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Introduction

Chemotherapy-induced neutropenia entails a series of major complications in patients with cancer. The appearance of neutropenia is a dose-limiting and regime-limiting factor in the therapy with antineoplastic agents, seriously threatening the life of patients with cancer [1]. Furthermore, a decrease of the granulocytes is associated with a high incidence of infectious and febrile episodes, directly related to the seriousness and duration of the neutropenia [2-4]. The morbidity caused by these infectious processes implies a higher risk of complications in immunosuppressed patients and, consequently, an increase in the costs associated with the treatment of these patients [5 6]. In fact, infection is the most frequent cause of mortality and morbidity in patients with cancer submitted to a combined treatment with radiotherapy and chemotherapy [7-10].

Recently, colony-stimulating factors (G-CSF or GM-CSF) have been successfully used both as an adjunct to cytotoxic cancer chemotherapy to attenuate the associated fall in neutrophil count, and after chemotherapy to accelerate the recovery of the neutrophil count to normal levels [11]. However, the high cost associated with these types of pharmacological agents obtained by biotechnological methods, makes it necessary not only to assess their efficacy and safety, but also to carry out a study of the economic implications of their use in the treatment of patients with cancer. This was the initial objective of the present study. However, the absence of a significant casuistry in our hospital as far as the use of these agents is concerned, and the lack of knowledge of the costs arising from a neutropenic episode, led us to reconsider the study. We thus carried out a preliminary examination to evaluate the repercussions on the health-service economy of a neutropenic episode induced by chemotherapy or radiotherapy in the absence of any other (prophylactic) treatment.

Methods

A retrospective evaluation of clinical histories corresponding to admissions of patients with cancer and neutropenia was carried out during the period 1 January to 31 December 1991. Selection of the clinical histories was performed according to the following criteria:

- cancer was histologically confirmed in all patients;
- patients had been admitted because of a neutropenia induced by chemotherapy or radiotherapy;
- neutropenia was defined as an absolute neutrophil count of less than 10^9/l.

Individuals who had been admitted with a clinical picture of infection with fever but had neutrophil counts within the normal range (values higher than 10^9/l) were excluded from the study.

We made an estimate of the cost that the recovery of such patients involved for the health-care system

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Abstract
This article describes the economic and social impact of neutropenia induced by myelotoxic chemotherapy in patients with cancer during the period 1 January-31 December 1991. Neutropenia is a life-threatening complication of chemotherapy in patients with cancer. The episodes of fever and infections originating from neutropenia require hospitalization of the patient until the granulocyte levels are restored. The calculation of the economic cost was based on the following parameters: length of stay in hospital, analytical tests performed on the patient, type and cost of drug therapy administered, blood transfusions performed, health assistance received, cost of isolation and absence from work. The overall economic cost of neutropenia in patients with cancer reached 329,775 pesetas ($2,893). Cost of the health-care staff was the largest budget item in relation to the total health resources estimated.

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estimation, the following parameters were assessed: length of stay in hospital, analytical tests performed on the patient, type and cost of therapy administered, blood transfusions performed, health assistance received, cost of isolation, and absence from work of patients with life-threatening neutropenia. The overheads of the hospital (food, electricity, water, maintenance of materials and apparatus, *etc.*) were not included in the calculation of the total cost, since the objective of the present study was to evaluate the costs from the clinical point of view and the cost of these overheads is relatively constant for all patients in the hospital, irrespective of their pathology or the reason for their admission. The cost of a neutropenic episode was evaluated for each hospital admission during the period of study, independently of the patient admitted. Thus the data reported always refer to admissions and not to patients.

To evaluate the economic parameters the clinical histories were reviewed in order to complete a form with a summary of data which was designed to take into account the following points.

- Patient's data (name, sex and age).
- Characteristics of the neutropenia. The neutrophil count was determined on admission and the number of days spent by the patient in isolation was recorded, as was the number of days spent in hospital as a result of the neutropenia alone, *i.e.* until the neutrophil counts reached levels higher than 10^9/l.
- Analytical tests and blood transfusions. All of the laboratory tests to which the patient was submitted in order to follow the development of the neutropenia and to determine the pharmacological treatment required, were taken into account. The following procedures were recorded: blood and urine analyses, blood, urine, faeces and sputum cultures, antibiograms, determinations of biochemical parameters, proteinograms, coagulation-time determinations, cross-tests, radiographs, sonographs and gasometries. In addition the number and type of blood transfusions performed on each admission were recorded.
- Pharmacological treatment. The therapy applied, the doses prescribed and the duration of treatment were all recorded. From these data the total amount of drug administered for each hospital treatment was calculated.
- Health assistance. Note was taken of the number of staff forming the medical team attending the patient (doctors, nurses and nursing auxiliaries) as well as the mean time each of them dedicated to the patient during each period in hospital.

The figures published yearly by the Spanish Association of Clinical Biopathology (SACB), and specifically those of 1991 [12], were used to calculate the costs of the analytical tests performed on these patients at the hospital. It should be noted that, regardless of the known existing budget differences between the public and the private health services, the economic data we present here (based on those published by SACB) are approximate but close to real costs.

Drug expenditure was assessed from the pricelist available at the Pharmacy Service at the time the study was carried out. Due to the difficulty of calculating the cost of the medicaments administered once a bottle is opened to be administered to a patient, it is never returned or reused, the cost derived from the administration of solutions, syrups, creams or pomades was estimated according to the price per tube or bottle. The same criteria have been adopted by other authors when trying to evaluate the drug cost per patient [13]. The use of other medicaments was calculated on the basis of the unit doses prescribed daily (number of tablets, ampoules, vials, sachets, *etc.*). The pharmacological treatment administered during each period in hospital was recorded in the patient's records and for this reason we have assumed that the pharmaceutical costs are those arising from medical prescriptions.

The materials, disposables or systems used by the health-service staff for the preparation and/or administration of certain drugs were not included in the study of the economic costs. Nevertheless, the time required for the performance of these tasks was considered when calculating the mean time that each member of staff attended each patient during each period in hospital.

The costs derived from the care given by the health staff (doctors, nurses and auxiliary nursing staff) have been calculated from the total number of hours that the staff worked per week. For this calculation, we took into account the three different shifts the nursing staff worked: mornings (7 hours), evenings (7 hours) and nights (10 hours). Given that the doctors were only in attendance in the mornings (7 hours), we have also considered the costs of the on-call doctors who covered the rest of each 24-hour period.

The cost of isolation arose, fundamentally, from the intensive health care required by these patients, for whom extreme care in the maintenance of total asepsis was necessary to minimize the risk of complications. Isolation always makes it impossible to admit another patient with cancer in the same room. Thus, it was assumed that the health-service costs for such patients were twice as much as those for other types of patients who do not need to be in isolation.

The costs arising from the patient's absence from work were estimated, assuming an average period of 15 days of absence per patient, which was estimated from the fact that the average period in hospital was about 12 days. The calculation was based on an average wage of 3,500 pesetas ($31) per day.

The data on the average cost per admission and on the total annual costs (Tables 1-3) were calculated independently. The mean costs per admission were calculated by first evaluating each parameter per admission and then calculating the corresponding mean. The total annual costs were calculated from the overall annual balance of each one of the parameters studied. We particularly wanted to establish this difference in carrying out the calculations so as to make the annual costs more representative for each of the parameters and thus eliminate errors that are invariably associated with the use of mean values.

The total annual costs of the health-service personnel and of the absence from work (Table 3) have been calculated after taking into account the total period of time – 343 days – spent in hospital by the 29 admissions. Similarly, the total annual costs corresponding to the period of time spent in isolation

(Table 3).

The data obtained were compiled in a data base and studied by the dBASE III PLUS program to be transferred to the program SPSS/PC+, V.3.1, for statistical analysis.

Results

During the year 1991, 197 hospital discharges were recorded at the Oncology Ward. Of these, 29 (15%) corresponded with admissions due solely to clinical manifestations caused by neutropenia in patients with cancer. 16 patients [7 females (44%) and 9 males (56%)] accounted for these 29 admissions. Their ages ranged from 16 to 76 years (mean age: 47.8 ± 21.2 years). From the sample population, 1 patient needed 2 admissions, 3 patients 3 admissions during the same period and 1 required admission 7 times. The 11 (69%) remaining patients were admitted once during the period studied.

The mean neutrophil count at the time of admission was 0.42 ± 0.40·10^9/l with a range of 0-0.9·10^9/l.

The mean duration of hospitalization was 11.8 ± 4.2 days, with a minimum of 6 days (3.4% of the admissions) and a maximum of 25 days (3.4%).

The laboratory tests performed on neutropenic patients on each admittance are shown in Table 1. The greatest overall expenditure corresponded to the haemogram with a cost of 615,325 pesetas ($5,398), due to the haematological toxicity of the chemotherapy. It was followed by haemoculture with a cost of 558,750 pesetas ($4,901). This cost arose from the high susceptibility of such patients to infection.

With respect to pharmaceuticals, the greatest consumption was of antimicrobial agents (Table 2).

The number of persons forming the health-service team in the Oncology Ward was 12, all of these were permanent hospital staff. The health-service staff who were in training and were constantly replaced were not considered. The medical team consisted of 2 doctors, 6 nurses and 4 nursing auxiliaries. The Oncology Ward recorded an average of 12 admissions per day throughout 1991. This implied an average dedication of 35 minutes per patient per day for each of the health-service personnel. This value was reduced to 25 minutes during the night shifts when the nursing staff were also responsible for the patients in the Haematology Ward on the same floor. From these data and from the different salaries of the distinct members of the teams we could establish that the average total cost of health service attention was 9,272 pesetas ($81) for each patient per day. Given that, as has been mentioned previously, the average length of hospital stays was 11.8 days, the mean cost of the health-service staff alone was 109,421 pesetas ($960) for each admission (Table 3).

Due to the appearance of severe neutropenia (less than 0.5·10^9/l, WHO grade IV), 59% of the admissions required isolation for periods of time between 3 and 12 days. Thus an additional cost of 9,272 pesetas ($81) per day had to be taken into account, as it was impossible to admit another patient in the same room. The mean time spent in isolation was 6.8 ± 2.6 days so that the additional cost represents about 63,056 pesetas ($553) (Table 3).

	Mean cost per admission		*Total annual cost*	
	pesetas	*dollars**	*pesetas*	*dollars**
Antibiogram	630	6	18,000	158
Biochemistry	13,872	122	401,112	3,519
Blood culture	19,296	169	558,750	4,901
Blood transfusion	2,716	24	78,750	691
Coagulation test	754	7	21,528	189
Cross-tests	600	5	17,500	154
Faecal culture	1,043	9	29,800	261
Gasometry	194	2	5,625	49
Glucose, ions and urea	5,232	46	151,902	1,332
Haemogram	21,231	186	615,325	5,398
Platelet transfusion	14,871	130	431,250	3,783
Proteinogram	911	8	26,325	231
Radiography	6,240	55	180,000	1,579
Red-cell transfusion	11,164	98	323,750	2,840
Sonography	453	4	15,100	132
Sputum culture	2,077	18	60,300	529
Urine analysis	366	3	10,569	93
Urine culture	1,647	14	47,817	419

*The rate of exchange at the time the study was done, was 1 $=114 pesetas.

Table 2 *Cost of pharmacological treatment*

	Mean cost per admission		*Total annual cost*	
	pesetas	*dollars*	*pesetas*	*dollars*
Analgesics	590	5.2	17,105	150.0
Antacids	400	3.5	11,591	101.7
Antiemetics	69	0.6	1,988	17.4
Antimicrobial agents	36,243	317.9	1,051,033	9,220
Anti-inflammatory drugs	518	4.5	15,016	131.7
Antitussives	34	0.3	997	8.7
Bronchodilators	111	1.0	3,217	28.2
Hypoglycaemic agents	37	0.3	1,064	9.3
Laxatives	27	0.2	772	6.8
Mucolytics	41	0.4	1,197	10.5

Table 3 *Health and social resource costs*

	Mean cost per admission		*Total annual cost*	
	pesetas	*dollars*	*pesetas*	*dollars*
Absence from work	52,500	461	1,200,500	10,531
Analytic tests	74,546	654	2,159,653	18,944
Health staff	109,421	960	3,180,639	27,900
Isolation	63,056	553	1,084,941	9,517
Pharmacological treatment	38,070	334	1,103,980	9,684
Transfusions	28,751	252	833,750	7,314
Total	9,563,463	83,890		
Mean	329,775	2,893		

total annual costs corresponding to the 29 admissions for neutropenia recorded for cancer patients in 1991 have been calculated. The final balance, including isolation costs, reached 9,563,463 pesetas ($83,890), which implies an average cost of 329,775 pesetas ($2,893) per neutropenic episode. If a neutropenic episode without isolation is considered, the cost is 292,363 pesetas ($2,565).

Discussion

Economic evaluation permits the efficiency of the different health-service procedures to be analysed so as to determine whether or not the resources available are being used well. Cost effectiveness studies are thus vital prior to establishing new therapeutic policies (often involving prophylactic therapy), that aim to improve the quality of health care while reducing or controlling the costs derived from their application.

The present study of the cost of a neutropenic episode is an example of economic analysis oriented towards the planning of future strategies to not only reduce the costs arising from treatment but also to improve the quality of life of the patients, the latter being a benefit which to some extent is rather intangible. Various economic studies on this theme have been published [14-16].

The Interdisciplinary Research Centre of St. Gallen (Switzerland) has performed an economic study on the costs of neutropenic episodes in Germany and Switzerland [14]. This group found that in patients with solid tumours the average cost of such episodes was $2,632-7,895 and $1,509-5,193 in the two countries, respectively. In the case of acute leukaemias, the costs per episode were $6,719-11,211 in Germany and $5,158-8,535 in Switzerland.

The University of Kuopio (Finland) evaluated the cost of a neutropenic episode in patients with solid, microcytic lung tumours and in patients with leukaemia and found that for the two types of patients, the costs were $9,694 and $18,596, respectively [15].

Studies carried out in Spanish hospitals [16] have calculated the cost of each neutropenic episode at 236,000-377,000 pesetas ($2,070-3,307) for patients with solid tumours and 391,000-667,000 pesetas ($3,430-5,851) for patients with acute leukaemia.

In the present study no differentiation has been made between neutropenic episodes in patients with solid tumours and those in patients with haematogenic neoplasias. We have only evaluated neutropenic episodes developed in patients with cancer submitted to chemotherapy and/or radiotherapy.

The methodology followed in the present study differs from that in others [14-16] that used the Delphi method [17] to determine the cost of a neutropenic episode. The Delphi method is based on the use of opinion polls among experts and doctors without reference to medical histories. The estimates are based on studies of the probability of neutropenic episodes in patients receiving chemotherapy. Such data, however, have to be judged with care since they consist of means established by oncologists and haematologists on the basis of their daily clinical therapy and other health-care measures not specified in the text [16], are the result of subjective evaluations made by the different persons polled who provide the frequency data. With our own methodology we aimed at being more rigorous. Thus our estimates of the costs of each neutropenic episode are based on studies of the clinical histories, the treatment regimes, analytical techniques and medical care received by the patients examined independently. Nevertheless, although the techniques of evaluation are different, our results do not differ substantially from those published by other authors. This does not, however, imply that the different methods employed are equally valid, but rather that our results fit easily into the very wide cost margins of a neutropenic episode described by these authors.

The studies based on the Delphi method fail to describe the procedures used to estimate the costs derived from the health care given by doctors and nursing staff. The calculation of the hospital costs per stay is based on the annual reports of the Social Security and those from certain hospitals [16], and therefore does not truly represent a neutropenic episode. It should not be forgotten that in certain cases the patients suffering such episodes require isolation which increases the amount of health care which must be given to them by doctors and nurses and, therefore, increases the associated costs. Such additional costs are not taken into account in the aforementioned reports.

The different budgets of various hospitals could contribute to the differences observed for each country. At the same time, although the treatment regimes are similar, the length of time for which they are applied, which always depends on the therapeutic policies of each hospital, may vary. Furthermore, many hospitals admit such patients to the intensive-care unit, which is generally more resource-intensive, and therefore more costly, than admission to a general medical ward.

The treatment used in a neutropenic episode will depend in principle on the potential myelotoxicity of the cycles of chemotherapy applied and on the complications of the infection arising from the fall in the number of circulating granulocytes. For this reason the duration of a neutropenic episode always varies, this is another factor which affects hospital costs.

In our study, antimicrobial agents represented the highest pharmaceutical costs. In fact, the greatest consumption of antimicrobial agents is directly related to the high incidence of febrile infection episodes that accompany the decrease in granulocytes. Initial antibiotic therapy is usually directed against Gram-negative organisms and often consists of an aminoglycoside combined with an antipseudomonal penicillin or cefalosporin [18-20]. Additional treatment costs may be incurred if patients fail to respond to antibacterial therapy, or require that an antifungal and/or an antiviral agent be added to the treatment regimen [21]. Furthermore, patients who have received prolonged antibiotic therapy may require treatment for fungal infection, caused by notably *Candida* and *Aspergillus* species [22]. Thus, the economic costs of antibiotic therapy can vary greatly, depending on the antibiotic used, the susceptibility of the patient to infections, possible microbial resist-

From this it can be deduced that the anti-infection policy followed by each hospital is an important factor to be taken into account when evaluating the economic cost of a neutropenic episode and can lead to differences in the budgets of different hospitals. For this reason we considered that the evaluation of a drug treatment should be done on an individual basis for each hospital admission. Other authors have not followed this reasoning but rather have calculated the cost of drugs on the basis of the net costs paid by each centre [14-16]. This latter criterion does not differentiate between patients requiring intensive antibiotic therapy and those who are hospitalized for observation. It therefore implies a significant error in the calculation of overall costs.

To the high costs of health care that neutropenia involves, other, no less important, social and economic costs should be added. The patient has to undergo repeated admissions to hospital whether for the administration of chemotherapy and/or radiotherapy or in order to recover from outbreaks of neutropenia. All of this diminishes the patient's quality of life and leads to high absenteeism from work. For this reason we thought it interesting, from the economic point of view, to include the social cost arising from absenteeism from work as an additional cost. This parameter has not been taken into account in the other studies, which is another factor which makes it impossible to compare our results with those obtained by other authors, who have used other criteria for estimating the cost of a neutropenic episode.

A reduction in health-care costs should focus on the establishment of prophylactic measures reducing the incidence of neutropenia in the oncological patient. For instance, a strict control of patients via regular blood tests would allow the establishment of antibiotic therapy protocols before the final decrease in white blood cell levels/counts. The additional costs derived from this type of health care would probably compensate hospital admittance costs due to neutropenia. At the same time, the risk of complications due to infections, and responsible for the majority of deaths in oncological patients suffering from neutropenia, would also disappear.

Furthermore, chemotherapy protocol application could contribute to an increase in treatment response and, as a result, to the total remission of the tumour [23], without the need to reduce the intensity of the treatment or to interrupt the administration guidelines when a neutropenic episode appears. Nevertheless, we should not rule out that this would increase costs linked to new chemotherapy cycles and the administration of high doses of antineoplastic agents. In this case, it is reasonable to think that the clinician is not going to consider making savings in health care if it is linked to a restriction of available resources to cure a neoplastic process. An adequate prophylaxis of the occurrence of a neutropenic episode could also entail a decrease in the number of hospital admittances and thus an improvement of the patient's quality of life, improving physical and psychological performance, which is an intangible advantage. This situation would also have the added social advantage of lowering consecutive labour absences.

Granulocyte colony-stimulating factors seem to penic episodes [24 25]. The studies carried out until now show that there is a decrease in the number of neutropenic episodes, in the length of the interruption of chemotherapy episodes, in hospital stays, in blood transfusions carried out and in antibiotic therapy requirements. The major direct biomedical cost savings would be derived from avoidance of hospital accommodation and medical-care charges, and costs related to the treatment of infection [26 27]. In fact, our results reveal that health-care costs are the highest compared to the other parameters considered, to the extent that any measure reducing hospital stay would have a direct repercussion on the global costs of a neutropenic episode.

Thus, the application of an adequate prophylactic therapy should be studied from the economic viewpoint but without forgetting the non-quantifiable, intangible benefits of such therapy, such as the possible improvement in the quality of life of the patients, or the tumoural processes of haematogenic origin that present a higher probability of the incidence of neutropenia.

The economic assessment of a neutropenic episode in our hospital makes it possible to establish from now on comparative studies with their prophylactic measures directed towards reducing health-care costs. It would be worthwhile to investigate in a further study the prevention of neutropenic processes in our hospital via the administration of colony stimulating factors (G-CSF or GM-CSF), with the objective of evaluating the possible reduction in the costs incurred as a result of neutropenia and hospitalization.

Conclusions

The methodology used for evaluating the economic costs of a neutropenic episode was based on data taken from the patients' clinical histories and for this reason the results obtained reflect real health-care costs.

The overall economic cost of neutropenia in a patient with cancer and isolation reached 329,775 pesetas ($2,893), and 292,363 pesetas ($2,565) without isolation.

Health staff care was the highest budget cost in relation to the total health resources estimated.

Antimicrobial agents represented the highest pharmaceutical costs.

Planning an adequate prophylactic regime against infection could decrease the appearance of infections and thereby reduce health-care costs.

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