treatment. The follow-up in these patients should mainly be one of care-taking and support-giving and can be made on an individual basis. A modest estimate reveals that approximately one-third of the follow-up consultations can be dropped without reducing the number of early detected recurrences that can be offered secondary treatment, and without reducing the care and support that we are obliged to give. The means, personnel and time hereby made available could be better utilised.

1. Bröyn T, Fröyen J. Evaluation of routine follow-up after surgery for breast carcinoma. *Acta Chir Scand* 1982, **148**, 401–404.
2. Cochrane JPS, Williams JT, Faber RG, Slack WW. Value of outpatient follow-up after curative surgery for carcinoma of the large bowel. *B M J* 1980, **280**, 593–595.
3. Ekman C-A, Gustavson J, Henning A. Value of follow-up study of recurrent carcinoma of the colon and rectum. *Surg Gynecol Obstet* 1977, **145**, 895–897.
4. Kolb E, Buchmann P. Erfahrungen bei Langzeitenuntersuchungen von patienten mit radikal operiertem Bronchuskarzinom. *Schweiz Rundschau Med (Praxis)* 1985, **74**, 1017–1020.
5. Boysen M, Natvig K, Winther FÖ, Tausjö J. Value of routine follow-up in patients treated for squamous cell carcinoma of the head and neck. *J Otolaryngol* 1985, **14**, 211–214.
6. Harmer MH, ed. *TNM Classification of Malignant Tumours*. 3rd edition, UICC, Geneva, 1987.
7. Warren S, Gates O. Multiple primary malignant tumors: a survey of literature and statistical study. *Am J Cancer* 1932, **16**, 1358–1414.
8. Dewar JR, Kerr GR. Value of routine follow-up of women treated for early carcinoma of the breast. *B M J* 1985, **291**, 1464–1467.
9. Queisser W, Maurer U, Schmidt H. Efficacy of German regional follow-up program of 5411 cancer patients. *J Cancer Res Clin Oncol* 1990, **116**, (Suppl, part 1), 206.
10. Wolfensberger M. Aufwand und Nutzen regelmässiger Nachkontrollen bei Patienten mit plasterzellkarzinomen des larynx, mundhölen und des pharynx. *HNO* 1988, **36**, 28–32.
11. Wagenfeld DJH, Harwood AR, Bryce DP, van Nostrand AWP, de Boer G. Second primary respiratory tract malignancies in glottic carcinoma. *Cancer* 1980, **46**, 1883–1886.
12. Tepperman BS, Fitzpatrick PJ. Second respiratory and upper digestive tract cancer after oral cancer. *Lancet* 1981, ii, 547–549.
13. Vikram B, Strong ES, Shah JP, Spiro R. Second malignant neoplasms in patients successfully treated with multimodality treatment for advanced head and neck cancer. *Head Neck Surg* 1984, **6**, 734–737.
14. Neel HB. Routine endoscopy—is it necessary every time? *Arch Otolaryngol* 1984, **110**, 531–532.
15. Schuller DE, Fritsch MH. An assessment of the value of triple endoscopy in the evaluation of head and neck cancer patients. *J Surg Oncol* 1986, **32**, 156–158.
16. Leipzig B, Zellmer JE, Klug D, *et al.* The role of endoscopy in evaluating patients with head and neck cancer: a multi-institutional prospective study. *Arch Otolaryngol* 1985, **111**, 589–594.
17. Shaha A, Hoover E, Marti J, Krespi Y. Is routine triple endoscopy cost-effective in head and neck cancer? *Am J Surg* 1988, **155**, 750–753.
18. Atabek U, Mohit-Tabatabai MA, Raina S, Rush BF, Dasmahapatra KS. Lung cancer in patients with head and neck cancer. Incidence and long-term survival. *Am J Surg* 1987, **154**, 434–438.

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Progressive Loss of Antiemetic Efficacy During Subsequent Courses of Chemotherapy

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The maintenance of the antiemetic efficacy of a combined protocol (intravenous methylprednisolone, oral thiethylperazine and oral amitriptyline) during six consecutive courses of adjuvant FAC chemotherapy (5-fluorouracil, doxorubicin, cyclophosphamide) was analysed in 107 female breast cancer patients who completed the six planned courses of treatment. A continuous decrease in complete (no vomiting episodes) and major protection rate (0–2 vomiting episodes) was evident during chemotherapy. Complete protection rate decreased from 62.6% in the first course to 48.6% in the sixth ($P<0.05$, χ^2 test). The respective figures for major protection rate were 76.6% and 58% ($P<0.01$, χ^2 test). These data, together with other from the literature, should be taken into consideration when reviewing the overall results of current antiemetic trials, which usually only mention the results obtained in the first course of chemotherapy.
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INTRODUCTION

WITH VERY few exceptions [1–5], antiemetic trials only report the results obtained during the first course of chemotherapy. A question which usually arises when reading the positive results of many recent antiemetic trials is whether or not the efficacy is maintained during subsequent cycles of chemotherapy.

Adjuvant FAC (5-fluorouracil, doxorubicin, cyclophosphamide) chemotherapy for breast cancer provides a useful model for answering this question, since it induces considerable emesis and the great majority of patients usually receive the planned six courses of chemotherapy.

In this paper, we present the results of a study in which the

Table 1. Characteristics of patients

Total	113
Evaluable for study purposes	107
Premenopausal	43
Postmenopausal	70
Age (years)	
Mean	53
Range	31–74

maintenance of antiemetic efficacy during subsequent courses of FAC chemotheapy was specifically analysed.

PATIENTS AND METHODS

Patients included in our study suffered from breast cancer in stages II to III-B and were referred to our Department in order to receive postsurgical adjuvant (stages II to III-A) or neoadjuvant (stage III-B) FAC chemotherapy, consisting of six courses of 5-fluorouracil 500 mg/m^2 intravenously, doxorubicin 50 mg/m^2 intravenously and cyclophosphamide 500 mg/m^2 intravenously 1 day every 3 weeks. Chemotherapy was given in an outpatient setting. In all patients, antiemetic treatment consisted of 250 mg of intravenous methylprednisolone immediately prior to FAC chemotherapy and oral thiethylperazine (6.5 mg three times a day on days 1–3) and oral amitriptyline (25 mg three times a day on days 1–3). This antiemetic protocol was selected in accordance with our previous controlled experience in FAC-induced emesis [6, 7], because it is able to provide adequate emetic control in nearly two thirds of the patients in the first course of therapy.

Patients with any kind of previous chemotherapy or with contraindications for FAC chemotherapy or corticosteroid therapy were not elegible for study purposes.

Patients received the same antiemetic treatment from the first to the sixth course of chemotherapy, in spite of the antiemetic results obtained, since efficacious drugs for antiemetic rescue, such as antiserotoninergic agents, were not available in Spain during the study period. Only those patients with important secondary effects due to antiemetics were given alternative antiemetics in subsequent courses of chemotherapy and, therefore, were excluded from analysis.

Patients received instructions on how to fill out a daily, special questionnaire on the evolution of their emesis, recording each episode of dry or ejective vomiting during the following 5 days after each of the six courses of chemotherapy treatment. Anticipatory vomiting, defined as vomiting which occurred before or during the infusion of chemotherapy, were also recorded in the questionnaire.

The aim of our study was to analyse the maintenance of antiemetic efficacy in terms of complete protection rate (no vomiting episodes over the 5 days following chemotherapy) and major protection rate (0–2 vomiting episodes over the same period of time) during the six courses of chemotherapy.

RESULTS

113 consecutive patients entered the study over a 3 year period (1987–1989). Patients' characteristics are shown in Table 1. 6 patients (5.3%) did not complete the overall period of six courses according to the protocol. Three of them received less than six courses of FAC themotherapy because of early disease progression and another 3 patients stopped antiemetic treatment as a result of contraindication for methylprednisolone administration (peptic ulcer). The remaining 107 patients were evaluable for study purposes and received the six planned courses of chemotherapy and the combination of antiemetics, according to the protocol.

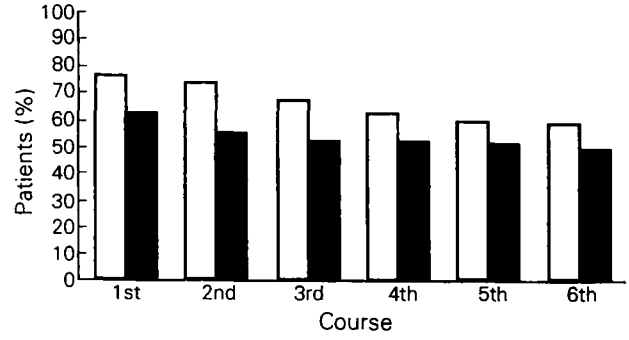

Fig. 1. Percentage of patients ($n=107$) with major (□) and complete control (■) of vomiting during the six courses of FAC chemotherapy. The differences between the first and sixth courses were statistically significant.

The results obtained in the 107 evaluable patients over the entire period of study (6 courses) are shown in Fig. 1. A continuous decrease in complete and major protection rate was evident during chemotherapy. Complete protection rate decrease from 62.6% in the first course to 48.6% in the sixth ($P<0.05$, χ^2 test).

21 patients (19.6%) presented anticipatory vomiting, usually after the fourth course of FAC chemotherapy. 7 of these patients had achieved a complete or major control of emesis in the first course of FAC chemotherapy.

DISCUSSION

As a consequence of methodological considerations, antiemetic trials usually only report the results obtained in the first course of chemotherapy and do not provide data on the evolution of emesis during the rest of chemotherapy treatment. A few antiemetic trials have analysed the maintenance of antiemetic efficacy in subsequent courses of chemotherapy and some of them did not find any loss of efficacy. However, a detailed analysis of the results of these studies does not support such a conclusion. Cognetti *et al.* [1] reported the results of antiemetic treatment with metoclopramide–dexamethasone during repeated courses of cisplatin chemotherapy in 18 patients. The majority of patients included in the study only received three courses of cisplatin. 12 out of 18 patients (67%) obtained complete protection from vomiting in the first course of chemotherapy, but this control was only maintained in 22 of the 53 subsequent courses of therapy (41.5%). In spite of the fact that statistical evaluation did not show any significant differences between the first and subsequent courses in this study, the power of the analysis to detect real differences was not defined and a clear trend towards worse results in repeated courses of treatment was evident. In another trial by Werner *et al.* [2], the maintenance of antiemetic efficacy of ondansetron was analysed during 132 retreatment courses of cisplatin in 56 selected patients who had experienced 0–2 emetic episodes during their initial

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treatment with the same drugs. After a median follow-up of three courses, a major control of emesis (0–2 vomiting episodes) was not maintained in 15% of the entire population.

Roila *et al.* [3] compared two different schedules of high-dose metoclopramide plus corticosteroids in cisplatin-treated patients. The protection from cisplatin-induced vomiting suffered a statistically significant decrease in subsequent courses of chemotherapy in both antiemetic arms under comparison. The complete protection rate with the most active of the antiemetic schedules dropped from 73.4% in the first course to 51.9% in the third course. Similarly, Abad-Esteve *et al.* [4] reported that the percentage of patients treated with cisplatin and metoclopramide–dexamethasone–diphenhydramine who presented three or less emetic episodes fell from 93% in the first course to 77.3% in the rest of the retreatment courses, after a mean follow-up of three. With a different combination of antiemetics (metoclopramide, droperidol and dexamethasone) 76.1% of cisplatin-treated patients experienced complete protection from nausea and vomiting in the first course of chemotherapy, but again this figure fell to 62.7% when all courses of subsequent chemotherapy were analysed [5]. The above mentioned results suggest a moderate but evident loss of efficacy of antiemetic treatment during subsequent courses of cisplatin chemotherapy. Nevertheless, their results cannot be accepted without reserve since the analysis of maintenance of antiemetic efficacy was not the major aim of many of the trials. Moreover, the methodology was rather inappropriate to analyse this problem, since an important number of the initial patients did not complete the follow-up due to unspecified reasons. On the other hand, our study was specifically designed to analyse the maintenance of efficacy of antiemetics in a population who had received an homogeneous number of courses of FAC chemotherapy. The great majority of the patients in our study completed the planned six courses of chemotherapy with the same antiemetic regimen and were evaluable for study purposes. Our study clearly showed that, despite the positive antiemetic results obtained in the first course of chemotherapy, there was a progressive loss of efficacy over the study period. The complete protection rate fell from 62.6% in the first course to 48.6% in the sixth, and the major protection rate showed a similar decrease (76.6% to 58%). The cause of this loss of efficacy of antiemetics is not clear. A psychological conditioning cannot be ruled out since some of the patients who achieved a major or complete control in the first course of chemotherapy subsequently developed overt anticipatory vomiting and lost their protection.

Our study, together with the data from the above mentioned trials, strongly suggests that a considerable percentage of patients (15–20%) who achieve a major or complete control of emesis during the first course of chemotherapy loses this antiemetic protection during subsequent retreatment courses. This fact should be taken into consideration when reviewing the overall results of current antiemetic treatments, which usually only mention the data obtained from the first course of chemotherapy.

1. Cognetti F, Carlini P, Pinnaro P, Ruggeri EM, Caporali C. Maintenance of antiemetic effect of a metoclopramide-dexamethasone combination during subsequent cisplatin courses. *Oncology* 1986, **43**, 292–294.
2. Werner K, Finn AL, Gandara DR. Maintenance of antiemetic effectiveness with multiple courses of GR 38032 F and cisplatin. Proc. *ASCO* 1989, **8**, 327.
3. Roila F, Tonato M, Basurto C, *et al.* Protection from nausea and vomiting in cisplatin-treated patients: High-doses metoclopramide combined with methylprednisolone versus metoclopramide combined with dexamethasone and diphenhydramine: A study of the Italian Oncology Group for Clinical Research. *J Clin Oncol* 1989, **7**, 1693–1700.
4. Abad-Esteve A, Rosell R, Moreno I, *et al.* Valoración del régimen antiemético con combinación de altas dosis de metoclopramida, dexamethasona y difenhidramina en regímenes de quimioterapia con cisplatino. *Med Clin* 1986, **87**, 796–798.
5. Sridhar KS, Donnelly E. Combination antiemetics for cisplatin chemotherapy. *Cancer* 1988, **61**, 1508–1517.
6. Martin Jimenez M, Diaz-Rubio E. Clinical evaluation of the simultaneous blockade of the dopamine D-2, Histamine H-1 and muscarinic cholinergic receptors in cancer chemotherapy-induced emesis. Results of a controlled trial. *Cancer Chemother Pharmacol* 1986, **18**, 168–171.
7. Martin Jimenez M, Diaz-Rubio E. Actividad antiemetica de las altas dosis de metoclopramida intravenosa en los vómitos inducidos por quimioterapia antineoplásica. Resultados de un estudio controlado. *Anales Med Intern* 1986, **3**, 525–528.