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Tetracosactrin vs. Methylprednisolone in the Prevention of Emesis in Patients Receiving FEC Regimen for Breast Cancer

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0.5 mg tetracosactrin is considered to be equivalent to 40 mg methylprednisolone with regard to the induced cortisol secretion. 97 female breast cancer patients who received their first two FEC courses (epirubicin 50–75 mg/m², 5-fluorouracil 500 mg/m², cyclophosphamide 500 mg/m²) entered this randomised crossover study (76 had previously received an adjuvant treatment); tetracosactrin was administered intramuscularly and methylprednisolone intravenously immediately before chemotherapy administration. The tolerability was evaluated using a diary card during 5 days and patients were asked for their preference at the end of the two cycles. There was no difference either for vomiting (dry heaves were included) or nausea between the two treatments (the analysis was performed on day 1, the worse day of days 2 and 3 and the worse day of days 4 and 5). At day 1, 49% of the patients experienced no or mild nausea after tetracosactrin and 62% after methylprednisolone (not significant) (first period analysis); a complete control of vomiting (including dry heaves) was observed in 49% of the patients after tetracosactrin and 53% after methylprednisolone (not significant). No difference was observed between patients with or without previous chemotherapy. However, slightly more patients preferred tetracosactrin ($P = 0.048$).
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INTRODUCTION

EPIRUBICIN, CYCLOPHOSPHAMIDE and 5-fluorouracil are widely used in the treatment of breast cancer either in the advanced stage or as an adjuvant treatment. Most patients experience grade 2 or 3 nausea and vomiting [1]. Glucocorticoids such as dexamethasone or methylprednisolone have been shown to be efficient in the prevention of nausea and vomiting in patients treated with moderately emetogenic chemotherapy agents [2, 3]. Tetracosactrin has been shown to be efficient as a salvage treatment in patients receiving FAC regimen in which doxorubicin was used instead of epirubicin [4]. Although difficult to evaluate, 0.5 mg tetracosactrin induces a cortisol secretion that is thought to be equivalent to 40 mg methylprednisolone [5]. The rationale for this trial was to use a tetracosactrin dose (0.5 mg) which induces a glucocorticoid secretion which is much less than 120 mg methylprednisolone.

PATIENTS AND METHODS

Patients

97 consecutive female breast cancer patients receiving the FEC regimen (epirubicin 50 or 75 mg/m², 5-fluorouracil 500 mg/m², cyclophosphamide 500 mg/m²) entered this trial; both epirubicin doses were accepted since it was a crossover study and since it had been shown that there was no difference in the intensity of nausea and vomiting between the two groups [6]. To be eligible patients should have received their first course with this

regimen (a previous treatment with the same regimen was not an exclusion criterion if at least 6 months had elapsed since the previous administration). 76 patients had previously received an adjuvant chemotherapy. 18 were chemotherapy-naive. Patients with concurrent illnesses, especially with digestive symptoms, were excluded.

Treatment

The study was a randomised crossover study comparing two antiemetic treatments administered immediately before chemotherapy: tetracosactrin (0.5 mg) intramuscularly and methylprednisolone (120 mg) intravenously. For the second course, patients received the other treatment.

Assessments

Assessment was carried out by the patient herself who had to complete a diary card daily for 5 days: the number of vomiting episodes and retches, the time of the first vomit, the intensity of nausea graded from 0 to 3 (absent, mild, moderate or severe) were recorded as well as the ability to eat (normal, limited, impossible), a general assessment of the course (good or tolerable, distressing, intolerable.) At the end of the two courses, each patient was asked for her preference.

Statistical analysis [7, 8]

Patients were considered fully evaluable if they completed both courses of treatment. For each course, treatment efficacy was assessed for day 1, the worse day of days 2 and 3, and the worse day for days 4 and 5.

A period interaction was looked for for each studied parameter. The evolution of the intensity of side-effects during the 5 days was studied by variance analysis and comparison of percentages by the χ^2 test. All results were interpreted with an α risk of 0.05.

Ethical approval

The protocol was reviewed and approved by the Medical Ethics Committee of the Centre Oscar Lambret (Lille) and was conducted according to the principles of the Declaration of Helsinki. All subjects gave informed consent.

RESULTS

As there was a period interaction for nausea ($P = 0.036$), only results of the first period were considered ($n = 47$). No period interaction was observed for vomits and retches ($P = 0.303$) and results of the two periods are thus presented.

Day 1

Results are presented in Table 1; no difference was observed between the two treatments for nausea. No difference was observed either in the control of vomiting between tetracosactrin and methylprednisolone. When comparing the antiemetic effect of the first period, no difference was observed between tetracosactrin and methylprednisolone for vomits and retches (major control was observed, respectively, in 62% and 75% of the patients); conversely a significant difference favouring methylprednisolone was observed in the percentage of patients with less than two vomiting episodes (66% vs. 85%; $P = 0.05$). The delay between chemotherapy administration and the first vomiting episode was the same in both groups: about 8 hours.

Table 1. *Efficacy of tetracosactrin and methylprednisolone in preventing nausea and vomiting (day* 1)

	Tetracosactrin	Methylprednisolone
Nausea*	$n = 47$	$n = 47$
None or mild	23 (49%)	29 (62%)
Moderate	18 (38%)	7 (15%)
Severe	6 (13%)	11 (23%)
Vomits (and/or retches)*	$n = 47$	$n = 47$
0	22 (47%)	29 (62%)
1–2	7 (15%)	6 (13%)
3–5	7 (15%)	3 (6%)
More than 5	11 (23%)	9 (19%)
Vomits (and/or retches)†	$n = 94$	$n = 94$
0	46 (49%)	50 (53%)
1–2	14 (15%)	12 (13%)
3–5	12 (13%)	9 (10%)
More than 5	22 (23%)	23 (24%)

* First period analysis only (period interaction for nausea, $P = 0.036$).
† Two period analysis (no period interaction, $P = 0.303$).

A major control of emesis was observed after tetracosactrin in 72% ($n = 18$) of chemotherapy-naive patients and 66% ($n = 76$) of patients with previous chemotherapy; the figures were 89% and 74% for methylprednisolone, respectively. The number of patients with no or mild nausea (first period analysis) was, respectively, in chemotherapy-naive patients 6 out of 8 after tetracosactrin and 5 out of 10 after methylprednisolone; in patients with previous chemotherapy, a major control of nausea was observed in, respectively, 17 out of 39 (44%) and 24 out of 37 (65%) patients.

No difference in complete control (no nausea, no vomiting) was observed between chemotherapy-naive (7 out of 18: 39%) and previously treated patients (29 out of 76: 38%).

Days 2 and 3

Results are presented in Table 2. No difference was observed between the two treatments either for nausea or for vomiting and retches.

Patient preference

When the two periods were considered, more patients preferred tetracosactrin than methylprednisolone (44.4% vs. 37.8%, $P = 0.048$). When each sequence was considered separately, the difference was of borderline significance when patients were given tetracosactrin first ($P = 0.07$) but no preference was expressed when they were given methylprednisolone first ($P = 0.474$).

Quality of life assessment

Patients reported normal eating after the first course in 34% after tetracosactrin and 42% of the cases after methylprednisolone (not significant); they were unable to eat in, respectively, 21.3% and 24.4% of the cases (not significant).

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Table 2. Efficacy of tetracosactrin and methylprednisolone in preventing nausea and vomiting (days 2 and 3)

	Tetracosactrin	Methylprednisolone
Nausea*	$n = 47$	$n = 47$
None or mild	29 (62%)	25 (53%)
Moderate	12 (25%)	13 (28%)
Severe	6 (13%)	9 (19%)
Vomits (and/or retches)*	$n = 47$	$n = 47$
0	24 (51%)	21 (45%)
1–2	13 (28%)	15 (32%)
3–5	7 (15%)	3 (6%)
More than 5	3 (6%)	8 (17%)
Vomits (and/or retches)†	$n = 94$	$n = 94$
0	48 (51%)	47 (50%)
1–2	20 (21%)	22 (23%)
3–5	12 (13%)	7 (8%)
More than 5	14 (15%)	18 (19%)

* First period analysis only (period interaction for nausea, $P = 0.036$).
† Two period analysis (no period interaction, $P = 0.303$).

The first chemotherapy course was felt tolerable in 70.2% after tetracosactrin and 68.9% after methylprednisolone (not significant); it was considered intolerable in, respectively, 29.8% and 31% of the cases (not significant).

The variations of nausea and vomiting during the 5 days of the study after each course were similar with tetracosactrin and after methylprednisolone.

Side-effects

Side-effects were reported with the same frequency in each treatment group ($n = 8$): all were minor due to corticoid (induced) treatment: face erythema (or oedema) ($n = 10$), headache ($n = 2$), hot flushes ($n = 3$) and vertigo ($n = 1$).

DISCUSSION

Dexamethasone as well as methylprednisolone has been shown to have antiemetic effect when used alone in moderately emetogenic regimens [2, 3]; it has been suggested by Lee [2] that 125 mg was as efficient as 250 mg with non-cisplatin, mechlorethamine and dacarbazine containing regimens. We thus used 120 mg methylprednisolone only once, since FEC is a moderately emetogenic chemotherapy regimen. To our knowledge, only one study compared two different methylprednisolone doses (375 and 120 mg) in the prevention of CMF-induced nausea and vomiting [9]. No difference was observed between the two groups. In another study, only published as an abstract, of escalating dexamethasone dose in patients receiving cisplatin, no apparent benefit in doses above 8 mg was observed [10]. An antiemetic efficiency of a low-dose of methylprednisolone cannot be excluded. In a previous study [4], we had shown that tetracosactrin when given intramuscularly at a dose of 0.5 mg was efficient as a salvage treatment in patients receiving FEC and failing currently used antiemetics.

The mechanism of action of tetracosactrin is not clearly understood. As it is a β-1-23 adrenocorticotropic hormone (ACTH) it may act through the induced glucocorticoid synthesis, and several studies comparing methylprednisolone to the "equivalent" dose of tetracosactrin suggest that this might be the case [8, 9]. The rationale for this study was to use a methylprednisolone dose three times higher than the "equivalent" tetracosactrin dose (it is generally accepted that 0.5 mg tetracosactrin intramuscularly is equivalent to 40 mg methylprednisolone).

The objective results obtained with these two treatments were not different with a major control of emesis in about 65% of the patients in both groups the first day. No difference was observed concerning nausea the first day or nausea and vomiting the other 5 days (especially days 2 and 3). These results on major control of emesis are better than those obtained in another trial with metoclopramide (80 mg day 1 and then 60 mg per day for 4 days): (42%), but less good than with the new anti-$5HT_3$ ondansetron (8 mg day 1, 24 mg per day for 4 days): (66%) [11]. Surprisingly, despite comparable objective results, more patients preferred tetracosactrin.

These results sugest that the antiemetic effect of tetracosactrin could be explained by a non-glucocorticoid mediated mechanism of action. Further, tetracosactrin has other actions, especially at the level of the central nervous system. The chemoreceptor trigger zone and the fasciculus solitarius are rich in neuropeptides [12] and their receptors; ACTH and especially 4-9 ACTH has been shown to bind to neuropeptide receptors and compete with metenkephalin [13]. An antagonism has been shown between ACTH and morphine in analgesia inhibition [14], prolactin secretion [15] and rat behaviour [16]. In any case, ACTH is a competitor of neuropeptides. It has been hypothesised that cytotoxic therapy-induced vomiting was mediated at least in part by enkephalin pathways [17]. It is thus possible that tetracosactrin, by antagonising neuropeptide action, may inhibit vomiting either directly or indirectly through the relations between dopaminergic and neuropeptidic systems [17].

The reason why patients preferred tetracosactrin in spite of no difference in the objective control of nausea and vomiting is unclear. Again, it suggests that tetracosactrin might act in the central nervous system in other areas than those involved in the control of vomiting, which could explain a more frequent feeling of wellbeing in patients receiving tetracosactrin. However, since the study was not a blind one, it cannot be excluded that patients preferred an intramuscularly administered drug.

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Phase II Study of Fotemustine in Recurrent Supratentorial Malignant Gliomas

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38 adults with recurrent supratentorial malignant gliomas, including glioblastoma multiforme (21), anaplastic astrocytomas (9), probably transformed low-grade astrocytomas (6), pinealoblastoma (1) and non-metastatic tumour of unknown histology (1), were treated with fotemustine 100 mg/m² intravenously every week for 3 consecutive weeks followed by a 5-week rest period. Maintenance treatment consisted of one infusion every 3 weeks. Patients were divided into three groups according to treatment effect. 10 objective responses (26%) with a median time without progression of 32.7 weeks, 18 stabilisations (47%) and 10 failures (26%) were observed. Pathological findings of the initial primary tumour and neurological functional status were unequally distributed in these groups. Haematological and liver toxicities were mild, delayed, transient and reversible. Thrombocytopenia and leukopenia were more frequent (30%) in patients treated with prior chemotherapy. Fotemustine is a well tolerated active drug in recurrent malignant gliomas with an original and short treatment schedule.
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INTRODUCTION

LIPOPHILIC NITROSOUREAS are the most important group of antineoplastic drugs in chemotherapy of malignant gliomas [1].

The standard drug is carmustine with a transient efficacy as monochemotherapy in recurrent gliomas and as adjuvant treatment combined with radiotherapy and surgery [2, 3]. Polychemotherapy with drugs crossing the blood–brain barrier does not increase efficacy compared to carmustine alone [4, 5]. Fotemustine, a new chloroethyl nitrosourea compound, is characterised by a high lipophilicity (log P = 1.25) and a chemical structure including a phosphonoalanine carrier group grafted onto the nitrosourea radical to achieve both a better penetration through the cell membrane and a better antitumoral activity [6]. In *in vivo* models fotemustine compared favourably with carmustine on intrathecal L1210 leukaemia grafted into mice and in xenografts of human glioma [7, 8]. A clinical phase I study with weekly administration for 3 consecutive weeks showed delayed, cumulative and dose-related thrombocytopenia, leukopenia and mild nausea and vomiting. The recommended dose for further phase II studies was 100 mg/m² [9]. Thus, a phase II study was initiated in recurrent malignant gliomas to assess the tolerance and antitumoral activity of fotemustine using this original fractionated schedule.

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MATERIALS AND METHODS

From October 1985 to October 1988, 38 patients with recurrent supratentorial primary brain tumour were treated by fotemustine in a multicentre study (Table 1). All patients had computed tomography (CT) findings of progressive disease in relation to earlier examination and 32 had significant neurological impairment. No biopsy was performed at recurrence.

According to the WHO classification [10], histological examination of initial tumours showed glioblastoma multiforme in 21 (55%), anaplastic astrocytoma in 9 (24%) and pinealoblastoma in 1 (3%). In 6 patients (16%) with primary low grade astrocytomas,