square tests. Results: In the first cycle, the prevalence of a complete response, no episodes of nausea or food intake in group B was significantly increased compared to group A. No significant difference in the prevalence of a complete response or food intake situation was found from the second cycle onwards. Conclusion: Combination of aprepitant with standard anti-emetic therapy may contribute to prevention of CINV in TC therapy for GC patients.*

Treatment with paclitaxel and carboplatin (TC) has been recognized to be standard therapy in patients with gynecologic-cancer (GC), including ovarian or endometrial cancer (1-3). In cancer chemotherapy, nausea or vomiting are the most distressing adverse effects. TC treatment is classified as carrying a moderate emetic risk within chemotherapy-induced nausea and vomiting (CINV) (4).

In Japan, anti-emetic guidelines recommend administration of a corticosteroid and a 5-hydroxytryptamine (HT)3 receptor antagonist before moderately emetogenic chemotherapy (MEC) to prevent CINV and to enhance the quality of life of cancer patients during chemotherapeutic treatment (5-7). However, the CINV owing to TC treatment tends to remain uncontrolled despite administration of corticosteroid and a 5-HT3 receptor antagonist. In general, CINV persists for 5 days.

One recent study showed that CINV can be classified by the onset period. That is, acute-phase CINV occurs within 24 h and delayed-phase CINV occurs 2-5 days after administration of an anticancer agent (5-9). Conversely, anticipatory nausea and vomiting can occur by conditioning mechanisms in patients who have experienced nausea and vomiting from chemotherapy (10).

Aprepitant is a neurokinin (NK)1 receptor antagonist. It represents a new class of anti-emetic agents and has a different effect from 5-HT_3 receptor antagonists (7, 8, 11-13). Such NK1 receptor antagonists have demonstrated efficacy against early (acute) and later (delayed) emesis (5). Several clinical trials have reported NK1 receptor antagonists to be most effective for highly emetogenic chemotherapy and MEC (3, 5-7). However, there is less evidence to support the efficacy of aprepitant in treatment regimens with MEC. To assess the efficacy of NK1 receptor antagonists for CINV, we conducted a randomized, open-labeled, parallel-designed, phase-II trial of aprepitant in GC patients during adjuvant TC therapy.

Patients and Methods

Study design. All patients provided written informed consent to participate in this randomized, open-label, parallel-design study. The Ethics Committee of the Fukuoka University Hospital (Fukuoka, Japan) approved the study protocol.

Patient selection. The study focused on patients undertaking their first TC therapy as postoperative adjuvant chemotherapy at the Fukuoka University Hospital from November 2010 to October 2012.

Patients were excluded from the study if they: carried a risk of vomiting for other reasons (symptomatic primary or metastatic malignancy in the central nervous system, active peptic ulcer or

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Key Words: Gynecological cancer, NK1 receptor, aprepitant, CINV.

gastrointestinal obstruction); had vomited in the 24 h before treatment; had abnormal laboratory values (white blood cell count <3,000/mm^3, absolute neutrophil count <1,500/mm^3, platelet count <100,000/mm^3, aspartate aminotransferase >2.5 × upper limit of normal range (ULN), alanine aminotransferase >2.5 × ULN, total bilirubin >1.5 × ULN or creatinine >1.5 × ULN. Patients under systemic corticosteroid therapy (at any dose) or taking pimozide were also excluded. In addition, patients who had the things (such as ileus, taking opioid, apparent infection and more), which the doctor judged to be unsuitable, were also excluded. Anti-emetic agents could not be administered within 48 h before treatment.

Procedures. Twenty-three eligible patients were divided randomly into two groups (A and B) using sealed opaque envelopes. Standard anti-emetic therapy comprised of 3 mg of a 5-HT$_3$ antagonist and 16 or 8 mg of dexamethasone administered *via* the intravenous route on day-1 followed by dexamethasone (8 or 4 mg) administered *via* the oral route on day-2 and day-3. Aprepitant regimen consisted of aprepitant (125 mg) administered *via* the oral route on day-1 and 80 mg on day-2 and day-3. Group A was treated with standard anti-emetic therapy only. Group B was treated with addition of aprepitant to standard anti-emetic therapy. Dexamethasone was used for the prevention of drug hypersensitivity, so we did not decrease its dose. From the second cycle of TC treatment onwards, all patients were treated with addition of aprepitant to standard anti-emetic therapy.

Assessments. Patients recorded the onset of vomiting and nausea in a symptom diary from day-1 to the morning of day-6. "Vomiting" was defined as at least one episode of emesis or gagging and was distinguished if emesis was not observed for at least 1 min. With regard to nausea, patients recorded the most severe intensity during the previous 24 h period based on a two-point scale ("nausea" or "no nausea"). Food intake was recorded based on a two-point scale ("eat as usual" or "not eat as usual"). If rescue therapy was received, patients recorded the drug and day of administration. Efficacy was evaluated from the start of administration of the anti-tumor agent on day-1 (also defined as "0 h") to the morning of day-6 ("120 h"). The primary endpoint was the percentage of patients with a complete response (CR), which was defined as no emesis and no rescue therapy. Secondary endpoints were either that the percentage of patients with CR in the overall phase since second cycle or that CR or no episode of nausea in the acute phase and delayed phase in all cycles. Safety was evaluated using general laboratory tests. Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events v4.0 set by the National Cancer Institute (Bethesda, MD, USA). In each cycle of TC treatment, AEs were recorded for the two groups. We compared CINV, rescue treatment and food intake situation in groups A and B. Furthermore, we compared CINV and rescue treatment in the first cycle and second cycle of group A. Moreover, we compared the overall prevalence of no episodes of nausea from two cycles to six cycles in groups A and B. Furthermore, we noted if patients could not continue chemotherapy. All patients received anti-emetic therapy based on guidelines set in Japan. All patients recorded their symptoms each day for six days.

Statistical analyses. Statistical analyses were carried-out using the McNemar test and Chi-square test. *p*-Values <0.05 were considered significant.

Table I. *Patients' characteristics*.

	Group A (n=12)	Group B (n=11)
Age	54.5±11.9	62.6±12.7
Primary diagnosis		
Ovarian cancer	9	9
Endometrial cancer	3	2
Stage of malignancy		
I	6	2
II	3	2
III	3	5
IV	0	2
Alcohol		
None	9	11
A few in month	2	0
Every day	1	0
Smoking	2	0
Motion sickness	3	2
Morning sickness	3	2
Pretreatment for CINV	3	2

Results

Twenty-six patients were enrolled in this study. Three patients were excluded because of a hypersensitivity reaction (HSR) against paclitaxel in the first cycle of TC treatment. Finally, twenty-three patients were randomized and allocated into two groups. Twelve patients were in the control group (group A) and eleven patients were in the aprepitant group (group B). Table I details the characteristics of patients in each group. There were no differences in age, stage of malignancy, alcohol consumption, smoking, motion sickness, morning sickness and pre-treatment with CINV between groups A and B.

To evaluate alterations in CINV after TC treatment, we compared the prevalence of a CR (no episodes of nausea and no rescue therapy), no episodes of nausea and food intake situation between the two groups in the first cycle of TC treatment. In group B, all patients had a CR in acute, delayed and overall phases. In overall and acute phases, the prevalence of a CR in group B was significantly increased compared to that in group A ($p<0.05$), whereas no significant difference in the prevalence of a CR was seen in the delayed phase (Figure 1A). In group B, all patients had no episodes of nausea and all had good food intake situation in overall, acute and delayed phases. In all phases, the prevalence of patients with no episodes of nausea or good food intake situation in group B was significantly increased compared to that in group A ($p<0.05$) (Figure 1B and C). These results suggested that addition of aprepitant to standard anti-emetic therapy (5-HT$_3$ receptor antagonist and a corticosteroid) completely suppressed the CINV mediated by MEC.

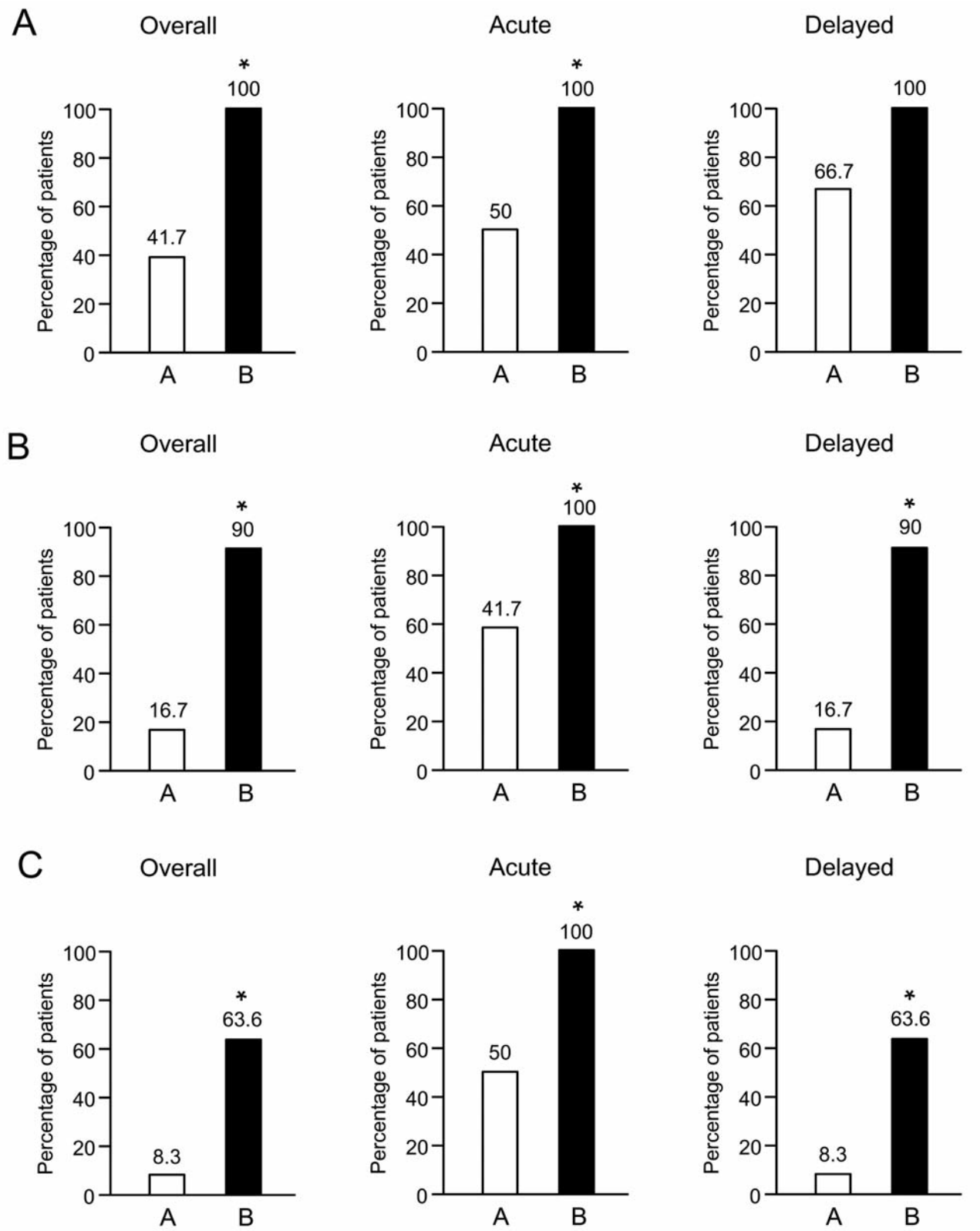

Figure 1. *Prevalence of patients in each treatment group who had a complete response in overall, acute and delayed phases. A: Prevalence of patients who had a complete response. B: Prevalence of patients who had no episodes of nausea. C: Prevalence of patients who had good food intake. *p<0.05 versus group A.*

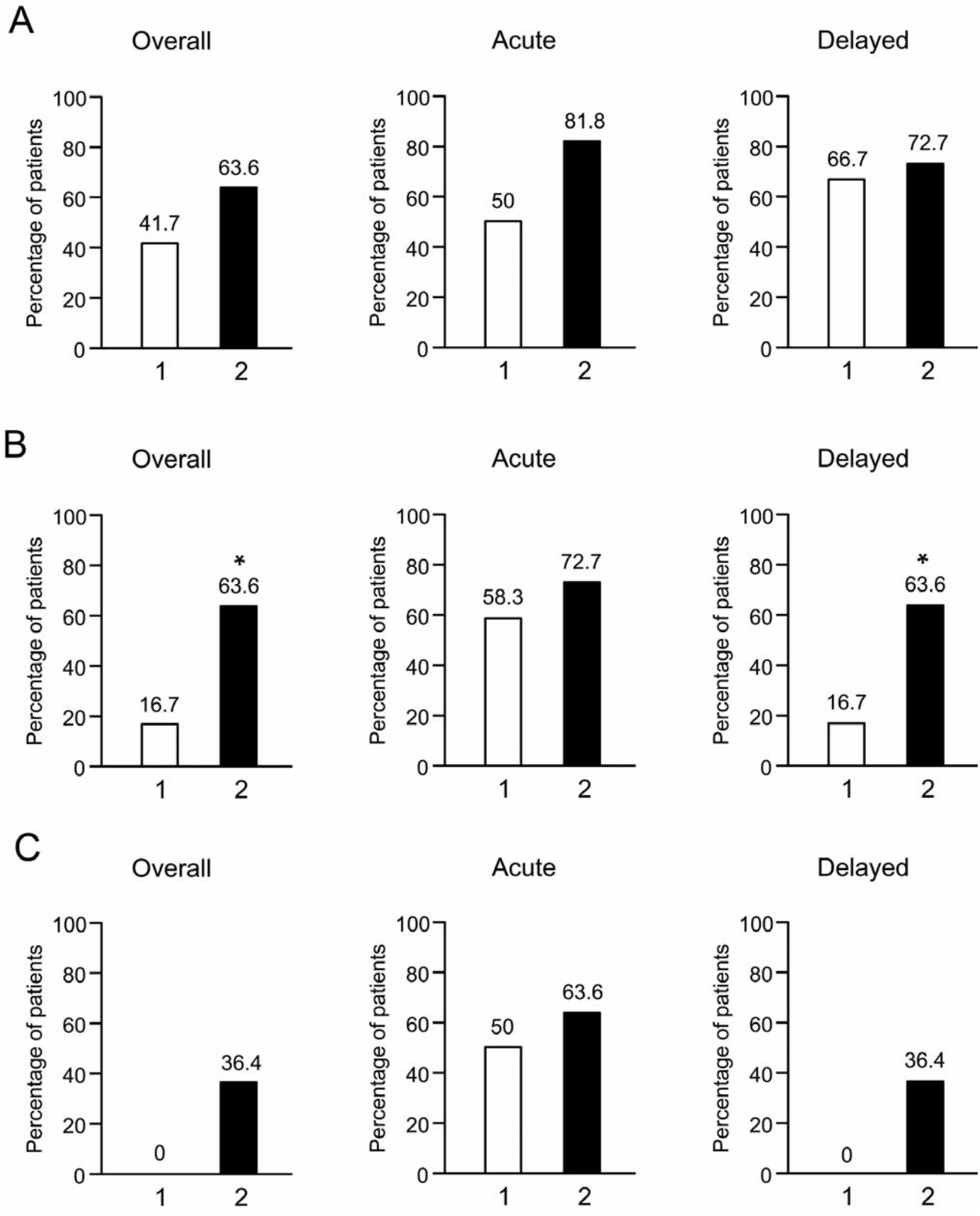

Figure 2. *Prevalence of patients in the first cycle and second cycle in group A. A: Prevalence of patients who had a complete response. B: Prevalence of patients who had no episodes of nausea. C: Prevalence of patients who had good food intake. *p<0.05 versus the first cycle.*

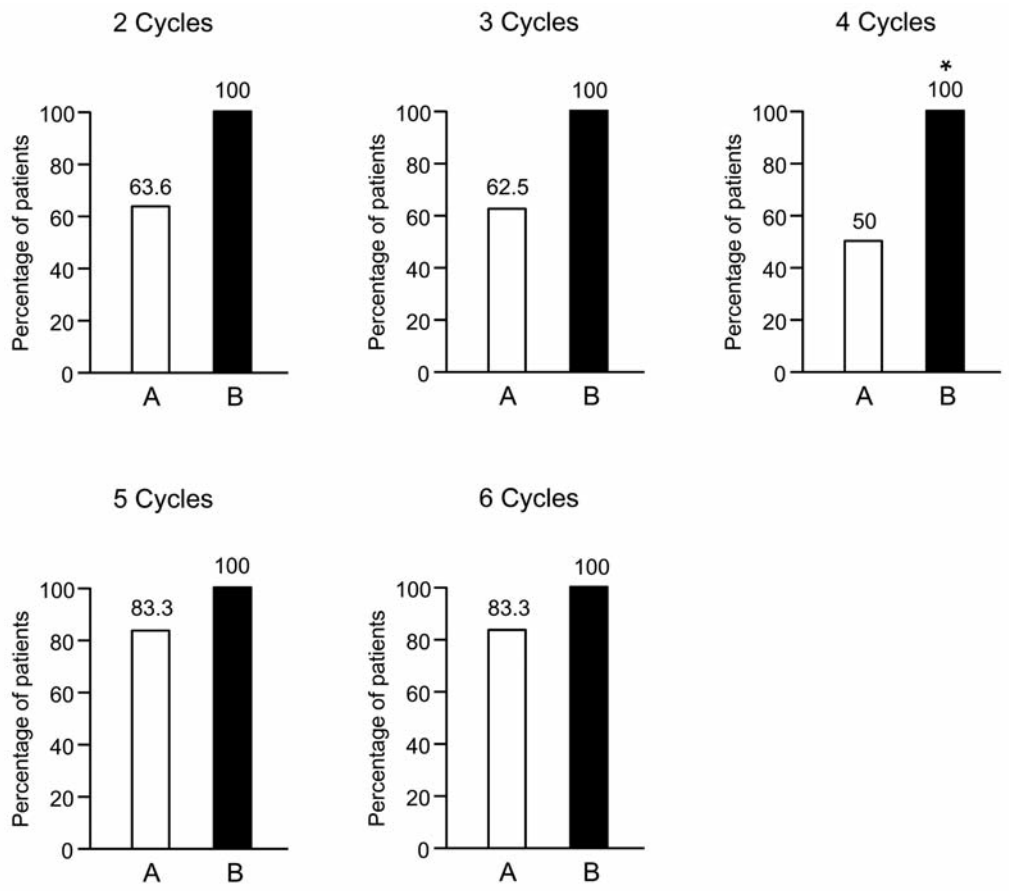

Figure 3. *Comparison of the prevalence of a complete response between the overall phase and from two cycles to six cycles in groups A and B. *p<0.05 versus group A.*

To confirm the efficacy of aprepitant on CINV, we examined alterations in the prevalence of a CR, no episodes of nausea and food intake situation between the first and second cycles of TC treatment in both groups. In group A, no significant difference in the prevalence of a CR or food intake situation was found between the first and second cycles of TC treatment, whereas addition of aprepitant tended to augment the prevalence of a CR and good food intake (Figure 2A and C). In the second cycle of TC treatment, the prevalence of no episodes of nausea increased significantly compared to that in the first cycle of TC treatment in overall and delayed phases ($p<0.05$), whereas there was little difference in the prevalence of no episodes of nausea in the acute phase between the first and second cycles of TC treatment (Figure 2B). In group B, the prevalence of a CR, no episodes of nausea and food intake situation in each phase was 100% in the first and second cycles of TC treatment. Taken together, these results suggested that addition of aprepitant improved CINV in MEC. Furthermore, these results suggested that use of aprepitant for CINV in the first cycle of TC treatment led to clinically significant results.

To further validate the continuous efficacy of aprepitant for CINV during the first six cycles of TC treatment, we compared alterations in the prevalence of a CR, no episodes of nausea or food intake situation in each cycle of TC treatment between groups A and B. In each cycle of TC treatment, the prevalence of a CR (Figure 3), no episodes of nausea (Figure 4) or food intake situation (Figure 5) in group B was almost 100%, whereas the prevalence of these parameters in group A did not reach 100%. In almost all cases, the prevalence in group B increased significantly compared to that in group A. These results suggested that addition of aprepitant to standard anti-emetic therapy from the first cycle of TC treatment may help to manage CINV.

Discussion

In the present study, we found that addition of the NK1 receptor antagonist aprepitant to standard anti-emetic therapy

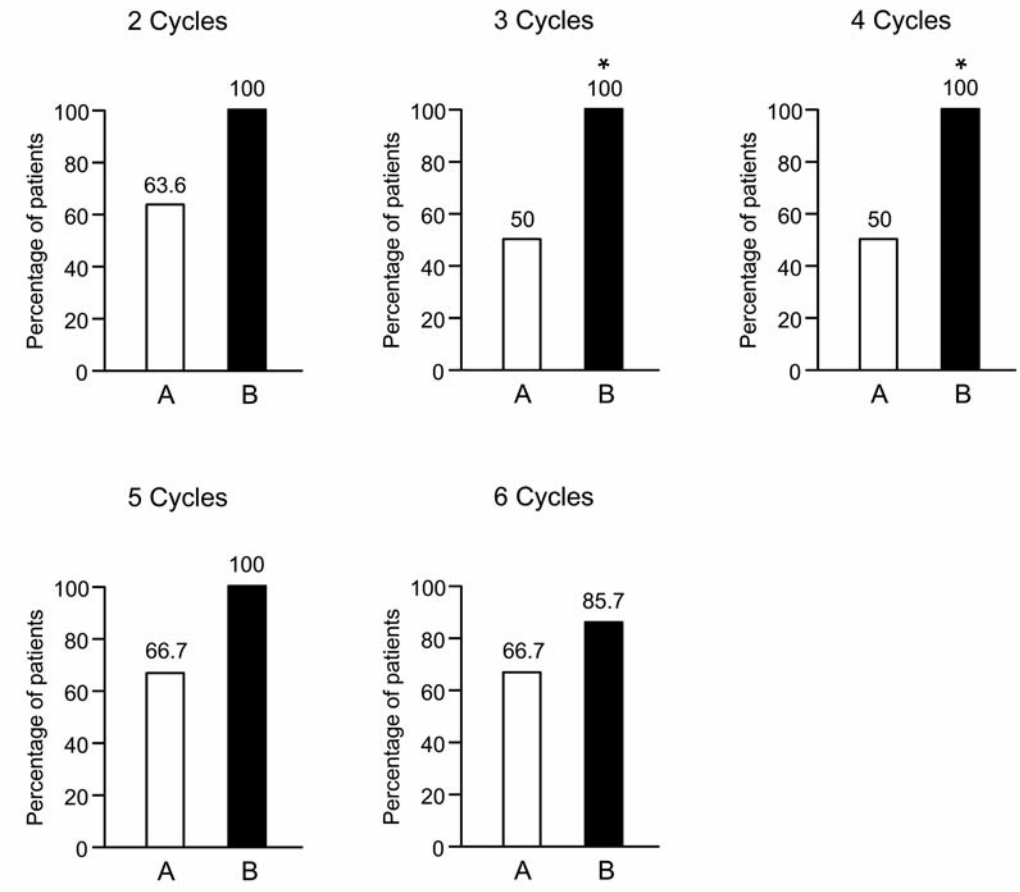

Figure 4. *Comparison of the prevalence of no episodes of nausea between the overall phase and from two cycles to six cycles in groups A and B. *p<0.05 versus group A.*

(5-HT_3 receptor antagonist and a corticosteroid) suppressed CINV in overall, acute and delayed phases. Furthermore, aprepitant used in combination was more efficacious than use of a 5-HT_3 receptor antagonist and a corticosteroid alone in TC treatment. These data suggest that aprepitant is a powerful and useful agent for preventing CINV in MEC.

Aprepitant is a potent and selective non-peptide antagonist of the NK1 receptor, which is known to play an important part in CINV (5). In early clinical trials, aprepitant was given in combination with a 5-HT_3 antagonist- and dexamethasone-enhanced protection against delayed emesis (12). This combination provided sustained anti-emetic protection over multiple cycles of chemotherapy and was, in general, well tolerated with few AEs (9). In the present study, group B displayed no episodes of nausea and no requirement for rescue treatment. CINV tends to become more severe over multiple cycles and the level of anti-emetic protection achieved in one cycle of chemotherapy has been noted to affect the severity of symptoms during, or even in anticipation of, subsequent cycles (14). Therefore, CINV must be prevented in the first cycle to decrease the risk of anticipatory nausea and vomiting.

Paclitaxel is an anti-neoplastic drug widely used for GC and thought to induce HSRs. In our study, three cases suffered HSRs in the first cycle and one patient suffered HSRs in the second cycle in the 26 cases enrolled in this study. Therefore, these subjects needed to change to other types of chemotherapy. HSR did not occur in group B, the group in which aprepitant was added to standard anti-emetic therapy from the first cycle onwards. In a recent study, substance P was shown to be involved in paclitaxel-induced HSRs (13). Substance P is the most likely endogenous ligand for the NK1 receptor. Therefore, it was hypothesized that aprepitant can prevent substance P-induced HSR and that an aprepitant regimen is more effective than standard anti-emetic therapy. However, in the present study, the prevalence of a CR and no episodes of nausea in the first cycle and second cycle were not significantly different between the two groups. In addition, we assessed the number of patients who

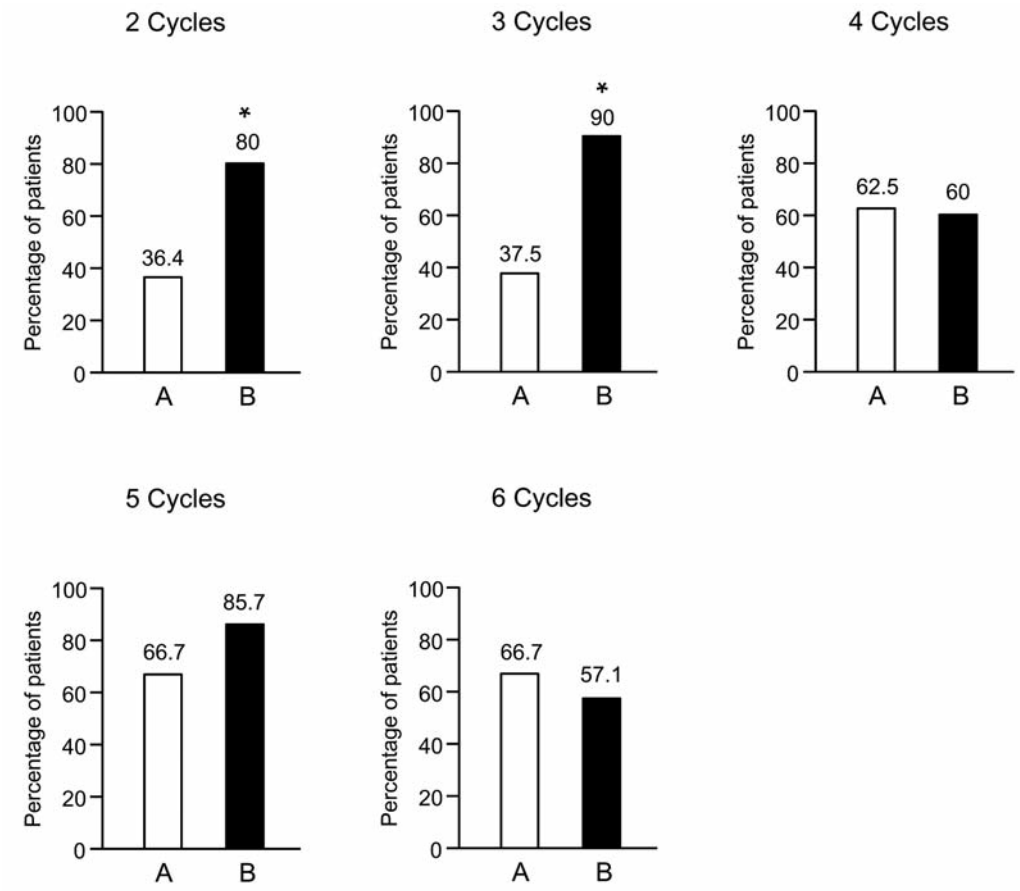

Figure 5. *Comparison of the prevalence of food intake between the overall phase and from two cycles to six cycles in groups A and B. *p<0.05 versus group A.*

completed six cycles. There was no significant difference between the two groups in terms of five cycles and six cycles. This result could have been because of the small number of patients in the study.

In conclusion, aprepitant used in combination with standard anti-emetic therapy (5-HT_3 receptor antagonist and corticosteroid) was well-tolerated and more effective in preventing the CINV associated with TC treatment. These results suggest that CINV can be controlled using aprepitant in combination with standard anti-emetic therapy from the first cycle onwards.

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Received April 3, 2015
Revised May 8, 2015
Accepted May 11, 2015