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ORIGINAL ARTICLE

Analysis of the effectiveness of an antiemetic protocol used in an oncology division☆

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KEYWORDS
Emesis;
Vomiting;
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Nausea;
Protocols

Abstract
Objective: To analyse the effectiveness of an antiemetic protocol in patients receiving chemotherapy treatment.
Method: Prospective study in patients with solid tumours receiving chemotherapy in an oncology day hospital between January 2006 and 2007.
We conducted a literature review and an evaluation of the recommendations of different clinical practice guidelines. The emetogenic potential was calculated according to the Hesketh level (HL), and the antiemetic premedication was determined for each regimen. We evaluated the effectiveness of an antiemetic protocol by using a survey as a method for measuring emetic episodes and nausea in the acute and delayed phases.
Results: 172 patients completed the survey. 13.4%vomited in the acute phase and 16.9%in the delayed phase; the median number of times was 2 (1-8) and 1 (1-5) for each respective phase. With treatment regimens classed as HL 4-5, 18.5% experienced vomiting in the acute phase and 20.2% in the delayed phase, with 46% experiencing nausea in the acute phase and 38.4% in the delayed phase. Control of vomiting in patients with treatment regimens classed as HL 1-3 was 100%in acute phase and 91.7%in the delayed phase; nausea was reported by 27%in the acute phase and 31%in the delayed phase. The factors that contributed the most to the presence of vomiting and nausea were the emetogenic potential of the treatment regimen ($P<.05$), vomiting in the previous cycle ($P<.05$) and age younger than 50 years ($P<.002$).

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Discussion: The proposed antiemetic protocol is effective for controlling vomiting in chemotherapy regimens with an HL of 1-3. For highly emetogenic regimens, the antiemetic protocol is also effective, but protection is not complete. This protocol seems less effective for controlling nausea, although this is a subjective symptom which is difficult to assess and not routinely measured in clinical trials.

PALABRAS CLAVE
Emesis;
Vómitos;
Antieméticos;
Quimioterapia;
Náuseas;
Protocolos

Análisis de la efectividad de un protocolo de antiemesis implantado en la Unidad de Oncología

Resumen

Objetivo: Analizar la efectividad de un protocolo antiemético en pacientes que reciben quimioterapia.

Método: Estudio prospectivo en pacientes con tumores sólidos con quimioterapia en el hospital de día de Oncología entre enero 2006-2007.

Se realizó una revisión bibliográfica analizando las recomendaciones de guías de práctica clínica. Se calculó el potencial emetógeno según nivel Hesketh (NH), estableciendo la premedicación antiemética de cada esquema. Se evaluó la efectividad de un protocolo antiemético mediante una encuesta como método de medida de episodios eméticos y náuseas en fase aguda y retardada.

Resultados: Ciento setenta y dos pacientes cumplimentaron la encuesta, 13,4%vomitaron en fase aguda y 16,9% en retardada, mediana número de veces 2 (1-8) y 1 (1-5) respectivamente. Con esquemas NH 4-5 18,5% experimentaron vómitos en fase aguda y 20,2% en retardada; náuseas en fase aguda 46% y 38,4% en retardada. El control de vómitos en pacientes con esquemas NH = 1-3 fue del 100% en fase aguda y de 91,7% en retardada; notificaron náuseas un 27% en fase aguda y 31%en retardada. Los factores que más contribuyeron a la presencia de vómitos y náuseas fueron potencial emetógeno ($p < 0,05$), vómitos en ciclo anterior ($p < 0,05$) y edad < 50 ($p < 0,002$).

Discusión: La pauta propuesta es eficaz en el control de vómitos para esquemas NH = −3. En esquemas altamente emetógenos, el protocolo antiemético es también eficaz aunque la protección no es completa. Este protocolo parece no ser tan efectivo en el control de náuseas, aunque éste es un síntoma subjetivo de valoración compleja que no se mide de forma sistemática en ensayos clínicos.

Introduction

Nausea and vomiting caused by chemotherapy treatment are two of the side effects that cause the most worry and discomfort in cancer patients. They occur in up to 70%-80% of patients who receive chemotherapy and greatly affect quality of life. In some cases, these symptoms force the postponement, change or suspension of treatment due to complications such as dehydration, electrolyte imbalance, etc.[1]

Although nausea and vomiting often occur at the same time, they are not always associated. Nausea refers to the unpleasant sensation in the back of the throat and stomach that can cause vomiting. Vomiting is strong contractions of the stomach muscles that cause the contents of the stomach to rise and exit through the mouth, both in the presence of nausea and in its absence.

Various types of chemotherapy-induced emesis are typically identified: acute emesis (AE), nausea and vomiting appearing in the first 24 hours after administration of chemotherapy; delayed emesis (DE), nausea and vomiting occurring after this period of time, in the following 6-7 days after administration of treatment; anticipatory emesis, nausea and vomiting prior to receiving chemotherapy in patients who have already received at least one previous cycle of treatment.[2]

Not all cytostatics have the same emetogenic potential, so much so that in the absence of antiemetic prophylaxis, over 90%of patients receiving cisplatin develop nausea and vomiting one to two hours after receiving chemotherapy, with the appearance of a second peak 48 to 72 hours later. Agents other than cisplatin, such as cyclophosphamide, carboplatin and anthrcyclines may also cause DE.[3-5]

The risk of developing nausea and vomiting after chemotherapy depends on several factors. They include sex, age, cystostatic dose, number of cycles received and history of alcohol consumption. Of all the known predictors however, it is the emetogenic potential of the chemotherapy regimen to be administered that should be considered the main risk factor when starting antiemetic therapy.[6]

The goal of treatment for nausea and vomiting induced by chemotherapy is, undoubtedly, the complete elimination of these symptoms, which is often very difficult to achieve. The ultimate goal is to achieve the greatest possible improvement in patient quality of life.[7]

Various response criteria are used to assess the emetic episodes. The most recent clinical trials use the term "complete response" for the absence of emetic episodes and the non-use of rescue treatment, "full protection" when at the same time there is no significant nausea and "total control" when there are no emetic episodes or nausea while at the same time employing no rescue medication.[8]

The best strategy for treatment of vomiting is prevention. This should begin with the first chemotherapy cycle since, once vomiting occurs, it is more difficult to control. Its effective treatment reduces not only patient morbidity but also the possible medical complications that may arise from repeated vomiting. This can also prevent premature withdrawal from treatment.

Although the incorporation of new drugs in the last decade has dramatically altered the prevention of nausea and vomiting, in many cases it is still an unsolved problem that is underestimated by various health professionals who treat these patients. However, nausea and vomiting caused by chemotherapy, along with death, often cause the most concern in patients, with no change in the perception of these events despite the introduction of highly effective drugs.[9,10]

We must keep in mind that approximately one of every three patients who undergo chemotherapy still experience vomiting at some point in treatment despite the progress made in the last decade.[11] Several authors have demonstrated the synergistic effect of the association of 5-HT3 antagonists and corticosteroids, both for vomiting as well as acute-phase nausea induced by both high and moderately emetogenic chemotherapy. Complete protection achieved with this regimen is around 70%-90%. The results obtained compared with the delayed phase are significantly worse, showing the low value of 5-HT3 in highly emetogenic chemotherapy (20%-22%). With moderately emetogenic chemotherapy regimens and treatment with corticosteroid plus metoclopramide or antiserotoninergic, a protection of around 50% is achieved in the delayed phase.[12,13]

The purpose of this study was to prospectively evaluate the effectiveness of an antiemetic protocol implemented in patients undergoing chemotherapy.

Methods

A literature review was conducted to analyse the recommendations in the various currently available clinical practice guidelines: American Society of Clinical Oncology (ASCO),[3] National Comprehensive Cancer Network (NCCN)[4] and American Society of Health-System Pharmacists (ASHP).[5]

The emetogenic potential of all chemotherapy regimens was calculated using the classification proposed by Hesketh,[14,15] which estimates the frequency of emesis expressed as a percentage when prophylaxis is not administered and categorises the cytostatics into five groups according to their emetogenic potential. For drug combinations, it establishes that those with an NH 1 Hesketh level do not contribute to the emetogenicity of the regimen. The addition of one of more NH 2 drugs increases the emetogenicity of the combination to a greater degree than the drug plus emetogenic of the combination. The addition of NH 3 or 4 drugs increases the emetogenicity of the combination by one level for each drug.

As stated in the clinical practice guidelines reviewed, the regimen that was followed for the decision regarding antiemetic treatment was as follows:

- NH 1: no need for prevention either in the acute or the delayed phase. If not controlled, treatment would proceed to that proposed for NH 2 in the acute and delayed phase respectively.
- NH 2: 8-20 mg dexamethasone intravenously (IV) in the acute phase and nothing in the delayed phase. If not controlled, treatment would proceed to that proposed for NH 3 in the acute and delayed phase respectively.
- NH 3: 8-20 mg IV dexamethasone and 8 mg IV ondansetron in the acute phase and 4-8 mg oral dexamethasone every 12 hours for 2 days. If not controlled, treatment would proceed to that proposed for NH 4 in the acute and delayed phase respectively.
- NH 4/5: 8-20 mg IV dexamethasone and 8 mg IV ondansetron in the acute phase and 4-8 mg oral dexamethasone every 12 hours for 3 days. In highly emetogenic platinum-based regimens, 8 mg oral ondansetron every 12 hours for 3 days is added to control the delayed phase.

For rescue therapy after treatment failure, 10-20 mg oral or IV metoclopramide every 6 hours is proposed and, if it does not abate, 0.5-2 mg oral or subcutaneous haloperidol every 8-12 hours. To control anticipatory emesis, treatment with a short-acting benzodiazepine, such as lorazepam, is proposed.

Tables 1-3 show the optimisation proposal, accepted by clinicians in 100% of the protocols, carried out according to the anatomical location of the tumour.

Once the antiemetic protocol was launched, the pharmacy department designed a survey, previously approved at the pharmacy and therapeutics committee, to evaluate its effectiveness (Figure 1).

We performed a prospective study that included patients with solid tumours who received chemotherapy in the Oncology Day Hospital during the period between January 2006 and January 2007. Inclusion criteria for patients were: histopathological diagnosis of cancer at any stage, treatment with IV chemotherapy, having received at least one treatment cycle and the ability to provide informed consent for participating in this study. Patients younger than 18 years of age were excluded as well as those that had received non-antineoplastic therapy as concomitant IV treatment.

The following independent variables were recorded from the medical history and from the survey: demographic data, susceptibility to vomiting and/or nausea (vomiting in the previous cycle, history of vomiting during pregnancy and

Table 1 Proposed optimisation of antiemetic treatment for gastrointestinal cancer

Gastrointestinal cancer					
TTT regimen	**Hesketh level**	**Acute emesis TTT**		**Delayed emesis TTT**	
		Current	**Proposed**	**Current**	**Proposed**
Gemcitabine 1.250 mg/ m^2 d 1 and 8 every 21 days 5-FU 225 mg/ m^2/ d inf. continue 6 weeks 5-FU 425 mg/ m^2 d 1-5 every 21 days (Mayo Clinic) Capecitabine 1,250 mg/ m^2/12 hx 14 d	2			Not required	
Irinotecan 150 mg/ m^2+5-FU 400 mg/ m^2 d 1 followed by 5-FU 2,400 mg/ m^2 inf. 48 h every 14 d (modified FOLFIRI)	4	DXM 10-20 mg IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/12x8hx2 d	DXM 4-8 mg oral/ 12 h x 3-4 d started after 24 h from CT
Cetuximab 400 mg/m^2 1st dose and follow with 250 mg/ m^2 weekly+modified FOLFIRI					
Oxaliplatin 85 mg/m^2+5-FU 400 mg/ m^2 d 1 followed by 5-FU 2400 mg/ m^2 inf. 48 h every 14 d (modified FOLFOX 4) Oxaliplatin 85 mg/m^2 d 1+capecitabine 850 mg/m^2/12 hx14 d every 21 d (xelox)		DXM 10-20 mg IV+ondansetron 8 mg IV			DXM 4-8 mg oral/ 12 hx3-4 d started after 24 h from CT
Cisplatin 75 mg/ m^2 d 1+5-FU 1.000 mg/ m^2/d inf. continued for 96 h every 28 d (Al Sarraf regimen)	5	DXM 20 mg IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8mg oral/8 hx3 d	
Epirubicin 50 mg/ m^2+cisplatin 60 mg/ m^2+5-FU 200 mg/ m^2/d inf. continued for 21 d, every 21 d					DXM 4-8 mg oral/ 12 hx3-4 d+ ondansetron 8 mg/12 hx3d oral

CT indicates chemotherapy; d, days; DXM, dexamethasone; inf., infusion; IV, intravenously; TTT, treatment.

kinetosis), anatomical location of tumour, chemotherapy regimens received, compliance with the antiemetic protocol and emetogenic potential of the treatment regimen received. The presence of vomiting and nausea in the acute and delayed phases was recorded as dependent variables.

The staff of the Oncology day hospital was in charge of randomly including patients in the study and explaining the reason for the survey as well as giving the necessary instructions for completing the survey. The patient filled out the survey at home and returned it the following cycle. In the survey, the patient had to indicate each day for days 1-5 if they had vomited and/or experienced nausea and how many times or days it lasted, as well as the need for rescue medication.

Statistical analysis of data was performed using SPSS® version 14.0. For the descriptive statistics, a frequency distribution was performed for the study's categorical variables as well as measurements of the central tendency and dispersion for the quantitative variables. In the bivariate analysis, for each categorical variable of interest the existence of association was determined between the respective independent variable and the four dependent variables of the study, by means of the Mantel-Haenszel chi-square statistical significance test. The magnitude of the association was calculated using the odds ratio (OR) and assessing the precision of the estimate using the 95%CI. To investigate the simultaneous effect of the independent variables as well as compare the various groups, we used

Table 2 Proposed optimisation of antiemetic treatment for breast cancer

Breast cancer					
TTT regimen	**Hesketh level**	**Acute emesis TTT**		**Delayed emesis TTT**	
		Current	**Proposed**	**Current**	**Proposed**
Trastuzumab 8 mg/kg (loading dose) follow with 6 mg/ kg every 21d Trastuzumab 4 mg/ kg (loading dose) and follow with 2 mg/ kg/ week	1	Not required		Not required	
Vinorelbine 30 mg/ m^2 d 1 and 8 every 21 d Vinorelbine 30 mg/ m^2 d 1 and 8 every 21 d+trastuzumab 4 mg/ kg (loading dose) and follow with 2 mg/ kg/ week					
Gemcitabine 1,000 mg/ m^2 d 1 and 8 every 21 d		Not required			
Docetaxel 35 mg/m^2 d 1 every week		Ondansetron 8 mg IV		Not required	
Docetaxel 100 mg/m^2 d 1 every 21 d		DXM 8 mg IV+ ondansetron 8 mg IV		Ondansetron 8 mg oral/12 hx2 d	Not required
Paclitaxel 80 mg/m^2 d 1 every week		DXM 20 mg IV+ ondansetron 8 mg IV		Ondansetron 8 mg oral/12 hx2 d	Not required
Paclitaxel 175 mg/ m^2 d 1 every 21 d		Ondansetron 8 mg IV		Not required	
Trastuzumab 8 mg/kg (loading dose) and follow with 6 mg/kg+ docetaxel 100 mg/m^2 d 1 every 21 d	2	DXM 8 mg IV+ ondansetron 8 mg IV	DXM 10-20 mg IV	Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/ 12 hx2 days	
Trastuzumab 4 mg/ kg (loading dose) and follow with 2 mg/kg+ paclitaxel 80 mg/m^2 d 1 every week		Ondansetron 8 mg IV		Not required	
Liposomal doxorubicin 50 mg/m^2 every 28 d Epirubicin 100 mg/ m^2 every 21 dx3 cycles followed by paclitaxel 225 mg/m^2 every 21 dx3 (NH 3 the first 3 cycles)					
Liposomal doxorubicin 50 mg/ m^2 d 1 every 21 d	3	DXM 20 mg IV+ ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/8 hx3 days	DXM 4-8 mg oral/ 2 hx2 days started 1 after 24 h from CT
Docetaxel 75 mg/m^2 d 1+capecitabine 1,250 mg/ m^2/12 hx14 d every 21 d					
Doxorubicin 60 mg/m^2 d 1+cyclophosphamide 600 mg/ m^2 d 1 every 21 dx4 cycles followed by paclitaxel 175 mg/m^2 every 21 dx4 (NH 4 the first 4 cycles)					

Table 2 *(continued)*

Breast cancer					
TTT regimen	**Hesketh level**	**Acute emesis TTT**		**Delayed emesis TTT**	
		Current	**Proposed**	**Current**	**Proposed**
Epirubicin 100 mg/ m^2 d 1+cyclophosphamide 600 mg/ m^2 d 1 every 21 d	4	DXM 20 mg IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/8 hx3d	DXM 4-8 mg oral/ 12 hx3-4 days started after 24 h from CT
Cyclophosphamide 600 mg/ m^2 d 1+methotrexate 40 mg/m^2 d 1 and 8+5-FU 600 mg/m^2 d 1 and 8 every 28 d				Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/8 hx3 d	DXM 4-8 mg oral/ 12 hx3-4 d started after 24 h from CT
Doxorubicin 60 mg/m^2 d 1+docetaxel 60 mg/m^2 d 1 every 21 d	4	DXM 20 mg IV+ ondansetron 8 mg IV			
Epirubicin 75 mg/ m^2 d 1+docetaxel 75 mg/ m^2 d 1 every 21 d					
Doxorubicin 60 mg/m^2+paclitaxel 175 mg/ m^2 every 21 d				Ondansetron 8 mg oral/12 hx2d	DXM 4-8 mg oral/ 12 hx3-4 days started after 24 h from CT
Epirubicin 90 mg/ m^2+paclitaxel 175 mg/ m^2 every 21 d					
5-FU 500 mg/ m^2+doxorubicin 50 mg/ m^2+cyclophosphamide 500 mg/ m^2 every 21 d		DXM 20 mg IV+ ondansetron 8 mg IV			
5-FU 600 mg/ m^2+epirubicin 90 mg/ m^2+cyclophosphamide 600 mg/ m^2 every 21 d		Ondansetron 8 mg IV	DXM 10 mg IV+ ondansetron 8mg IV		
Trastuzumab 4 mg/kg (loading dose) and follow with 2 mg/kg/ week+paclitaxel 80 mg/m^2 d 1, 8, and 15+carboplatin AUC 2 d 1, 8, and 15 each 21 d	5			Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/ 8 hx3d	DXM 4-8 mg oral/ 12 hx3-4 days started after 24 h from CT

CT indicates chemotherapy; d, days; DXM, dexamethasone; IV, intravenously; NH, nivel Hesketh; TTT, treatment.

logistic regression in the multivariate analysis. The statistical criteria for acceptance of variables in the model was statistical significance at $P<.05$ and an exit criteria of $P>.10$. The Forward-Wald method was used for selecting predictive variables.

Results

Intravenous chemotherapy was administered to 554 patients during the study period. A total of 172 surveys were completed, not counting the total number of surveys distributed. The gender distribution was 139 women and 33 men with a median age of 55 years (range 49, 31-80). Table 4 shows the patient profiles.

Seventy-two percent of the chemotherapy regimens administered were highly emetogenic (NH 4-5) while the remaining 28% were classified as low-moderately emetogenic (NH 1-3). Figure 2 shows the regimens used and the NH assigned to each one.

Tables 5-7 list the results obtained for vomiting and nausea in the acute and delayed phases as well as the degree of statistical significance achieved for each independent variable (bivariate analysis).

Generally, 13.4%of the patients vomited in the acute phase and 16.9%vomited in the delayed phase with a median occurrence of 2 (1-8) and 1 (1-5) episodes respectively with the antiemetic protocol implemented. The incidence of nausea was 40.7%in the acute phase and 47.1%in the delayed phase with a median occurrence of 4 episodes (1-10). Also, of

Table 3 Proposed optimisation of antiemetic treatment for lung cancer

Lung cancer					
TTT regimen	**Hesketh level**	**Acute emesis TTT**		**Delayed emesis TTT**	
		Current	**Proposed**	**Current**	**Proposed**
Gemcitabine 1000 mg/ m^2 d 1 and 8+vinorelbine 25 mg/m^2 d 1 and 8 every 21 d	2	DXM 8 mg IV+ ondansetron 8 mg IV	DXM10-20 mg IV	Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/8 hx2d	Not required
Gemcitabine 2500 mg/ m^2+ irinotecan 150 mg/ m^2 every 15 d	5	DXM 20 mg IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/8 hx2d	DXM 4-8 mg oral/ 12 hx3-4 d started after 24 h from CT
Docetaxel 75 mg/m^2+carboplatin AUC=5 every 21 d		DXM 20 mg IV+ondansetron tron 8 mg IV	Ondansetron 8 mg IV+DXM 8 mg/ 12 h previous day	Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/8 hx2d Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/8 hx3d	DXM 4-8 mg oral/ 12 hx3-4 d started after 24 h from CT+ondansetron 8 mg/12 hx3 d
Docetaxel 75 mg/m^2+cisplatin 75 mg/ m^2 every 21 d					
Paclitaxel 175 mg/m^2+carboplatin AUC=5 every 21 d		DXM 20 mg IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/ 8 hx2d	DXM 4-8 mg oral/ 12 hx3-4 d started after 24 h from CT+ondansetron 8 mg/12 hx3 days
Paclitaxel 80 mg/m^2+carboplatin AUC=2 every 7 d		DXM 10 mg IV in 1st admin and after 4 mg	DXM 10 mg IV	Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/8 hx2d	DXM 4-8 mg oral/ 12 hx3-4 d started after 24 h from CT+ondansetron 8 mg/12 h x 3d
Paclitaxel 175 mg/m^2+cisplatin 80 mg/m^2 every 21 d		DXM 20 mg IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/8 hx2d	DXM 4-8 mg oral/ 12 hx3-4 d started after 24 h from CT+ondansetron 8 mg/12 hx3d
Carboplatin AUC=6 d 1+etoposid 100 mg/ m^2 d 1-3 every 21 d	2 days 2 and 3	DXM 4 mg IV+ondansetron 8 mg IV	DXM 20 mg IV	Not required	
	5 day 1	DXM 20 mg IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/ 12 hx3 d	DXM 4-8 mg oral/ 12 hx3-4 d started after 24 h from CT+ondansetron 8 mg/12 hx3 days
Cisplatin 80 mg/m^2 d 1+etoposid 100 mg/ m^2 d 1-3 every 21 d	2 days 2 and 3	DXM 4 mg IV+ondansetron 8 mg IV	DXM 20 mg IV	Not required	
	5 day 1	DXM 20 mg IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/ 12 hx3d	DXM 4-8 mg oral/12hx3-4 d started after 24 h from CT+ondansetron 8 mg/12 hx3d

Table 3 *(continued)*

Lung cancer					
TTT regimen	**Hesketh level**	**Acute emesis TTT**		**Delayed emesis TTT**	
		Current	**Proposed**	**Current**	**Proposed**
Gemcitabine 1000 mg/ m^2 d 1 and 8+carboplatin AUC=5 every 21 d	2 day 8	Ondansetron 8 mg IV	DXM 20 mg IV	Not required	
	5 day 1	DXM 20 IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/ 12 hx2d	DXM 4-8 mg oral/ 2 hx3-4 d started 1 after 24 h from CT+ondansetron 8 mg/12 hx3 d
Gemcitabine 1250 mg/ m^2 d 1 and 8+cisplatino 100 mg/m^2 every 21 d	2 day 8	Ondansetron 8 mg IV	DXM 20 mg IV	Ondansetron 8 mg oral at 4 and 8 h from CT and after 8 mg oral/8 hx3d	Not required
	5 day 1	DXM 20 mg IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT and after 8 mg oral/8 hx3 d	DXM 4-8 mg oral/ 2 hx3-4 d started 1 after 24 h from CT+ondansetron 8 mg/12 hx3d
Cisplatin 100 mg/ m^2 d 1+vinorelbine 30 mg/ m^2 d 1, 8 and 15 every 21 d	1 days 8 and 15	Ondansetron 8 mg IV	Not required	Not required	
	5 day 1	DXM 20 mg IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/8 hx3 d	DXM 4-8 mg oral/ 12 hx3-4 d started after 24 h from CT+ondansetron 8 mg/12 hx3 d
Vinorelbine 25 mg/ m^2 d 1 and 8+carboplatin AUC=5 every 21 d	1 day 8	Ondansetron 8 mg IV	Not required	Not required	
	5 day 1	DXM 8 mg IV+ondansetron 8 mg IV		Ondansetron 8 mg oral at 4 and 8 h from CT followed by 8 mg oral/8 hx3 d	DXM 4-8 mg oral/ 12 hx3-4 d started after 24 h from CT+ondansetron 8 mg/12 hx3d

CT indicates chemotherapy; d, days; DXM, dexamethasone; IV, intravenously; TTT: treatment.

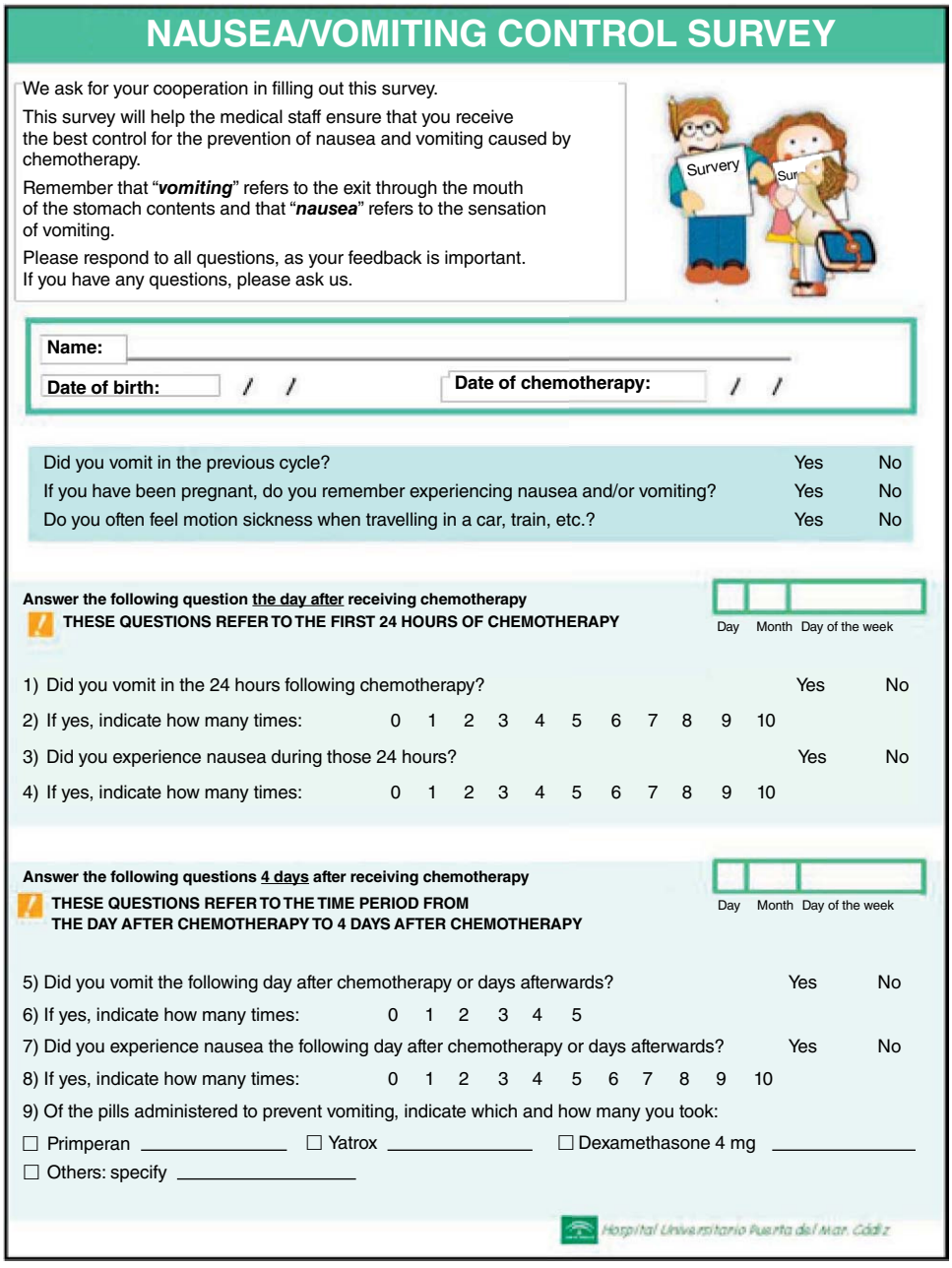
those patients that vomited in the delayed phase, 17 had also suffered vomiting in the acute phase (89.5%).

We observed a relationship between the emetogenic potential of the chemotherapy regimen and probability of emesis both in the acute and delayed phases. The probability of AE in highly emetogenic regimens is 10.4 times higher (Confidence Interval [CI] 95%1.4-79.9, P=.006) than in low-moderately emetogenic regimens. There is also a correlation in the delayed phase between the emetogenic level of the chemotherapy regimen and the presence of vomiting and nausea, OR 2.8 (CI 95%, 0.9-8.4, P=.06) and 2.5 (CI 95%, 1.2-5, P=.01) respectively.

Fifteen percent of the patients did not meet the prescribed antiemetic protocol with 26.9%(7/26) of them vomiting. Two patients vomited in both the acute and delayed phases, three only in the acute phase and two only in the delayed phase although this did not reach statistical significance in the bivariate analysis.

Seventy-four patients had one or more of the predisposing factors for presenting post-chemotherapy emesis (vomiting in the previous cycle, history of kinetosis and hypermesis). Vomiting in the previous cycle was the most important predictive factor and the only one that achieved statistical significance, since 78% of the patients who vomited in the acute phase and 72.4%of the patients who vomited in the delayed phase had also vomited in the previous cycle. A low proportion (5/98) of the remaining patients (98/172) presented vomiting; almost all were young women and with highly emetogenic treatment regimens.

Table 8 shows the results of the multivariate analysis where we can see that the emetogenic potential of the chemotherapy regimen to be administered and having vomited in the previous cycle are two of the factors that most contribute to the presence of vomiting and nausea in the acute phase (P<.05). The age of the patients, being under 50 years, was also a negative predictive factor for the



NAUSEA/VOMITING CONTROL SURVEY

We ask for your cooperation in filling out this survey.

This survey will help the medical staff ensure that you receive the best control for the prevention of nausea and vomiting caused by chemotherapy.

Remember that "***vomiting***" refers to the exit through the mouth of the stomach contents and that "***nausea***" refers to the sensation of vomiting.

Please respond to all questions, as your feedback is important. If you have any questions, please ask us.

Survery

Name:

Date of birth: / /

Date of chemotherapy: / /

Did you vomit in the previous cycle?	Yes	No
If you have been pregnant, do you remember experiencing nausea and/or vomiting?	Yes	No
Do you often feel motion sickness when travelling in a car, train, etc.?	Yes	No

Answer the following question the day after receiving chemotherapy

THESE QUESTIONS REFER TO THE FIRST 24 HOURS OF CHEMOTHERAPY

Day Month Day of the week

1) Did you vomit in the 24 hours following chemotherapy?	Yes	No
2) If yes, indicate how many times: 0 1 2 3 4 5 6 7 8 9 10		
3) Did you experience nausea during those 24 hours?	Yes	No
4) If yes, indicate how many times: 0 1 2 3 4 5 6 7 8 9 10		

Answer the following questions 4 days after receiving chemotherapy

THESE QUESTIONS REFER TO THE TIME PERIOD FROM THE DAY AFTER CHEMOTHERAPY TO 4 DAYS AFTER CHEMOTHERAPY

Day Month Day of the week

5) Did you vomit the following day after chemotherapy or days afterwards?	Yes	No
6) If yes, indicate how many times: 0 1 2 3 4 5		
7) Did you experience nausea the following day after chemotherapy or days afterwards?	Yes	No
8) If yes, indicate how many times: 0 1 2 3 4 5 6 7 8 9 10		

9) Of the pills administered to prevent vomiting, indicate which and how many you took:

☐ Primperan _____ ☐ Yatrox _____ ☐ Dexamethasone 4 mg _____

☐ Others: specify _____

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Figure 1 Survey for evaluating effectiveness of antiemetic protocol.

presence of nausea in the acute phase with an OR 3.1 (CI 95%1.5-6.2, *P*=.002). In the delayed phase, having vomited in the previous cycle had a statistically significant correlation both for the presence of vomiting and for nausea. The emetogenic potential of the regimen only had a statistically significant correlation for nausea.

Furthermore, approximately half of the patients who received highly emetogenic chemotherapy regimens (NH 4-5) reported nausea both in the acute and delayed phases.

The control of vomiting in patients with low-moderately emetogenic treatment regimens was complete in the acute phase and 91.7%in the delayed phase while 27%had nausea in the acute phase and 31%in the delayed phase.

Discussion

Choosing the most appropriate antiemetic regimen is based primarily on the emetogenic potential of the regimen to be administered, although the individual risk factors of each patient may lead to variations in the dosage and even in the choice of drug. These factors include: age, sex, stress, depression and alcohol consumption. In particular, younger patients (<50 years), females, those with low alcohol consumption (<100 g/ day) and those with a history of vomiting during pregnancy and for motion sickness (kinetosis) are more likely to experience vomiting.[16] However, the most important predictor factor is having

Table 4 Patient characteristics

	Patients, %	No. patients (n=172)
Sex		
Women	80.8	139
Men	19.2	33
Age		
≤50 years	34.9	60
>50 years	65.1	112
Predictor factors		
Kinetosis	14	24
Emesis gravidarum	25	43
Previous cycle emesis	22.7	39
Diagnostic		129
Breast cancer	75	14
Gastrointestinal cancer	8.1	9
Lung cancer	5.2	20
Others	11.6	
Hesketh level		
1	3.5	6
2	17.4	30
3	7	12
4	43.6	75
5	28.5	49
Completion of protocol		
Yes	84.9	146
No	15.1	26

nausea and vomiting in previous cycles.[17] This has also been verified in our study except in young patients (<50 years) where we observed a lower incidence of vomiting in the acute phase. Although the incidence of acute and delayed emesis was greater in women than in men, this difference was not statistically significant. This is probably due to the lack of homogeneity that exists in terms of the proportion of patients older than 50 years and who are female, a limitation that we accepted.

There are numerous published studies examining post-chemotherapy emetic episodes although fewer examine nausea. Not all of these studies publish the results using the criteria of standardised response (complete response, total protection and total control) that evaluate nausea using an visual analogue scale (VAS) or a descriptive scale, which makes it much harder to compare the results.[8] Although most clinical trials tend to use the term "complete response" to refer to emetic episodes and the need for rescue medication without assessing the incidence of nausea, other studies define their own response criteria such as incidence of emetic episodes, greater response and lesser response. In national studies similar to ours, such as the one carried out on patients with gynaecological tumours[18] treated with chemotherapy, complete protection (absence of vomiting and nausea) was achieved in the acute phase in 87.3% of the patients with moderately emetogenic chemotherapy without cisplatin, decreasing to 78.4% in those regimens that include cisplatin. However, as expected, the results achieved in the delayed phase are somewhat lower since complete protection is achieved in 69.3% of the patients with moderately emetogenic chemotherapy and 26.1% in those that receive cisplatin. It is difficult to compare these results with ours, firstly because they analyse global cycle data and not individual patient response, and secondly because they use different response variables from ours. In our study, due to the lack of assessment of the appearance of nausea by means of the validated VAS or another descriptive scale, and the subjective value of them, we have conducted a separate tracking of the emetic episodes and nausea both in the acute and delayed phases, justifying the non-use of standardised response criteria.

Other current studies show that the incidence of post-chemotherapy nausea and vomiting in patients who receive antiemetic treatment considered effective is significant even in the first 24 hours, both in observational studies based on real life[10,19] and in controlled clinical trials.[20,21] Between 13%-32% of patients experienced emesis or a need for rescue treatment during the acute phase and more than 35% experienced nausea. The incidence of nausea and vomiting in the delayed phase in routine practice in patients treated with moderately to highly emetogenic chemotherapy and appropriate antiemetic prophylaxis is 52%-60% for nausea and 28%-50% for vomiting.[10,22] These data do not highly divers from those found in our study in the acute phase. With the antiemetic protocol implemented, the incidence of vomiting was 86.6% among patients. Nevertheless, the control of vomiting in the delayed phase was much greater in our case since only 17% of the patients needed a rescue treatment. Perhaps this difference lies in the low number of patients treated with cisplatin, considered the standard drug with the highest emetogenicity, who completed the survey undervaluing vomiting in the delayed phase.

An observational study published by Grunberg et al,[10] which included 298 patients, showed that of the 32% of patients who suffered vomiting in the delayed phase and 54% of those who suffered nausea, 23% and 24% respectively, occurred in the absence of nausea and vomiting in the acute phase. In our study, of the 29 patients (16.9%) who vomited in the delayed phase, almost half occurred in the absence of vomiting in the acute phase (12/29).

Another observational study published[23] in 2008 that included 102 patients who received antiemetic treatment considered effective, determined the incidence of nausea and vomiting due to chemotherapy in routine practice. Some 15.7% of the patients vomited in the acute phase in the first cycle and 14.7% did so in the delayed phase. Nevertheless, the incidence of nausea is greater, 37.3% and 47.1% respectively, increasing in later cycles. These results reveal that while vomiting is well controlled, the same does not occur with nausea. We must again emphasise the similarity of our data with those reported in this study since in 40.7% and 47.1% of the patients, acute and delayed phase respectively, we were unable to control nausea.

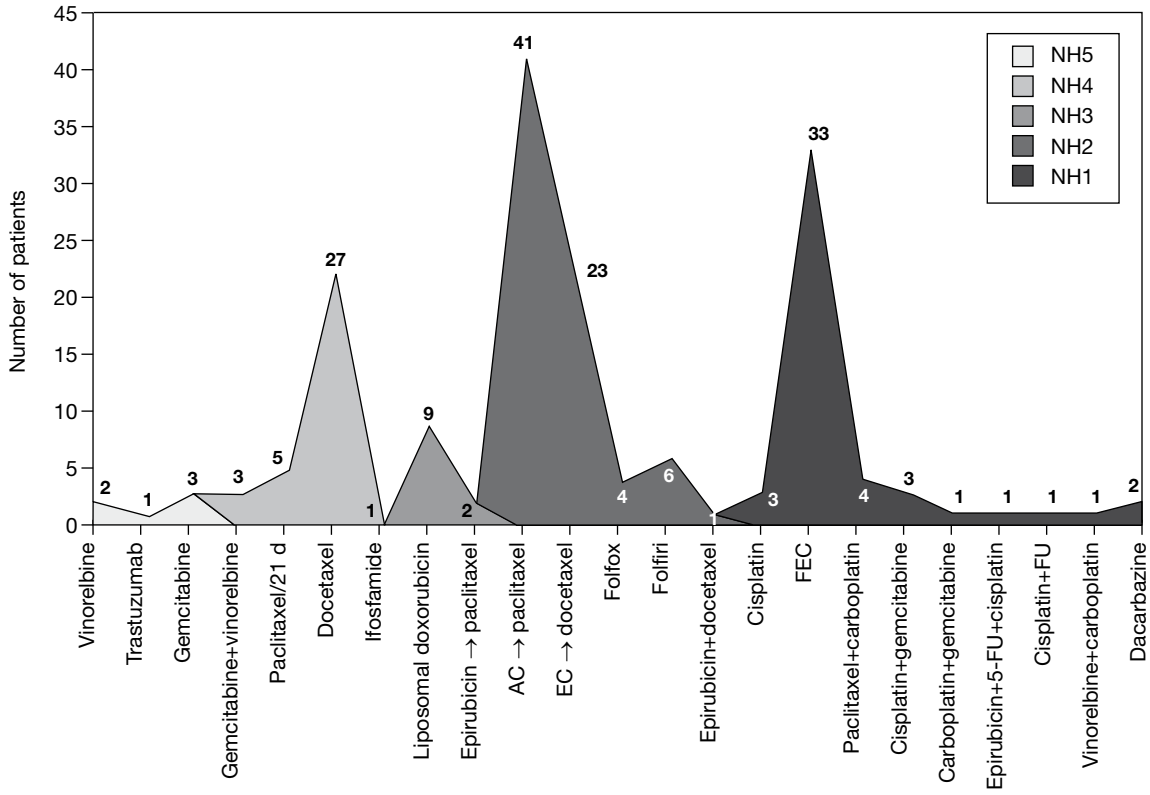

Figure 2 Patient distribution according to treatment regimens and Hesketh level. d indicates days; NH; nivel Hesketh.

Table 5 Emetic episodes in acute and delayed phase by patient subgroup

	Acute phase %(n)		Delayed phase %(n)	
	Vomiting	**Nausea**	**Vomiting**	**Nausea**
Sex				
Women	15.1% (21)	45.3% (63)	18% (25)	54% (75)
Men	6.1% (2)	21.2% (7)	12.1% (4)	18.2% (6)
Age				
≤50 years	10% (6)	56.7% (34)	21.7% (13)	60% (36)
>50 years	15.2%(17)	32.1%(36)	14.3%(16)	42.2%(45)
Predictor factors				
Kinetosis	29.2% (7)	62.5% (15)	25% (6)	58.3% (14)
Emesis gravidarum	23.3% (10)	55.8% (24)	23.3% (10)	67.4% (29)
Previous cycle emesis	46.2% (18)	66.7% (26)	53.8% (21)	76.9% (30)
Hesketh level				
1	–	–	–	–
2	–	30% (9)	6.7% (2)	36.7% (11)
3	–	33.3% (4)	16.7% (2)	33.3% (4)
4	18.7% (14)	49.3% (37)	20% (15)	54.7% (41)
5	18.4% (9)	40.8% (20)	20.4% (10)	51% (25)
Completion of protocol				
Yes	0.7% (1)	41.8% (61)	17.1% (25)	48.6% (71)
No	19.2% (5)	34.6% (9)	15.4% (4)	38.5% (10)

Table 6 Acute phase emesis. Bivariate analysis

	Vomiting		Nausea	
	OR (CI 95%)	*P*	OR (CI 95%)	*P*
Sex				
Men/ women	2.7 (0.6-12.4)	.17	3.1 (1.2-7.6)	.011
Age				
≤50/>50 years	1.6 (0.6-4.3)	.342	0.4 (0.2-0.7)	.002
Predictor factors				
Kinetosis	3.4 (1.2-9.4)	.014	2.8 (1.2-6.9)	.019
Emesis gravidarum	2.7 (1.1-6.7)	.028	2.3 (1.1-4.6)	.02
Previous cycle emesis	21.9 (7.3-65.5)	.000	4 (1.9-8.6)	.000
Hesketh level				
1-3/ 4-5	10.4 (1.4-79.9)	.006	2.3 (1.1-4.7)	.024
Completion of protocol				
No/ yes	0.6 (0.2-1.7)	.341	1.4 (0.6-3.2)	.493

CI indicates Confidence Interval; OR, odds ratio.

Table 7 Delayed phase emesis. Bivariate analysis

	Vomiting		Nausea	
	OR (CI 95%)	*P*	OR (CI 95%)	*P*
Sex				
Men/ women	1.6 (0.5-4.9)	.4	5.3 (2-13.6)	.000
Age				
≤50/>50 years	0.6 (0.3-1.3)	.2	0.4 (0.2-0.8)	.01
Predisposing factors				
Kinetosis	1.8 (0.6-5)	.2	1.7 (0.7-4)	.2
Emesis gravidarum	1.7 (0.7-4.1)	.2	3.1 (1.5-6.3)	.002
Previous cycle emesis	18.2 (7-47.2)	.000	5.3 (2.3-12.2)	.000
Hesketh level				
1-3/4-5	2.8 (0.9-8.4)	.06	2.5 (1.2-5)	.01
Completion of protocol				
No/yes	1.1 (0.4-3.6)	.8	1.5 (0.6-3.5)	.3

CI indicates Confidence Interval; OR, odds ratio.

Cisplatin is considered the most emetogenic drug by all clinical practice guidelines and is able to cause a biphasic emetic profile composed of an AE phase and a DE phase. When used in low doses (40-60 mg/ m^2), cisplatin-induced DE is rare, contrary to what occurs when the doses exceed 100-120 mg/ m^2. In two multicentric clinical trials that included more than 1000 patients who received cisplatin (dosage ≥70 mg/m^2) and prophylaxis based on 5-HT3 receptor antagonists and dexamethasone, between 44%-53% of the patients experienced emesis or the need for rescue treatment during the delayed phase.[20,21] In our study, three patients received cisplatin in monotherapy. One of them received 40 mg/ m^2 and the other two received 100 mg/ m^2. They did not vomit either in the acute nor delayed phase although they did experience nausea, which became more evident in the delayed phase. Additionally, five patients received cisplatin combined with other cytotoxic agents. Of these, two vomited in both the acute and the delayed

Table 8 Logistic regression model (multivariate analysis)

	Coefficient	*P*	OR	(CI 95%)
Vomiting in acute phase				
Previous cycle emesis	2.992	.000	19.9	(6.5-60.7)
Hesketh level				
1-3/4-5	2.102	.052	8.2	(1-68.4)
Vomiting in acute phase				
Age				
≤50/>50	1.121	.002	3.1	(1.5-6.2)
Hesketh level				
1-3/4-5	0.812	.043	2.3	(1-5)
Previous cycle emesis	1.269	.002	3.6	(1.6-7.9)
Vomiting in delayed phase				
Previous cycle emesis	2.903	.000	18.2	(7-47.3)
Nausea in delayed phase				
Hesketh level				
1-3/4-5	0.759	.049	2.1	(1-4.6)
Previous cycle emesis	1.698	.000	5.5	(2.3-13.1)

phases with the regimens that contained high doses of cisplatin (100 mg/m^2). Due to the low number of patients treated with cisplatin who completed the survey (8/172), it is difficult to make conclusions as to the actual incidence of vomiting in these patients or the effectiveness of our protocol. We also cannot make comparisons with those found in the literature.

Type S-3 serotonin receptors (5-HT3) are considered the most important mediators of post-chemotherapy emesis. However, other receptors, including D-2 dopaminergic, endorphinergic, and muscarinic-cholinergic, may also play a role in the transmission of afferent nerve stimuli of the emetic reflex arc. Recently, the substance P (neurokinin-1) has also been implicated in the transmission of emetic signals.[24] Clinical practice guidelines published after our study[17] now recommend a new drug for the antiemetic prophylaxis of highly emetogenic chemotherapy regimens that contain cisplatin. This new drug, Aprepitant, has a different mechanism since it acts as an antagonist of the neurokinin-1 receptors. At the time this study was carried out, this drug had not yet been requested by the pharmacy and therapy committee of our hospital. Currently, it has been included as a prophylactic antiemetic in those patients who receive highly emetogenic chemotherapy with cisplatin and anthracyclines and who are refractory to the protocol implemented in the hospital.

Even though there are studies on the efficacy and safety of Aprepitant,[13,21] we do not currently have conclusive information on the standard practices that should be followed in patients with platinum-based chemotherapy regimens for several days or chemotherapy regimens with radiotherapy.

There is controversy at present about the role of 5-HT$_3$ antagonists in the prevention of DE.[25] The results of a meta-analysis[26] show a slight reduction (4.6%) in the absolute proportion of patients in whom DE is controlled using these drugs, independently of antiemetic treatment received in the different clinical trials analysed. In fact, the American Society of Clinical Oncology, in their most recent clinical practice guideline,[27] does not recommend the combination of a 5-HT$_3$ antagonist with dexamethasone for the prevention of DE after highly emetogenic chemotherapy.

However, in our hospital we continue to use a combination of both drugs for preventing DE in regimens that contain platinum, possibly due to the fact that this type of emesis continues to be a problem that is far from being resolved. It may be also due to the use restrictions of Aprepitant in the pharmacotherapeutic guideline, which determines its use in those patients in whom there is no control of emesis with the proposed antiemetic protocol.

Nausea and vomiting induced by chemotherapy are adverse side effects that should be completely controlled in the majority of cancer patients. The objective should be to prevent its appearance rather than treating it with the aim of improving quality of life, avoiding complications and aiding in the completion of the chemotherapy. Despite significant progress in the control of emesis induced by chemotherapy, current antiemetic treatments do not protect all cancer patients from one of the most feared side effects. The available resources need to be optimised to ensure that no patient undergoing chemotherapy suffers from nausea or vomiting.

The results of our study cannot be extrapolated due to the low number of patients included, but it demonstrates the need for continuing work in updating the antiemetic protocol in order to increase the control of nausea and vomiting in all patients who receive chemotherapy and, thereby, preserve quality of life in these patients.

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References

1. National Comprehensive Cancer Network (NCCN) [Main webpage]. United States: Nausea and vomiting. Treatment guidelines for patients with cancer. Version IV.2007 [updated June, 2007; accessed 4 February, 2009]. Available from: http://www.nccn.org/patients/patient_gls/_spanish/pdf/NCCN_náuseas.pdf
2. Jordan K, Kasper C, Schmoll HJ. Chemotherapy-induced nausea and vomiting: current and new standards in the antiemetic prophylaxis and treatment. European Journal of Cancer. 2005;41:199-205.
3. Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW, et al. Recommendations for the use of antiemetics: evidence based, clinical practice guidelines. J Clin Oncol. 1999; 17:2971-94.
4. National Comprehensive Cancer Network (NCCN) [Main webpage]. United States: Antiemesis clinical practice guidelines in oncology. Version 2.2003 [updated June, 2005; accessed 4 July, 2008]. Available from: http://www.nccn.org/patients/patient_gls/_spanish/pdf/NCCN_náuseas.pdf

5. American Society of Health-System Pharmacists. ASHP. Therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health-Syst Pharm. 1999;56:729-64.
6. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC) [Main webpage]. Perugia Consensus Conference on Antiemetic Therapy. Antiemetic guidelines [updated version March, 2008; accessed 3 August, 2008]. Available from: http://data.memberclicks.com/site/mascc/MASCC_Guidelines_Update.pdf
7. Vera R, Martínez M, Salgado E, Láinez N, Illarramendi JJ, Albístur JJ. Tratamiento de la emesis inducida por quimioterapia. An Sist Sanit Navar. 2004;27:117-23.
8. Gralla R, Lichinitser M, Van der Vegt S, Sleeboom H, Mezger J, Peschel C, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Annals of Oncology. 2003;14:1570-7.
9. Aldaco F, Cervantes G, Torrecillas L, Cortés P, Valle AE. Evaluación y prevención de la emesis aguda y/o tardía asociada a quimioterapia: no todo es una receta de cocina. Gamo, Jan-Feb. 2007;6:16-23.
10. Grunberg S, Deuson R, Mavros P, Geling O, Hansen M, Cruciani G, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. Perception versus reality. Cancer. 2004;100:2261-8.
11. Ginés J, Sánchez A. Antieméticos y quimioterapia: evolución histórica y estudio comparativo de los antagonistas de la serotonina. Recomendaciones actuales. Farm Hosp. 2000;24:187-214.
12. Hesketh P. Chemotherapy-induced nausea and vomiting. N Engl J Med. 2008;358:2482-94.
13. Noguera A, Massó J, Codina C, Ribas J. Terapia antiemética de rescate y perspectivas de futuro en la prevención y tratamiento de los vómitos post-quimioterapia. Farm Hosp. 2002;26:340-9.
14. Hesketh PJ, Kris MG, Grünberg SM, Beck T, Hainsworth JD, Harker G, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol. 1997;15:103-9.
15. Hesketh PJ. Defining the emetogenicity of cancer chemotherapy regimens: relevance to clinical practice. Oncologist. 1999;4:191-6.
16. Tsavaris N, Kosmas C, Mylonakis N, Bacoyiannis C, Kalergis G, Vadiaka M, et al. Parameters that influence the outcome of nausea and emesis in cisplatin based chemotherapy. Anticancer Res. 2000;20:4777-84.
17. Roila F. Control of acute cisplatin-induced emesis over repeat courses of chemotherapy. Italian Group for Antiemetic Research. Oncology. 1996; 53(Suppl 1):65-72.
18. Arrizabalaga MJ, Ayerdi B, Sainz de Rozas C, García M, De Juan A, Ibarra O. Control de náuseas y vómitos, agudos y retardados, en pacientes con tumores ginecológico tratadas con quimioterapia. Farm Hosp. 1997;21:21-7.
19. Pérez JJ, Llopis MC, Casabo VG, Jiménez V. Factores de riesgo asociados con la emesis postquimioterapia en pacientes con cáncer de mama (II): análisis de la duración de la emesis. Farm Hosp. 2002;26:275-82.
20. Poli-Bigelli S, Rodriguez-Pereira J, Carides AD, Julie G, Eldridge K, Hipple A, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in latin America. Cancer. 2003;97:4112-9.
21. Hesketh PJ, Grunberg SM, Gralla RI, Warr DG, Roila F, De Wit R, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin. The aprepitant Protocol 052 Study Group. J Clin Oncol. 2003;21:4112-9.
22. Gómez-Raposo C, Feliú-Batle J, González-Barón M. Prevención y control de las náuseas y vómitos inducidos por quimioterapia. Med Clin. 2006;126:143-51.
23. Molassiotis A, Saunders MP, Valle J, Wilson G, Lorigan P, Levine E, et al. A prospective observacional study of chemotherapy-related nausea and vomiting in Soutine practice in a UK cancer centre. Support Care Cancer. 2008;16:201-8.
24. Martín M, López S. Tratamiento de la emesis inducida por citotóxicos. Psicooncología. 2004;1:131-6.
25. Geling G, Eicler HG. Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. J Clin Oncol. 2005;23:1289-94.
26. Cance Care Ontario Practice Guideline Initiative [Main webpage]. United States: use of 5-HT3 receptor antagonists in patient receiving moderately or highly emetogenic chemotherapy. Practice Guideline Report 12-3 [accessed 11 February, 2009]. Available from: http://www.cancercare.on.ca/pdf/pebc12_3f.pdf
27. Kris MG, Hesketh PJ, Somerfield M, Feyer P, Clark-Snow R, Koeller JM, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol. 2006;24:2932-47.