Economic impact of the preparation scenario for cytotoxic drugs: an observational study

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Abstract
Aim: To evaluate the financial impact of three different preparation and conservation scenarios for cytotoxic drugs.
Method: In scenario one we discarded the residual fraction of the drug after each preparation. In scenario two we used the residual fraction of the vial until the end of the day. In scenario three we used the residual fraction of the vial until the chemical/physical expiry date.
To analyse the economic impact of the three scenarios, we looked at 3,086 preparations during July and August 2006.
Results and discussion: A major difference in cost was found between the three scenarios, namely:
Euros 872,413, Euros 807,309 and Euros 754,442 for scenarios one, two and three respectively. Savings varied between a minimum of Euros 52,867 (7%) and a maximum of Euros 117,971 (15%) for the observation period of two months, or an average of Euros 17 to Euros 38 per preparation.
Conclusion: When cytotoxic medicines are prepared under rigorous conditions, pharmacists can contribute to substantial economic savings.

Introduction

The central pharmacy of Ghent University Hospital prepares approximately 28,500 cytotoxic drugs per year in a centralised preparation unit. This unit is equipped with biological safety cabinets placed in a controlled work zone (which includes, for example, negative pressure, high efficiency particulate air (HEPA), filtered air and limited access). The unit and procedures comply with ISO 9001 of the International Organization for Standardization, as part of the hospital pharmacy certification.

For the protection of the employees and the product, we use the closed-transfer device, PhaSeal (complying with the International Society of Oncology Pharmacy Practitioners standards definition of being airtight and leak-proof), during the preparation of all our cytotoxic drugs. In another study (Microbiological challenge of protective devices for the reconstitution of cytotoxic agents – submitted for publication in *Letters in Applied Microbiology*), we demonstrated the advantage of the PhaSeal system over other transfer devices by a microbiological challenge test.

In daily practice, in order to define the expiry date for the reconstituted products, we must consider several factors:

1. The expiry date of the product itself regarding its physical and chemical properties.
2. The internal procedures of the hospital and hospital pharmacy.
3. The level of safety for the sterility of the product because of the "hardware" such as the location, equipment, air quality of the clean room and use of special devices.
4. The level of safety for sterility of the product because of the "software" such as the training, education and skills of personnel.
5. National laws or guidelines.

After assessing the outcome of risk analysis of the above parameters, the pharmacist can decide either to:

1. Discard the rest of the vial after each single preparation.
2. Discard the rest of the vial at the end of the day.
3. Use the vials until the expiry date of the product with regard to its physical and chemical properties.

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The goal was to estimate the financial impact of these three scenarios by considering the cost of the cytotoxic products and other costs such as that of the closed-transfer device (PhaSeal).

Methods

For the study we analysed the preparation data in July and August 2006 and simulated for each day the theoretical use of drug vials belonging to each scenario as follows:

Scenario one

We used the drug vials available in the Belgian market and calculated for each preparation the optimum number of vials needed to prepare each dose individually.

Scenario two

We calculated the number of different vials needed to prepare the prescribed dose, for all patients attending the oncology unit that day.

Scenario three

We calculated the number of vials needed, based on the highest volume and/or concentration available on the market for the total period, paying attention to the time that the next preparation was required and the maximum time before expiry found in the literature. When the internal expiry date set by the department was shorter than the interval between two consecutive preparations of that product, the remaining volume of the vial was discarded and a new vial was used to start the second preparation.

At the end of the observation period, we counted up all the used vials in the different scenarios and multiplied them with the tariff price of each vial to obtain the total cost of the products.

For each vial, one specific transfer device (PhaSeal Protector), adapted to the size of the vial and the diameter of the aluminium cap, was used. We have included the cost of only the different protector devices used, because the use of the connector and injector (two other parts of the PhaSeal system) are comparable for each scenario.

Appendix 1: Maximum expiry date vial of reconstituted stock solution

Generic product	Brand name	Maximum expiry date	Reference
Amsacrine	Amsidine	RTU	
Bevacizumab	Avastin	RTU	
Bleomycin	Non-proprietary	28 D	1
Bortezomib	Velcade	8 H	
Carboplatin	Carbosin	RTU	
Cetuximab	Erbitux	RTU	
Cisplatin	Platosin	RTU	
Cyclophosphamide	Endoxan	7 D	5
Cytarabine	Non-proprietary	RTU	
Dacarbazine	Non-proprietary	4 D	6
Dactinomycin	Cosmegen Lyovac	8 H	
Daunorubicin	Cerubidine	7 D	1
Docetaxel	Taxotere	28 D	7, 8
Doxorubicin		RTU	
Liposomal doxorubicin	Caelyx	RTU	
Epirubicin	Farmorubicine	RTU	
Etoposide	Eposin	RTU	
Fludarabine	Fludara	14 D	1
Fluorouracil	Fluracedyl	RTU	
Gemcitabine	Gemzar	36 D	9
Idarubicin	Zavedos	1 D	
Ifosfamide	Holoxan	7 D	1
Irinotecan	Campto	RTU	
Melphalan	Alkeran	1 H	
Methotrexate low dose		RTU	
Methotrexate high dose		RTU	
Mitomycin		14 D	2
Mitoxantrone	Xantrosin	RTU	
Oxaliplatin	Eloxatin	28 D	10
Paclitaxel	Taxol	RTU	
Pemetrexed	Alimta	3 D	11
Teniposide	Vumon	AMP	
Topotecan	Hycamtin	17 D	12
Trastuzumab	Herceptin	2 D	13
Vinblastine		7 D	14
Vincristine		RTU	
Vindesine	Eldesine	7 D	14
Vinorelbine	Navelbine	RTU	

Key: RTU: ready to use, D: days, H: hours, AMP: ampoule for immediate use

We calculated the number of the different protectors used in the different scenarios, multiplied them with their unit cost and added this sum to the products cost.

Various books, journals and electronic databases [1-4], as well as the injectable medication administration guidelines for adults used at the MD Anderson Cancer Center, University of Texas, USA, were consulted to establish the physical and chemical expiry dates of the products. For each drug, the maximum stability was defined and is listed in Appendix 1.

Results

During the study period, 3,086 preparations were evaluated. These were prepared from 39 different products; the top 10 most-used products are shown in Table 1.

The details of the number of vials and protectors used in the three scenarios are presented in Appendix 2 that summarises: the product, number of preparations and total amount prescribed (dose administered during the observation period). For each scenario, the total number of vials used (expressed in mg), the percentage compared with the administered dose, the number of vials and specific dosages used, and the number of protectors used are also shown.

Details of the cost for each drug in the three scenarios are presented in Appendix 3.

The differences for the top 10 drugs, in terms of losses in scenario one compared with scenario three, are presented in Table 2.

The differences for the top 10 drugs, in terms of losses in scenario two compared with scenario three are presented in Table 3.

Table 1: The top 10 most-used cytotoxic preparations

Product	Number of preparations
Fluorouracil	718
Cyclophosphamide	229
Etoposide	182
Cisplatin	178
Doxorubicin	177
Cytarabine	166
Gemcitabine	151
Vincristine	133
Oxaliplatin	116
Irinotecan	103

The total cost and difference between the three scenarios are presented in Table 4.

We also calculated the number and cost of the closed-transfer devices we used during the preparation of the cytotoxic drug (Table 5).

The overall cost was calculated and is shown in Table 6.

Discussion

In recent years, more and more research has been done on the chemical and physical stability of cytotoxic drugs after dissolving and in dilution [1-14]. Given conflicting interests, this type of research is mostly done by, for example, academics or hospital pharmacists rather than the pharmaceutical industry. Most often, the expiry time is limited to 24 hours, arguing that sterility cannot be guaranteed over a longer period. It cannot be emphasised enough that strict sterile procedures must be implemented in order to conserve the product over a longer period, which will then result in substantial savings.

Different scenarios for preparation and conservation can lead to a minimum saving of 7% and a maximum of 15% on the total accumulated cost of drug and transfer device.

The contribution of the use of closed-transfer devices to savings is limited and represents, depending on the scenario, only 2.2% to 4.3% of the cost of the drugs.

Conclusion

The use of multi-dose vials until the end of their physical and chemical expiry dates can save a substantial amount of money in the range of Euros 300,000 to Euros 700,000 per year for our hospital.

On average, the overall cost of cytotoxic preparation can be decreased by 7% to 15% depending on the applied scenario.

The challenges in using this beneficial scenario are the availability of devices, the necessary setting (apparatus and environment), methods and procedures that are validated to ensure that the contents of the vials remain sterile and that sterility can be guaranteed until the expiry date.

The possible savings can be a supplementary argument for investing in a better work-setting (such as a clean room and flow cabinets) and devices to ensure the safe and sterile handling of cytotoxic drugs.

Appendix 2: Details of the three scenarios: the total number of vials used (expressed in mg), the percentage compared with the administered dose, the number of vials and specific dosages used, and the number of protectors used are shown

Product	N	mg	Scenario 1: Amounts used per preparation							Scenario 2: Amounts used per day							Scenario 3: Amounts used until the expiry date						
Amsacrine	13	2,262	mg	%	75				Prot	mg	%	75				Prot	mg	%	75				Prot
			2,925	129	39				39	2,925	129	39				39	2,400	106	32				32
Bevacizumab	29	11,283	mg	%	100	400			Prot	mg	%	100	400			Prot	mg	%	100	400			Prot
			12,400	110	36	22			58	12,100	107	33	22			55	11,600	103	0	29			29
Bleomycin	30	493	mg	%	15				Prot	mg	%	15				Prot	mg	%	15				Prot
			555	113	37				37	555	113	37				37	495	100	33				33
Bortezomib	64	143	mg	%	3,5				Prot	mg	%	3,5				Prot	mg	%	3,5				Prot
			221	154	63				63	203	142	58				58	203	142	58				58
Carboplatin	84	47,880	mg	%	150	450			Prot	mg	%	150	450			Prot	mg	%	150	450			Prot
			53,850	112	89	90			179	50,850	106	36	101			137	48,150	101	0	107			107
Cetuximab	92	43,465	mg	%	500				Prot	mg	%	500				Prot	mg	%	500				Prot
			59,000	136	118				118	48,500	112	97				97	43,500	100	87				87
Cisplatin	179	15,403	mg	%	10	50	100		Prot	mg	%	10	50	100		Prot	mg	%	10	50	100		Prot
			16,350	106	390	83	83		556	15,950	104	105	26	136		267	15,500	101	0	0	155		155
Cyclophosphamide	230	266,165	mg	%	500	1,000			Prot	mg	%	500	1,000			Prot	mg	%	500	1,000			Prot
			325,500	122	139	256			395	278,000	104	32	262			294	267,000	100	0	267			267
Cytarabine	166	133,432	mg	%	100	500	1,000	2,000	Prot	mg	%	100	500	1,000	2,000	Prot	mg	%	100	500	1,000	2,000	Prot
			145,300	109	353	44	24	32	453	136,000	102	140	28	48	48	264	134,000	100	0	0	0	67	67
Dacarbazine	63	25,938	mg	%	500				Prot	mg	%	500				Prot	mg	%	500				Prot
			31,500	121	63				63	31,500	121	63				63	26,500	102	53				53
Dactinomycin Cosmegen	7	4,826	µg	%	500				Prot	µg	%	500				Prot	µg	%	500				Prot
			7,500	155	15				15	7,500	155	15				15	7,500	155	15				15
Daunorubicin	8	712	mg	%	20				Prot	mg	%	20				Prot	mg	%	20				Prot
			800	112	40				40	800	112	40				40	740	104	37				37
Docetaxel	78	9,868	mg	%	20	80			Prot	mg	%	20	80			Prot	mg	%	20	80			Prot
			10,540	107	99	107			206	10,160	103	48	115			163	9,920	101	0	124			124
Doxorubicin	177	10,978	mg	%	10	50	200		Prot	mg	%	10	50	200		Prot	mg	%	10	50	200		Prot
			11,690	106	294	175	0		469	11,760	107	86	66	38		190	11,000	100	0	0	55		55
Liposomal doxorubicin	25	1,316	mg	%	20	50			Prot	mg	%	20	50			Prot	mg	%	20	50			Prot
			1,450	110	10	25			35	1,390	106	12	23			35	1,350	103	0	27			27
Epirubicin	99	16,468	mg	%	10	50	200		Prot	mg	%	10	50	200		Prot	mg	%	10	50	200		Prot
			17,070	104	222	241	14		477	16,810	102	71	66	64		201	16,600	101	0	0	83		83
Etoposide	182	34,311	mg	%	100	200	500		Prot	mg	%	100	200	500		Prot	mg	%	100	200	500		Prot
			42,200	123	34	149	18		201	37,000	108	24	63	44		131	34,500	101	0	0	69		69
Fludarabine	20	900	mg	%	50				Prot	mg	%	50				Prot	mg	%	50				Prot
			1,150	128	23				23	1,150	128	23				23	900	100	18				18
Fluorouracil	718	1,293,279	mg	%	500	1,000	5,000		Prot	mg	%	500	1,000	5000		Prot	mg	%	500	1,000	5,000		Prot
			1,500,000	116	190	1,095	62		1,347	1,306,500	101	19	107	238		364	1,295,000	100	0	0	259		259
Gemcitabine	151	266,885	mg	%	200	1,000			Prot	mg	%	200	1,000			Prot	mg	%	200	1,000			Prot
			281,200	105	271	227			498	270,200	101	96	251			347	267,000	100	0	267			267
Idarubicin	26	552	mg	%	10				Prot	mg	%	10				Prot	mg	%	10				Prot
			720	130	72				72	690	125	69				69	570	103	57				57
Ifosfamide	45	108,569	mg	%	1,000				Prot	mg	%	1,000				Prot	mg	%	1,000				Prot
			160,000	147	160				160	128,000	118	128				128	109,000	100	109				109
Irinotecan	103	31,470	mg	%	40	100			Prot	mg	%	40	100			Prot	mg	%	40	100			Prot
			33,220	106	133	279			412	32,040	102	41	304			345	31,500	100	0	315			315
Melphalan	5	1,530	mg	%	50				Prot	mg	%	50				Prot	mg	%	50				Prot
			1,600	105	32				32	1,600	105	32				32	1,600	105	32				32
Methotrexate low dose	42	881	mg	%	5	50			Prot	mg	%	5	50			Prot	mg	%	5	50			Prot
			920	104	124	6			130	920	104	124	6			130	920	104	94	9			103

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Appendix 2: Continued

Product	N	mg	Scenario 1: Amounts used per preparation						Scenario 2: Amounts used per day						Scenario 3: Amounts used until the expiry date					
Methotrexate high dose	15	160,442	mg	%	500	1,000	5,000	Prot	mg	%	500	1,000	5,000	Prot	mg	%	500	1,000	5,000	Prot
			164,000	102	6	31	26	63	164,000	102	4	32	26	62	165,000	103	0	0	33	33
Mitomycin	12	105	mg	%	2	10		Prot	mg	%	2	10		Prot	mg	%	2	10		Prot
			110	105	30	5		35	110	105	25	6		31	110	105	0	11		11
Mitoxantrone	12	249	mg	%	20	25		Prot	mg	%	20	25		Prot	mg	%	20	25		Prot
			265	106	7	5		12	265	106	7	5		12	250	100	0	10		10
Oxaliplatin	116	19,215	mg	%	50	100		Prot	mg	%	50	100		Prot	mg	%	50	100		Prot
Eloxatin			22,050	115	45	198		243	19,950	104	17	191		208	19,300	100	0	193		193
Paclitaxel	24	7,151	mg	%	30	100	300	Prot	mg	%	30	100	300	Prot	mg	%	30	100	300	Prot
			7,550	106	45	20	14	79	7,500	105	40	18	15	73	7,200	101	0	0	24	24
Pemetrexed	19	17,212	mg	%	500			Prot	mg	%	500			Prot	mg	%	500			Prot
			21,500	125	43			43	21,500	125	43			43	18,000	105	36			36
Teniposide	9	1,691	mg	%	50			Prot	mg	%	50			Prot	mg	%	50			Prot
			1,900	112	38			0	1,900	112	38			0	1,900	112	38			0
Topotecan	5	30	mg	%	4			Prot	mg	%	4			Prot	mg	%	4			Prot
			40	133	10			10	40	133	10			10	32	107	8			8
Trastuzumab	62	25,916	mg	%	150			Prot	mg	%	150			Prot	mg	%	150			Prot
			30,150	116	201			201	28,500	110	190			190	26,400	102	176			176
Vinblastine	20	196	mg	%	10			Prot	mg	%	10			Prot	mg	%	10			Prot
			200	102	20			20	200	102	20			20	200	102	20			20
Vincristine	133	203	mg	%	1	2		Prot	mg	%	1	2		Prot	mg	%	1	2		Prot
			232	114	34	99		133	218	107	20	99		119	204	100	0	102		102
Vindesine	8	33	mg	%	5			Prot	mg	%	5			Prot	mg	%	5			Prot
			40	121	8			8	40	121	8			8	40	121	8			8
Vinorelbine	12	526	mg	%	10	50		Prot	mg	%	10	50		Prot	mg	%	10	50		Prot
			580	110	13	9		22	570	108	12	9		21	550	105	0	11		11

Key: N: number of vials used, Prot: number of protectors used

Appendix 3: The cost of used drug vials for each scenario (in Euros)

Product	Scenario 1	Scenario 2	Scenario 3
Amsacrine	1,771	1,771	1,453
Bevacizumab (study product)	0	0	0
Bleomycin	1,085	1,085	968
Bortezomib	76,777	70,684	70,684
Carboplatin	36,647	33,791	31,418
Cetuximab (Erbitux)	25,730	21,151	18,970
Cisplatin	12,645	10,983	10,137
Cyclophosphamide	2,207	2,076	2,061
Cytarabine	5,851	5,807	3,723
Dacarbazine	1,594	1,594	1,341
Dactinomycin	28	28	28
Daunorubicin	587	587	543
Docetaxel	84,337	81,043	78,878
Doxorubicin	14,139	12,191	10,420
Liposomal doxorubicin	34,575	33,214	31,920
Epirubicin	33,255	30,153	28,662
Etoposide	4,681	4,864	5,196
Fludarabine	3,237	3,237	2,534
Fluorouracil	11,498	8,942	8,728
Gemcitabine	40,766	38,052	36,955
Idarubicin	12,866	12,330	10,186
Ifosfamide	2,747	2,198	1,872
Irinotecan	65,332	62,640	61,412
Melphalan	386	386	386
Methotrexate low dose	531	531	465
Methotrexate high dose	20,491	20,469	19,902
Mitomycin	365	359	327
Mitoxantrone	1,696	1,696	1,588
Oxaliplatin	97,121	87,787	84,868
Paclitaxel	34,717	34,437	32,640
Pemtrexed	66,123	66,123	55,359
Teniposide	203	203	203
Topotecan	2,771	2,771	2,217
Trastuzumab	134,853	127,473	118,080
Vinblastine	410	410	410
Vincristine	1,934	1,796	1,648
Vindesine	851	851	851
Vinorelbine	1,390	1,365	1,296

Table 2: The top 10 drugs and the differences in cost (in Euros), in scenario 1 compared with scenario 3

Product	Loss in scenario 1
Trastuzumab	16,773
Oxaliplatin	12,253
Pemtrexed	10,764
Cetuximab	6,760
Bortezomib	6,093
Docetaxel	5,460
Carboplatin	5,228
Epirubicin	4,593
Irinotecan	3,919
Gemcitabine	3,810

Table 3: The top 10 drugs and the differences in cost (in Euros), in scenario 2 compared with scenario 3

Product	Loss in scenario 2
Pemtrexed	10,764
Trastuzumab	9,393
Oxaliplatin	2,919
Carboplatin	2,372
Cetuximab	2,181
Docetaxel	2,165
Idarubicine	2,144
Cytarabine	2,084
Paclitaxel (Taxol)	1,798
Doxorubicin	1,770

Table 4: Total drug cost (in Euros) and difference for each scenario

	Scenario 1	Scenario 2	Scenario 3
Financial value of used drug vials	836,198	785,079	738,329
Difference compared with scenario 3	97,869	46,750	
Per cent	**+13%**	**+6%**	

Table 5: Number and cost (in Euros) of the closed-transfer devices used in cytotoxic preparation

	Scenario 1		Scenario 2		Scenario 3	
Protector type	Number	Cost	Number	Cost	Number	Cost
Total p14	272	1,523	258	1,445	211	1,181
Total p21	4,119	20,183	2,632	12,897	1,695	8,306
Total p50	2,459	14,508	1,337	7,888	1,123	6,626
Total	**6,850**	**36,214**	**4,227**	**22,230**	**3,029**	**16,113**
Per cent		**+125%**		**+40%**		

Table 6: Total cost (in Euros)

	Scenario 1	Scenario 2	Scenario 3
Product	836,198	785,079	738,329
Protector	36,214	22,230	16,113
Total	**872,412**	**807,309**	**754,442**
Difference with scenario 3	**117,970**	**52,867**	
Difference in % with scenario 3	**+15.6%**	**+7.0%**	

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