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Original

The Impact on Quality of Life of Highly Effective Antiemetic Therapy among Breast Cancer Patients Receiving Anthracycline Plus Cyclophosphamide-based Regimen

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Abstract: Treatment for chemotherapy-induced nausea and vomiting (CINV) has improved significantly with the development of antiemetic drugs. We conducted a prospective observational study to clarify the quality of life (QOL) impact of antiemetic therapy recommended by the Japanese Cancer Therapy Association (JSCO) guidelines for Japanese breast cancer patients receiving an anthracycline plus cyclophosphamide regimen (ACR). This was an open, single-center, prospective observational study conducted in Yokohama City University Medical Center. Antiemetic therapy recommended by the JSCO guidelines was implemented for all cases treated therein (i.e., aprepitant, dexamethasone, and palonosetron). The primary endpoint was no impact on daily living (NIDL) rate during a 120-hour period following chemotherapy (i.e., overall phase). We use the Japanese version of the Functional Living Index–Emesis (FLIE) to evaluate the impact of CINV on QOL. There were 118 analyzable cases. The NIDL rate during the overall phase was 44.9%, and was significantly lower than the complete response (CR) rate of 58.5% (i.e., no emetic responses and no rescue medication; $P = 0.037$). Age < 55 years ($P = 0.008$) and a history of morning sickness ($P = 0.005$) were identified as independent risk factors of NIDL ($P < 0.05$). Among Japanese breast cancer patients receiving ACR and a combination of aprepitant, dexamethasone, and palonosetron, the NIDL rate was relatively low at approximately 45%. A more effective antiemetic therapy should therefore be developed for patients' QOL that takes NIDL risk factors into account. In addition, our results suggested that the CR rate is insufficient for evaluating the effect of antiemetic therapy on a patient's QOL.

Key words: breast cancer, chemotherapy-induced nausea and vomiting, quality of life, Functional Living Index Emesis

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) can have major adverse effects on a patient's quality of life (QOL)[1,2]. The development of novel classes of antiemetic drugs such as aprepitant, neurokinin 1 (NK1) receptor antagonists, and palonosetron, a second-generation $5HT_3$ receptor antagonist[3,4], has significantly improved the treatment outcomes for CINV, and several guidelines on recommended antiemetic therapy for the prevention of CINV have been published[5–7]. Guidelines published in 2010 by the Japanese Cancer Therapy Association (JSCO)[8] led to standardized antiemetic therapy in Japan, and anticancer drugs have been classified into four groups based on their risk of inducing emesis, with an optimal antiemetic therapy recommended for each of these groups. For instance, the recommended antiemetic therapy for a highly emetogenic chemotherapy is a combination of aprepitant or fos-aprepitant, dexamethasone, and a $5HT_3$ receptor antagonist.

The anthracycline plus cyclophosphamide regimen (ACR) is used to treat breast cancer patients and is classified as a highly emetogenic chemotherapy. In addition, the risk of CINV can be influenced by various patient-specific risk factors such as female sex, age $<$ 55 years, no alcohol intake, and having a history of morning sickness or motion sickness[10,11].

Objective indicators such as complete response (CR; i.e., no emetic responses and no use of rescue medication) and complete control (CC; i.e., no emetic responses and no nausea) are widely used in the symptom assessment of CINV. Then in 2009, the US Food and Drug Administration published the "Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims"[12], a set of guidelines[5–7] that recommend the use of patient-reported outcomes (PROs). For outpatient chemotherapy, it is also important to consider the subjective patient-reported and daily life outcomes alongside the objective indexes[13], and many studies have employed the Functional Living Index–Emesis (FLIE)[14,15] to evaluate the QOL impact of CINV subjectively. Indeed, the Japanese version of the FLIE has shown good reliability and validity[16], and several survey studies using the FLIE have demonstrated that CINV leads to a notable decrease in QOL[13,17,18]. Nevertheless, there has not yet been a detailed report on the QOL impacts of the antiemetic therapy recommended by the JSCO guidelines (a combination of aprepitant, palonosetron, and dexamethasone), with their improved treatment outcomes, for Japanese breast cancer patients receiving a highly emetogenic chemotherapy.

Therefore, herein we conducted a prospective observational study to clarify the QOL impact and reported risk factors of the antiemetic therapy recommended by the JSCO guidelines for Japanese breast cancer patients receiving ACR. We also compared the QOL impact by FLIE, with the CR or the CC rates as objective indicators.

Patients and methods

Study design

This was an open, single-center, prospective observational study involving a patient diary and conducted at the Yokohama City University Medical Center. The protocol was approved by

the Research Ethics Committee of Yokohama City University Medical Center, and the study was conducted in line with the Declaration of Helsinki (as revised in October 2013). This trial was registered with the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN000018544).

Patient selection

All patients received the combination of antiemetics recommended in the 2010 JSCO Guidelines for Antiemetics in Oncology[8]. This treatment is targeted for patients undergoing chemotherapy regimens of FEC (fluorouracil 500 mg/m^2 + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2), EC (epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2), and AC (doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2). Enrolled patients had to fulfill the following inclusion criteria: (a) ≥ 18 years of age and receiving a highly emetogenic chemotherapy that includes cyclophosphamide and anthracycline for the first time; (b) no experience of nausea or vomiting within 24 hours before receiving an anticancer agent; (c) provided written informed consent; (d) had an Eastern Cooperative Oncology Group Performance Status of 0–2; and (e) capable of understanding all study procedures and completing a patient diary. The exclusion criteria were as follows: (a) presence of brain metastases; (b) presence of hypercalcemia; (c) presence of gastrointestinal obstruction; and (d) taking drugs that can influence the antiemetic effect or participating in other studies involving protocols other than standard antiemetic agents.

Antiemetic treatment

The 5HT$_3$ receptor antagonist called palonosetron has a superior inhibitory effect on CINV in the delayed phase compared to another such drug, granisetron[9], thus we used palonosetron in this study. During the first course of chemotherapy, all patients received oral aprepitant 125 mg, intravenous dexamethasone 9.9 mg, and intravenous palonosetron 0.75 mg before chemotherapy on day 1. On days 2 and 3, patients received oral aprepitant 80 mg and oral dexamethasone 8 mg. On day 4, patients received oral dexamethasone 8 mg. Patients were also prescribed oral prochlorperazine 5 mg as a rescue antiemetic medication, to be used only when nausea and vomiting developed over the 120-hour observation period. We focused solely on the first course of chemotherapy, and patients were allowed to change their antiemetic therapy from the second course onwards.

Outcome assessment

The acute phase was defined as 0–24 hours following chemotherapy, the delayed phase as 24–120 hours following chemotherapy, and the overall phase as 0–120 hours following chemotherapy. Patients completed a patient diary once per day from days 1 to 5, wherein they recorded emetic episodes, intensity of nausea, and number of times that a rescue antiemetic was needed. Patients also completed the FLIE in order to assess their QOL from days 1 to 5.

Vomiting was defined as one or more emetic episodes or retching (dry heaves), and episodes were considered as separate if they occurred at least 5 min apart. Nausea intensity was evaluated

on a 4-point Likert-type scale (0, none ; 1, mild ; 2, moderate ; 3, severe) once a day from days 1 to 5, with significant nausea defined by a rating of 2 or more.

We used the Japanese version of the FLIE to assess the impact of CINV on QOL[16]. The FLIE is a modified version of the Functional Living Index–Cancer, which is a representative measure of QOL for cancer patients with established reliability and validity[14]. The FLIE contains 18 items assessing the effect of CINV on patients' daily lives, and contains separate domains for the impacts of nausea and vomiting. The first item in each domain asks the patient to rate how much nausea (vomiting) they have experienced, and then the remaining eight items assess the impact of nausea (vomiting) on the following aspects of a patient's daily life : ability to enjoy meals / liquids, ability to prepare meals / do household tasks, ability to perform daily functions, ability to perform usual recreation, ability to enjoy leisure activities, willingness to spend time with family and friends, extent to which the side effect has caused personal hardship and / or hardship on others.

For each item, participants rate the impact of both nausea and vomiting on daily life, thus producing two scores for each item, and all items are rated on a visual analogue scale (VAS) ranging from 1 ("not at all") to 7 ("a great deal"). The total score ranged from 18 to 126, and we defined a total score of less than 36 as indicating no impact on daily living (NIDL). For each domain, scores ranged from 9 to 63, and we defined a total score of less than 18 as indicating NIDL of nausea or vomiting.

The CR rate was defined as the proportion of patients with no emetic episode and no use of rescue antiemetic medication. Furthermore, the complete control (CC) rate was defined as the proportion of patients with no emetic episode, no use of rescue medication, and no nausea.

The primary endpoint in this study was NIDL rate during the overall study phase. Other endpoints included differences in NIDL, CR, and CC rates in the acute, delayed, and overall phases. We also investigated the influence of certain risk factors on NIDL rate (including age $<$ 55 years, no alcohol intake, history of motion sickness, and history of morning sickness) in the acute, delayed, and overall phases.

Statistical analysis

A χ^2 test was used to compare NIDL rate with the CR or CC rate in each phase. To assess the influence of the risk factors on NIDL rate, we conducted a multivariate logistic regression analysis with NIDL as the outcome variable and each risk factor as an explanatory variable. We specifically examined whether the risk factors were associated with not achieving NIDL. We also examined the relationship between number of risk factors and NIDL rate using the Cochran-Armitage trend test. Analyses were carried out with SPSS Statistics 24.0, and JMP Pro 12 was used to conduct the Cochran-Armitage trend test. All reported *P*-values were two-sided, and only *P*-values $<$ 0.05 were considered statistically significant.

Results

Patient characteristics

From June 2014 to December 2016, we enrolled 121 patients were enrolled in the study, and 118 of these were included in the analysis. Three patients were excluded because they either failed to complete the patient diary (n = 2) or changed hospitals (n = 1). Table 1 lists the characteristics of the analyzed patients. All patients were women, and the median age of patients was 54 years (range 27-76). Across the treatment regimens, 71 patients were on FEC, 44 patients on EC, and 3 patients on AC. The aim of treatments included perioperative adjuvant chemotherapy (89.0%, n = 105) and Suppression of advance or recurrence (11.0%, n = 13).

Table 1. Patient baseline characteristics

	Number	%
Total	118	
Gender		
Female	118	100.0
Aim of chemotherapy		
Adjuvant chemotherapy	25	21.2
Neoadjuvant chemotherapy	80	67.8
Suppression of advanced or recurrence	13	11.0
Age (year)		
Median (range)	54 (27-76)	
Body mass index		
Median (range)	23.4 (15.2-44.3)	
Regimen of chemotherapy		
FEC	71	60.2
EC	44	37.3
AC	3	2.5
Subtype		
ER (+)	65	55.1
HER2 (+)	40	33.9
Clinical stage		
Ⅳ	12	10.2
Risk factor		
Age < 55	46	39.0
No alcohol intake	34	28.8
History of motion sickness	22	18.6
History of morning sickness	62	52.5

FEC : Fluorouracil + Epirubicin + Cyclophosphamide,
EC : Epirubicin + Cyclophosphamide,
AC : Doxorubicin + Cyclophosphamide

Table 2. Number of patients who experienced nausea, vomiting, and use of rescue medication by phase

	acute phase		delayed phase		overall phase	
	N	%	N	%	N	%
Vomiting	26	22.0	17	14.4	29	24.6
Nausea	83	70.3	84	71.2	94	79.7
Significant nausea*	31	26.3	20	16.9	36	30.5
Use of rescue medication	33	20.0	34	28.8	46	39.0

*Significant nausea was defined as nausea with a severity of greater than 2 on the Likert scale.

Antiemetic outcomes

The antiemetic outcomes are shown in Table 2. The acute phase had the highest rates of vomiting and significant nausea, and they tended to decrease with time.

Impact on QOL

Figure 1 details the FLIE-based QOL assessment results. During the overall phase, the prevalence of patients with NIDL was 53 (44.9%), and in all phases, the NIDL of nausea tended to be lower than that of vomiting. Figure 2 shows the comparison between the NIDL rate and the CR or CC rate. The NIDL rate was significantly lower than the CR rate in all phases, but was significantly higher than the CC rate in all phases.

Risk factors

Table 3 shows the univariate comparisons of NIDL rate by the presence or absence of risk factors for the different phases. The results indicated that age $<$ 55 years and history of morning sickness were significantly associated with a low NIDL rate in the acute, delayed, and overall phases. The multivariate logistic regression analyses are also detailed in Table 3. Again, age $<$ 55 years and a history of morning sickness were extracted as independent risk factors of a failure to achieve NIDL ($P < 0.05$).

Table 4 shows the relationship between the number of reported risk factors and NIDL rate in each phase. The NIDL rate tended to decrease significantly as the number of reported risk factors increased in all three phases ($P < 0.05$).

Discussion

This was a single-center, prospective, observational study on the QOL impact of aprepitant, dexamethasone, and palonosetron combination therapy for ACR in Japanese breast cancer patients. Notably, the NIDL rates in this study remained at 44.9% in the overall phase (Figure 1).

In Japan, the most recommended antiemetic therapy for a highly emetogenic chemotherapy is the combination of NK-1 receptor antagonist, dexamethasone, and $5HT_3$ receptor antagonist (preferred one is palonosetron)[19]. The CR rate in the overall phase of a randomized double-blind comparative study on the effectiveness of this particular therapy among 326 breast cancer

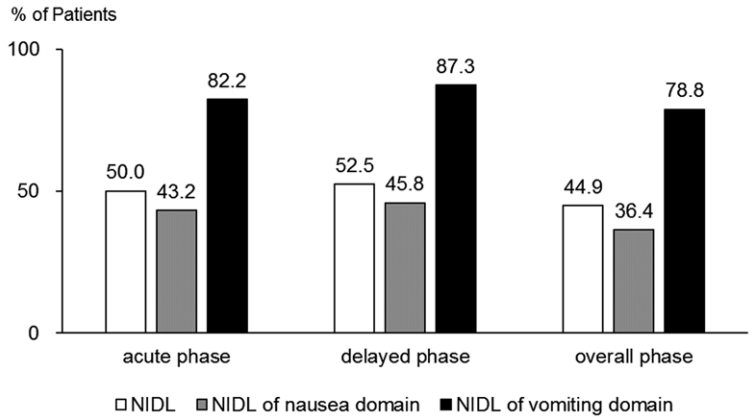

Fig. 1. Percentage of patients with no impact on daily living (NIDL), NIDL in the nausea domain, and NIDL in the vomiting domain

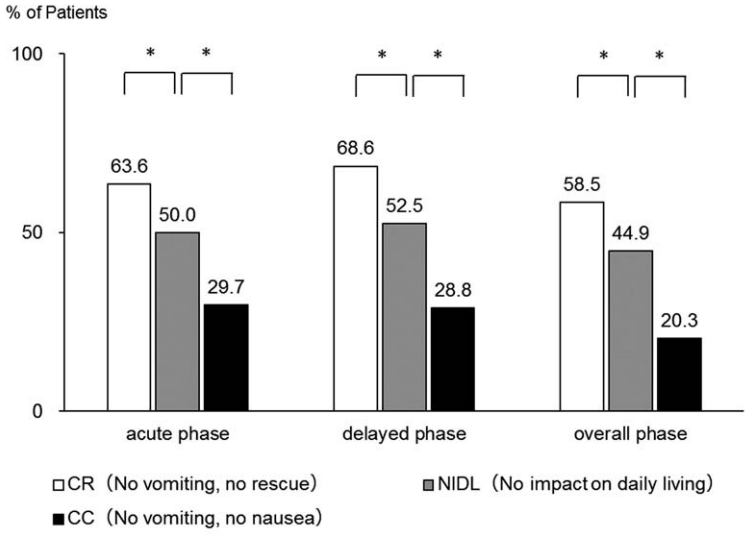

Fig. 2. Percentage of patients with complete response (CR), no impact on daily living (NIDL), and complete control (CC). $^{*}P < 0.05$ by χ^2 test.

patients undergoing ACR in Japan was 54.9%[20], which is similar to the CR rate of this study. In contrast, another randomized double-blind comparative study[9] on the effectiveness of this combination therapy for patients receiving Japanese cisplatin treatment reported a CR rate of 65.7%, which is substantially higher than that of the previous study[20] targeting ACR and the present study. In addition, in an integrated analysis of randomized controlled trials[21], the incidence of CINV with ACR was higher than that for patients receiving a cisplatin regimen. Therefore, while both cisplatin and ACR are highly emetogenic chemotherapies, the latter seems to need more attention for CINV management when it is used to treat breast cancer.

Several survey studies that investigated QOL using the FLIE questionnaire targeted highly or moderately emetogenic chemotherapy involving a combination of corticosteroid and $5HT_3$ receptor

Table 3. Factors associated with no impact on daily living (NIDL) in the (a) acute phase, (b) delayed phase and (c) overall phase

(a) acute phase

	N	NIDL		Univariate analysis	Multivariable analysis		
		N	%	p	OR	95% CI	p
Age (year)							
＜55	61	22	36.1	0.002	0.252	0.075–0.665	0.005
55≦	57	37	64.9				
No alcohol intake							
(+)	34	17	50.0	1.000	1.070	0.388–2.955	0.896
(−)	84	42	50.0				
History of motion sickness							
(+)	22	8	36.4	0.156	0.691	0.210–2.269	0.542
(−)	96	51	53.1				
History of morning sickness							
(+)	62	24	38.7	0.013	0.241	0.082–0.706	0.009
(−)	25	17	68.0				

(b) delayed phase

	N	NIDL		Univariate analysis	Multivariable analysis		
		N	%	p	OR	95% CI	p
Age (year)							
＜55	61	26	42.6	0.026	0.309	0.120–0.799	0.015
55≦	57	36	63.2				
No alcohol intake							
(+)	34	18	52.9	0.956	1.070	0.394–2.908	0.894
(−)	84	44	52.4				
History of motion sickness							
(+)	22	10	45.5	0.460	0.954	0.301–3.029	0.937
(−)	96	52	54.2				
History of morning sickness							
(+)	62	24	38.7	0.013	0.253	0.089–0.721	0.010
(−)	25	17	68.0				

(c) overall phase

	N	NIDL		Univariate analysis	Multivariable analysis		
		N	%	p	OR	95% CI	p
Age (year)							
＜55	61	20	32.8	0.006	0.252	0.091–0.695	0.008
55≦	57	33	57.9				
No alcohol intake							
(+)	34	16	47.1	0.766	1.263	0.445–3.583	0.661
(−)	84	37	44.0				
History of motion sickness							
(+)	22	6	27.3	0.065	0.436	0.118–1.610	0.213
(−)	96	47	49.0				
History of morning sickness							
(+)	62	20	32.3	0.009	0.210	0.071–0.625	0.005
(−)	25	16	64.0				

Table 4. The number of risk factors associated with no impact on daily living (NIDL)

Number of risk factors	Number of patients	NIDL					
		acute phase		delayed phase		overall phase	
		N	%	N	%	N	%
0	15	14	93.3	13	86.7	13	86.7
1	47	26	55.3	27	57.4	24	51.1
2	24	13	54.2	14	58.3	11	45.8
3	25	5	20.0	6	24.0	4	16.0
		*$p < 0.05$		*$p < 0.05$		*$p < 0.05$	

*Cochran-Armitage tests.

antagonist. Most studies have reported a decrease in QOL by CINV[13, 17, 18]. Among these, Fernández-Ortega *et al*[13] analyzed 160 patients treated with highly or moderately emetogenic chemotherapy with steroids and $5HT_3$ receptor antagonist as CINV prophylaxis, and reported that QOL was not affected by nausea in 55% of patients. In another study, Ballatori *et al*[18] evaluated 152 patients receiving cisplatin followed by appropriate prophylaxis according to Multinational Association of Supportive Care in Cancer (MASCC) guidelines and reported QOL effects due to vomiting in 67.3% of the patients and due to nausea in 76.6% of the patients. For the first time in this study, we targeted Japanese patients with breast cancer receiving an ACR regimen of aprepitant, dexamethasone, and palonosetron, and investigated QOL using FLIE questionnaires. And we found that NIDL for nausea was 36.4% and NIDL for vomiting was 78.8% in the overall phase. Therefore, we found no significant improvement in QOL compared to previous studies.

We also found that the incidence of significant nausea during the overall phase was higher than the incidence of vomiting (30.5% vs. 24.6%), and that NIDL could not be achieved for nausea (36.4%), but could generally be achieved for vomiting (78.8%). Together, these results indicate that the influence of nausea on QOL was considerable. Furthermore, the NIDL rate, which is an index of QOL, was significantly lower than the CR rate, possibly because nausea was not included as an evaluation indicator when measuring CR rate. A previous study investigating the effect of CINV on QOL similarly presumed that nausea has a greater negative impact on QOL than does vomiting because vomiting is a short-term event, whereas nausea is a prolonged feeling[13]; however, since the NIDL rate in this study was significantly higher than the CC rate (no emetic responses and no nausea), we might infer that the CC rate is not the most ideal goal of antiemetic therapy and that mild nausea probably did not lead to a lower QOL.

By contrast, significant nausea might have a large influence on QOL, and our results indeed suggest that the CR rate is insufficient for evaluating the QOL effects of antiemetic therapy. Consequently and with the growing use of outpatient chemotherapy, proper assessment of QOL using subjective indexes, including nausea, is essential for CINV management, and it might be necessary to calculate NIDL rates using the FLIE to effectively evaluate the impact of CINV on patient QOL.

One previous study investigating CINV and QOL among breast cancer patients undergoing ACR conducted in Canada, which also used the FLIE, reported a CR rate of 51% and an NIDL rate of 63.5%[22]; also, in contradiction to the present study results, the NIDL rate was higher than the CR rate. A previous study in Japan using the FLIE Japanese version attributed this difference in rates to the period used to define NIDL[23]; in the Canadian study, the FLIE was obtained 120 hours following treatment, and participants were asked to rate the last 5 days, whereas in the FLIE Japanese version, the questionnaire was administered to patients every 24 hours. In addition, the FLIE is a subjective evaluation of QOL and thus possibly affected by memory, which is likely to become increasingly ambiguous over time. Thus, the FLIE Japanese version used in our study might more accurately measure QOL[23].

For Japanese patients receiving ACR for breast cancer, the NIDL rate remained at about 50%, despite the use of effective antiemetics. This might be because a large number of the cases had risk factors of CINV, such as being young and female, and in this study, the NIDL rate of individuals aged＜55 years or with a history of morning sickness was significantly lower (Table 3). In addition, the NIDL rate tended to decrease as the number of known risk factors increased in this study (Table 4). On the other hand, the NIDL rate was over 90% for cases without any risk factors. Thus, the antiemetic therapy seemed adequate only when no risk factors were present. Therefore, individualized antiemetic therapy taking risk factors into account should be considered. Recently, the usefulness[24] of combined antiemetic treatment of olanzapine with aprepitant, dexamethasone, and a $5HT_3$ receptor antagonist has been demonstrated. Thus, patients with many risk factors might improve their QOL by adding olanzapine in conjunction with other antiemetics.

Since this study is a single-arm, single-center observational study, we cannot deny the possibility of omitting other confounders affecting QOL, or the possibility of influencing factors within the treatment environment. Thus, a more detailed and larger-scale study is warranted.

In summary, among Japanese patients with breast cancer receiving ACR, even usiug the recommended combination therapy of aprepitant, dexamethasone, and palonosetron, the NIDL rate was only about 45%. It is therefore necessary to develop a more effective antiemetic therapy that takes patient-level risk factors into account to improve overall patient QOL. In addition, the NIDL rate was significantly lower than the CR rate in this study, suggesting that the CR rate is insufficient for evaluating the effect of antiemetic therapy on a patient's QOL.

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Compliance with Ethical Standards

Conflicts of interest

No potential conflicts of interest to disclose.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and / or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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