Comparative Study of Low-Dose Oral Granisetron Plus Dexamethasone and High-Dose Metoclopramide Plus Dexamethasone in Prevention of Nausea and Vomiting Induced by CHOP-Therapy in Young Patients with Non-Hodgkin's Lymphoma

TONTANAI NUMBENJAPON, M.D.*,
WICHEAN MONGKONSRITRAGOON, M.D.*,
WICHAI PRAYOONWIWAT, M.D.*
CHANTRAPA SRISWASDI, M.D.*,
APICHAI LEELASIRI, M.D.*,

Abstract

Standard-dose (2 mg/day) oral granisetron seems to have more antiemetic efficacy than that of high-dose (0.5-1 mg/kg/dose) metoclopramide in moderately emetogenic chemotherapy. However, the cost of oral granisetron is much higher than that of metoclopramide so the authors tried to overcome this disadvantage by dose reduction and adding dexamethasone to enhance the antiemetic effect of oral granisetron. Twenty four young patients (aged < 50 years), with non-Hodgkin's lymphoma receiving CHOP-therapy were enrolled and evaluated in a randomized, double-blind, crossover study comparing the antiemetic efficacy, toxicity and patients' preference of a combination of low-dose oral granisetron plus intravenous dexamethasone (gran/dex) with a combination of high-dose metoclopramide plus intravenous dexamethasone (met/dex) on days 1-5 after chemotherapy. The acute, delayed (day 2-5) and 5-day total control of nausea and vomiting in the gran/dex group were significantly higher than those of the met/dex group (75.0% *vs* 25.0%; p-value = 0.004, 79.2% *vs* 33.3%; p-value = 0.007 and 75.0% *vs* 25.0%; p-value = 0.004, respectively). Except for extrapyramidal reactions in the met/dex group, the side effects in both groups were comparable. The mean total score of antiemetic preference in the gran/dex group was also significantly higher than that of the met/dex group (9.0 *vs* 7.5; p-value = 0.004). In conclusion, low-dose oral granisetron combined with intravenous dexamethasone had significantly higher protective effects against both acute and delayed nausea and vomiting induced by CHOP-therapy. Thus, this regimen may be considered as an alternative outpatient antiemetic treatment for young patients with non-Hodgkin's lymphoma.

Key word : Granisetron, Metoclopramide, Dexamethasone, Chemotherapy, Nausea, Vomiting

NUMBENJAPON T, SRISWASDI C, MONGKONSRITRAGOON W, LEELASIRI A, PRAYOONWIWAT W
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* Department of Medicine, Phramongkutklao Hospital, Bangkok 10400, Thailand.

Nausea and vomiting are the most common undesirable side effects in cancer patients treated with combination chemotherapy[1,2]. The incidence of chemotherapy induced nausea and vomiting in so-called moderately high emetogenic regimens such as cyclophosphamide ≥ 600 mg/m^2 and doxorubicin ≥ 50 mg/m^2 is 60-90 per cent[3-5].

These side effects are the main reasons for diminishing cancer patients' quality of life and treatment compliance.

Metoclopramide, a conventional antiemetic in chemotherapy treatment, not only has an unimpressive efficacy but also has many side effects. Incomplete antiemetic prophylaxis of metoclopramide has occurred in approximately 40 per cent of patients who received moderately high emetogenic chemotherapy regimens[2,6].

Both intravenous and oral forms of granisetron, a 5-hydroxy tryptamine$_3$ (5-HT$_3$) receptor antagonist, a novel potent antiemetic, became available in March 1994 and April 1995, respectively[7,8]. The principal site of action is 5-HT$_3$ receptor located on the vagal afferent neuron adjacent to the enterochromaffin cell in the gut mucosa[9]. 5-HT$_3$ receptor antagonist is effective in controlling nausea and vomiting associated with both highly and moderately emetogenic combination chemotherapy regimens[10-15].

Many randomized clinical trials to compare 5-HT$_3$ receptor antagonist and high-dose intravenous metoclopramide in either highly or moderately emetogenic regimens have shown significant superiority of the former over the latter[10,11].

Some moderately emetogenic chemotherapy regimens are scheduled in an outpatient treatment manner, such as CHOP-therapy for non-Hodgkin's lymphoma, COPP/ABVD-therapy for Hodgkin's disease and CMF-therapy for adjuvant post-operative breast cancer. Hence, an oral antiemetic is more convenient and suitable than an intravenous one in this outpatient setting.

A preliminary report established that the optimal dosage for oral granisetron in highly emetogenic chemotherapy regimens was between 0.25 mg and 2.5 mg daily[16].

In the current study, oral granisetron in moderately emetogenic regimens recommended that a 1 mg twice daily dose was more effective than a 0.25 mg and a 0.5 mg twice daily dose for preventing acute nausea and vomiting[17]. One study supported the feasibility of using an orally administered granisetron in a single daily dose because it showed that the antiemetic benefit in 1 mg twice daily dose and 2 mg once daily dose were comparable[18].

Recently, some studies have indicated that corticosteroids may enhance the antiemetic effect of 5-HT$_3$ receptor antagonist in highly emetogenic chemotherapy induced both acute and delayed nausea and vomiting[19-23].

Despite the high antiemetic efficacy of oral granisetron in moderately emetogenic chemotherapy regimens, the expense of this agent is very high. As a result, the authors conducted a crossover randomized controlled trial to compare the clinical efficacy and safety of modified low-dose oral granisetron (1 mg daily) plus intravenous dexamethasone and high-dose metoclopramide (0.5-1 mg/kg) plus intravenous dexamethasone for controlling both acute and delayed nausea and vomiting induced by CHOP-therapy in young patients (aged ≤ 50 years) with non-Hodgkin's lymphoma who are at risk of nausea and vomiting[24,25].

MATERIAL AND METHOD

Patients

From July 1998 to May 2001, consecutive patients with non-Hodgkin's lymphoma scheduled to receive the first course of CHOP-therapy were enrolled in the study. Each patient received cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), vincristine (1.4 mg/m^2) and prednisolone (100 mg/day for 5 days). The only inclusion criterian was patients between 15 to 50 years old. The criteria for exclusion before randomization were poor performance status (ECOG > 2), the presence of nausea or vomiting regardless of the causes in 24 hours before receiving 1st CHOP-therapy, GI lymphoma, primary CNS lymphoma, severe hepatic or renal functions, concurrent treatment with benzodiazepine or phenothiazine or butyrophenones or radiotherapy and consuming regular alcohol[26].

Design of the study

A comparative study with a randomized, double blind, crossover design was conducted at the outpatient hematology clinic, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand. The study was approved by the ethics committee of Phramongkutklao Hospital and all patients gave written informed consent.

The sample size was calculated on the assumption that total and major control of acute nausea and vomiting would be achieved in at most 25 per

cent of patients receiving high-dose metoclopramide plus intravenous dexamethasone and in at least 70 per cent of those receiving oral granisetron plus intravenous dexamethasone. As the result, at least 23 patients would be enrolled into this study. However, expected loss was 8 per cent and a total of 25 patients were enrolled. An overall p-value (two-sided) ≤ 0.05 was considered to indicate statistical significance.

Antiemetic therapy

With blind fashion, each patient was randomly assigned to receive one of the two antiemetic treatment protocols then he/she was crossover to receive the other with at least a 3 weeks washout period. The granisetron/dexamethasone (gran/dex) consisted of a red capsule containing 1 mg of granisetron tablet (Kytril, SmithKline Beecham, Harlow, Essex, United Kingdom) given orally plus 8 mg of dexamethasone injection and 20 ml of normal saline given intravenously (as a placebo for intravenous metoclopramide) half an hour before chemotherapy, followed by a white capsule containing 2 tablets of placebo given before lunch, dinner and at bed time on the day of chemotherapy. From day 2-5, a red capsule containing 1 mg of granisetron tablet was given before breakfast, followed by a white capsule containing 2 tablets of placebo given before lunch, dinner and at bed time. The metoclopramide/dexamethasone (met/dex) consisted of a 1 mg/kg of metoclopramide injection diluted in 20 ml of normal saline administered as an intravenous infusion over a period of 10 minutes, 8 mg of dexamethasone injection given intravenously and a red capsule containing a tablet as a placebo for oral granisetron half an hour before chemotherapy, followed by a white capsule containing 10 mg of metoclopramide tablet at a dose of 0.5 mg/kg/dose given before lunch, dinner and at bed time on the day of chemotherapy. From day 2-5, a red capsule containing 10 mg of metoclopramide tablet at a dose of 0.5 mg/kg/dose was given before breakfast, followed by a white capsule containing 10 mg of metoclopramide tablet at a dose of 0.5 mg/kg/dose given before lunch, dinner and at bed time. According to the potential extrapyramidal reactions of high-dose metoclopramide, each patient was given 2 capsules of 25 mg diphenhydramine HCL at bedtime to diminish such side effects for 5 consecutive days in both treatment protocols.

Clinical assessment

Episodes of nausea and vomiting were recorded by the patients or their relatives on the record forms for the first 24 hours after chemotherapy (acute phase) and for the following 4 consecutive days (delayed phase). Nausea was rated on a grading scale as none (absence of nausea), mild (did not interfere with normal daily life), moderate (interfered with normal daily life), severe (bed ridden due to nausea).

An episode of vomiting was defined as a single instance of vomiting or retching or continuous vomiting or retching within 5 minutes. Complete protection was defined as the absence of vomiting episode and nausea, major protection as only one episode of vomiting, minor protection as 2-4 episodes and failure as > 4 episodes of vomiting. Total control was defined as no vomiting, no nausea and no use of rescue therapy and major control was defined as no vomiting or major response and no or mild nausea.

Other potential adverse reactions, number of rest days caused by nausea or vomiting, and patient's antiemetic preference were also recorded by each patient for 5 days.

Statistical analysis

Analyses were performed using the Statistical Package for the Social Science for Windows version 10.0 (SPSS, Chicaco, IL, USA). Analyses of nausea and vomiting were performed separately for total effects (day 1 through day 5), acute effects (day 1), and delayed effects (day 2 through day 5). The nausea grade, emetic rate and side effects were reported in percentage and analyzed using Mcnemar Chi-Square test. The number of rest days and antiemetic preference score were reported in mean and analyzed using Paired *t*-test. The p-value (2-sided) less than 0.05 referring to test was considered statistically significant.

RESULTS

Twenty-four of 25 patients enrolled into the study completed the consecutive antiemetic treatment protocols and were evaluated. The characteristics of the patients are shown in Table 1.

Acute antiemetic effects

The acute antiemtic effects are shown in Table 2 and 4. The 24-hour total control of nausea and vomiting after chemotherapy in patients receiving gran/dex was significantly higher than those receiving met/dex (75.0% *vs* 25.0%; p-value = 0.004). Among patients receiving met/dex, 14 patients (58.3%) without total control still responded to gran/dex administration whereas 4 patients (16.7%) failed to have

Table 1. Characteristics of the patients.

Characteristics	Gran/dex then Met/dex (n = 13)	Met/dex then Gran/dex (n = 11)
Age : mean (range)	38.1 (15-49)	39.9 (19-50)
Male : Female	8 : 5	4 : 7

Gran/dex = Granisetron/dexamethasone
Met/dex = Metoclopramide/dexamethasone

total control after both antiemetic regimens. Two patients (8.3%) who failed to respond to gran/dex had total control during met/dex treatment.

The 24-hour major control of nausea and vomiting after chemotherapy was also significantly superior in patients receiving gran/dex than those receiving met/dex (95.8% *vs* 50.0%; p-value = 0.003).

Table 2. Number of patients with complete and major protection from acute nausea and vomiting*.

Treatment	Gran/dex		Met/dex		P-value
	n	%	n	%	
Complete protection from					
Nausea	20	83.3	7	29.2	0.001
Vomiting	21	87.5	14	58.3	0.039
Major protection from					
Nausea	23	95.8	12	25.0	0.003
Vomiting	24	100.0	17	70.8	0.023

* First 24 hours after chemotherpy
Gran/dex = Granisetron/dexamethasone; Met/dex = Metoclopramide/dexamethasone

Table 3. Number of patients with complete and major protection from delayed nausea and vomiting*.

Treatment	Gran/dex		Met/dex		P-value
	n	%	n	%	
Complete protection from					
Nausea					
Day 2	20	83.3	9	37.5	0.007
Day 3	20	83.3	9	37.5	0.007
Day 4	21	87.5	10	41.7	0.003
Day 5	21	87.5	11	45.8	0.006
Day 2-5	20	83.3	9	37.5	0.007
Vomiting					
Day 2	23	95.8	18	75.0	NS
Day 3	24	100.0	19	79.1	NS
Day 4	24	100.0	23	95.8	NS
Day 5	24	100.0	23	95.8	NS
Day 2-5	23	95.8	17	70.8	NS
Major protection from					
Nausea					
Day 2	23	95.8	16	66.7	0.039
Day 3	23	95.8	17	70.8	NS
Day 4	23	95.8	19	79.2	NS
Day 5	23	95.8	19	79.2	NS
Day 2-5	23	95.8	16	66.7	0.039
Vomiting					
Day 2	24	100.0	20	83.3	NS
Day 3	24	100.0	22	91.7	NS
Day 4	24	100.0	23	95.8	NS
Day 5	24	100.0	23	95.8	NS
Day 2-5	24	100.0	20	83.3	NS

* Day 2-5 after chemotherpy
Gran/dex = Granisetron/dexamethasone; Met/dex = Metoclopramide/dexamethasone

Regarding major control, however, it was found that all patients responded to gran/dex or met/dex or both antiemetic treatment protocols.

Delayed antiemetic effects

The delayed antiemtic effects are shown in Table 3 and 4. The delayed total and major control of nausea and vomiting after chemotherapy in patients receiving gran/dex were also significantly higher than those receiving met/dex (79.2% *vs* 33.3%; p-value = 0.007 and 95.8% *vs* 66.7%; p-value = 0.039, respectively). Thirteen patients (54.2%) had total control during gran/dex administration but they had no such protection during met/dex administration. However, only 2 patients (8.3%) had the opposite outcome. For major control, all patients responded to gran/dex or met/dex or both antiemetic treatment protocols. Interestingly, 23 patients (95.8%) receiving gran/dex had major control whereas only 16 patients (66.7%) receiving met/dex had such protection.

Acute and delayed antiemetic effects

Again, 5-day total and major control of nausea and vomiting after chemotherapy were achieved in a significantly larger number of patients receiving gran/dex (75.0% and 95.8%, as compared with 25.0% and 50.0% in those receiving met/dex; p-value = 0.004 and p-value = 0.003, respectively).

Anticipatory nausea and vomiting

As shown in Table 5, one patient receiving met/dex had anticipatory nausea and vomiting but no one receiving gran/dex had that event.

Number of rest days

The authors also analyzed the impact of the sequence of antiemetic treatment protocols on the number of rest days caused by nausea and vomiting episodes and found no significant difference between them. In contrast, patients receiving gran/dex had a significantly fewer number of mean rest days than those receiving met/dex (1.4 days *vs* 2.8 days; p-value = 0.029).

Side effects

As shown in Table 5, except for the extrapyramidal reactions in patients receiving met/dex, the side effects in both antiemetic treatment protocols were comparable and well tolerated.

Antiemetic preference

The mean total score of antiemetic preference of patients receiving gran/dex was significantly higher than those receiving met/dex (9.0 *vs* 7.5; p-value = 0.004).

DISCUSSION

As an outpatient setting, the present study indicated that low-dose oral granisetron plus intravenous dexamethasone on the day of chemotherapy followed by low-dose oral granisetron on subsequent days was able to control both acute and delayed CHOP-therapy induced nausea and vomiting in the majority of the patients. In the acute phase, 75.0% and 95.8% of patients receiving low-dose oral granisetron plus intravenous dexamethasone achieved total and major control, respectively. These results were supported by the previous studies[19,23]. Moreover, in the delayed phase, low-dose oral granisetron combined with prednisolone in CHOP-therapy at a dose of 100 mg/day (equal to 20 mg of dexamethasone), had a significantly higher total control (79.2%) and major control (95.8%) compared with moderate-dose oral metoclopramide combined with prednisolone. These results could be explained by the study which indicated that granisetron combined with dexametha-

Table 4. Number of patients with total and major control from both nausea and vomiting.

Treatment	Gran/dex		Met/dex		P-value
	n	%	n	%	
Acute and delayed total control	18	75.0	6	25.0	0.004
Acute and delayed major control	23	95.8	12	50.0	0.003
Acute total control	18	75.0	6	25.0	0.004
Acute major control	23	95.8	12	50.0	0.003
Delayed total control	19	79.2	8	33.3	0.007
Delayed major control	23	95.8	16	66.7	0.039

Gran/dex = Granisetron/dexamethasone; Met/dex = Metoclopramide/dexamethasone

Table 5. Side effects of the two antiemetic treatment protocols.

Side effects	Gran/dex		Met/dex		P-value
	n	%	n	%	
Headache	7	29.2	9	37.5	NS
Constipation	14	58.3	11	45.8	NS
Dry mouth	9	37.5	14	58.3	NS
Sleepiness	12	50.0	17	70.8	NS
Extrapyramidal reactions	0	0.0	9	37.5	0.008
Allergic reactions	1	4.2	2	8.3	NS

Gran/dex = Granisetron/dexamethasone; Met/dex = Metoclopramide/dexamethasone

Table 6. Comparing the total costs of the two antiemetic treatment protocols (based on Phramongkutklao Hospital's drug price list, 2002).

Met/dex	Gran/dex (1 mg/day)	Gran/dex (2 mg/day)
2.68 US$	62.13 US$	124 US$

Met/dex = Metoclopramide/dexamethasone
Gran/dex = Granisetron/dexamethasone;

sone had more protective effect than metoclopramide combined with dexamethasone against delayed nausea and vomiting in highly emetogenic chemotherapy regimens[23]. However, the authors still cannot draw any conclusion that administration of low-dose oral granisetron on day 2-5 after chemotherapy will be truly beneficial and cost effective in terms of delayed antiemetic protection since the previous study demonstrated that the protective efficacy of dexamethasone (not prednisolone) was higher than that of 3 mg intravenous granisetron in moderately emetogenic chemotherapy regimens[19].

Comparing side effects during treatment with granisetron and those reported by previous studies[19,23], constipation was the most common side effect in our patients and those reported by previous studies during treatment with granisetron one among the presented patients receiving gran/dex. However, it was found that the incidence of both side effects were equal to those receiving met/dex.

Quality of life in young non-Hodgkin's lymphoma patients treated with chemotherapy is very meaningful. Results from this study suggested that oral low-dose granisetron combined with intravenous dexamethasone can be recommended as an alternative outpatient antiemetic treatment in CHOP-therapy because it was able to help these active working patients continue their jobs during chemotherapy. Although the cost of oral granisetron is much higher than that of metoclopramide as shown in Table 6, the disadvantage may be offset by dose reduction, its ease of administration as a single daily dose and the antiemetic preference of the patient, in particular younger individuals in whom high-dose metoclopramide is likely to have substantial toxic effects[27]. In the future, some studies to evaluate the quality of life and cost benefit of oral low-dose granisetron to prevent delayed nausea and vomiting compared with dexamethasone in patients treated with CHOP-therapy should be conducted.

SUMMARY

The authors concluded that low-dose oral granisetron (1 mg/day) plus intravenous dexamethasone is much more effective than high-dose intravenous metoclopramide plus intravenous dexamethasone for total control and major control of nausea and vomiting in the day of CHOP administration. In the delayed phase, low-dose oral granisetron also had a significantly higher total control of nausea and vomiting than that of high-dose oral metoclopramide. As result, this regimen may be considered as an alternative treatment and may also improve the quality of life in young patients who may not be able to afford antiemetic therapy.

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การศึกษาเปรียบเทียบประสิทธิภาพของยาแกรนิซีตรอนในขนาดต่ำร่วมกับยาเด็กซาเมทาโซนเปรียบเทียบกับยาเมทโทโคลพามาดในขนาดสูงร่วมกับยาเด็กซาเมทาโซนในการป้องกันอาการคลื่นไส้และอาเจียนที่เกิดจากเคมีบำบัด (CHOP-therpay) ในการรักษาผู้ป่วยอายุน้อยที่เป็นมะเร็งต่อมน้ำเหลืองชนิด Non-Hodgkin's lymphoma

ต้นตนัย นำเบญจพล, พ.บ., จันทราภา ศรีสวัสดิ์, พ.บ.*,*
วิเชียร มงคลศรีตระกูล, พ.บ., อภิชัย ลีละสิริ, พ.บ.*, วิชัย ประยูรวิวัฒน์, พ.บ.**

จากการศึกษาที่ผ่านมาพบว่าผู้ป่วยที่ได้รับเคมีบำบัดกลุ่มที่ก่อให้เกิดอาการคลื่นไส้และอาเจียนรุนแรงปานกลางนั้น ยาแกรนิซีตรอนชนิดรับประทานในขนาดมาตรฐาน (2 มก/วัน) สามารถควบคุมอาการคลื่นไส้และอาเจียนที่เกิดขึ้นได้ดีกว่ายาเมโทโคลพามายด์ในขนาดสูง (0.5-1 มก/ครั้ง) เนื่องจากยาแกรนิซีตรอนมีราคาแพงกว่ายาเมทโทโคลพามายด์มาก ดังนั้น คณะผู้ทำการวิจัยจึงได้ทำการศึกษาถึงประสิทธิภาพในการป้องกันอาการคลื่นไส้และอาเจียน โดยใช้ยาแกรนิซีตรอนชนิดรับประทานในขนาดต่ำ (1 มก/วัน) ร่วมกับยาเด็กซาเมทาโซนเปรียบเทียบกับยาเมทโทโคลพามายด์ในขนาดสูงร่วมกับยาเด็กซาเมทาโซน

ผู้ป่วยจำนวน 24 ราย อายุน้อยกว่า 50 ปีซึ่งได้รับการวินิจฉัยว่าเป็นมะเร็งต่อมน้ำเหลืองชนิด Non-Hodgkin's lymphoma และได้รับการรักษาด้วยเคมีบำบัด CHOP-therapy ได้เข้ารับการศึกษาแบบสุ่มตัวอย่างแบบปิด 2 ทางและสลับกลุ่ม เพื่อเปรียบเทียบประสิทธิภาพในการป้องกันอาการคลื่นไส้และอาเจียน ผลข้างเคียงและความพึงพอใจของผู้ป่วยที่มีต่อยาแก้อาเจียน 2 กลุ่มคือ กลุ่มที่ 1 ยาแกรนิซีตรอนชนิดรับประทานในขนาดต่ำ (1 มก/วัน) ร่วมกับยาเด็กซาเมทาโซน เทียบกับกลุ่มที่ 2 ยาเมทโทโคลพามายด์ขนาดสูง (0.5-1 มก/ครั้ง) ร่วมกับยาเด็กซาเมทซาโซนในวันที่ 1-5 หลังจากได้รับเคมีบำบัด พบว่าการควบคุมอาการคลื่นไส้และอาเจียนในระยะเฉียบพลัน (วันที่ 1), ระยะหลัง (วันที่ 2-5) และทั้ง 5 วันของยาในกลุ่มที่ 1 มีประสิทธิภาพสูงกว่าในกลุ่มที่ 2 อย่างมีนัยสำคัญทางสถิติ (75.0% *vs* 25.0%; p-value = 0.004, 79.2% *vs* 33.3%; p-value = 0.007 และ 75% *vs* 25%; p-value = 0.004 ตามลำดับ) สำหรับผลข้างเคียงของยาทั้งสองกลุ่มพบว่าไม่แตกต่างกัน ยกเว้นในกลุ่มที่ 2 ที่มีอาการของ extrapyramidal reactions มากกว่า นอกจากนี้ยังพบว่าผู้ป่วยมีความพึงพอใจต่อประสิทธิภาพของยาในกลุ่มที่ 1 มากกว่ากลุ่มที่ 2 อย่างมีนัยสำคัญทางสถิติ (9.0 *vs* 7.5; p-value = 0.004) โดยสรุป ยาแกรนิซีตรอนชนิดรับประทานในขนาดต่ำ (1 มก/วัน) ร่วมกับยาเด็กซาเมทาโซนมีประสิทธิภาพดีกว่ายาเมทโทโคลพามายด์ในขนาดสูงร่วมกับยาเด็กซาเมทซาโซนในการป้องกันอาการคลื่นไส้และอาเจียนในระยะเฉียบพลันและระยะหลังจากให้เคมีบำบัด CHOP-therapy โดยเฉพาะในผู้ป่วยอายุน้อย (< 50 ปี) ซึ่งได้รับการวินิจฉัยว่าเป็นมะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin's lymphoma ซึ่งน่าจะเป็นอีกทางเลือกหนึ่งของผู้ป่วยกลุ่มนี้ได้

คำสำคัญ : แกรนิซีตรอน, เมทโทโคลพามายด์, เด็กซาเมทาโซน, เคมีบำบัด, คลื่นไส้, อาเจียน

ต้นตนัย นำเบญจพล, จันทราภา ศรีสวัสดิ์,
วิเชียร มงคลศรีตระกูล, อภิชัย ลีละสิริ, วิชัย ประยูรวิวัฒน์
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* กองอายุรกรรม, โรงพยาบาลพระมงกุฎเกล้า, กรุงเทพ ฯ 10400