Farm Hosp. 2009;**33(4):**217-223

Farmacia
HOSPITALARIA

www.elsevier.es/farmhosp

ORIGINAL ARTICLE

Management of returned anti-neoplastic treatments and their reuse in oncology patients

D. Yuste-Vila,[a,*] A. Albert-Mari,[a,b] V. Jiménez-Arenas,[c] and N.V. Jiménez-Torres[a,b]

[a]*Servicio de Farmacia, Hospital Universitario Dr. Peset, Valencia, Spain*
[b]*Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Valencia, Spain*
[c]*Unidad de Investigación Epidemiológica (EPIFARM), CSISP, Conselleria de Sanitat, Valencia, Spain*

Received October 16, 2008; accepted May 11, 2009

KEYWORDS
Return;
Reuse;
Recycling;
Anti-neoplastic treatments;
Quality criteria

Abstract
Objective: Analyse the profile of parenteral preparation and treatment (anti-neoplastic and supplementary) that were dispensed and returned to the Pharmacy Department, the reasons why they were not administered, their reuse and the associated direct costs.
Method: Longitudinal study over 8 months (October 2004-May 2005) in a tertiary hospital with centre for preparing anti-neoplastic agents (including supplementary treatment) in its Pharmacy Department. The variables studied, downloaded from the Oncofarm® application, are as follows: a) patients and diagnostics; b) returned treatments, classified by reason returned, pharmaco-therapeutic scheme, cycle, and day; c) returned preparations (anti-neoplastic and supplementary) that were reused; and d) direct costs.
Data is presented with its absolute and relative frequencies and confidence intervals of 95% normalised at 1000 patients/day.
Results: Eighty-four treatments were returned by 66 patients for a total of 139 preparations corresponding to 3429 patients/day. This figure represents 24.5 (95% CI, 19.6-30.2) treatments that were prepared and not administered per 1000 patients/day, mainly due to clinical causes (n=47). Colon neoplasia and treatment with 5-fluorouracil and levofolinic acid presented the highest number of returns. The returned preparations made up 1.45% (95% CI, 1.2-1.7) of those produced. The percentage of reuse is 98%, which results in savings of €10 432.55 (90% of the cost of the treatments that are returned).
Conclusions: The application of quality, effectiveness, and safety criteria to anti-neoplastic treatments that are prepared and returned to the Pharmacy Department allows a more efficient preparation process.

This project has been presented partially as a poster at the 50th National Conference of the Spanish Society of Hospital Pharmacy held in Oviedo on September 27-30, 2005.

*Corresponding author.
E-mail address: yuste_marvil@gva.es (D. Yuste Vila).

1130-6343/$ - see front matter

PALABRAS CLAVE
Devolución;
Reutilización;
Reciclaje;
Tratamientos antineoplásicos;
Criterios de calidad

Gestión de la devolución de tratamientos antineoplásicos y de su reutilización en pacientes oncológicos

Resumen
Objetivo: Analizar el perfil de tratamientos y preparaciones parenterales (antineoplásicas y de soporte) dispensados y devueltos al servicio de farmacia, las causas de no administración, su reutilización y los costes directos asociados.
Método: Estudio longitudinal, prospectivo, durante 8 meses (octubre 2004-mayo 2005) en un hospital terciario con centralización de la preparación de esquemas antineoplásicos (incluye tratamiento de soporte) en el servicio de farmacia. Las variables estudiadas, descargadas del aplicativo Oncofarm®, fueron: a) pacientes y diagnósticos; b) tratamientos devueltos, diferenciando por causa, esquema farmacoterapéutico, ciclo y día; c) preparaciones devueltas (antineoplásicos y soporte) y reutilizadas, y d) costes directos. Los datos se presentan con sus frecuencias absolutas, relativas e intervalos de confianza (IC) del 95 %, normalizado a 1.000 pacientes/día.
Resultados: 84 tratamientos devueltos de 66 pacientes con un total de 139 preparaciones correspondientes a 3.429 pacientes/día. Este dato representa 24,5 (IC del 95 %, 19,6 a 30,2) de tratamientos preparados y no administrados por 1.000 pacientes/día, debido, mayoritariamente, a causas clínicas (n = 47).
La neoplasia de colon y el esquema de 5-fluorouracilo y ácido levofolínico presentan el mayor número de devoluciones. Las preparaciones devueltas suponen el 1,45% (IC del 95%, 1,2 a 1,7) de las elaboradas. El porcentaje de reutilización es del 98 %, con un coste ahorrado que asciende a 10.432,55 € (90 % del coste de los tratamientos devueltos).
Conclusiones: La aplicación de criterios de calidad, eficacia y seguridad a los tratamientos antineoplásicos preparados y devueltos al servicio de farmacia permite incrementar la eficiencia en el proceso de preparación.

Introduction

The dose of each drug, finally received by the patient, independent from the dosage parameters handled, makes it possible to quantify the compliance of the prescribed treatment and its potential consequences. In the non-oncologic ambulatory patient, the percentage of drugs returned does not reach 1% of the total of difference prescribed medications.[1] This percentage is found between 8% and 15% when referring to intravenous mixtures (IVM) prepared in the hospital setting,[2,3] without any information on the return of antineoplastic treatments.

Oncologic patients rarely comply with all of the dosage parameters of programmed chemotherapy treatments; sometimes days are modified, other time the number of cycles, and others, the components of the pharmacotherapeutic regimen (PTR). In adjuvant therapy for breast cancer (FEC and AC), only about 30% to 40% of the patients reach a compliance of 100%.[4] The modification of doses in these PTR under the demonstrated effective levels is correlated with a loss of benefit.[5]

Thus, sometimes, due to logistic criteria failure, other times from adverse effects or lack of response in the patient, a percentage of the confirmed programmed treatments, prepared and dispensed, are not actually administered to the patient.

Operatively, regarding the return of chemotherapy treatments, there are 2 main interventions: try to recuperate them or facilitate their direct disposal. Ethical considerations weigh on this decision, for which it has been proposed that any treatment, complete or portion thereof, that is not administered to the patient for whom it was prepared, must be destroyed by incineration.[1] The contrary option (recuperate) is also defended as, due to their high cost, potential reduction of assistance load in the pharmacy department (PD), costs for its disposal and potential environmental contamination, facilitating its reuse, once its therapeutic validity is guaranteed regarding effectiveness and safety, there is no doubt that this is a licit practice, professionally respectable and cost effective.[2,6,7] Logically, any condition that alters the criteria of quality of these returned IVM, (physical-chemical, microbiologic and dosage), is a reason for its destruction, following the established criteria to do so.[8]

In this area, the JCAHO (MM.4.80)[9] standards, and more recently, the ISOPP (section 20)[8] standards, establish that the antineoplastic IVM, prepared and returned to the centralized unit of the PD, should comply with the quality criteria established if their posterior reuse is considered, in the same patient or in a different patient. This situation is applicable in a general manner, given that one same drug can be used in different chemotherapy protocols.

The aim of this study is to understand the profile of the parenteral preparations (antineoplastic and supportive) returned to the PD. In addition to this, the causes that lead to them not being administered to the cancer patient are analysed along with its final destination (reuse or disposed) and the direct costs. With the objective to provide the bases for the management of the return of chemotherapy treatments that are not administered and their posterior reuse.

Method

Longitudinal, prospective study conducted over a period of 8 months (October 2004-May 2005), carried out in a tertiary university hospital (535 beds). The preparation of all of the treatments is done in a centralised manner in the intravenous therapy unit of the PD, following the quality standards (5901 treatments, 18 290 preparations, and 632 cancer patients/year). The PTR required to treat cancer patients include antineoplastic drugs as well as those needed as support to guarantee the effectiveness and safety of the treatment, and they have been designed in manner that follows the protocol and that has been agreed upon between the clinical pharmacy department and the medical oncology department.

The patients included in this study were cared for in the day hospital (10 armchairs/3 beds) as well as in the hospitalisation unit (20 beds). At least once, their confirmed, prepared, dispensed and non-administered treatment was returned to the PD according to the normalised working protocol (NWP).

The processes of the therapeutic chain, from programming up to administration of the treatments and, their justified return, are registered electronically and doubly validated with auxiliary devices (bar-code technology). Figure 1 shows the map of the processes included for the reuse of the parenteral preparations of antineoplastic regimens. Among them, we must point out:

1. Information system of the preparations not administered and returned to the PD.

   – The pharmaco-therapeutic history of the patient that does not receive his/her treatment is electronically updated with the help of bar-code technology handling the following variables: *a)* of the patient (name of patient, medical record number, department to which he/she belongs, diagnosis); *b)* of the treatment (acronym of the regimen used, cycle and day of the treatment, medication, date and hour of preparation, date and hour of return, cost; and *c)* of the preparations (identifying codes, stability of drug substances, possibility to reuse, expiration, and cause of return). The combination of preparations has been considered treatment (antineoplastic and supportive drugs) corresponding to a day of PTR prescribed to the patient.

   – Pharmaceutical validation (PV) of the returned preparation and quality and safety criteria handled.[10]

2. Technology: integrity of packaging, correct and legible label, and functioning of the administrative system, if applicable (infusers, etc).
3. Physical-chemical: visual control (colour and/or precipitation), conservation conditions of the preparation outside of the PD (temperature, humidity, and photo-protection, if photosensitive), and expiration date, established in an individualised manner for each preparation depending on the database of bibliographic sources regarding stability and approved technical sheet, depending on the state of final concentration, vehicle, and recommended storage conditions.
4. Microbiologic: minimised risk by using the quality standards.[11] There are 3 levels of risk established regarding safety for the patient.[12-16] The IVM that are made by the PTR are classified at risk level I (low): simple mixtures prepared in sterile conditions (laminar flow hood), stored at room temperature and administered within 24 h since being prepared or conserved at 2-8°C for a maximum of 7 days, before their complete administration to the patient in a maximum period of 24 h. The established reuse criteria include levels I and II.

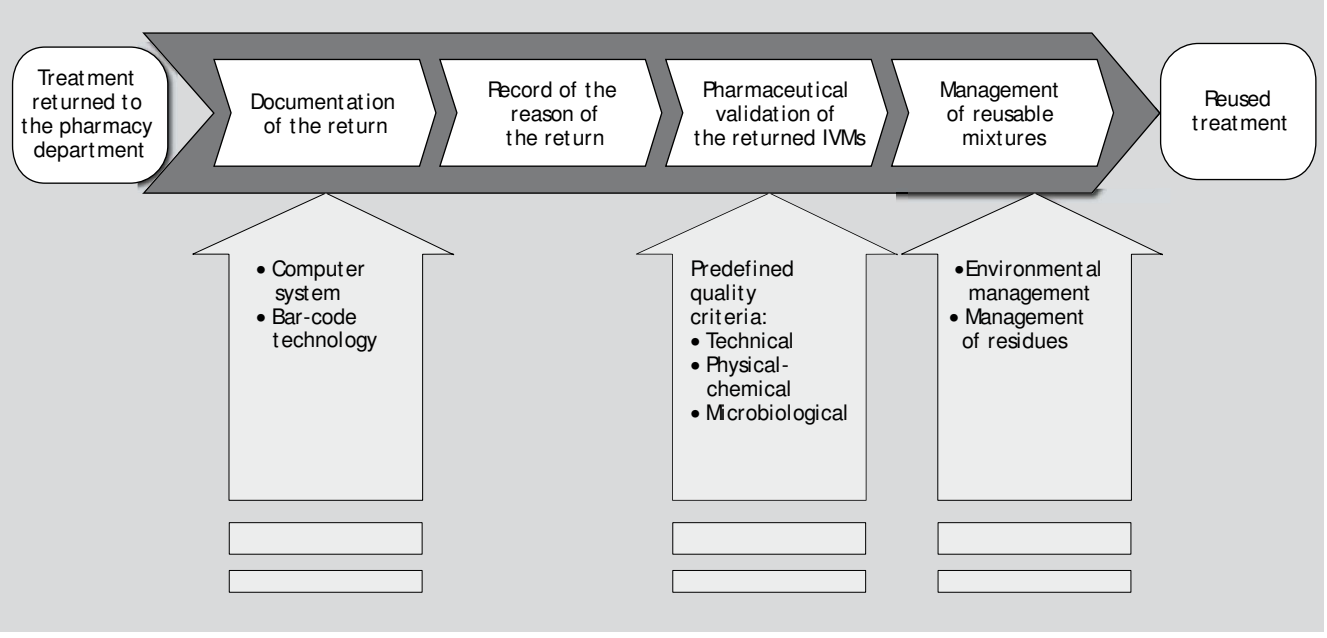

Figure 1 Flow diagram of the integrated process to reuse preparations of antineoplastic regimens IVM indicates intravenous mixtures.

The FV of the returned preparations determines their potential to be reused (conformity of all criteria) or disposed of (non-conformity with any one of the criteria). The result of the FV is recorded and facilitated with the Oncofarm® application, version 4.0 (IMF SL, Valencia, Spain).

5. Management of the returned and potentially reusable preparations. The Oncofarm® computer system manages the expiration date and the reuse possibility of the mixtures returned and of the preparations available in the database of the program. The process is activated and made visible to the pharmacist at the moment they validate the antineoplastic treatment of any patient, where at least one of its components (drug) coincides and is available in a mixture ready to be reused. The indicated data are the vehicle, volume and administration system (for example elastomeric infuser). The dose of the drug substance in the preparations that are offered to the validator should be located in the accepted interval (dose band) (±5% of the prescribed dose); they also offer those preparations whose dose is inferior than the prescribed dose, as they are susceptible to adding the remaining amount to them. Once the preparation that should be recuperated is accepted, the responsible professional, the date and time, the patient, the pharmaco-therapeutic regimen, the cycle and the day of treatment are recorded.

The variables studied, downloaded from Oncofarm® were:

– Total patients cared for and that had not received any component of the prescribed treatment.
– Total prepared and returned treatments, differentiated by type of predefined cause: technological (difficult identification and loss of air-tightness of packaging), clinical (adverse effects from chemotherapy, progression of disease or clinical situation of the patient), and logistic (programming error or error in assignment of patient) and non-specified or unknown cause, diagnosis, regimen type, cycle, and day.

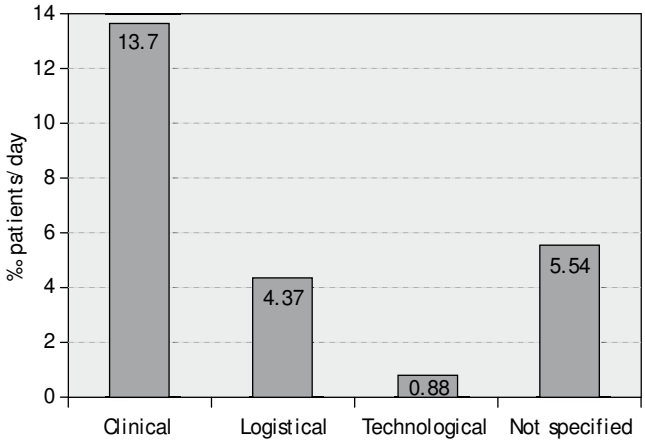

Figure 2 Cause incidence of antineoplastic treatment return (October 1, 2004-May 31, 2005).

– Total and returned preparations, differentiated by drug substance, percentage of reuse, and drugs involved.
– Total direct and differentiated costs for the preparations that are reused and disposed of.

All of the data extracted from the program have been exported (Excel) to validate their security and that of the information system used. This process enables the elimination of the treatments corresponding to non-oncologic patients (Oncofarm® manages patients with conditions other than cancer). Once the database is filtered, the SPSS® program, version 12.0, is used to obtain absolute frequencies, relative frequencies and 95% confidence intervals (CI) (macros designed for SPSS),[17] as a precision measurement.

The data have been normalised to 1000 patients/ day, which is equivalent to 1000 treatments/ day.

Results

Four hundred and forty-eight oncologic patients received antineoplastic and supportive treatment during the study period (8 months) which, when normalised to patients/ day, reaches a value of 3429 patients/ day.

Close to 15% of the patients (n=66) did not receive complete treatment in at least one of the days of the total of confirmed cycles. From this subgroup of patients, 23% (n=15) were not administered the foreseen treatment in 2 or more of the days of the confirmed cycle.

In this time period, 84 of the 3429 confirmed, prepared and dispensed treatments were not administered and were returned to the PD. This value represents 2.45% (95% CI, 1.96-3.02).

The reasons for returning these treatments, normalised to 1000 patients/ day, are shown in Figure 2.

Clinic-related motives stand out (n=47) as the most common causes, followed by logistic motives (n=15) and technological motives (n =3). No motive was specified for 19 returned treatments when recording the return of the treatment not administered to the patient.

By diagnosis, the prepared and returned treatments are collected in Table 1. The absolute and relative frequencies of the returned treatments describe the differences between the different diagnoses treated.

Table 2 summarises the raw and adjusted data (normalised to 1000 patients/ day) of the prepared and returned treatments, grouped by type of antineoplastic regimen.

Overall, the regimen with the greatest number of returns is one that combines 5-fluorouracil (5-FU) with levofolinic acid; however, when adjusting the data for PTR, the combination of gemcitabine/ cisplatin presents the greatest probability of non-administration of the prepared treatment.

When analysing the non-administered treatments regarding the number of the cycle, treatments have been returned to the PD from the first to the ninth cycles. 20 (23.81%) treatments corresponding to the first cycle stand out along with 15 (17.86%) from the fourth cycle of the antineoplastic regimen.

The evaluation of the days of the cycle indicate that for the 2 PTR with greater incidence of returns according to

Table 1 Returned antineoplastic treatments. Raw data and data adjusted to local diagnosis per 1000 patients/day (October 1, 2004-May 31, 2005)

Local diagnosis	Dispensed treatments	Non-administered treatments	
	Total No.	No.	Adjusted ‰ patients/day (95% CI)
Colon cancer	907	26	28.7 (18.8-41.7)
Rectum cancer	395	14	35.4 (19.5-58.7)
Non small cell lung cancer	441	12	27.2 (14.1-47.0)
Urinary bladder cancer	154	9	58.4 (27.1-108.0)
Stomach cancer	250	7	28.0 (11.3-56.8)
Other cancers (n≤4[a])	1282	16	12.4 (7.1-20.2)
Total treatments	3429	84	24.5 (19.6-30.2)

CI indicates confidence interval.
[a]Neoplasias/cancers: small-cell lung, breast, unknown origin, pancreas, ovary, and prostate.

Table 2 Returned antineoplastic treatments. Raw data and data adjusted to pharmaco-therapeutic regimen per 1000 patients/day (October 1, 2004-May 31, 2005)

Regimens	Dispensed treatments	Non-administered treatments	
	Total No.	No.	Adjusted ‰ patients/day (95% CI)
Fluorouracil (5FU) + LV[a]	692	26	37.6 (24.7-54.6)
Oxaliplatin + 5FU[b]	234	9	38.4 (17.7-71.7)
Cisplatin + gemcitabine[c]	107	7	65.4 (26.7-130.1)
Other regimens (n≤4)	2396	42	17.5 (12.7-23.6)
Total treatments	3429	84	24.5 (19.5-30.2)

CI indicates confidence interval; FU, fluorouracil; LV, levoflovinic acid.
[a](5FU 425 mg/m^2+ levofolinic acid 10 mg/m^2) × 5 days, every 28 days.
[b](Oxaliplatin 130 mg/m^2 day 1 + 5FU 2600 mg/m^2 PIV 24 h days 1, 8 + levofolinic acid 250 mg/m^2 days 1, 8) every 21 days with anti-vomiting regimen.
[c](Cisplatin 100 mg/m^2 day 1 + gemcitabine 1250 mg/m^2 days 1, 8) every 21 days or (cisplatin 70 mg/m^2 day 2 + gemcitabine 1000 mg/m^2 days 1, 8, 15) every 28 days with anti-vomiting regimen + hydration + manitol + supplements kg/mg.

adjusted data (oxaliplatin + 5FU and cisplatin + gemcitabine), the treatment corresponding to day 8 of the cycle is the one that is more frequently returned (preparations of 5FU or gemcitabine, respectively).

When analysing the dispensed and non-administered treatments regarding the total number of dispensed parenteral preparations, 139 preparations are calculated to be returned (81 antineoplastics and 58 supportive) compared with 9575 parenteral preparations elaborated during the study period, which represents 1.45% (95% CI, 1.22-1.7) of the preparations. This information is equivalent to 40.54 preparations returned by 1000 patients/day (95% CI, 34.18-47.69) or 4.05 returns for every 100 patients with treatment per day; of these 23.62 per 1000 patients/day (95% CI, 18.8-29.27) correspond to antineoplastics and 16.92 per 1000 patients/day to supportive treatment (95% CI, 12.87-21.81).

Similar to the previous Tables, Tables 3 and 4 show the drug substances used, for the antineoplastics and supportive treatments, in the preparations returned to the PD, normalised to 1000 preparations/day.

After applying the predefined reuse criteria, 133 (97.84%; 95% CI, 93.82-99.55) preparations that were dispensed and returned to the PD were recycled for other patients in antineoplastic treatment. The 3 preparations that were disposed of did not comply with the technological criteria of the integrity and air-tightness of the packaging.

The direct cost in antineoplastic and supportive medications handled for the preparation of the prepared treatments for oncologic patients cared for in the oncology department, during the study period, ascended to €1 274 718.14 (€371 746.32 per every 1000 patients/day). The direct costs of the returned treatments represented 0.91% of the total of the study period. Of this amount, 90% is saved (€10 432.55) by reusing these preparations. The losses from the non-administration of treatments ascended to €1219.92.

Discussion

In this study, the low percentage of the return of treatments (2.45%) recorded illustrates the high degree of compliance with the confirmed treatment regimen for oncology patients.

Table 3 Returned preparations. Raw data and data adjusted for drug substance per 1000 preparations/day (October 1, 2004-May 31, 2005)

Antineoplastic drug substance	Dispensed treatments	Non-administered treatments	
	Total No.	No.	Adjusted ‰ patients/day (95% CI)
5FU	1720	43	25.0 (18.1-33.5)
Gemcitabine[a]	3567	21	5.9 (3.6-9.0)
Cyclofosfamide	180	3	16.7 (3.4-47.9)
Docetaxel[a]	187	3	16.4 (3.3-46.2)
Etoposide	220	3	13.6 (2.8-39.3)
Irinotecan	210	3	14.3 (3.0-41.2)
Epirubicin	147	2	8.1 (0.9-28.9)
Carboplatin	217	1	4.6 (0.1-25.4)
Cetuximab	50	1	20.0 (0.5-106.5)
Cisplatin	341	1	2.9 (0.1-16.2)
Total preparations	5180	81	15.6 (12.4-9.4)

CI indicates confidence interval; FU, fluorouracil.
[a]Corresponds to drug substances disposed of.

Table 4 Returned preparations. Raw data and data adjusted for drug substance per 1000 patients/day (October 1, 2004-May 31, 2005)

Supportive drug substance	Dispensed treatments	Non-administered treatments	
	Total No.	No.	Adjusted ‰ patients/day (95% CI)
Levofolinic acid[a]	1174	23	19.5 (12.5-29.2)
Dexamethasone	1380	16	11.6 (6.6-18.7)
Ondansetron	1125	10	8.9 (4.3-16.3)
Atropine	196	6	30.6 (11.3-65.4)
Granisetron	238	3	12.6 (2.6-36.4)
Total preparations	4395	58	13.2 (10.0-17.0)

CI indicates confidence interval.
[a]Corresponds to drug substances disposed of.

The return of oncologic treatments is, mostly, for clinic-related reasons (56%) and includes causes that are not always predictable. Thus, the regimen change as the disease progresses, the adverse effects associated to chemotherapy and any non-optimal situation of the patient to receive chemotherapy (for example: a cold or stomach flu) are evaluated, in general, after the confirmation of the treatments by the oncologist.

As strategies to improve budgets, the integration of the computer program with the supportive systems for decision-making and electronic patient medical records[18] are useful. Also, having an integrated working procedure available facilitates the interdisciplinary communication and the recording of the reasons for returns in the program; however, in this study, up to 23.6% of the returns had no known reason, as the default term "unspecified" was used, which led to a review, update and diffusion of the actual procedure in the framework of the quality program implanted.[19] The reasons recorded for returns in this study are not different than those published in primary or hospital care (adverse effects and change of treatment).[20]

The diagnoses with greater numbers of returned preparations are colon and rectum cancers, a fact that explains why the 2 drug substances most frequently returned are the 5FU and levofolinic acid. These data correlate with the cancers with greatest prevalence[21] and justifies the high percentage of reuse of these IVM. This situation has been seen in previous publications about medication returns.[10]

The adjusted analysis of the returns indicates that bladder cancer is the diagnosis with the greatest probability with 5.8 returned treatments for every 100 prepared treatments (Table 1).

Regarding the cycles, it is observed that cycles 1 and 4 stand out coinciding with the inadequate clinical situation of patients when initiating treatment (time difference between programming and confirmation) and with secondary toxicity to the chemotherapy in the fourth cycle, respectively.

In the hospital setting, the return of treatments represents between 8% and 15% of the total of prepared parenteral mixtures.[2,3,10] In this study the percentage of returned units is 5 to 10 times less than that published. This difference can

be explained by an integrated working procedure and by the use of computer systems for key processes, between the PD and medical oncology departments.[22]

A second dimension that should be evaluated in the process of returning antineoplastic and supportive treatments is their potential reuse that is located in the non-hospital setting between 20% and 46% of the returns, after applying the period of validating quality criteria[1,23]; this percentage rises to 80%-83% in hospital settings.[10,24]

In this study, the reuse of non-administered treatments is of 97% of the preparations due to the fact that the medication is kept in controlled environmental conditions from the moment it is dispensed until it is returned. To this finding, also, the normalisation of concentration, and the type and volume of the vehicle also contribute, similar to what happens with the IVM with dexamethasone and ondansetron that are reused in 100% of the returns.

In oncology, it has been documented that 1.33% of the cytostatics can be reused for other patients, similar to that described in this study.[25]

The established reuse process makes it possible to save 1% of the cost for this medication (€15 000 per year), which leads to support from various authors[2,26,27] for an adequate reuse program.

All of the ISOPP criteria for the reuse of antineoplastic drugs are met in this study.[8] However, we must point out the limited sample size of the treatments and preparations returned to the PD as a bias, and, as found in other studies, the fact that only direct costs of the medication have been considered.[2]

References

1. Mackridge AJ, Marriott JF. Returned medicines: waste or a wasted opportunity? J Public Health (Oxf). 2007;29:258-62.
2. Tullio CJ. Minimizing i.v. admixture waste in a 70-bed hospital. Hosp Pharm. 1987;22:994-1001.
3. Jiménez Torres NV. Unidad de mezclas intravenosas. In: Jiménez Torres NV, editor. Mezclas intravenosas y nutrición parenter al. 3rd ed. Valencia: ECUSA; 1988.
4. Jiménez Arenas V. Evolución de la terapia adyuvante en cáncer locorregional [tesis doctoral]. Valencia: Universidad de Valencia; 2006.
5. Wood WC, Budman DR, Korzun AH, Cooper MR, Younger R, Hart RD, et al. Dose and dose intensity of adjuvant chemotherapy for Stage II, node-positive breast carcinoma. N Engl J Med. 1994;330:1253-9.
6. Thompson CA. Oklahoma allows limited medication recycling: Program aims to help indigent patients. Am J Health Syst Pharm. 2005;62:1437-8.
7. Pomerantz JM. Recycling expensive medication: why not? Med Gen Med. 2004;6:4.
8. International Society of Oncology Pharmacists Practitioners (ISOPP). ISOPP standards of practice. Safe handling of cytotoxic. J Oncol Pharm Practice. 2007;13 Suppl 1:1-81.
9. Rich DS. New JCAHO Medication Management Standards for 2004. Am J Health Syst Pharm. 2004;61:1349-58.
10. Llopis Salvia P, Jiménez Torres NV. Normalización y mejora de la calidad en la administración intravenosa de medicamentos. In: Jiménez Torres NV, editor. Mezclas intravenosas y nutrición parenteral. 4rt ed. Valencia: CONVASER CEE; 1999.
11. Conselleria de Sanidad. Criterios de calidad para la acreditación de los servicios de farmacia hospitalaria. 1st ed. Valencia: Generalitat Valenciana; 2005.
12. USP (U.S. Pharmacopeia) Pharmaceutical compounding-sterile preparations (general test chapter 797). In: The United States Pharmacopeia 28 rev., and The National Formulary, 23rd ed. Rockville: United States Pharmacopoeial Convention; 2005. p. 2471-7.
13. Kastango ES, Bradshaw BD. USP chapter 797: Establishing a practice standard for compounding sterile preparations in pharmacy. Am J Health-Syst Pharm. 2004;61:1928-38.
14. Buchanan EC, McKinnon BT, Scheckelhoff DJ, Schneider PJ. Principles of sterile product preparation. Bethesda: American Society of Health-System Pharmacists; 2002.
15. Okeke CC, Bailey L, Medwick T, Grady LT. Revised USP standards for product dating, packaging, and temperature monitoring. Am J Health-Syst Pharm. 2000;57:1441-5.
16. ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products. Am J Health-Syst Pharm. 2000;57:1150-69. 17. Domenech JM, Sesma R, Bonillo A, Granero R. Confidence intervals for proportions (exact and asymptotics) Macro CIPV2007.01.10(c). In: Doménech JM, editor. Fundamentos de diseño y estadística. Barcelona: Signo; 2007.
18. Schiff GD. Computerized prescriber order entry: models and hurdles. Am J Health-Syst Pharm. 2002;59:1456-60.
19. Yuste Vila D, Vila Torres E, Albert Marí A, Marquez Peiró JF, Campos Moreno E, Jiménez Torres NV. Mejora en la calidad del registro informatizado de los motivos de devolución de los tratamientos antineoplásicos. Farm Hosp. 2005;29:104-5.
20. Langley C, Marriott J, Mackridge A, Daniszewski R. An analysis of returned medicines in primary care. Pharm World Sci. 2005; 27:296-9.
21. López-Abente G, Pollán M, Aragonés N, Pérez-Gómez B. Informe sobre la salud de los españoles. Cáncer. Área de Epidemiología Ambiental y Cáncer. Centro Nacional de Epidemiología. Instituto de Salud Carlos III. 2003. [Accessed Mar 1, 2008]. Available from: www.isciii.es/htdocs/pdf/salud-cancer-2003.
22. Almenar Cubells D. Procesos integrados en oncología. [Tesis Doctoral]. Valencia: Universidad de Valencia; 2005.
23. Marchiset-Ferlay N, Gerbaud L, Sauvant MP, Jaffeux P, Manhes G, Leblanc N, et al. Description of unused drugs collected in pharmacies in the Puy-de-Dôme region in France. Rev Epidemiol Sante Publique. 2001;49:551-8.
24. Martínez-Tutor MJ. Evaluación económica de la centralización de mezclas intravenosas. Farm Hosp. 2006;30:351-8.
25. Martínez Rodriguez OA, Rivas Bocanegra RE, Ascencio-Pérez IS, Zapata Sánchez LA. Costes de una unidad de preparación de citostáticos en un hospital de México. Farm Hosp. 2007;31: 375-8.
26. Bronder E, Klimpel A. Unused drugs returned to the pharmacy-new data. Int J Clin Pharmacol Ther. 2001;39:480-3.
27. Hauser JM, Chen L, Paice J. Down the drain: the cost of medications wasted in hospice. J Pain Symptom Manage. 2006; 31:379-80.