Antiemetic effect of granisetron NK, a generic 5-HT<sub>3</sub> receptor antagonist in comparison with azasetron for prevention of chemotherapy-induced nausea and vomiting in cancer patient

- A crossover randomized controlled clinical trial -

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Abstract

Purpose: Five-hydroxytryptamine-3 (5-HT<sub>3</sub>) receptor antagonists (RAs) are widely used to control chemotherapy-induced nausea and vomiting in cancer chemotherapy. Several 5-HT<sub>3</sub> RAs could be available, there are some important points to select agents, like as efficacy, adverse events and their costs. In this study, we compared an originator drug, azasetron with a generic version, granisetron NK, to evaluate their anti-emetic efficacy and quality of life in crossover randomized setting. 

Patients and Methods: Patients treated with a highly emetic FEC100 regimen are registered in this study. Patients randomly assigned to 2 groups, which treated with granisetron NK in first course followed second course treated with azasetron, or vice versa. Efficacy, adverse events and quality of life (QOL) were evaluated with patient self-reporting questionnaires.

Results: Twenty seven patients were recruited to this study. Fourteen patients were assigned to receive azasetron in first course followed by granisetron NK in second course, and 13 patients were assigned to receive granisetron NK in first course followed by azasetron in second course. There was no significant difference in grade and frequency of nausea, vomiting, eating status and defecation between two treatment groups. In addition, analysis of QOL showed no significant difference in two groups.

Conclusion: A generic 5-HT<sub>3</sub> RA granisetron NK which reduce 31% cost showed no significant differences in terms of efficacy, adverse events and QOL in comparison with originator drug azasetron. Effective and high cost-performance supportive therapy should be chosen.

Key Words: generic drug, emesis, azasetron, granisetron, 5-HT<sub>3</sub> receptor antagonist, randomized clinical trial

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is based on the assumption that a generic product displays essentially the same kinetic and dynamic profile as that of its brand-name counterpart\(^5\).

Azasetron is a 5-HT\(_3\) RA and its antiemetic potency is reported as similar to those of granisetron and ondansetron, although the cost is about 10% lower than granisetron\(^6-8\)\). Therefore, in Japan, azasetron is widely used to prevent CINV in cancer chemotherapy. Granisetron NK is one of generic subscription of 5-HT\(_3\) RA and which cost is 69% of azasetron. In this study, we compared granisetron NK and azasetron in terms of their efficacy to prevent CINV. This is first prospective randomized crossover study comparing efficacy and adverse events of generic drug granisetronNK and originater drug azasetron.

**Patients and Methods**

This study was designed as a single-institution, randomized, single-blind, crossover trial, and approved by Institutional Review Board of Aizawa Hospital based on ethical norms presented in Helsinki Declaration of the World Medical Association as well as under the provisions of Act on the Protection of Personal Information in Japan. Informed consent was obtained from each participant.

**Patients**

Patients 20 years or older with breast cancer who were preparing to initiate FEC100 (high emetic risk) treatment with a Performance Status score of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale were enrolled. Study exclusion criteria were ECOG PS 3 or 4, with severe hepatic, renal, or cardiac diseases as complications, pregnancy or breastfeeding, other cause of nausea or vomiting and receiving radiotherapy during this study.

**Treatment**

Eligible patients were randomly assigned to 2 treatment groups which receiving granisetronNK in first course of FEC100 regimen followed by receiving azasetron in second course and the other patients receive azasetron in first course followed by granisetronNK in second course. GranisetronNK 3 mg and azaseteron 10 mg were mixed with dexamethasone and intravenously infused over 30 minutes before administration of FEC100 regimen (5-FU (500 mg/m\(^2\)), Epirubicin Hydrochloride (100 mg/m\(^2\)) and Cyclophosphamide Hydrate (500 mg/m\(^2\)) on day 1, every 3 weeks). Granisetron hydrochloride 2 mg and dexamethasone 8 mg were per orally administered for three days after FEC100 regimen. Patients permitted to use additional granisetron hydrochloride 2 mg and/or metoclopramide when they feel CINV, and instructed to record the time and frequency of use their drugs in questionnaire.

**Evaluation**

Anti-emetic efficacy and adverse events were evaluated using patient questionnaire. Patients were instructed to record their nausea, vomiting, eating status, constipation and additional use of granisetron hydrochloride 2 mg or metoclopramide over a 24-hour period after FEC100 regimen (Table 1). Patients’ QOL during treatment were scored by Numerical Rating Scale (NRS) with 11 scores from 0 to 10. Score 0 represents QOL did not suffered from CINV, and score 10 represents maximum QOL suffering from CINV.

**Statistical Analysis**

Primary end point was grade and number of CINV treating with granisetronNK compared with that of azasetron. As secondary end points, we analyzed adverse events and QOL.

The severity and frequency of nausea, vomiting, constipation and eating status were analysed using \(\chi^2\)-test. QOL was analysed by unpaired t-test. Differences were considered significant if \(P < 0.05\).

**Results**

**Patient characteristics**

Between March 2009 and April 2010, 27 breast cancer patients were randomly assigned to receive granisetronNK in first course followed by azasetron in second course and to receive azasetron in first course followed by granisetronNK in second course on the same day of initiation of FEC100 treatment. Thirteen patients first received granisetronNK, and 14 patients first received azasetron. There were no significant differences between the granisetronNK treatment-first group and azasetron treatment-first group in terms of age, sex, body weight, body mass index (BMI), treatment period (neoadjuvant or adjuvant) and dose reduction of FEC100 regimen (Table 2).

**Anti-emetic efficacy**

All patients received FEC100 regimen felt nausea in two groups. There were no significant differences about grade and frequency of CINV in both between 2 groups, and between first course and second course (Table 3). About vomiting, same tendencies were observed (data not shown). Eating status was evaluated as grade 1; could eat just like usual amount, grade 2; could eat half of usual mount and grade 3; could not eat. In the view of comparison of granisetronNK first group and azasetron first group, and comparison of first course and second course, there was no significant difference (Table 4).
Antiemetic effect of granisetron NK

Table 1. Patient self-reporting questionnaire form. Questionnaire is consisted with part of investigate anti-emetic efficacy, adverse events and Quality of Life during treatment.

QUESTIONNAIRE

Please complete this Questionnaire within 24 hours of the injection you received at hospital (i.e., by ___ o'clock on ___ [month] ___ [day]).
Date of FEC 100 therapy: ___ (month) ___ (day), ___ (year)
ID: __________ Name __________
Please circle the number that best represents your situation. If there is anything that you are concerned about, please indicate in the space provided near the bottom.

Did you feel nausea?
1. I did not feel nausea.
2. I felt slight nausea.
3. I felt nausea.

Did you vomit?
1. I did not vomit.
2. I vomited (___ times).
   At: _____ (a.m. or p.m.) on ___ (month) ___ (day)

Did you take the PRN (as needed) antiemetic?
1. I took it.
2. I took it once at: _____ (a.m. or p.m.) on ___ (month) ___ (day).
3. I took it twice at: _____ (a.m. or p.m.) on ___ (month) ___ (day)
   and at: _____ (a.m. or p.m.) on ___ (month) ___ (day).

Did you eat meals?
1. I ate about the usual amount.
2. I ate about half the usual amount.
3. I could not eat.

Defecation
1. I defecated as usual.
2. I found it more difficult to defecate than usual.
3. I found it much more difficult to defecate than usual.

Please indicate any other concern you may have:

Please answer the following question regarding the extent of your suffering within 24 hours of the infusion. With the score of 10 representing the worst suffering related to vomiting and feeling nausea that you can imagine, how do you rate your current suffering? Please mark the location on the scale that best represents your situation with a circle.

No suffering 0 5 10 Worst suffering

Table 2. Patient characteristics. There were no significant differences between the granisetronNK first group and azasetron first group in each variable. Four patients in each group reduced chemotherapy doses.

<table>
<thead>
<tr>
<th></th>
<th>Azasetron First group</th>
<th>Granisetron NK First group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>51 (36-73)</td>
<td>50 (42-68)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>0/14</td>
<td>0/13</td>
</tr>
<tr>
<td>Median Body weight (range)</td>
<td>58.5 (46.0-71.8)</td>
<td>57.9 (46.3-68.7)</td>
</tr>
<tr>
<td>Neoadjuvant/Adjuvant</td>
<td>14/0</td>
<td>13/0</td>
</tr>
<tr>
<td>Dose-down case</td>
<td>4/14</td>
<td>4/13</td>
</tr>
</tbody>
</table>

Table 3. Nausea within 24 hours of FEC100 regimen and anti-emetic treatment. Nausea was rated on a 3-grade scale on the Questionnaire. Grade 1. Did not feel nausea; 2. Felt slightly nausea; 3. Felt nausea. Abbreviation: n.s.; not significant.

<table>
<thead>
<tr>
<th>Grade (1/2/3)</th>
<th>Azasetron First group</th>
<th>Granisetron NK First group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First course</td>
<td>(4/5/5)</td>
<td>(5/5/3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Second course</td>
<td>(5/7/2)</td>
<td>(5/7/1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>p value</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
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</tbody>
</table>

Table 4. Eating status within 24 hours of FEC100 regimen and anti-emetic treatment. Eating status was rated on 3-grade scale on the Questionnaire. Grade 1. Ate about the usual amount; 2. Ate about half the usual amount; 3. Could not eat. Abbreviation: n.s.; not significant.

<table>
<thead>
<tr>
<th>Grade (1/2/3)</th>
<th>Azasetron First group</th>
<th>Granisetron NK First group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First course</td>
<td>(5/5/4)</td>
<td>(7/4/2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Second course</td>
<td>(4/9/1)</td>
<td>(6/4/3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>p value</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
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</tbody>
</table>

Table 5. Defecation within 24 hours of FEC100 regimen and anti-emetic treatment. Grade 1. Defecated as usual; 2. Found it more difficult to defecate than usual; 3. Found it almost impossible to defecate when compared with usual. Abbreviation: n.s.; not significant.

<table>
<thead>
<tr>
<th>Grade (1/2/3)</th>
<th>Azasetron First group</th>
<th>Granisetron NK First group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First course</td>
<td>(4/6/4)</td>
<td>(3/4/6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Second course</td>
<td>(4/9/1)</td>
<td>(4/4/5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>p value</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>
Adverse events

Adverse events including constipation which is considered as inhibitory action of intestinal movement caused by 5-HT3RAs were investigated\(^5\). There was no difference between 2 groups (Table 5). No patients discontinued treatment due to adverse events and all of them completed the scheduled treatment.

QOL analysis during treatment

In QOL analysis, granisetronNK first group showed score 1.8 (+-1.9) and azasetron first group showed score 3.1(+2.3) in first course of treatment (Fig. 1). Statically analysis using unpaired \(t\)-test showed no difference between two groups.

Discussion

This randomized crossover study revealed no significant differences between Granisetron NK (a generic) and azasetron (an originator drug) in terms of efficacy, adverse events and QOL.

In this study, we selected FEC regimen classified as high emetic risk to investigate of preventing effect of two 5-HT3 RAs. After 2006, even though NK-1 inhibitors have been recommended for high emetic risk groups, 5-HT3 RAs and corticosteroids are also needed\(^2\), \(^3\), \(^9\). Currently 5-HT3 RAs are recommended as an established regimen for moderate emetic risk combined with corticosteroids\(^3\), \(^4\). Thus 5-HT3 RAs play important roles in anti-emetic treatment for cancer chemotherapy.

Although, several 5-HT3 RAs can be commercially available, it is important to confirm their efficacy and adverse event in clinical use\(^3\). Therefore we conducted this clinical trial to compare a generic anti-emetic drug and an originator drug in crossover design.

The reasons we selected a crossover design are follows. At first, nausea and vomiting are subjective symptoms with extremely high individual variability, it is desirable to implement the trial with the same subject; second, that their maximum drug concentration time (Tmax) of two arms are post-dosage, and are quickly eliminated thereafter with half-lives within five hours, therefore washout period are provided in the 21-day dosage interval of FEC100 treatment.

In the view point of medical economy, cost of granisetronNK is 69% of that of azasetron. About 1500 Japanese yen (about 12-18 US dollars) was saved per one vial. Four cycles of FEC100 regimen could save about 6000 Japanese yen (about 48-72 US dollars) for one patient. As described above, 5-HT3 RAs are widely used for low to high emetic risk chemotherapy regimens for various cancers. Even though cost reduction for one patient is not so big, whole of society, the cost reduction effect might be very big. It will be more important to investigate generic drugs in terms of the balance of their efficacy and drug cost.

Limitation of this study is first, the patient number is too small to make a conclusion that granisetronNK is clinically equal to azasetron, and second, lack of view point of QOL including not only physical status but also patient’s economical feeling. Although balance of drug efficacy and cost is very important, we don’t have adequate scale or criteria to evaluate both factors. If the adequate scale or criteria were added, research and develop of generic drugs will be clearer.

Conclusions

A generic 5-HT3 RAs granisetronNK which reduce 31% drug cost showed no significant difference in efficacy, adverse events and QOL compared with originator drug azasetron in randomized crossover study.

![Fig. 1. QOL during first treatment course in 2 groups. Patients’ QOL during treatment were scored by Numerical Rating Scale (NRS) with 11 scores from 0 to 10. Score 0 represents QOL did not suffered from CINV, and score 10 represents maximum QOL suffering from CINV. There was no significant difference between granisetronNK first group and azasetron first group (unpaired t-test; n.s.).](image-url)
Acknowledgments

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References


