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ORIGINAL ARTICLE

A Cost Saving and Waste Minimization Study About Handling of the Antineoplastic Agents

Antineoplastik İlaç Hazırlamada Tıbbi Malzeme Tasarrufu ve Atık İlaç Miktarının Azaltılması

Metin Deniz KARAKOÇ*

Denizli State Hospital, Zafer Gökşin Oncology Centre, Denizli, Turkey

ABSTRACT

Objectives: As a cancer treatment option, chemotherapy costs make up a large part of the budgets of social insurance foundations and related expenditures are increasing continuously annually. Cost saving and waste minimizing strategies are required to reduce the expenditures in the field of oncology. The study aimed to reduce the amount of wasted antineoplastic drugs and medical supply consumption.

Materials and Methods: The study explains why vials with a larger size and drugs in liquid form should be preferred over various smaller sizes and powder forms of antineoplastic preparations.

Results: Amounts of drug wastage, vial adaptor, and transfer set consumption data were recorded regularly for a period of seven months. The average vial adaptor consumption per patient in the last three months decreased from 5 to 3.3. The preference of liquid forms as much as possible instead of powder forms, which has a shorter stability time after dilution, and the choice of larger package sizes of frequently used drugs decreased vial adaptor consumption. Potential savings were calculated as around 31.660 USD annually. Costs of total wasted doses were 8.699.87 USD, and the whole antineoplastic drug consumption was 515.500 USD during the study. A decrease of 0.58 USD was observed per capita when the first and last three-month periods were compared in terms of waste costs.

Conclusion: These values indicate that the reduction of wasted drugs have potential annual savings of 3.375 USD. It is shown that total potential savings of 35.000 USD could be made per year. By implementing the same principles in all hospitals in Turkey, approximately 2.8 million USD could be made annually. The pharmaceutical industry and hospital pharmacists have important responsibilities in this issue.

Key words: Antineoplastic, cost saving, chemotherapy, drug waste, pharmacoeconomy

ÖZ

Amaç: Günümüzde kanser kemoterapisi giderleri sosyal güvenlik kurumlarının bütçelerinden önemli bir pay almakta ve harcamalar yıldan yıla sürekli olarak artmaya devam etmektedir. Onkolojideki giderleri azaltmak için tasarruf sağlayıcı ve atık ilaç miktarını azaltıcı stratejilere ihtiyaç vardır. Çalışma, hem tedaviden arta kalan yarım doz antineoplastik ilaçların hem de tedavide kullanılan tıbbi malzeme sarfiyatının azaltılmasını amaçlamaktadır.

Gereç ve Yöntemler: Çalışmada çeşitli ambalaj boyları ve toz formdaki flakonlar yerine mümkün olduğunca büyük boy flakonlar ve konsantre sıvı formdaki ilaçlar tercih edilmiştir. İmha edilen ilaç miktarı ile flakon adaptörü ve transfer seti sarfiyatları yedi ay müddetince düzenli olarak kaydedilmiştir.

Bulgular: Çalışmanın son üç ayında ortalama olarak hasta başına harcanan flakon adaptörü sayısının 5'ten 3.3'e düştüğü belirlenmiştir. Sulandırıldıktan sonraki stabilite süresi daha kısa olan toz formdaki antineoplastiklerin mümkün olduğunca konsantre sıvı form ilaçlarla değiştirilmesi ve sık kullanılan ilaçlarda daha büyük boy flakonlar kullanılmasıyla flakon adaptörü sarfiyatı azaltılarak tasarruf sağlanmıştır. Yıllık potansiyel tasarrufun 31.660 $ civarında olduğu hesaplanmıştır. Çalışma sırasında kullanılan antineoplastik ilaçların maliyeti 515.500 $ olurken bunun 8.699.87 $ tutarındaki kullanılmayan kısmının imha edildiği belirlenmiştir. Çalışmanın ilk üç aylık dönemi ile son üç aylık dönemi karşılaştırıldığında imha edilen ilaç miktarında hasta başına ortalama 0.58 $ azalma olduğu görülmüştür.

Sonuç: Çalışmada imha edilen ilaç miktarının azaltıldığı ve yılda 3.375 $ potansiyel tasarruf sağlamanın mümkün olduğu gösterilmiştir. Toplamda ise yılda 35.000 $ potansiyel tasarruf sağlanabileceği belirlenmiştir. Türkiye çapında bütün hastanelerde aynı prensipler uygulanarak yıllık 2.8 milyon $ tasarruf sağlanması mümkündür. Bu konuda ilaç endüstrisi ve hastane eczacılarına önemli sorumluluklar düşmektedir.

Anahtar kelimeler: Antineoplastik, maliyet tasarrufu, kemoterapi, ilaç imhası, farmakoekonomi

*Correspondence: **E-mail:** metindeniz.karakoc@saglik.gov.tr, **Phone:** +90 258 263 93 11 **ORCID-ID:** orcid.org/0000-0003-3188-8738
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INTRODUCTION

Cancer is one of the leading causes of human deaths all over the world. According to the latest data reported from the International Agency for Research on Cancer, the estimated incidence will continue to increase in coming years. Therefore, cancer treatment has gained importance rapidly in the medical world, especially in recent years. Surgery, radiotherapy, and chemotherapy are commonly applied methods for cancer treatment. These treatments can be administered to patients with cancer individually, sequentially or in combination. Among these treatments, chemotherapy is the most frequently performed method, it is used all over the world as in our country, and stands out as the costliest treatment option.

Chemotherapy is the major treatment for most patients with cancer, even when other treatment options can not be applicable. There are many different chemotherapy administering protocols for several cancer types. According to the selected protocol, administered antineoplastic drug numbers and administration frequencies vary among patients. The number of administered antineoplastic drugs, existing dose forms on the market, and the administering frequency affects both the total cost of medical supplies and the amounts of wasted drugs during preparation. Antineoplastic drug doses are calculated for each patient by physicians using many criteria such as body surface area, renal and hepatic function, age, and sex.[1] Therefore, drug doses vary between patients. Generally, it is not possible for the pharmaceutical industry to determine ideal doses that would be sufficient for a patient in a single vial. Consequently, there is an amount of unavoidable drug waste if it is not possible to use the remaining dose for another patient within the stability period.[2,3]

The costs of anticancer drug developments and licensing are increasing rapidly, approximately 1 billion-1.8 billion USD in the United States of America.[4,5] In recent years, the expenditure for cancer treatment has increased, largely due to the increase in cancer prevalence, demographic changes, and the incorporation of new and expensive drugs into clinical practice. It was reported in a study that a seven-fold increase was seen in anticancer drug expenditure in Australia between 2000 and 2012.[6] This result is consistent with the results of another study conducted in Europe between 1993 and 2004.[7] It is a huge burden on government budgets and also individual cancer patients' expenditure. The current status brings responsibilities for health workers in relation to rational use of drugs and medical supplies.

The study aimed to reduce the amount of drug waste and medical supplies consumption by preferring larger size vials and liquid form drugs instead of various sizes and formulations of antineoplastic preparations and to achieve savings.

EXPERIMENTAL

The study was conducted in Denizli State Hospital Oncology Center. First, written permission (24.12.2015 - 16661972) was obtained from the hospital management for the study. In the study, we classified patients in Denizli State Hospital in terms of administered antineoplastic solution numbers as single, double, and three or more for a period of seven months (January - July, 2016) to determine the most economical chemotherapy administering sets. Each vial adaptor and transfer set that was used in the drug preparation was purchased for 3.2 USD before the study. Vial adaptor and transfer set consumption data per patient were recorded daily and regularly. Furthermore, total medical supply consumption and amount of drug waste was calculated in US dollars. All antineoplastic drug preparations in the study were performed in a bio-safety cabinet inside a validated negative pressure clean room using closed-system vial adaptors and transfer sets. Exposure to antineoplastic drugs during preparation and administration can present a health risk to medical staff.[8] According to the National Institute for Occupational Safety and Health, a closed-system transfer device is defined for use in compounding and administering sterile doses of chemotherapy and other hazardous drugs, as a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system, and the escape of hazardous drugs or vapor concentrations outside the system. The benefits of using closed-system transfer devices has been described in several previous studies.[8-13]

It is only possible to use a drug inside an opened vial to maintain both its microbiologic and physicochemical stability. No solution is added to the unused amount of concentrated liquid form drug vials. Thus, the drug's physicochemical stability continues as long as it is microbiologically stable. Manufacturing companies that provide medical supplies ensure that their products maintain a microbiologic barrier for seven days and support it with literature.[14] Therefore, concentrated liquid form drugs are accepted as microbiologically stable for seven days after setting the adaptors to the vials, and unused drugs at the end of seventh day are wasted. On the other hand, the physicochemical stability of lyophilized powder form drugs generally deteriorates rapidly after reconstitution. According to the manufacturer's instructions of drugs used in the study, the maximum stability period varied between 8 to 24 hours. Therefore, in compliance with the manufacturer's instructions, unused powder form drugs were wasted at the end of their maximum stability period.

A total of 32 different drugs were used throughout the study. Various dose form changes were made for 14 drugs. Larger sized and concentrated liquid forms were preferred instead of lyophilized powder forms that required dilution before use for 3 of 14 drugs (epirubicin, gemcitabine, and oxaliplatin). The use of docetaxel preparations that required ethanol as solvent stopped and 'ready to use' solutions were preferred that needed no dilution. For the other 10 of 14 drugs (bevacizumab, carboplatin, cisplatin, doxorubicin, etoposide, ifosfamide, irinotecan, paclitaxel, pemetrexed, and panitumumab), it larger sized vials with no formulation change were preferred. Concentrated liquid form drugs and larger sized packages were preferred in order to reduce vial adaptor consumption, achieve the greatest possible economic saving, and also shorten the drug preparation time by reducing the workload of medical staff. On the other hand, no dose form changes were made for 18 of 32 antineoplastic drugs used in the study (5-fluorouracil, azacitidine, bortezomib, dacarbazine, eribulin, liposomal doxorubicin, nab-paclitaxel,

raltitrexed, topotecan, trastuzumab, vinblastine, vincristine, fludarabine, cetuximab, cyclophosphamide, methotrexate, rituximab, and vinorelbine). The first thirteen drugs were devoid of alternative dose forms on the market, and the last five are rarely used and lesser consumed drugs compared with the others.

Each drug's consumption rate was taken into account separately. Purchasing procedures for the designed saving scheme started in January 2016, but the new drugs came to the hospital in late March 2016. The list of used intravenous antineoplastic drugs during the study, dose forms, and frequency scores (Table 1) are given below. The differences between the groups were

Table 1. List of used intravenous antineoplastic drugs and dosage forms during the study

	Drug name	Using frequency score*	First dose forms	Modified dose forms
1	5-Fluorouracil	5	1 g	1 g
2	Azacitidine	1	100 mg	100 mg
3	Bevacizumab	3	100 mg	100 and 400 mg
4	Bortezomib	1	3.5 mg	3.5 mg
5	Carboplatin	4	50 and 150 mg	450 mg
6	Cetuximab	2	100 mg	100 mg
7	Cisplatin	4	10 and 50 mg	100 mg
8	Cyclophosphamide	3	0.5 g	0.5 g
9	Dacarbazine	1	100 mg	100 mg
10	Docetaxel	4	20 and 80 mg	80 mg (ready to use)
11	Doxorubicin	3	10 mg	10 and 50 mg
12	Epirubicin	4	10 and 50 mg	50 mg
13	Eribulin	1	0.88 mg	0.88 mg
14	Etoposide	3	50 mg	100 mg
15	Fludarabine	1	50 mg	50 mg
16	Gemcitabine	4	200 mg and 1 g	1 g
17	Ifosfamide	1	0.5 g	1 g
18	Irınotecan	3	40 mg and 100 mg	300 mg
19	Liposomal doxorubicin	1	20 mg	20 mg
20	Methotrexate	1	50 mg	50 mg
21	Nab-paclitaxel	1	100 mg	100 mg
22	Oxaliplatin	3	50 mg	200 mg
23	Paclitaxel	4	30 and 100 mg	300 mg
24	Panitumumab	3	100 mg	100 and 400 mg
25	Pemetrexed	2	100 mg	100 and 500 mg
26	Raltitrexed	1	2 mg	2 mg
27	Rituximab	2	100 and 500 mg	100 and 500 mg
28	Topotecan	1	4 mg	4 mg
29	Trastuzumab	5	150 mg	150 mg
30	Vinblastine	1	10 mg	10 mg
31	Vincristine	2	1 mg	1 mg
32	Vinorelbine	1	50 mg	50 mg

*Scale of using frequency; 5: Every day, 4: At least 3 days per week, 3: At least 2 days per week, 2: Average 1-2 patient per week, 1: Average 1-3 patient per month

investigated using chi-square (χ^2) and the Kruskal-Wallis tests in the Statistical Package for the Social Sciences (SPSS) version 22.

RESULTS

At the beginning of the study, drugs were prepared according to the present inventory (Table 1- first dose forms) in January, February, and March 2016. The purchasing processes of new dose forms were completed in late March. In early April, newly purchased drugs and previous inventory drugs were used together. At the end of April, it was observed that a number of savings had been achieved despite the use of old and new type drugs together. Vial adaptor savings were observed (Table 2) in the months following April when compared with the previous months. The decrease in vial adaptor consumption in May, June, and July showed statistically significance when compared with January ($p<0.05$) and February ($p<0.001$).

It was determined that 51.94% of patients were administered single drugs, 34.07% were administered double, and 13.99% of patients were administered three or more antineoplastic drugs. The average consumption of transfer sets per patient was calculated as 1.63. Neither changes in treatment regimens nor numbers of patients caused a statistically significant difference ($p>0.05$) in average transfer set consumption. The preference of liquid forms as much as possible over powder forms and larger package size drugs decreased vial adaptor consumption. The average consumption of vial adaptors reduced to 3.3 from 5 in the last three months of the study compared with the first three months. During the study, an average of 485 patients were administered chemotherapy monthly. Considering that each vial adaptor bought for 3.2 USD, the potential annual savings of the hospital was calculated as 31.660 USD.

Beside the monetary savings, although it could not be shown by the numeric data, it was determined that using larger size packages and liquid form drugs significantly shortened the preparation time. Shortening of preparation time reduces the risk of exposure to cytotoxic agents on medical staff and also accelerates the services offered to patients.

Active ingredients of bortezomib, topotecan, bleomycin, cyclophosphamide, and ifosfamide were wasted in every month of the study. Although whole doses of 5-fluorouracil, cisplatin, trastuzumab, carboplatin, cetuximab, bevacizumab, docetaxel, etoposide, irinotecan, paclitaxel, panitumumab, raltitrexed, vinblastine, and vincristine agents were all used, none was wasted throughout the study. Using concentrated liquid form drugs that do not require dilution, enables longer storage for remaining doses and reduces the amount of wasted drugs. There were no wasted doses of epirubicin, oxaliplatin, and gemcitabine after we began to use liquid forms instead of powder forms. It was determined that there was a reduction in the cost of total wasted drugs (Figure 1) in the last four months of the study when compared with previous months.

The total cost of wasted doses was 8.699.87 USD, and the total antineoplastic drug consumption was 515.500 USD during the study. It was determined that 1.69% of the antineoplastic drugs that were prepared in the unit could not be used for other patients and wasted. A 0.58 USD decrease was observed

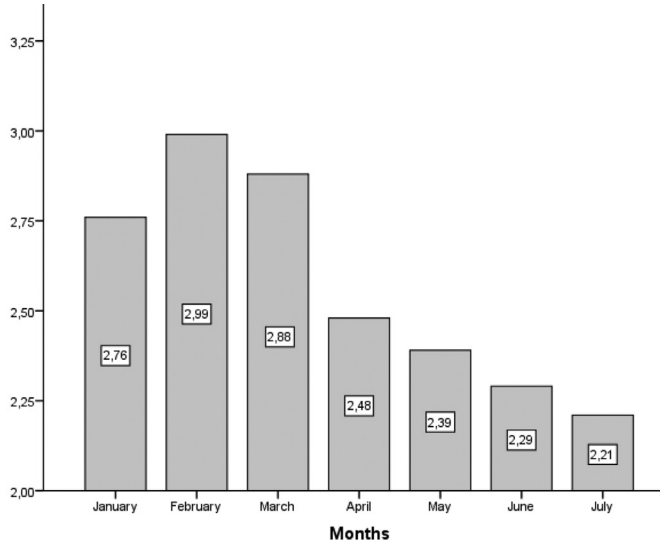

Figure 1. Monthly average of wasted drug costs ($) per chemotherapy

Table 2. Administered parenteral antineoplastic drug numbers and distributions with medical supply consumption and amounts of wasted drugs

Month	1 agent	2 agent	3 and 3+ agent	Total patient number	Vial adaptor consumption per patient	Average vial adaptor consumption per patient	Average transfer set consumption per patient	Wasted drug amount ($)	Wasted drug amount per patient ($)
January	248	145	68	461	2.306	5.00	1.64	1.272.36	2.76
February	253	130	80	463	2.320	5.01	1.62	1.384.37	2.99
March	262	142	75	479	2.402	5.01	1.59	1.379.52	2.88
April	239	183	63	485	2.086	4.30	1.64	1.202.80	2.48
May	246	182	59	487	1.554	3.19	1.61	1.163.93	2.39
June	256	187	63	506	1.786	3.53	1.62	1.158.74	2.29
July	260	188	67	515	1.637	3.18	1.69	1.138.15	2.21
Total	**1764**	**1157**	**475**	**3.396**	**14.091**			**8.699.87**	

per capita when the first and last three-month periods were compared in terms of waste costs. It was determined that the amount of wasted drugs could be reduced and 3.375 USD per year could potentially be saved when considering the monthly average number of patients administered chemotherapy during the study.

DISCUSSION

In recent years, many researchers aimed at cost saving and minimizing waste in oncology by using different methods. One of these was the dose rounding method, which may be an alternative way to reduce waste. It was reported in a study that 15.922 USD cost savings were achieved in a period of three months by dose rounding of biologic anticancer agents to an amount within 10% of the ordered dose.[15] In addition, it was shown in a recent study that using a computer for storing data on amount and stability of unused chemotherapy drugs could contribute to reducing total anticancer drug expenditure by about 5%.[16]

It was reported in a study that daily monitoring of antineoplastic drug consumption and an internal waste minimization protocol were able to achieve savings of 15.700 Euros every month. The projection of an annual cost-saving result of 188.000 Euros corresponds to a recovery of 4% on the spending for oncologic drugs.[17] These savings are relatively higher when compared with ours. The difference is probably based on the patient numbers and chemotherapy protocol differences between the studies. Similarly, in an another study, it was reported that 8.3% of antineoplastic drugs were wasted annually before applying a planned cost-saving protocol, and the authors observed a 45% reduction in drug waste expenditure.[18] Despite gaining great success as the monetary amount, the rate of wasted drug costs were much higher even in the final status than the average of our study (1.69%). Savings can be maximized by applying the dose rounding method together with the model that we applied in the study. However, we did not apply dose rounding, which is one of the shortcomings of the present study. Besides, administering rarely used and quite expensive specific medicines (e.g., bortezomib, eribulin, liposomal doxorubicin, nab-paclitaxel, pemetrexed) only in certain hospitals in a city can contribute to achieving savings by reducing the total amount of unused doses after opening vials instead of administering these drugs in every hospital.

The average cost of wasted drugs per month was calculated as 1.242.84 USD in the present study. However, a Turkish study performed about unused chemotherapy drugs reported a cost of 6.406.93 USD for wasted drugs within two months.[19] The disparity between the studies is probably due to different patient numbers or short storage times because of using needles in the other study instead of closed-system transfer devices.

There are three types of antineoplastic drug administering sets on the market; single, double, and four inlets. Increasing the inlet number raises the price of administering sets, which leads to elevated costs in chemotherapy. Therefore, it is not rational to administer single anticancer agents to patients with double or four inlet administration sets. Classifying patients according to the administered antineoplastic agent numbers and determining the use ratios enables more rational purchasing processes of the antineoplastic drug administering sets.

In coming years, it is possible that we will see a decrease in the use of intravenous antineoplastic agents because of the increasing administration of oral formulations. It has been shown in some studies that oral antineoplastic drugs improve patient treatment adherence and reduces waste.[20-22] On the other hand, an amount of oral antineoplastic drugs also become waste because of the inability to read and understand complex instructions; compliance risks, which may reflect inadequate treatment adherence; over adherence or reduced persistency; unanticipated drug interactions with food and other medications; and apparent non-responsiveness to the drug regimen.[23] Despite some of the disadvantages described above, the increase in oral antineoplastic drug use can make savings in health expenditures by reducing the waste when compared with intravenous antineoplastics.

Some drugs are marketed only in one package size, which leads to heavy spending on vial adaptors during preparation in some situations. Similarly, 5-fluorouracil and cisplatin are frequently used drugs for chemotherapy and the maximum marketed vials are 1 g and 100 mg, respectively. Solutions for the market such as 10 g 5-fluorouracil and 500 mg cisplatin vials would provide lower vial adaptor consumption and shorter preparation times.

Remaining doses in an opened vial can only be used if it is stable both microbiologically and physicochemically. In the study, the manufacturer's instructions were strictly followed regarding the maximum stability period for dilution-requiring drugs. However, there are conflicting results between manufacturer's instructions and some scientific studies for many antineoplastic drugs. For instance, the manufacturer of bortezomib advises a maximum stability period of 8 hours after dilution; however, a 2014 study reported that bortezomib diluted with isotonic sodium chloride maintained its physicochemical stability for up to 21 days.[24] Another study reported that bortezomib remained stable for five days in the vial after dilution.[25] Conflictingly, another study showed that bortezomib maintained its stability for up to 33 days at 2.5 mg/mL concentration at room temperature.[26] Moreover, there is an ongoing debate about the stability of topotecan. The manufacturer recommends using topotecan within 24 hours after dilution. However, it has been shown that topotecan remained stable for 28 days when diluted with sterile water.[27] The results of a different study were consistent with these results, although the authors tested at a different temperature.[28] On the other hand, in another study conducted by the same research team, topotecan hydrochloride was stable for up to 24 hours at room temperature and for up to 7 days at 5˚C in PVC and polyolefin infusion bags and glass bottles containing either 5% dextrose injection or 0.9% NaCl injection.[29]

There are numerous similar conflicts for most antineoplastic drug stability periods. It is observed that drug companies generally indicate in the instruction manuals that drugs maintain their stability for 8 to 24 hours after opening the

vials. Nevertheless, stability studies that have been conducted by many researchers revealed that the stability period of drugs were longer than those notified in the manufacturer's instruction manuals. The drug companies probably do not want to take risk about the patient's health and therefore indicate deliberately short-term stability periods for the opened vials. This subject merits further studies.

In Turkey, bortezomib and topotecan are marketed only in single dose forms as 3.5 mg and 4 mg vials, respectively. These expensive drugs are less consumed in terms of number when compared with the other drugs used in the study, and it is observed that the total doses of these drugs in a single vial are usually too much for one patient. Due to the lower circulation of patients and shorter storage time after dilution, the remaining doses of topotecan and bortezomib are constantly being wasted. It is thought that launching 2 mg and 0.5 mg for bortezomib and 1 mg for topotecan would reduce the amount of wasted drugs in chemotherapy units. Similarly, in a study that was published in 2011, it was reported that the average bortezomib dose per patient was 2.1 mg and the average amount of waste was 39.5%. Therefore, in the same study, it was recommended that the most convenient vial doses of bortezomib were 2.5 mg and 0.5 mg.[30]

There are very few studies about antineoplastic drug preparation and waste minimization in Turkey. In one of these studies, it was reported that preparing antineoplastic solutions was generally the responsibility of nurses.[19] However, in the last few years, this duty has been performed by hospital pharmacists in Turkey. The performance of this task by hospital pharmacists will increase the amount of savings by allowing more efficient evaluation of unused doses of antineoplastic drugs. Pharmacists are more competent about storage conditions and the maximum stability periods of opened antineoplastic drug vials. This situation can contribute to obtaining better results both economically and with patient health.

In the present study, it was shown how the application of a simple waste minimization model could reduce drug waste expenditure. Moreover, classifying patients according to the administered antineoplastic agent numbers gives an idea about selecting the most convenient chemotherapy administering sets for the future. Larger size and liquid form drug selections provided a cost saving via enabling more storage time and reduced vial adaptor consumption. Marketing larger sized vials for 5-fluorouracil and cisplatin would improve savings by reducing vial adaptor consumption and shortening the drug preparation period. Moreover, it should be more economical to launch smaller dose forms for bortezomib and topotecan in terms of reducing drug waste. Despite showing the reduction in vial adaptor consumption and amounts of wasted drugs, this is a single-center study and it is limited by its short duration. There is need for multi-center, long-term studies in the future.

CONCLUSION

High costs in cancer chemotherapy can be reduced with pharmacoeconomic approaches and rational use of drugs. It was shown that with 3.375 USD savings of waste drug reduction and 31.660 savings from medical supply consumption, a total of 35.000 USD potential savings could be made per year in our hospital. By applying the same principles countrywide in all hospitals that administer chemotherapy, it is possible to save approximately 2.8 million USD annually in Turkey.

The pharmaceutical industry and hospital pharmacists have important responsibilities in this issue. The medical industry has to redefine the dose forms of rarely used and expensive antineoplastic medicines considering the average application doses. Launching smaller dose forms of such medicines on the market would have a positive effect for the country's budget. On the other hand, as explained above, frequently used drugs in chemotherapy such as cisplatin and fluorouracil should be available in larger dose forms. This situation will reduce the number of vials used and lead to lesser consumption of medical supplies.

Drug preparation staff must be strictly controlled by pharmacists so as to ensure use of unused doses. Moreover, pharmacists should observe the usage frequency of all antineoplastic drugs to determine the most convenient dose forms for their hospital; keeping all forms of antineoplastic medicines in pharmacy stocks burdens hospital's financial balance and increases the workload of drug preparation staff. Preference of larger dose forms for frequently used liquid form drugs reduces vial adaptor consumption. Furthermore, for rarely used drugs, preferring smaller dose forms over larger forms will provide less unused medicine disposal and provide cost savings.

Conflict of Interest: No conflict of interest was declared by the authors.

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