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## Original Paper

# A Randomised Dose-comparison Trial of Granisetron in Preventing Emesis in Children with Leukaemia Receiving Emetogenic Chemotherapy

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**This randomised study was performed to assess the anti-emetic efficacy and tolerability of two-dose regimens of granisetron in children with leukaemia. 49 children with leukaemia were treated with three consecutive courses of high-dose methotrexate or cytarabine regimen. During the first course, patients were evaluated regarding the emetogenicity of each regimen. They were randomised in a crossover manner to receive 20 or 40 μg/kg of granisetron before the second and third course of chemotherapy. Neither emesis nor severe appetite loss were observed in over 80% of patients within the first 24 h in all treatment groups. There was no significant difference in the anti-emetic efficacy between the two-dose regimens of granisetron. However, complete protection was achieved less frequently on days 2 and 3. Older children and girls appeared to be less well protected. No adverse events attributable to granisetron were observed. Granisetron dose regimens of 20 and 40 μg/kg are, comparably, well tolerated and effective in controlling chemotherapy-induced emesis in the first 24 h, though this protection fails thereafter, particularly in older patients and girls** 

**Key words: granisetron, emesis, children with leukaemia, chemotherapy, crossover study**
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## INTRODUCTION

With the increasing use of intensive high-dose (HD) chemotherapy regimens for treatment of childhood cancer, nausea and emesis are the most distressing and commonly encountered adverse symptoms [1–3]. Severe emesis may cause electrolyte imbalance, dehydration, delay the clearance of methotrexate (MTX) after HD infusion therapy, and potentiate the nephrotoxicity of anticancer drugs [4]. Furthermore, it may result in a patient's refusal to continue treatment [5]. Therefore, effective and well-tolerated anti-emetic therapies are vital for children with cancer undergoing intensive HD chemotherapy. Unfortunately, control of chemotherapy-induced emesis in paediatrics poses particular problems, as conventional anti-emetics including chlorpromazine, metoclopramide and prochlorperazine are either ineffective or associated with significant side-effects [6–8].

Recently, specific 5-hydroxytryptamine (5-HT3) receptor antagonists, such as granisetron [9–11], have been developed and have been shown to prevent nausea and emesis in animals and human adults receiving cancer chemotherapy [12–14]. Clinical studies on the use of granisetron have been conducted mainly in adult patients [15–20]. Only a limited number of studies have been undertaken in children with cancer [21–26]. The recommended dose for prophylaxis of chemotherapy-induced emesis is 10 μg/kg for both adult and children in the U.S.A. However, in European countries, three prophylactic doses of granisetron (10, 20, and 40 μg/kg) were compared and doses of 20 to 40 μg/kg of granisetron were reported safe and appropriate in children [21, 22]. The efficacy and safety of granisetron in Japanese children have also been evaluated at doses of 20 and 40 μg/kg [23, 25]. It is noteworthy that the frequency, severity, and onset of emesis are reportedly dependent on treatment regimen and individual

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patient variables [27]. The present controlled crossover study was undertaken to assess the efficacy and tolerability of two-dose (20 and 40 μg/kg) regimens of granisetron in Japanese children with leukaemia receiving uniform emetogenic chemotherapy.

## PATIENTS AND METHODS

*Patients and study design*

From March 1994 to June 1996, Japanese patients aged 1 to 14 years who were undergoing treatment with the Tokai Paediatric Oncology Study Group (Tokai POSG) Acute Lymphoblastic Leukaemia (ALL) 9104 Protocol [28], entered the study. All patients had B-precursor ALL. Written informed consent was obtained from parents and/or patients, and the study received institutional approval from the respective institutional ethics committees before entering the trial. Patients had to meet the following criteria: no signs and symptoms of central nervous system leukaemia, no other serious illness, no elevation of serum bilirubin, aspartate aminotransferase (AST), creatinine, or urea, no nausea and emesis for 1 week before the study, and no other anti-emetic therapy during the study period.

The chemotherapy protocols used in this study were either HD-MTX regimen in remission induction phase (MTX 3 g/m$^2$ and vincristine 1.5 mg/m$^2$ on day 1, intrathecal injection of MTX 12 mg, cytarabine 30 mg, and hydrocortisone 20 mg on day 2, and cyclophosphamide 600 mg/m$^2$ and L-asparaginase 20 000 U/m$^2$ on day 3), or HD-cytarabine (CA) regimen in the maintenance phase (CA 3 g/m$^2$ on day 1, daunorubicin 30 mg/m$^2$ and L-asparaginase 20 000 U/m$^2$ on day 3, and dexamethasone 12 mg/m$^2$ for 7 days). Tokai POSG 9104 protocols have been previously reported in detail [28]. Children were eligible for this study if they were scheduled to receive three courses of the same chemotherapy regimen described above. From March 1994 to June 1996, 74 and 25 patients received three courses of HD-MTX and HD-CA chemotherapy, respectively. During the first course of chemotherapy, patients were evaluated regarding the emetogenicity of each regimen without prophylactic administration of granisetron. The ethical committees did agree to patients specifically receiving no anti-emetogenics before HD-MTX and HD-CA chemotherapy. When the patients developed emesis and appetite loss, rescue administration of granisetron was allowed as needed.

Eligible patients were randomly divided into two groups (A or B). There were separate randomisation procedures for HD-MTX and HD-CA patients. Patients in Group A received 20 μg/kg of granisetron in the second course of scheduled chemotherapy regimen and 40 μg/kg of granisetron in the third course. Patients in Group B received 40 μg/kg in the second course and 20 μg/kg in the third course. Granisetron was given on day 1 immediately before the start of chemotherapy by a 30-min intravenous (i.v.) infusion. The patients who did not receive any additional administration of granisetron or other conventional anti-emetics were evaluable on days 2 and 3.

*Evaluation of anti-emetic efficiency*

The effectiveness of anti-emetic therapy was measured using the number of retches and vomits which were recorded on patient diary cards during days 1–3. The following definitions were used: complete response, no emetic episode per day; partial response, one to four emetic episodes per day; and failure, more than five emetic episodes per day. Emesis included any episode of vomiting and retching. In addition, overall appetite and food intake were also recorded on patient diary cards. Appetite loss was rated as none, mild, or severe. In patients who experienced severe appetite loss, no food intake was possible. In patients who experienced mild appetite loss, food intake was reduced between 25 and 75% of usual intake. The efficacy parameters used in the present study were the percentage of patients experiencing complete response (no emesis) and the percentage of patients with severe appetite loss (no food intake). The effectiveness of anti-emetic therapy was assessed by the investigating physicians on each day during the 3-day study period following the initiation of chemotherapy.

*Safety assessments*

To monitor possible toxic effects of granisetron, a full blood count, creatinine and urea, serum electrolyte, and liver function tests were performed during the week before treatment, 24 h post treatment and at 7 and 14 days post treatment. Liver function tests included serum bilirubin, alanine aminotransferase (ALT), AST, alkaline phosphatase, and gamma glutamyltransferase. Safety assessments conducted throughout the study period also included reports of any adverse experience and vital signs. The investigating physicians graded the intensity of the adverse events and were asked to comment on the possible association between granisetron and the events.

*Statistical analysis*

Statistical analysis of anti-emetic efficacy was done for days 1, 2, and 3, respectively. The major response parameters were the occurrence of emesis and severe appetite loss. These parameters were compared for the two doses of granisetron between boys and girls; and between younger ($<$6 years) and older patients ($\geq$6 years). Fisher's test and the chi-square test were used to compare these subgroups regarding complete response and severe appetite loss.

## RESULTS

From March 1994 to June 1996, 74 and 25 patients aged 1 to 14 years received three courses of HD-MTX and HD-CA chemotherapy, respectively. During the first course of either HD-MTX or HD-CA chemotherapy regimen, patients did not receive any prophylactic administration of granisetron. Approximately one third (35%, 26/74 cases), who received HD-MTX treatment, experienced no emetic episode or severe appetite loss, whilst the same was true for only 2/25 (8%) of those who received the first course of HD-CA chemotherapy. Anti-emetic intervention therapy with granisetron was immediately administered to the other patients who developed emesis and appetite loss. The patients who experienced no emetic episode or severe appetite loss during the first course of chemotherapy were not eligible for subsequent randomisation. In addition, 22 patients (12 and 10 patients on HD-MTX and HD-CA, respectively) were not randomised because the chemotherapy regimens were significantly modified in half of them and the other patients did not consent to randomisation. This left 49 patients who were eligible. 36 patients were scheduled for HD-MTX chemotherapy and 13 for HD-CA chemotherapy. This represented approximately 50% of the patients who received three courses of HD chemotherapy for this study period. The anti-emetic

efficacy was evaluated in the patients who received single prophylactic administration of granisetron alone on day 1 before the start of chemotherapy. The 49 patients were randomly divided into two groups (A and B). The treatment groups were similar for sex, age, and body weight (Table 1). Total anti-emetic efficacy and side-effects of granisetron were analysed on 72 and 26 occasions in subsequent courses of HD-MTX and HD-CA chemotherapy, respectively. After review of the defined eligibility criteria, 15 and 9 patients on HD-MTX chemotherapy who received any additional granisetron administration on day 2 and day 3, respectively, were excluded from the subsequent analysis: prophylactic granisetron was given to 6 and 7 patients on day 2 and day 3, respectively; the other patients, in whom anti-emetic control was lost, received rescue administration of granisetron. A total of 15 and 24 occasions on day 2 and day 3, respectively, could not be evaluated.

*Anti-emetic efficacy*

The complete response rates during the 3-day interval following the start of chemotherapy are shown in Figure 1. Complete response (no emesis) was observed in over 80% of patients on day 1 in all treatment groups. In particular, granisetron completely protected against acute emesis in patients receiving highly emetogenic HD-CA chemotherapy. There was no significant difference in complete response rates between patients receiving 20 μg/kg of granisetron and those receiving 40 μg/kg of the agent in both chemotherapy regimens. Similarly, severe appetite loss (no food intake) developed only in a small number of patients on day 1 (Figure 2) with the majority of the patients experiencing only mild appetite loss.

However, complete emesis protection was less frequently achieved on days 2 and 3 following the start of HD-MTX chemotherapy. Complete response rates on day 2 were clearly lower than those on day 1, irrespective of the dose of granisetron administered before chemotherapy. Moreover, on day 3 when additional emetogenic i.v. chemotherapy was given, complete response rates were further decreased and severe appetite loss was observed in a considerable proportion of the patients. The difference in the anti-emetic efficacy on days 2 and 3 between two doses (20 and 40 μg/kg) of granisetron was not significant. It is of note that severe appetite loss was experienced in only 9 of 57 and 13 of 48 occasions on days 2 and 3 of HD-MTX therapy, respectively (Figure 2).

In contrast, very few patients who received HD-CA chemotherapy experienced emesis and severe appetite loss on days 2 and 3. The patients were well protected even on day 3, when additional i.v. chemotherapy was given. Note that these patients received no additional granisetron infusion. They were, however, receiving dexamethasone.

Both age and gender were found to affect the anti-emetic efficacy of granisetron in patients receiving HD-MTX chemotherapy. Severe appetite loss was more often observed in girls than in boys on days 2 and 3 (Figure 2). Moreover, there was an indication that older patients ($\geq$6 years) experienced severe appetite loss more frequently than did younger patients, although the difference was not statistically significant. Neither sex nor age was a significant variable for complete response (Figure 1).

*Side-effects*

None of the patients enrolled in this study were drowsy during treatment nor experienced the distressing extra pyramidal reactions that are often associated with dopamine antagonists such as metoclopramide. No patient withdrew from the trial because of an adverse event. As might be anticipated when considering the severity of illness of the patient population and nature of chemotherapy, laboratory parameters outside the normal range were observed in 5 patients receiving HD-MTX chemotherapy. However, none

*Table* 1. *Demographic characteristics for randomised patients*

| | Group A | Group B | Total cases |
|---|---|---|---|
| HD-MTX chemotherapy | | | |
| Total eligible cases | 18 | 18 | 36 |
| Gender | | | |
| Boys | 8 | 8 | 16 |
| Girls | 10 | 10 | 20 |
| Age | | | |
| Mean ±S.D. | 5.9±3.6 years | 6.7±3.9 years | 6.3±3.7 years |
| (Range) | (2–14) | (1–13) | (1–14) |
| Body weight | | | |
| Mean ±S.D. | 21.9±12.5 kg | 24.3±10.5 kg | 23.1±11.4 kg |
| (Range) | (10–60.2) | (10–41) | (10–60.2) |
| HD-CA chemotherapy | | | |
| Total eligible cases | 6 | 7 | 13 |
| Gender | | | |
| Boys | 3 | 2 | 5 |
| Girls | 3 | 5 | 8 |
| Age | | | |
| Mean ±S.D. | 5.5±3.5 years | 6.8±4.0 years | 6.2±3.7 years |
| (Range) | (2–14) | (1–13) | (1–14) |
| Body weight | | | |
| Mean ±S.D. | 19.1±8.3 kg | 26.3±13.0 kg | 23.0±11.3 kg |
| (Range) | (14.5–47) | (13–47) | (13–47) |

HD-MTX, high-dose methotrexate; HD-CA, high-dose cytarabine; S.D., standard deviation.

of these patients had changes in laboratory parameter that were assessed by the investigating physician as possibly related to granisetron. Headache, fever, transient somnolence, and constipation, seen in other studies [21–23], were not observed.

## DISCUSSION

The prevention of nausea and vomiting is an important quality of life issue for children receiving antineoplastic chemotherapy. A few previous studies have shown that selective 5-HT3 receptor antagonists, such as granisetron and

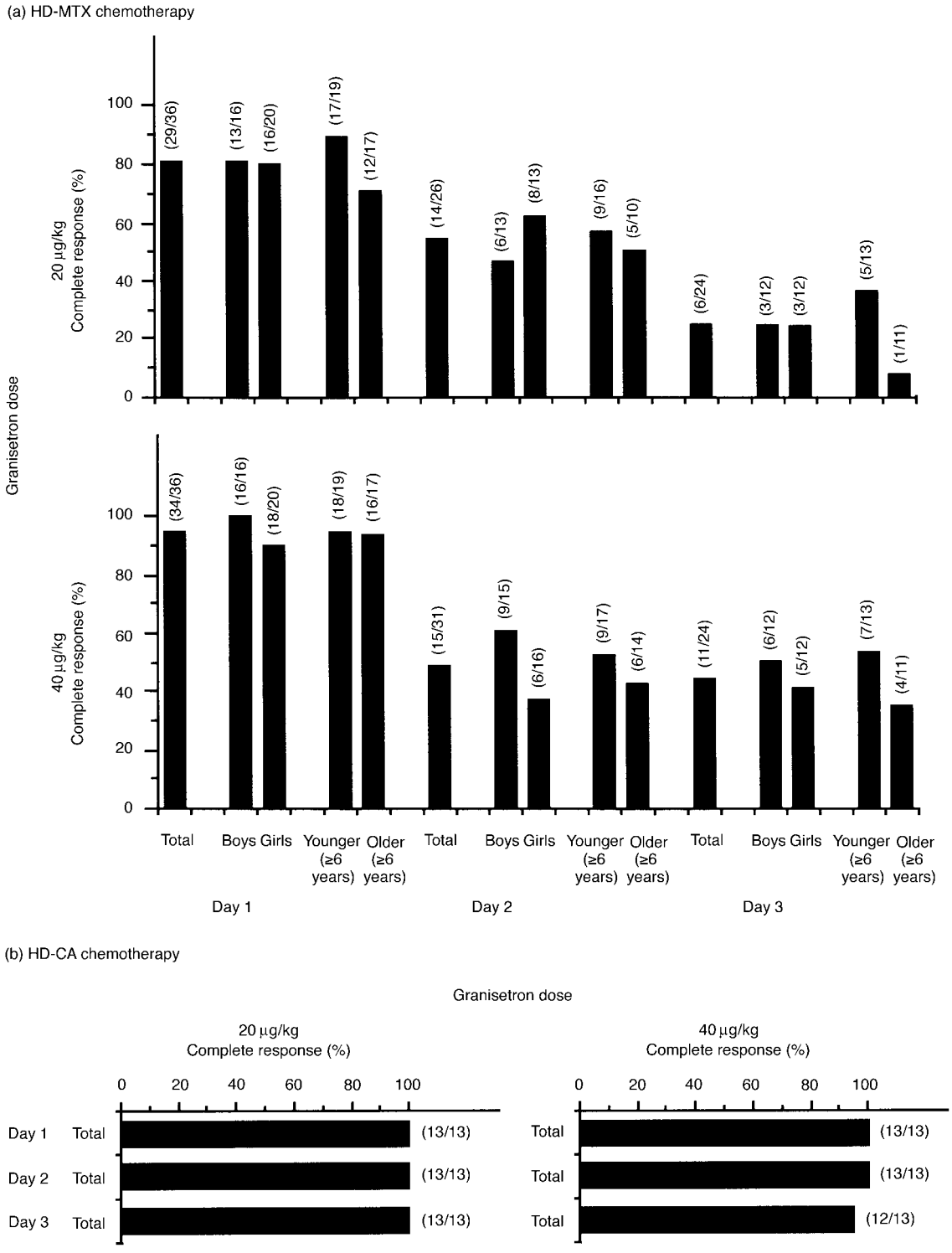


**Figure 1. Complete response rate in children with leukaemia receiving HD-MTX (a) and HD-CA (b) chemotherapy. The percentage of patients experiencing a complete response during a 3-day study period is shown in each subgroup. The values in parentheses indicate the numbers of patients experiencing no emesis out of all eligible patients. A few ineligible patients receiving HD-MTX chemotherapy were excluded from the analysis of anti-emetic efficacy on days 2 and 3 owing to the additional use of granisetron**

ondansetron, are safe, well tolerated and effective anti-emetics in the treatment of children receiving a wide variety of chemotherapy regimens [9, 10, 21–26]. However, analysis of efficacy was complicated by the variety and complexity of the chemotherapy regimens given and the individual patients' variables [27]. Indeed, in our study one third of patients who received the first course of HD-MTX therapy experienced no emetic episode or severe appetite loss without any anti-emetic treatment. Therefore, it was necessary to evaluate individual patients regarding the emetogenicity of chemotherapy

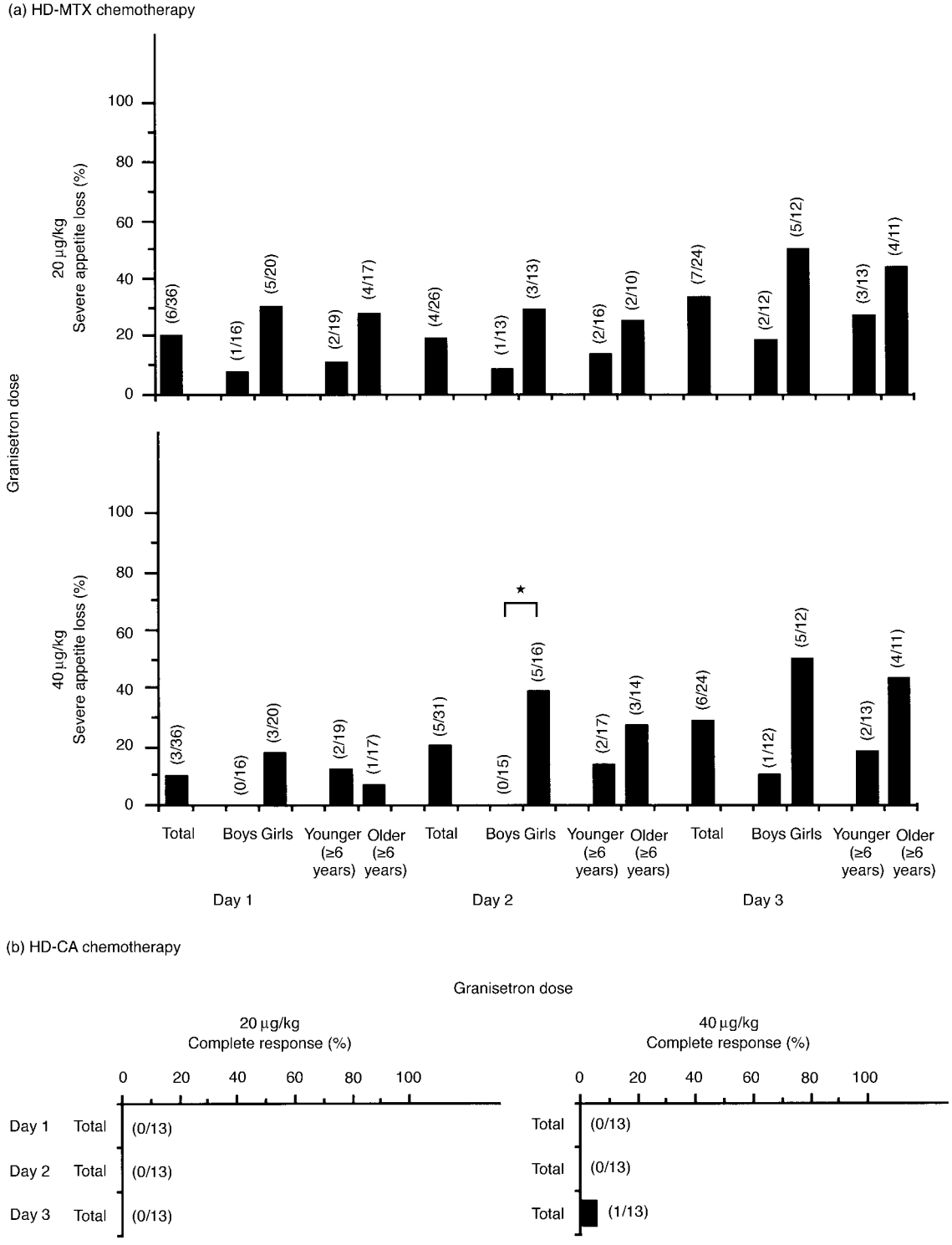


**Figure 2. Severe appetite loss in children with leukaemia receiving HD-MTX (a) and HD-CA (b) chemotherapy. The percentage of patients experiencing severe appetite loss during the 3-day study period is shown in each subgroup. The values in parentheses indicate the numbers of patients experiencing severe appetite loss out of all eligible patients. A few ineligible patients receiving HD-MTX chemotherapy were excluded from the analysis of anti-emetic efficacy on days 2 and 3 owing to the additional use of granisetron. *$P$=0.017 (Fisher's test).**

regimens without prophylactic administration of granisetron before they were enrolled in the present trial. As far as we know, no controlled study of granisetron has been undertaken in children with *all* receiving uniform emetogenic chemotherapy. In addition, granisetron at doses of 20 and 40 μg/kg was compared in a crossover manner, examining efficacy and tolerance. This unique design distinguishes the present study from others and provides a solid base for the conclusion drawn, despite the fact that the numbers of randomised patients were relatively small. Furthermore, this study was not blinded and data were evaluated by the investigating physicians making it difficult to rule out bias in the interpretation of the results. However, the potential of such bias is probably minimal taking account of the uniqueness of the study design.

49 patients were eligible for randomisation and 36 patients were scheduled for HD-MTX regimen. Prophylactic administration of granisetron at doses of 20 and 40 μg/kg was equally effective for the complete protection of acute emesis. The complete response rates were invariably over 80% on day 1 in all treatment groups. In the present study, patients were evaluated regarding the emetogenicity of HD-MTX chemotherapy regimen during the first course. Only the patients who developed emesis and appetite loss were eligible for subsequent randomisation. It is well known that emesis in the first course of chemotherapy is the most important risk factor for anticipatory emesis in the second and third course of chemotherapy. Considering that all eligible patients did experience emesis and appetite loss during the first course of HD-MTX chemotherapy, achieving a 80% complete response in the second and third courses is indeed excellent.

However, we found that the protection against emesis and appetite loss was frequently lost on days 2 and 3 in patients under HD-MTX treatment. These findings suggest that IV granisetron was highly effective in protecting patients from chemotherapy-induced emesis and appetite loss in the first 24 h following the start of chemotherapy but its protective efficacy clearly decreased thereafter. A study on the use of ondansetron consistently showed that delayed vomiting, retching, or nausea considerably reduced anti-emetic responses on day 2–5, although a complete or major response (fewer than 2 vomiting episodes) was achieved in 87% of children in a 24 h period after starting chemotherapy [29]. The emesis observed on day 2 and day 3 would be delayed emesis induced by HD-MTX infusion on day 1. Alternatively, intrathecal injection and i.v. infusion of additional antineoplastic agents could induce acute emesis on day 2 and day 3. Considering that the mean terminal half-life of granisetron was reported to be approximately 9–10 h in cancer patients [30, 31], more frequent dosing, i.e. daily dosing for the duration of chemotherapy, would be required.

Single prophylactic administration of granisetron appeared to be quite effective for preventing emesis and appetite loss induced by HD-CA regimen. However, it has been reported that the combination of a 5-HT3 receptor antagonist and dexamethasone is superior to a 5-HT3 receptor antagonist alone for controlling emetic episodes after cisplatin or cyclophosphamide in children, increasing response rates by approximately 15% [32, 33]. Since the patients were under dexamethasone treatment, we assumed that concomitant administration of dexamethasone could also improve the anti-emetic efficacy of granisetron in children receiving HD-CA therapy.

Craft and colleagues reported that the complete response rate was highest in younger children, and pharmacokinetic studies showed an association between some pharmacokinetic parameters and age [34]. In addition, clinical studies on the use of granisetron in adult patients indicated that males experienced less nausea and vomiting than females [5, 35, 36]. The present study also revealed that sex and age might be risk factors for severe appetite loss on day 2 and day 3 after HD-MTX chemotherapy. Prophylactic use of granisetron had less anti-emetic efficacy in girls and older patients ($\geq$6 years), compared with boys and younger patients ($<$6 years), respectively, although the difference was not statistically significant. It might be worthwhile investigating whether more frequent anti-emetic medication, i.e. daily dosing of granisetron, could prevent emesis and appetite loss especially in older girls receiving HD-MTX chemotherapy, since they were most likely to experience severe appetite loss on days 2 and 3.

Granisetron in doses of 20–40 μg/kg was well tolerated by children with leukaemia undergoing HD chemotherapy. There were no clinically important changes in any vital signs and laboratory tests considered or possibly related to study medication. Headache, fever, transient somnolence and constipation, seen in other studies [21–23], were not experienced in the present study. The extra pyramidal symptoms observed after dopamine antagonists such as metoclopramide were not observed at all. Furthermore, granisetron was devoid of sedative effects associated with chlorpromazine and chlorpheniramine. We conclude that a single prophylactic dose of 20 or 40 μg/kg granisetron provides excellent and safe anti-emetic control within the first 24 h.


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