Reducción del gasto en cáncer disminuyendo el desperdicio en drogas

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Resumen

Objetivo: El cáncer es uno de los principales problemas de salud pública a nivel mundial debido a la morbilidad, mortalidad y costes asociados. Las presentaciones farmacéuticas de medicamentos antineoplásicos en general no se ajustan exactamente a la dosis requerida, generándose sobrantes de fármaco no utilizado. Reducir al mínimo el desperdicio de medicamento teniendo en cuenta la estabilidad físicoquímica y microbiológica del vial puede reducir los costes. El objetivo de este estudio es establecer el ahorro derivado de esta práctica aplicada en el ámbito hospitalario.

Métodos: Se calculó el número de viales necesarios para los tratamientos de cáncer en nuestro centro durante un periodo de un mes. El gasto total en medicamentos (€) se estimó de acuerdo con los siguientes escenarios: la cantidad residual es desechada inmediatamente tras la preparación, al final del día, después de 24 horas o transcurrido el tiempo máximo antes de la fecha límite encontrada en la literatura (hasta un máximo de siete días). Los costes fueron calculados según el precio de venta del laboratorio sin impuestos.

Resultados: El ahorro osciló entre el 8,2 y 18,2 por ciento del gasto total en fármacos antineoplásicos durante periodo de estudio. El número de viales necesarios disminuyó hasta un 18%. Los mayores ahorros se produjeron en bevacizumab, bortezomib, trastuzumab, y azacitidina.

Conclusiones: La extensión de vida útil de los viales abiertos y/o reconstituidos de medicamentos antineoplásicos una vez se ha validado técnica aséptica empleada en la elaboración puede conducir a un importante ahorro de recursos en el tratamiento antineoplásico.

Palabras clave: **Gasto sanitario, ahorro de costes, agentes antineoplásicos.**

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Reduction of cancer expenditure by diminishing drug wastage

Summary

Objective: Cancer is a major public health problem worldwide due to morbidity, mortality, and great associated cost. Pharmaceutical products of antineoplastic drugs usually do not exactly fit to the dose required in a specific patient generating residual amounts of unused drugs. Minimizing the drug wastage according to microbiological and physicochemical stability could reduce cancer cost. The aim of this study is to establish savings derived from this practice in the hospital outpatient setting.
Methods: We calculated the number of vials needed for cancer treatments in our centre for a one month period. Drug expenditure (€) was estimated according to the following scenarios: the residual amount is discarded immediately, at the end of the day, after 24 hours, or after the maximum time before expiry found in the literature (up to seven days). Costs were computed before taxes.
Results: Total savings ranged from 8.2 and 18.2 per cent of the total antineoplastic drug budget for the study period. Number of vials needed could be declined by 18%. Greatest savings occurred with drugs such as bevacizumab, bortezomib, trastuzumab, and azacitidine.
Conclusions: Extending shelf-life of reconstituted or opened vials of antineoplastic drugs once the aseptic technique has been validated can lead to relevant financial savings in cancer treatment.

Key Words: **Health expenditures, cost savings, antineoplastic agents.**

Introduction

Cancer is a major public health problem worldwide and has an elevated social impact due to morbidity and mortality, and the substantial increases in cost to a level that is now causing a serious financial burden to society.

Overall, an estimated 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008 worldwide[1].

The number of total cancer deaths in Spain in 2012 was estimated at 102,639, and more than 208,000 new cancer cases were diagnosed. The crude incidence rates vary across sexes between 482 and 463 per 100,000 person-years and the total number of cases is growing gradually[2].

Even with current rates of incidence and mortality, the burden of cancer will continue to increase. Therefore, cancer will be one of the greatest health challenges for the next few years and will require the use of a large amount of resources including antineoplastic agents.

The advance in cancer knowledge is one of the greatest achievements of scientific research in the field of medicine in the last few years. These progresses have permitted the development of new molecules and treatment schedules which currently offer our patients greater expectations in terms of response, prolonged survival, or improved quality of life. However, we must bear in mind that, sometimes, these new tools are very expensive and the availability of resources is limited, so they should be used in an efficient and equitable manner[3].

Furthermore, current tendency suggests that the growing cost of cancer treatment will accelerate in the coming years due to the de-

velopment of new, more expensive treatments, the continuing growth and ageing of the world's population, the increased life expectancy by improvements in therapeutic outcome, and more effective diagnostic procedures[4].

Health professionals have implemented numerous strategies to contain the aforementioned increasing expenditure and improving efficiency, such as the use of generic and biosimilar molecules[5], the outpatient management of cancer patients, and optimizing treatment selection based on pharmacogenetics[6].

Other approaches are directly related to the drug preparation process. It should be noted that most anticancer drugs are individually dosed according to a patient´s body surface. Therefore, pharmaceutical products do not exactly fit the dose required in a specific patient, generating, to a greater or lesser extent, residual amounts of unused drugs. The problem is more pronounced when marketed vials don't correspond to the average dose used generally. For example, bortezomib vials (Velcade®, Janssen-Cilag), a drug used in the treatment of multiple myeloma, contain 3.5 mg of active drug, while the usual dose administered per patient is 1.3 mg/m^2, and the maximum dose to be administered is 2.6 mg[7,8].

Some other possible saving approaches have been proposed, such as dose rounding of chemotherapy to the nearest vial size[9] or the dose standardisation of anticancer drugs *("dose-banding")*[10].

Using residual amounts of vials in cytostatic drug compounding is another tool which can allow substantial savings by diminishing the quantity of drug discarded. This system can reduce cancer expenditure without impacting health outcomes. As already mentioned, the dosage individualization means that most of our patients receive only a portion of vial contents. The unused medication is disposed of if it can not be used in another patient during the lifetime of the vial. Drug wastage is variable depending on several factors: vial dose, the amount remaining after the preparation of the day's doses, the shelf life of the drug and the duration of the interval between patients requiring the same drug, and microbiological stability.

Manufacturers frequently quote stability after dilution or opening as being stable for short times, reflecting the application of the 'care principle' considering possible bacterial contamination, or the fact that stability tests were only conducted over a very short period[11].

Shelf-life extension, based on well-designed physicochemical stability studies along with the assurance of a proper aseptic technique, could lead to a decrease drug expenditure[12]. Recently our team demonstrated that vials manipulated using a closed-system drug transfer device (PhaSeal®) inside a biological safety cabinet remain sterile for a week instead several punctures[13]. The main hypothesis of this study is that the use of residual amounts of reconstituted or diluted vials of antineoplastic agents through an extended shelf-life on the basis of validated physicochemical stability data and the use of appropriate aseptic technique to maintain sterility throughout this period can result in significant savings of resources.

The aim of this study is to establish savings derived from this practice in the hospital outpatient setting.

Methods

We analyzed the economic data associated with the cytostatic drug elaboration over a period of one month in a tertiary hospital with a production of approximately 6.000 parenteral antineoplastic treatments per year.

For each preparation the optimal number of vials needed was calculated depending on product availability in our centre through the automatically generated elaboration guidance by the outpatient medication management software (Farmatools®, Dominion).

In a similar way to Vandenbroucke et al.[14], we calculated the theoretical use of drug vials according to several scenarios as follows:

- Scenario one (S1). We calculated the optimum number of vials needed to prepare each dose individually discarding the rest of the vial immediately.

- Scenario two (S2). We calculated the number of different vials needed to prepare the prescribed dose if vials are shared by patients whose treatments are elaborated in the same day.

Table 1
Number of vials needed for each scenario during study period

	S 1	S 2	S 3	S 4
Azacitidine 100 mg	18	18	13	13
Bevacizumab 25 mg/ml 16 ml	21	19	18	17
Bevacizumab 25 mg/ml 4ml	15	12	9	8
Bleomycin 15 UI	3	3	3	3
Bortezomib 3,5 mg	10	9	9	6
Carboplatin 150 mg	33	27	23	22
Carboplatin 450 mg	22	22	22	22
Cetuximab 5 mg/ml 20 ml	85	82	80	76
Cyclophosphamide 1 g	29	28	28	20
Cisplatin 100 mg	23	21	21	19
Dacarbazine 1.000 mg	2	2	2	2
Docetaxel 20 mg	17	12	8	5
Docetaxel 80 mg	5	5	5	5
Docetaxel 160 mg	13	13	13	13
Doxorubicin 50 mg	34	33	30	28
Epirubicin 50 mg	4	4	4	4
Etoposide 20 mg/ml 5 ml	52	51	46	46
Fluorouracil 50 mg/ml 100 ml	46	35	26	25
Gemcitabine 1 g	41	41	37	34
Irinotecan 100 mg 5 ml	27	26	26	26
Methotrexate 25 mg/ml 2 ml	4	4	4	4
Oxaliplatin 100 mg	44	42	41	40
Paclitaxel 300 mg 50 ml	45	36	35	31
Pemetrexed 100 mg	17	17	17	14
Pemetrexed 500 mg	4	4	4	4
Rituximab 100 mg	15	13	13	13
Rituximab 500 mg	6	6	6	6
Topotecan 4 mg 5 ml	11	11	11	11
Trastuzumab 150 mg	64	59	56	55
Vinblastin 10 mg	2	2	2	2
Vincristin 2 mg 2 ml	5	5	5	5
Vinorelbine 50 mg 5 ml	3	3	3	3
Total	**720**	**665**	**620**	**582**
Absolute saving (n vials)		**55**	**100**	**138**
% Savings		**7,6%**	**13,9%**	**19,2%**

Table 2
Drug cost for each scenario

	S 1	S 2	S 3	S 4
Azacitidine 100 mg	6.372,0	6.372,0	4.602,0	4.602,0
Bevacizumab 25 mg/ml 16 ml	26.730,7	24.184,9	22.912,0	21.639,1
Bevacizumab 25 mg/ml 4 ml	4.930,8	3.944,6	2.958,5	2.629,8
Bleomycin 15 UI	44,3	44,3	44,3	44,3
Bortezomib 3,5 mg	11.201,4	10.081,3	10.081,3	6.720,8
Carboplatin 150 mg	1.414,1	1.157,0	985,6	942,7
Carboplatin 450 mg	2.735,0	2.735,0	2.735,0	2.735,0
Cetuximab 5mg/ml 20 ml	16.345,5	15.768,6	15.384,0	14.614,8
Cyclophosphamide 1 g	224,5	216,7	216,7	154,8
Cisplatin 100 mg	513,8	469,1	469,1	424,5
Dacarbazine 1.000 mg	30,1	30,1	30,1	30,1
Docetaxel 20 mg	1.628,8	1.149,7	766,5	479,1
Docetaxel 80 mg	1.605,8	1.605,8	1.605,8	1.605,8
Docetaxel 160 mg	6.262,6	6.262,6	6.262,6	6.262,6
Doxorubicin 50 mg	465,8	452,1	411,0	383,6
Epirubicin 50 mg	90,4	90,4	90,4	90,4
Etoposide 20 mg/ml 5 ml	261,6	256,5	231,4	231,4
Fluorouracil 50 mg/ml 100 ml	654,6	498,1	370,0	355,8
Gemcitabine 1 g	2.067,2	2.067,2	1.865,5	1.714,3
Irinotecan 100 mg 5 ml	2.186,5	2.105,5	2.105,5	2.105,5
Methotrexate 25 mg/ml 2 ml	8,0	8,0	8,0	8,0
Oxaliplatin 100 mg	7.136,8	6.812,4	6.650,2	6.488,0
Paclitaxel 300 mg 50 ml	20.147,9	16.118,3	15.670,6	13.879,6
Pemetrexed 100 mg	4.080,0	4.080,0	4.080,0	3.360,0
Pemetrexed 500 mg	4.800,0	4.800,0	4.800,0	4.800,0
Rituximab 100 mg	3.619,2	3.136,6	3.136,6	3.136,6
Rituximab 500 mg	7.197,7	7.197,7	7.197,7	7.197,7
Topotecan 4 mg 5 ml	1.293,5	1.293,5	1.293,5	1.293,5
Trastuzumab 150 mg	38.177,3	35.194,7	33.405,1	32.808,6
Vinblastin 10 mg	12,3	12,3	12,3	12,3
Vincristin 2 mg 2 ml	28,4	28,4	28,4	28,4
Vinorelbine 50 mg 5 ml	94,5	94,5	94,5	94,5
Total	**172.361**	**158.268**	**150.504**	**140.873**
Absolute Saving (€)		**14.093**	**21.857**	**31.487**
% Savings		**8,9%**	**13,8%**	**19,9%**

- Scenario three (S3): We calculated the number of vials needed when residual amounts of the vials are stored for a maximum of 24 hours.

- Scenario four (S4): We calculated the number of vials needed considering the maximum time before expiry found in the literature up to seven days

We calculated in a comprehensive manner and for each drug savings in absolute terms as well as the net percentage of savings. All costs were calculated before taxes.

Results

During the study period vial consumption data were obtained for the different scenarios (Table 1). Absolute savings expressed as number of vials and the percentage of savings for each scenario with respect to the worst case scenario (scenario 1) are also indicated. All costs expressed as euros are showed in Table 2.

Total savings ranged from 8.9 and 19.9 per cent of total antineoplastic drug budget for the study period. Number of vials needed declined by 19% when the best scenario was considered. Greatest savings occurred with drugs such as bevacizumab, bortezomib, trastuzumab, and azacitidine.

Discussion

Our research has confirmed that the use of the residual amounts of the vials while drug remains stable and for a maximum of a week, diminishes drug wastage and represents a major reduction in cancer treatment budget.

Minimizing the overall health expenditure without adversely impacting patient's health outcomes is one of the biggest future challenges of health systems in the current economic environment[15].

Several initiatives have been undertaken in the field of pharmacotherapy such as formulary policies, therapeutical interchange, intravenous-to-oral sequential therapy, generic drug utilization or dose rounding.

Decreasing inappropriate disposal of unused or partially used vials is an attractive cost-cutting strategy, since it neither limits specific drug use nor affects quality of care. Walker et al. calculated that extending shelf-life period reduced drug wastage about 42%[12].

In our study, cost savings varied between 8% and 19% depending on the considered scenario. These results imply an overall cost reduction which ranged between 120,000 and 250,000 euros approximately. Our results are consistent with those previously described by Vandenbrouke et al.[14] who estimated potential savings around 7% and 15%. These findings demonstrate that this practice is economically advantageous regardless of the setting in which it is applied.

Leftover amounts may reach 10% of the used drug depending on the number of patients attended, anthropometric characteristics, time between patients who receive the same drug, marketed vials and their established shelf-life[16]. Certain factors can be controlled, for instance through a citation system matching the patients with the same treatment. However, this is not always possible because treatment delays due to toxicity are common and some patients can not wait for their treatment.

Finally, the use of residual amounts necessarily implies that stability must be maintained. In terms of physicochemical stability, a lot of studies support the extension of the utility period[17]. In terms of microbiological stability, a proper aseptic technique must be achieved. Our group previously validated this issue[13]. Other authors have confirmed that vials manipulated inside biological safety cabinets and using closed-system drug transfer device remain sterile for at least for a week[18]. This kind of devices exerts a microbiological barrier function[19]. In any case, microbial growth is hampered by anticancer drugs[20,21]. Roy et al.[22] studied 25 commonly used antineoplastic drugs concluding that most of them could be considered microbiologically stable once opened. All this suggests that extending vial lifetime is feasible in normal practice.

Conclusions

Extending shelf-life of reconstituted or opened vials of antineoplastic drugs once aseptic technique has been validated can lead to relevant financial savings in cancer treatment.

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