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ORIGINAL ARTICLE

Measuring the impact of guideline-based antiemetic therapy on nausea and vomiting control in breast cancer patients with multiple risk factors

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Abstract
Purpose The objective of this exploratory analysis was to determine if individual patient risk factors could be used to optimize chemotherapy-induced nausea and vomiting (CINV).
Methods Through validated risk prediction models which quantify patient risk factors, 152 patients with early-stage breast cancer scheduled to received adjuvant anthracycline-based chemotherapy were categorized as being at low (level 0) or high-risk (level 1) for CINV. Prior to the first cycle of chemotherapy, low-risk patients received ondansetron and dexamethasone, while high-risk level 1 patients also received aprepitant. For subsequent cycles, patients who experienced CINV had their antiemetics changed in a stepwise manner to level 2 (extended-duration dexamethasone) or level 3 (extended-duration dexamethasone and low-dose olanzapine).
Results The study enrolled 152 patients who received 484 cycles of chemotherapy. Forty patient cycles were classified as low risk (level 0) compared to 201, 162 and 81 that were classified as high-risk levels 1, 2 and 3, respectively. Complete control of acute and delayed vomiting was comparable and was achieved in over 85 % of patients across all risk levels ($p = 0.56$ and $p = 0.99$). In contrast, complete control of acute and delayed nausea was reduced in risk levels 1 to 3 compared to level 0 (acute = 51.2, 58.0, 45.7 vs. 70.0 %; $p = 0.013$)—(delayed = 32.8, 45.7, 34.6 vs. 62.5 %; $p < 0.001$).
Conclusions Despite the addition of aprepitant, extended-duration dexamethasone and olanzapine, patients at high risk for CINV due to personal risk factors failed to achieve good nausea control.

Keywords Nausea · Vomiting · Chemotherapy · Risk prediction · Randomized trial · Aprepitant

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Background

An important clinical advance in cancer supportive care over the past 25 years was the approval of the serotonin receptor (5HT3) antagonist class of antiemetics (e.g. ondansetron, granisetron) for the prevention of chemotherapy-induced nausea and vomiting (CINV) [1]. Further progress was then made with the approval of the neurokinin-1 (NK-1) receptor antagonists (e.g. aprepitant), the better use of agents such as dexamethasone and olanzapine and through evidence-based antiemetic guidelines developed by the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) [2–6].

The guidelines have been invaluable in the selection of optimal antiemetic therapy secondary to classifying chemotherapy based on its potential for emesis [5, 6]. As an illustration, both sets of guidelines categorize doxorubicin as being moderately emetogenic with the risk of emesis being less than 90 % [5, 6]. However, doxorubicin administered to a female patient having underlying risk factors for CINV such as a young age, a non-drinker and with a history of morning sickness should be reclassified as being highly emetogenic [7, 8]. In contrast, a 75 year old patient receiving doxorubicin who is a high-alcohol consumer and has no underlying risk factors for nausea and vomiting (N&V) would be at a lower risk compared to the first patient. Hence, the latter patient may not need additional agents added to standard ondansetron and dexamethasone.

In an era of increasingly personalized medicine, antiemetic guidelines were developed based on the results of randomized trials evaluating highly emetogenic single-cycle chemotherapy. However, the guidelines do not appear to incorporate individual patient risk factors into their guidance. This is in contrast to guidelines on the use of granulocyte colony-stimulating factors for the prevention of febrile neutropenia, which do incorporate patient risk factors such as advanced age and patient performance status into their recommendations [9, 10].

To help incorporate patient factors with the emetogenic potential of the chemotherapy over a full course of treatment, we previously developed repeated measures cycle-based models to determine which patients are at high-risk for CINV [7, 8]. Major predictors for acute (within the first 24 h) and delayed (from days 2 to 5) CINV were consistent with the published literature and included age less than 40 years, platinum- or anthracyline-based chemotherapy, low alcohol consumption, emesis in earlier cycles of chemotherapy and previous history of motion/morning sickness [7, 8]. The models were subsequently used to develop numerical scoring systems (indices) that are able to accurately identify patients at high-risk CINV prior to each cycle.

From the initial development studies, patients with risk scores of ≥7 and >16 were classified as being at "high-risk" for acute and delayed CINV [7, 8]. To externally validate the models, two prospective validation trials were undertaken in cancer centres that were not part of the initial development studies [11, 12]. The clinical utility of the risk models was subsequently demonstrated in a randomized trial comparing risk model-guided (RMG) antiemetic therapy to a physician's choice (PC) control group in breast cancer patients receiving anthracycline-based adjuvant chemotherapy [13]. The data from the physician's choice control group is not presented in the current paper because in contrast to the RMG experimental group, protocol-mandated adjustments in antiemetics were not based on the presence of patient risk factors. For patients randomized into the physician's choice control group, physicians were free to choose any antiemetic prophylaxis based on their clinical judgment.

From data collected as part of the randomized trial, the current exploratory analysis sought to determine if the addition of guideline-based antiemetics such as aprepitant, extended-duration dexamethasone and low-dose olanzapine to standard ondansetron and dexamethasone can improve CINV control in patients with multiple risk factors.

Patients and methods

Patients who were 18 years of age and older with a new diagnosis of early-stage breast cancer and scheduled to receive anthracycline-based adjuvant chemotherapy at The Ottawa Hospital Cancer Centre and the Irving Greenburg Cancer Centre in Ontario were enrolled into the study. Permission to conduct the study was received by the ethics review boards of each centre. Adjuvant chemotherapy consisted of four cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 500 mg/m^2 (AC) or three cycles of 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2 (FEC).

Study design and treatments

Eligible and consented patients were randomized (1 to 1) to a physician's choice (PC) antiemetic control group or to a RMG experimental group. All randomized patients had acute and delayed antiemetic risk scores calculated prior to each cycle of chemotherapy. In the physician's choice control group, the treating oncologist could choose whatever combination, dose and duration of antiemetic therapy he/she wished. The current exploratory analysis focused on patients who received antiemetic therapy in the RMG group.

Patients randomized into the RMG group received antiemetic therapy based on their calculated risk scores. Patients considered to be at low risk (acute risk score <7 and/or a delayed score of ≤16) by the models [7, 8], received dexamethasone and ondansetron based on provincial antiemetic guidelines and were categorized as level 0. This consisted of dexamethasone and ondansetron (day 1, dexamethasone 10 mg IV and ondansetron 8 mg PO before chemotherapy; dexamethasone 4 mg PO and ondansetron 8 mg 8 h later; days 2 and 3, dexamethasone 4 mg PO BID and ondansetron 8 mg BID). Patients considered at high risk for CINV by the models (acute risk score ≥7 and/or a delayed score of >16) were categorized as level 1 and received guideline-based antiemetic prophylaxis for a highly emetogenic chemotherapy and consisted of dexamethasone, ondansetron and aprepitant (day 1, dexamethasone 12 mg IV, ondansetron 8 mg PO and aprepitant 125 mg PO before chemotherapy, and ondansetron 8 mg 8 h later; days 2 and 3, aprepitant 80 mg PO daily). If patients had poorly controlled CINV in subsequent cycles, then additional dexamethasone (level 2) and low-dose olanzapine (2.5 mg daily for 7 days) were added in subsequent cycles (level 3).

Study endpoints and data collection

The co-primary endpoints were complete control of nausea and vomiting at 24 h and from days 2 to 5. Complete control was defined as no patient reported nausea or vomiting over the 5-day period. Secondary endpoints measured at day five post chemotherapy consisted of patient quality of life (QOL) and the use of rescue medication at home. QOL was assessed using the Functional Living Index-Emesis (FLIE) index (version that has been modified for a 5-day recall), which is a validated questionnaire designed to measure the impact of CINV on a patient's daily life [14]. The FLIE index is

composed of two domains, using nine items for each domain with a 5-day recall. Each domain has a score ranging from 9 to 63, with higher scores indicating better control of CINV and improved QOL [15].

At study enrollment, data collection consisted of patient demographic and disease-related information, risk factors for CINV such as history of motion sickness, history of morning sickness during a previous pregnancy and daily alcohol consumption. Just prior to each cycle of chemotherapy, additional information was collected such as the scheduled antiemetic prophylaxis, patient's expectation to become nauseous following chemotherapy, food intake the morning of chemotherapy and number of hours slept the night before. Anxiety levels were also measured just before receiving each cycle using a 4-point Likert scale (graded as none, mild, moderate and high). All patients were then provided with a diary to record the number of episodes as well as the intensity and duration of N&V during the first 24 h and during days 2 to 5 following chemotherapy. This was supplemented with a telephone call by the study nurse on days 1 and 5 post chemotherapy. The collection of patient risk factor data beyond what was required for the application of the CINV risk models was mandated in the randomized trial protocol in order to provide evidence that balance existed between patients randomized into the RMG and the physician's choice control group [13].

Sample size and statistical analysis

The sample size for the randomized trial required that 152 patients be randomized into each group to provide an 80 % power to detect a 60 % relative reduction in the risk of acute emesis within the first 24 h following chemotherapy between the RMG and the physician's choice control group. Therefore, in this exploratory analysis, data on 152 patients in the RMG group who received a total of 490 cycles was available.

Patient demographic, clinical and treatment characteristics were presented descriptively as mean, medians or proportions. The risk of acute and delayed CINV between levels 0, 1, 2 and 3 over all cycles of chemotherapy were compared using generalized estimating equations (GEE), with an adjustment for clustering on the patient. The independent variables in the GEE model were risk "level" and "cycle number". Repeated measures mixed models were used to compare differences in QOL (measured by the FLIE index) between risk levels over the full course of treatment. Independent variables in the mixed models consisted of risk level, cycle number and FLIE scores at baseline and 24 h post chemotherapy. All of the statistical analyses were performed using Stata, V11.0 (Stata Corp., College Station, TX, USA).

Results

From April 2012 to November 2014, 152 patients were randomized into the RMG group, which made up the sample for the current exploratory analysis (Table 1). Median patient age was 54 and approximately 90 % of patients had stage II or III disease. Overall, 81 % of patients reported drinking less than

Table 1 Characteristics of patients and treatments

Characteristic	Breast cancer patients (n = 152)
Median age (range)	54 (26–76)
Disease stage	
I	9.2 % (14)
II	48.7 % (74)
III	42.1 % (64)
History of alcohol intake	
Less than 1 drink/day	80.9 % (123)
1 drink/day	5.9 % (9)
More than 1 drink/day	7.9 % (12)
Missing	5.3 % (8)
History of motion sickness	42.7 % (65)
History of morning sickness (if applicable)	55.9 % (89)
Concomitant medical conditions[a]	61.2 % (93)
Planned chemotherapy	
AC × 4	34.9 % (53)
FEC × 3	64.5 % (98)
FAC × 3	0.7 % (1)
Median number of cycles (range)	2 (1 to 4)
Cycles of chemotherapy delivered	
One	152
Two	145
Three	145
Four	48
Total	490
Planned chemotherapy completed	95.4 % (145)
CINV risk level at cycle 1	
Level 0[b]	15.8 % (24)
Level 1[c]	80.9 % (123)
Missing	3.3 % (5)
Antiemetic prophylaxis at cycle 1	
5HT3 + Dex (pre and post)	15.8 % (24)
5HT3 + Dex + NK1 (pre and post)	80.9 % (123)
Missing	3.3 % (5)

A doxorubicin, C cyclophosphamide, F 5-fluorouracil, E epirubicin, 5HT3 serotonin 5-HT3 receptor antagonist, Dex dexamethasone, NK1 neurokinin 1 receptor antagonist

[a] Cardiovascular disease, diabetes, gastrointestinal, musculoskeletal, thyroid, other

[b] Only ondansetron and dexamethasone

[c] Ondansetron, dexamethasone and aprepitant

one alcoholic beverage per day and 42.7 and 55.9 % reported having a positive history for motion sickness and morning sickness respectively (Table 1). Approximately 65 % of patients received FEC chemotherapy and the remainder was treated with AC. Overall, 490 cycles of chemotherapy were delivered, which translated to 95.4 % of treatment being completed as planned (Table 1).

The risk models were then applied to each patient before each cycle. At cycle 1, 15.8 and 80.9 % of patients were deemed by the models to be low (level 0) and high risk (level 1) for CINV, respectively. Hence, the assigned risk levels reflected the type of antiemetic prophylaxis received prior to cycle 1 (Table 1). Since 80.9 % of patients were assigned to risk level 1, triple antiemetic therapy (i.e. ondansetron, dexamethasone and aprepitant) was provided prior to cycle 1. Lower risk level 0 patients only received ondansetron and dexamethasone according to provincial practice guidelines (Table 1).

Prior to each cycle, some patients acquired additional risk factors for CINV. These included nausea before treatment, anticipatory nausea and vomiting as well as anxiety and reduced sleep before a given cycle of chemotherapy (Table 2). Over 490 cycles of chemotherapy, 26.3 % of patients had moderate to high levels of anxiety. These risk factors as well as subsequent vomiting episodes contributed to patients moving into the higher risk levels (i.e. levels 2 and 3), in which the study protocol mandated the addition of extended-duration dexamethasone and low-dose olanzapine (Table 2).

The complete control of CINV, defined as no nausea and vomiting was then compared between risk levels. In the first 24 h following chemotherapy, there was no significant difference in the proportion of patients developing acute vomiting between risk levels ($p = 0.56$), where the prevalence of acute vomiting was 5 % or less (Fig. 1). In contrast, there was a significant difference in the development of acute nausea between risk levels (Fig. 1). Using risk "level 0" as the reference category and controlling for cycle number, the GEE regression model indicated that patients in levels 1 to 3 were 2 to 4 times more likely to suffer from acute nausea, despite the addition of aprepitant, extended-duration dexamethasone and low-dose olanzapine (Table 3). It was also interesting to note that the risk of acute nausea was significantly lower compared to the first cycle of chemotherapy, but remained elevated from cycles 2 to 4 (Table 3). Approximately 83 of 146 evaluable patients (56.8 %) developed acute nausea in the first cycle compared to 46.9, 33.1 and 25.0 % in cycles 2, 3 and 4, respectively.

Similar results were also observed in the case of delayed nausea and vomiting. There were no significant differences in

Table 2 Predictive factors and risk level for CINV prior to each cycle

Characteristic	Breast cancer patients ($n = 490$)
Nausea before chemotherapy	5.7 % (28)
A meal prior to chemotherapy	91.0 % (441)
Median number hours sleep night before chemotherapy (range)	7 (0–12)
Patient expectation of nausea/vomiting prior to each chemotherapy cycle	
Yes	33.9 % (166)
No	58.6 % (287)
Missing	7.6 % (37)
Patient anxiety prior to each chemotherapy cycle	
None	30.0 % (147)
Mild	38.2 % (187)
Moderate	21.2 % (104)
High	5.10 % (25)
Missing	5.5 % (27)
CINV risk level over all chemotherapy cycles	
Level 0[a]	8.2 % (40)
Level 1[b]	41.0 % (201)
Level 2[c]	33.1 % (162)
Level 3[d]	16.5 % (81)
Missing	1.2 % (6)

CINV chemotherapy-induced nausea and vomiting

[a] Only ondansetron and dexamethasone

[b] Ondansetron, dexamethasone and aprepitant

[c] Ondansetron, aprepitant and additional dexamethasone

[d] Ondansetron, additional dexamethasone, aprepitant and olanzapine

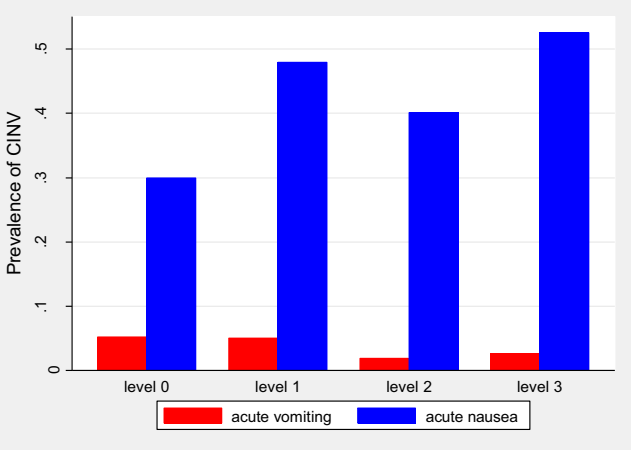

Fig. 1 Prevalence of acute nausea and vomiting by CINV risk level

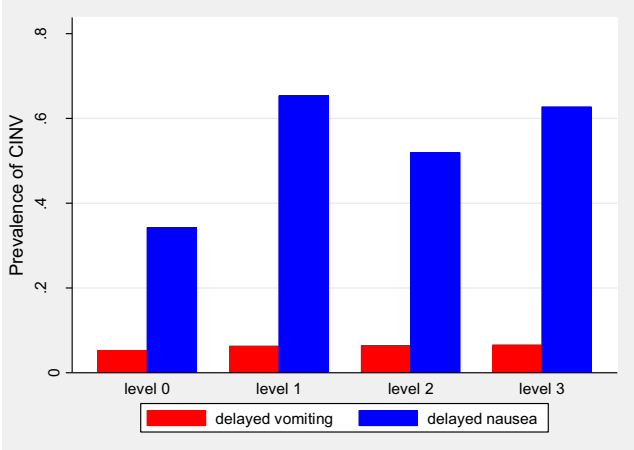

Fig. 2 Prevalence of delayed nausea and vomiting by CINV risk level

the development of delayed vomiting between the difference risk levels (Fig. 2; $p = 0.99$). However, the risk of delayed nausea was significantly higher in levels 1, 2 and 3 when compared to level 0 (Table 3). What was particularly interesting was that patients in risk level 3 were eight times more likely to develop delayed nausea compared to level 0 (OR = 8.0; $p < 0.001$), despite the use of ondansetron, extended-duration dexamethasone, aprepitant and low-dose olanzapine (Table 3). These findings imply that nausea continues to be problematic is a substantial number of patients, even after the use of our most powerful antiemetics. The final observation was that the risk of delayed nausea was also decreased beyond cycle 1 (Table 3).

Table 3 Risk of acute and delayed nausea by risk level and cycle number

Variable	Odds ratio	95%CI	*p* value	Impact on acute nausea
Acute Nausea				
Risk level (vs. 0)				
1	2.00	0.94 to 4.39	0.072	NS
2	2.32	0.90 to 5.93	0.08	NS
3	4.22	1.46 to 12.2	0.008	↑ by 4.2 times
Cycle number (vs. 1)				
2	0.56	0.34 to 0.95	0.032	↓ risk by 44 %
3	0.25	0.14 to 0.48	<0.001	↓ risk by 75 %
4	0.21	0.09 to 0.47	<0.001	↓ risk by 79 %
Delayed Nausea				
Risk level (vs. 0)				
1	3.93	1.75 to 8.76	0.001	↑ by 3.9 times
2	3.90	1.51 to 10.2	0.005	↑ by 3.9 times
3	8.00	2.74 to 23.3	<0.001	↑ by 8.0 times
Cycle number (vs. 1)				
2	0.42	0.23 to 0.78	0.006	↓ risk by 58 %
3	0.18	0.09 to 0.37	<0.001	↓ risk by 72 %
4	0.11	0.04 to 0.25	<0.001	↓ risk by 89 %

NS = not significant at the $p = 0.05$ level

Approximately 105 of 146 evaluable patients (71.9 %) developed delayed nausea in the first cycle compared to 56.6, 42.8 and 31.2 % in cycles 2, 3 and 4, respectively.

The final endpoint assessed in the current study was patient QOL between risk levels using the FLIE index. There were no significant differences in mean FLIE scores for vomiting between the four risks levels (data not shown). However, there was a statistically significant difference in mean FLIE scores for nausea between risk levels (mean FLIE scores at 5 days post chemotherapy: risk level 0 = 56.7 vs. 49.8, 52.7 and 52.9 in risk levels 1, 2 and 3, respectively), indicating a decline in QOL in levels 1, 2 and 3 relative to level 0 (Fig. 3).

Discussion

Randomized trials evaluating new drugs for the prevention of CINV have typically used complete response (CR), defined as

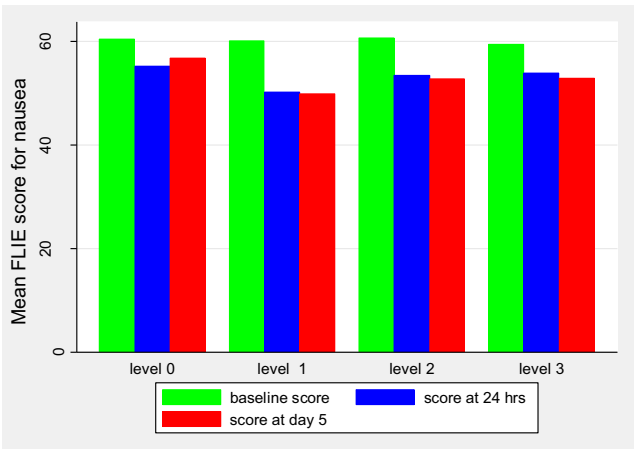

Fig. 3 Functional Living Index-Emesis for nausea by CINV risk level. The drop in mean FLIE score for nausea was statistically significant between risk levels 1, 2 and 3 relative to level 0 (p = 0.023, p = 0.007 and p = 0.005)

no vomiting or rescue medication as the primary trial endpoint [16–18]. In most studies, this endpoint has been evaluated in chemotherapy-naïve patients after the first cycle of highly emetogenic chemotherapy. These trials have reported impressive CR rates, in excess of 80 %, in patients receiving triple antiemetic therapy consisting of a 5HT3 receptor antagonist, dexamethasone and an NK1 receptor antagonist [16–18]. The findings from these trials have provided the core evidence for the development of the ASCO and ESMO guidelines [5, 6].

The current study confirms that even after multiple cycles of chemotherapy, complete control of acute and delayed vomiting is in excess of 90 %, even in high-risk patients with multiple risk factors. However, nausea remains poorly controlled, especially in patients with multiple risk factors for CINV. Furthermore, nausea control was not improved, even after the addition of multiple agents such as aprepitant, extended-duration dexamethasone and low-dose olanzapine. As a result, patient QOL was significantly compromised over the entire course of chemotherapy. These findings imply that nausea remains the critical unmet medical need, especially in patients with multiple risk factors. Therefore, the choice of primary endpoints of randomized trials evaluating new antiemetics need to be refocused on improving nausea control [19, 20].

We recommend that future randomized trials incorporate patient risk factors into the inclusion criteria and have complete control of nausea over 5 days post chemotherapy as the primary endpoint, evaluated over multiple cycles. In addition, guidelines committees need to incorporate patient risk factors and make nausea control their primary objective. Failure to revise antiemetic randomized trial design and guideline development activities will continue to neglect nausea, the real unmet medical need [20].

There are a number of limitations in the current study that need to be acknowledged. The current analysis was a secondary evaluation of data that were collected as part of a prospective randomized trial. Therefore, the findings should be seen as exploratory. Despite the best efforts of the clinical trial staff, CINV acute and delayed outcomes data were missing in 3 to 6 % of patients. The study enrolled a homogenous sample of breast cancer patients receiving AC of FEC adjuvant chemotherapy. Almost 50 % of patients in the trial were less than 50 years of age, approximately 80 % consumed less than one alcoholic beverage per day and 55 % had a history of morning sickness. As a result, 81 % of these patients were categorized by the models as "high-risk" prior to the first cycle of chemotherapy. Therefore, the hypotheses generated in this study should be tested in different tumour types and in a more heterogeneous sample of patients.

In conclusion, this exploratory evaluation suggested that vomiting, even in high-risk patients with multiple risk factors appears to be well controlled using evidence-based antiemetic therapy. However, nausea was poorly controlled in high-risk patients, leading to significant reductions in QOL. Furthermore, nausea continued to be poorly controlled, even after the addition of aprepitant, extended-duration dexamethasone and low-dose olanzapine. Therefore, future clinical trials evaluating new antiemetics need to preselect patients with multiple risk factors and designate nausea control as the primary trial endpoint. The findings from such trials can then be used to create guidelines that can better serve our patients.

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Conflict of interest None of the authors has a financial relationship with the organization that sponsored the research. The lead author had full control of all primary data and will allow the journal to review the data if requested.

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