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Clinical report

Antiemetic treatment with two different doses of methylprednisolone in breast cancer patients: a double-blind randomized cross-over study with evaluation of efficacy parameters

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This randomized double-blind cross-over study followed a previous one which showed an antiemetic efficacy from methylprednisolone (MP) 250 mg superior to placebo. The present study compared MP 40 mg with 250 mg in breast cancer patients treated with non-cisplatin chemotherapy. Preference after course II was the determining parameter. Participation in two courses was compulsory for evaluation, participation in four courses was optional. Interim analyses were performed after each 12 patients to a maximum of 60 patients. As there was no significant difference in preference in 60 patients the study was closed. Patients treated with the CEF regimen, patients who requested rescue antiemetics and patients completing four study courses had a better effect from high-dose MP reflected in preference and other parameters. Global assessments, measurement of emetic volumes and the visual analog scale for nausea gave a fair coherence with patents' preference. The numbers of emetic episodes and observer registered nausea were of no value. The stability of preference and other parameters after course II and IV, respectively, was low. The present study did not prove superiority from high-dose MP. This hypothesis must be tested in patients more severely bothered by emesis after chemotherapy. These results show the complexity of evaluation of antiemetic effect and demonstrate the dependency of a given result on the parameter used.

Key words: Antiemetic, chemotherapy, dosage, methylprednisolone.

Introduction

Steroids have antiemetic effect in patients treated with non-cisplatin chemotherapy[1] and in cisplatin-treated patients they are useful in combination with other antiemetics.[2–4] Traditionally doses of steroids have varied from 40 to 500 mg i.v. of methylprednisolone (MP) and from 8 to 100 mg of dexamethasone. The lack of precise dose recommendations may be due to the fact that different doses only cause small differences in efficacy. Therefore a dose finding study must apply fairly accurate methods of evaluation. These methods must be easy to handle and should not bother the patient more than necessarily.

In a previous randomized double-blind cross-over study we found a significantly superior antiemetic effect from MP 250 mg compared with placebo in breast cancer patients treated with CMF or CEF chemotherapy.[1] Moreover, we found that hourly recordings of emetic volumes and hourly recordings of nausea on the visual analog scale as well as global assessments of nausea and vomiting for 24 h were valid parameters. They cohered with patients' preference and were able to detect antiemetic differences.

As a continuation of the previous study we performed the present one with the following aims: (i) to compare the antiemetic efficacy of high-dose (HD) MP (250 mg) with low-dose (LD) MP (40 mg) with respect to preference and other efficacy parameters, (ii) to investigate the stability of patients' preference after two and four study courses, and (iii) to investigate if we could confirm the findings in the previous study regarding coherence of other efficacy parameters with preference.

Material and methods

Patients

All patients received emetogenic chemotherapy for breast cancer; 22 patients received adjuvant CMF

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Table 1. Patient characteristics: study course I and II

	No. of patients
Evaluable after study course II	60
Excluded and currently substituted	20
reasons	
protocol violation	4
own wish	2
progressive disease	1
lack of cooperability	1
chlorpromazine in both study arms	10
unidentical doses of diazepam in the two study arms	2
Adjuvant therapy (CMF)	22
Relapse therapy (CEF)	29
Relapse therapy (epirubicin)	9
First study course on HD MP	30
First study course on LD MP	30

CMF: cyclophosphamide 500 mg/m^2, methotrexate 50 mg/m^2, 5-fluorouracil 600 mg/m^2 i.v. every 3 weeks. CEF: cyclophosphamide 500 mg/m^2, epirubicin 40 mg/m^2, 5-fluorouracil 600 mg/m^2 i.v. every 3 weeks. Epirubicin: 45–145 mg/m^2 every 3 weeks.

treatment. Thirty eight patients had disseminated disease; among these, 29 patients received the CAF regimen and nine patients received single drug treatment with epirubicin. For drug and dose specifications see Table 1. The patients had all received at least one chemotherapy course before inclusion in the study as we wanted them to be familiar with after-treatment emesis. The patients gave informed consent in accordance with Helsinki Declaration II and the study was approved by the local Ethical Committee.

Patients with known CNS metastasis, tuberculosis, diabetes, psychiatric disorders, concomitant steroid therapy, other reasons for nausea or vomiting and unability to cooperate were excluded.

Design and antiemetic treatment

The study was designed as a randomized double-blind cross-over study. The patients were randomly allocated to receive either HD or LD MP in the first study course and the opposite dose level in the second study course. Participation in two study courses was a prerequisite for analysis, participation in four courses with identical sequence of HD and LD MP was optional. This design gave the opportunity to compare the high and the low dose after study course II and again after study course four. Moreover, it was possible to calculate an 'overall' comparison of high and low dose in patients who completed four study courses and the stability of preference could be tested by comparison of data after course II and course IV.

Table 2. Time schedule for observations

Hospitalization	9 a.m.
i.v. methylprednisolone	9.30–9.45 a.m.
Chemotherapy	10 a.m.
Registrations	
VAS scores	hourly for 24 h
Emetic amount	hourly for 24 h
Dry heaves	hourly from 9 a.m. to 5 p.m.
Nausea intensity	hourly from 9 a.m. to 5 p.m.
Emetic episodes	hourly from 9 a.m. to 5 p.m.
Global assessment	5 p.m. and 9 a.m.
Preference	9 a.m.
Acceptance	9 a.m.
Blood pressure	9 a.m., 5 p.m. and 9 a.m.

MP was given as a 15 min infusion 30 min before chemotherapy. The patients were hospitalized on the day of chemotherapy and antiemetic efficacy was evaluated regularly for 24 h.

Chlorpromazine 100 mg rectally was used as rescue medication.

Rules for exclusion of patients already included

The patients were excluded from analysis if chemotherapy doses were changed more than ± 25%, if chemotherapy was stopped before study course II or if the patients refused further participation before completion of study course II. Because of difficulty in analyzing preferences in patients treated with other antiemetics and/or tranquilizers we also excluded patients who received chloropromazine in both of the two first or both of the two last study courses and patients treated with benzodiazepines, who did not receive identical doses during the two first or the last two study courses.

Patients who were excluded from analysis before the end of study course II were currently substituted with patients who received MP in the same dose sequence. Patients who left the study after course two were not substituted, and data from course I and II only were used in the analysis.

Other medications

Usual medication other than antiemetics and steroids was allowed. Tranquilizers were administered in identical doses from one study course to another.

Parameters for efficacy

The following variables for efficacy were obtained in all study courses. Time schedule is shown in Table 2.

Primary efficacy variable

(1) Patients' preference after study course II for the antiemetic success in either course I or course II.

Secondary efficacy variables

(2) Patients' assessment of nausea on a visual analog scale (VAS), a 100 mm long horizontal line, endbarred, but otherwise unmarked, the ends of which were marked 'no nausea' and 'unbearable nausea', respectively. Patients were not allowed to see their previous recordings when marking VAS.
(3) A trained nurse observer's recordings of the current nausea intensity (NI) registered on a categorical scale from 0 to 3 (no, slight, moderate, severe).
(4) A categorical global assessment scale for nausea intensity (GN) for the first 8 h and for all 24 h marked by the patient 0–3 (no, slight, moderate, severe).
(5) Acceptance of nausea (AN): the patients were asked whether they considered the nausea acceptable or not.
(6) Emetic amounts (Em Am) per hour measured in grams.
(7) The number of emetic episodes (Em Ep) per hour.
(8) The number of dry heaves (DH) (feeling like vomiting without bringing up gastric contents) per hour.
(9) A categorical global assessment scale for vomiting (GV) like the one for nausea and recorded at the same hours.
(10) Acceptance of vomiting (AV): the patients were asked whether they considered the vomiting acceptable or not.
(11) Blood pressure and heart rate were measured three times; urine analysis for glucose was done in the evening.
(12) Patients' preference after study course III and IV in those patients who completed four study courses.

VAS scores and emetic amounts were measured hourly for 24 h when the patients were awake.

Nausea intensity, emetic episodes and dry heaves were recorded hourly in the day time until 5 p.m.

Global assessments for nausea and vomiting were obtained at 5 p.m. for the previous 7–8 h and the next morning for the previous 24 h together with acceptance and preference. After this evaluation the patients left the hospital.

Statistical analysis

Patients preference after course II was the determining parameter. The study was planned with interim analysis of preference after course II for every 12 patients (Prescott's test) to a maximum of 60 patients, thereafter the study was stopped if no significant difference between HD and LD MP was found.

Patient who received rescue therapy with chlorpromazine in one study course were assumed to prefer the opposite one regardless of the actual answer.

For all the secondary efficacy variables, differences in scores between HD and LD MP were calculated for each patient after the second and fourth study course. For each comparison of two periods, the preferred one was assumed to be the one with the lowest score.

Average VAS was analyzed by means of overall differences (two-sided Mann–Whitney *U*-test on a 5% significance level).

Coherence of secondary efficacy variables with preference was analyzed by means of Kendall's rank correlation coefficient, T_b.

For VAS scores, Em Am and Em Ep, the following methods were used. Analysis of carry-over effect, effect of periodicity and effect of treatment were performed by analysis of variance with 'treatment sequence' and 'type of chemotherapy' as factors. Effect of treatment (HD or LD) was supplementarily tested by the non-parametric Wilcoxon signed rank test without assumption of normally distributed data but assuming that no effect of periodicity exists. For all other tests, Fisher's two-sided exact test in $r \times c$ unordered tables or Kruskal–Wallis two-sided exact test in $r \times c$ ordered tables was applied.

The level of significance was 5%.

Results

Eighty patients were included in the study, but 20 were not evaluable: eight were excluded due to concomitant steroid therapy (1), diabetes (1), planned cessation of chemotherapy before study course

Table 3. Patient characteristics: study course III and IV

	No. of patients
Completed study course I and II	60
Left the study before course IV	16
reasons	
chemotherapy stopped	5
own wish	3
unidentical doses of diazepam in course III and IV	3
procedure error in chemotherapy	3
chlorpromazine in both course III and IV	1
reduced dose of chemotherapy due to leukopenia	1
Evaluable for course III and IV	44
Adjuvant therapy (CMF)	17
Relapse therapy (CEF)	20
Relapse therapy (epirubicin)	7

II (1), lack of recordings (1), own wish (2), progression of disease (1), and unability to cooperate (1). Twelve patients were excluded before the end of course II because of treatment with chlorpromazine in both of the two first study courses[10] or because of unidentical doses of diazepam.[2] After the inclusion of 60 evaluable patients, the study was terminated. Twenty-two patients received CMF (cyclophosphamide, methotrexate and 5-fluorouracil), twenty-nine received CEF (same as CMF but with methotrexate replaced by epirubicin) and nine patients received epirubicin (E) as a single drug. All regimens were administered every 3 weeks. See Table 2, doses and patient characteristics.

Among the 60 patients, 16 patients did not complete course III and IV due to termination of treatment (5), own wish (3), unidentical dosage of diazepam in course III and IV (3), procedure error in chemotherapy (3), chlorpromazine in both course III and IV (1), and reduced dose of chemotherapy due to leucopenia (1). Thus 44 patients completed four study courses (20 CEF, 17 CMF and seven E patients) (Table 3).

Evaluation of efficacy

Main results are shown in Table 4.

After course I and II (60 patients)

Preference. Thirty-two patients preferred HD (53%), 21 preferred LD (35%) and seven patients (12%) had no preference ($p = 0.084$). No significant difference according to chemotherapy groups was found.

Table 4. The most important treatment results: all significant differences are in favor of HD

Parameter	Study course no. I and II (60 patients) (p value)	III and IV (44 patients) (p value)	All four (44 patients) (p value)
Preference	0.084	0.05	0.007
Average Em Am	0.23	0.06	0.003
Average VAS	0.46	0.013	0.119
GV 9 a.m.	0.029	0.059	0.008
GN 9 a.m.	0.109	0.075	0.126
AN 9 a.m.	0.131	0.031	0.008
AV 9 a.m.	0.440	0.004	0.024

Abbreviations: see text.

Secondary parameters. Global assessments for vomiting the next morning showed better effect from HD ($p < 0.05$). No difference was found in other efficacy parameters.

After course III and IV (44 patients)

Preference. In the subgroup of patients who completed four study courses, 26 patients (59%) preferred HD, 14 (32%) preferred LD ($p < 0.05$) after the first two courses; after course IV 55% preferred HD and 30% LD ($p = 0.05$).

Secondary parameters. The following secondary parameters showed superior effect from HD compared with LD ($p < 0.05$): average VAS scores, acceptance of nausea and vomiting the next morning. No parameter showed a better effect from LD than from HD.

Overall results

In patients who completed four study courses data from course I and II were compared with data from course II and IV in order to exploit the full amount of data.

Preference. Overall preference was calculated for each patient from the preferences after study course II and IV. Each preference was scored +1, −1 or 0

(preference for HD, LD or no preference). The scores were added with the possible values from −3 to +3, where +3 and −3 represented a patient's unanimous preference for HD and LD, respectively. A better effect from HD compared with LD was revealed ($p = 0.007$).

Secondary parameters. Overall differences in average emetic amounts after four study courses were in favor of HD ($p < 0.005$), as well as global assessment of vomiting and acceptance of both nausea and vomiting the next morning. For emetic amounts a significant treatment effect from HD was only seen in overall results. In the data from course III and IV a significant carry-over effect occurred, due to CMF patients having large emetic volumes when starting on LD. This effect disappeared in the overall results.

The effect from chlorpromazine on treatment results

Fifteen patients received chlorpromazine in one study course, nine in course I or II and six in course III or IV (seven on LD and eight on HD). Regardless of their actual preference the patients were assumed to prefer the course in which they did not receive chlorpromazine. This was true in seven patients (six on LD and one on HD), but eight patients (seven on HD and one on LD) had their preference overruled.

The patients who received chlorpromazine in one of the first two courses had an average VAS score of 13.5 mm compared to 5.7 mm in other patients. In the chlorpromazine group the average decrease in VAS was 5.9 mm with HD compared with an increase of 1 mm in the other patients ($p < 0.05$).

Six patients received chlorpromazine in course III or IV, there was no difference in VAS between chlorpromazine-treated patients and other patients.

CEF patients

After course II, global assessment for nausea the next morning showed better effect from HD ($p < 0.05$). Sixty per cent of CEF patients who completed all four study courses had an overall preference for HD ($p < 0.03$).

Emetic episodes, dry heaves and nausea intensity

Emetic episodes, dry heaves and observer registered nausea intensity were rated during an 8 h period, and were only above zero in 27, 20 and 25% of the study hours, respectively, and they were of no value in detecting emetic effect.

Conclusion on antiemetic effect

No significant difference between HD and LD MP was detected in preference after study course II. CEF patients, patients who needed chlorpromazine and the 44 patients who completed four study courses had a benefit from HD MP in some situations but this finding was inconsistent.

The value of different efficacy parameters for the 8 h period when Em Ep and NI were recorded

As nausea intensity and emetic episodes were only recorded until 5 p.m. we took into consideration the limited period where all measurements were done.

Non-parametric tests were used because of many recordings being equal to zero. There was no significant difference between HD and LD MP, which was to be expected as nausea and vomiting did not commence before 7–9 h after chemotherapy.

Agreement between variables

Agreement between preference and other efficacy variables was tested by means of Kendall's T_b (Table 5). It appears that T_b values calculated for comparisons between preference and emetic amounts and global assessments for nausea and vomiting in the morning are statistically significantly greater than zero. This holds true both for preferences after study course II and IV and for overall preferences. For all other variables T_b is statistically significant at it's best in one or two sessions. The actual value of T_b, however, does not indicate good agreement; statistical significance is obtained only because of a large number of observations.

Table 5. Agreement between patients' preference and secondary parameters measured by Kendall's rank correlation coefficient T_b, together with its level of significance (p value)

	Study course no.					
	I and II		III and IV		all four	
	T_b	p value	T_b	p value	T_b	p value
Parameters						
VAS	0.166	0.091	0.246	0.047	0.330	0.011
emetic volume	0.545	0.001	0.344	0.007	0.432	0.001
emetic episodes	0.270	0.013	−0.084	0.289	0.194	0.091
dry heaves	0.319	0.005	−0.210	0.089	0.128	0.240
nausea intensity	0.072	0.277	0.186	0.119	0.179	0.108
Global assessments						
nausea 5 p.m.	0.360	0.001	0.125	0.223	0.192	0.094
nausea 9 a.m.	0.420	0.001	0.418	0.001	0.433	0.001
vomiting 5 p.m.	0.186	0.069	−0.064	0.358	0.134	0.190
vomiting 9 a.m.	0.588	0.001	0.397	0.002	0.483	0.001
Acceptance						
nausea 5 p.m.	0.216	0.104	0.174	0.317	0.157	0.167
nausea 9 a.m.	0.289	0.008	0.075	0.366	0.219	0.065
vomiting, 5 p.m.	0.080	0.313	−0.155	0.251	−0.141	0.242
vomiting, 9 a.m.	0.346	0.002	0.111	0.279	0.289	0.022

Reproducibility of preferences

The design with four study courses made it possible to test the stability of preferences and the reproducibility of the changes in other study parameters from study course I–II and from course III–IV. For the purpose of this analysis the use of chorpromazine was ignored. The measure to quantify reproducibility is Cohen's weighted κ. For a reproducibility to reasonable κ should be >0.33.

The reproducibility of preference for all patients was low ($\kappa = -0.0342$) but fair for CEF patients ($\kappa = 0.4643$).

VAS showed a fair reproducibility for all patients and for CEF patients ($\kappa = 0.3462$ and 0.5483, respectively).

Emetic amount, emetic episodes, nausea intensity, dry heaves and global assessments had a low grade of reproducibility.

It should be noted that a $\kappa < 0.7$ only indicates a modest agreement between parameters.

Side effects

The 80 patients included in the trial completed a total of 255 study courses. In 13 courses (11 HD and two LD) ($p = 0.8\%$) side effects were recorded, comprising a metallic taste, swollen face or throat, euphoria and vertigo.

Discussion

The antiemetic effect from steroids has been shown in several studies. Parry[5] found a better antiemetic effect from dexamethasone than from placebo in a randomized single-blind cross-over study in 31 patients receiving non-cisplatin chemotherapy. In a randomized double-blind cross-over study in 100 patients treated with non-cisplatin-containing chemotherapy, Jones[6] showed that dexamethasone was equal to ondansetron in controlling acute nausea and vomiting, but better than ondansetron concerning late side effects.

Zaglama *et al.*[7] showed effect from dexamethasone 40 mg/m^2 in patients treated with doxorubicin-based combination chemotherapy but no effect from dexamethasone 95 mg/m^2 in cisplatin-treated patients.

Concerning dose, conflicting results exist. Gez *et al.*[8] compared 125 mg of MP with the same dose given twice in 20 CMF patients. Thirty per cent in the HD group and 17% in the LD group had complete protection, 15 and 44%, respectively, had no protection. There was no significant difference in side effects. Drapkin *et al.*[9] conducted a trial in 22 patients treated with cisplatin with or without cyclophosphamide and adriamycin. Dexamethasone 8 mg in conjunction with hydroxyzine and prochlorperazine showed better effect than hydroxyzine and prochlorperazine alone. Thereafter the

dose of dexamethasone was escalated at 8 mg increments to 40 mg. Five of 22 patients had better antiemetic control with doses of dexamethasone above 8 mg, but in 17 patients there was no benefit from doses above 8 mg.

Chiara *et al.*[10] compared MP 375 mg and 120 mg i.v. divided in three equal doses in 68 CMF patients and found no difference in emesis or nausea intensity, but significantly more side effects in the HD group.

Coleman *et al.*[11] in a double-blind randomized parallel study investigated dexamethasone 5 or 20 mg in conjunction with haloperidol 3 mg and lorazepam 2 mg in 57 cancer patients treated with non-cisplatin-containing chemotherapy. No significant difference was found. Pieters *et al.*[12] treated 39 patients with MP 250 mg versus 500 mg 30 min before non-cisplatin chemotherapy. The trial used a randomized double-blind cross-over design. No significant difference was found. Seventeen patients out of 56 were unevaluable, a problem often seen in cross-over studies and experienced in our study as well.

Evaluation in the above four studies comprised nausea, vomiting and appetite recorded after 24 h, and in Pieter's study patients' preference. These methods are regarded as fully sufficient but not designed to elucidate minor differences in efficacy.

The present study did not show a major difference between HD and LD solumedrol. The determining parameter was patient' preference after two study courses and, according to the study protocol, the study was closed after inclusion of 60 patients. However, it was observed that patients severely bothered by nausea and vomiting benefitted from HD in some parameters. Moreover, patients who went through all four study courses turned out with less nausea on HD than on LD. No results were in favor of LD solumedrol.

In a previous study with a similar design[1] comparing MP 250 mg with placebo we found that VAS and emetic amounts were superior to nausea intensity and emetic episodes in registering antiemetic efficacy. The results in the present study may seem disappointing regarding the exploration of different efficacy variables, but may be explained by the fact that we are dealing with rather small differences in antiemetic efficiency.

Global assessments were able to detect differences in antiemetic efficacy after two study courses. VAS and emetic amounts did not show any difference in the present study. However, after course III and IV the average VAS was significantly lower in the HD than in the LD series and emetic amounts after four courses also showed better effect from HD. Moreover, VAS decreased more with HD treatment than with LD in patients who needed chlorpromazine. As nausea intensity and emetic episodes were only recorded for 8 h, no estimation of the value of these parameters could be done.

Coherence between preference and the secondary efficacy parameters was modest, presumably because of the small differences in efficacy.

It can be argued that the present study was hampered by some methodological problems, especially the inclusion of patients receiving different kinds of chemotherapy. As the patients were planned to be their own controls we did not consider this a major obstacle, but it must be admitted that the interpretation of results would have been easier and more reliable if the patient population had consisted of only one chemotherapy group.

Many studies only accept patients who are chemotherapy naive, but our patients were to participate in up to four consecutive study courses, and we found that the greatest changes in emetic capacity was to be expected from study course I to II, and therefore we preferred patients who were not chemotherapy naive.

The primary parameter, preference after course II, did not show any superiority from HD MP and great care must be employed in the interpretation of the many results from the secondary parameters. These results can only be hypothesis generating.

If HD MP was clearly better than LD MP, we are convinced that this would be revealed by preference in a reasonable number of patients and one or more of the secondary efficacy variables would have been able to detect a difference too. On the contrary, neither preference nor the other efficacy parameters showed consistent superiority of HD MP after two study courses.

As there was no difference in side effects it could be argued that one might just as well start with HD MP at least in patients receiving heavily emetogenic chemotherapy as a marginal effect from the high dose seems to be possible.

Conclusion

In conclusion, HD MP may be more efficacious in patients heavily bothered by nausea and vomiting but this hypothesis must be tested in further randomized studies with HD and LD MP in a well defined homogenous group of patients treated with severely emetogenic chemotherapy.

References

1. Havsteen, Kjaer M. Double-blind randomized cross-over trial comparing methylprednisolone with placebo in chemotherapy-induced nausea and vomiting: a study with special reference to study parameters. *Anti-Cancer Drugs*, 1991; **2**: 571–9.
2. Smyth JF, Coleman RE, Nicholson M, *et al.* Does dexamethasone enhance control of acute cisplatin induced emesis by ondansetron? *Br Med J* 1991; **303**: 1423–6.
3. Kris MG, Gralla RJ, Tyson LB, *et al.* Improved control of cisplatin-induced emesis with high-dose metoclopramide and with combinations of metoclopramide, dexamethasone and diphen-hydramine. Results of consecutive trials in 255 patients. *Cancer* 1985; **55**: 527–34.
4. Schmidt M, Sorbe B, Högsberg T, *et al.* Efficacy and tolerability of tropisetron and dexamethasone in the control of nausea and vomiting induced by cisplatin. *Ann Oncol* 1993; **4**: S31–4.
5. Parry H, Martin K. Single dose i.v. dexamethasone—an effective anti-emetic in cancer chemotherapy. *Cancer Chemother Pharmacol* 1991; **28**: 231–2.
6. Jones AL, Hill AS, Soukop M, *et al.* Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. Lancet 1991; **338**: 483–7.
7. Zaglama NE, Rosenblum SL, Sartiano GP, *et al.* Single, high dose intravenous dexamethasone as an antiemetic in cancer chemotherapy. *Oncology* 1986; **43**: 27–32.
8. Gez E, Strauss N, Vitzhaki N, *et al.* Methylprednisolone as antiemetic treatment in breast-cancer patients receiving cyclophosphamide, methotrexate and 5-fluorouracil: a prospective crossover, randomized blind study comparing two different dose schedules. *Cancer Chemother Pharmacol* 1992; **30**: 229–32
9. Drapkin RL, Sokol GH, Paladine WJ, *et al.* The antiemetic effect and dose response of dexamethasone in patients receiving *cis*-platinum. *Proc Am Soc Clin Oncol* 1982; **62**: C-236.
10. Chiara S, Campora E, Lionetto R, *et al.* Methylprednisolone for the control of CMF-induced emesis. *Am J Clin Oncol* 1987; **10**: 264–7.
11. Coleman RE, Twelves CJ, O'Reilly SM, *et al.* Influence of dexamethasone on the control of chemotherapy-induced nausea and vomiting. *Eur J Cancer* 1991; **27**: 1062–3.
12. Pieters RC, Vermorken JB, Gall HE, *et al.* A double-blind randomized crossover study to compare the antiemetic efficacy of 250 mg with 500 mg methylprednisolone succinate (solu-medrol) as a single intravenous dose in patients treated with noncisplatin chemotherapy. *Oncology* 1993; **50**: 316–22.

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