Health economics of targeted cancer therapies

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CHAPTER 7

MICRO-COSTING STUDY OF RITUXIMAB SUBCUTANEOUS INJECTION VERSUS INTRAVENOUS INFUSION

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Micro-costing study of rituximab subcutaneous injection versus intravenous infusion.
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Abstract

Introduction: The goal of this study is to identify and compare all direct costs of intravenous (IV) and subcutaneous (SC) rituximab given to the diffuse large B-cell lymphoma (DLBCL) patients in the Netherlands.

Methods: Using a prospective, observational, bottom up, micro-costing study we collected primary data on the direct medical costs of the preparation, administration and acquisition of rituximab. Drug costs and spillage, labor costs, material costs and daycare costs were identified using standardized forms, structured using prices from official pricelists and compared for the IV and SC forms of rituximab.

Results: Measurements were done on 53 rituximab administrations (33 IV and 20 SC) and on 13 rituximab preparations (7 IV and 6 SC). The mean total costs of the IV infusion were €2176.77, and €1911.09 for the SC injection. The estimated difference of €265.17 (95% confidence interval: 231.99-298.35) per administration was mainly due to differences in time spent in chemotherapy unit, related daycare costs, spillage and drug costs.

Conclusion: Rituximab administered in the form of SC injection is less costly than its IV form. Taking into account their equal effectiveness, economic SC rituximab administration can result in significant savings when transferred to the total DLBCL population in the Netherlands.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of Non-Hodgkin Lymphoma (NHL) comprising 30-58% of NHL cases [1]. It affects 3-4 people of all ages in 100,000 in the European Union (EU) and its incidence increases with age [1]. In 2012, there were 3,922 newly diagnosed patients with different types of NHL in the Netherlands, out of which around 1,000 had DLBCL. These figures have shown an inclining trend during the last decade [2]. The disease is frequently presented in an aggressive form, which results in lower survival rates for DLBC than in other NHLs and requires more intensive treatment [3].

Rituximab (MabThera®) combined with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) is the standard initial treatment of DLBCL [4]. In several clinical trials this therapeutic regimen has shown a significant increase in effectiveness and a comparable toxicity profile when compared with previous mainstay chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine and prednisolone only (CHOP) [5-7]. A regular full R-CHOP treatment consists of 8 cycles rituximab combined with 6 (for elderly patients) or 8 cycles of CHOP, once every fourteen or twenty-one days. A dose of 375 mg/m^2 of rituximab is applied. An exception applies to younger patients with a favorable prognostic profile, receiving only 6 cycles. Premedication before R-CHOP is generally applied, consisting of analgesic/anti-pyretic and antihistaminic drugs. Each first infusion of rituximab takes three to five hours, during which the infusion speeds up each half an hour. Subsequent treatments take less time because infusion rates are increased according to the Summary of Product Characteristics (SmPC) [8]. Prior, during and after the infusion, several health checks are performed to make sure there are no complications related to the infusion. Taking all of the above into account, the normal intravenous (IV) treatment of a single patient with rituximab is very time and health-care resource consuming. Some sources support the feasibility and safety of a 90-minute regimen for the subsequent administrations for NHL patients [9,10] and hospitals have adopted such practice; however, this infusion rate is formally not in accordance with the European SmPC [8].

Furthermore, the preparation of IV infusion of rituximab may involve a considerable time investment. As the compounding of rituximab as concentrate for solution for infusion is based on the body surface area (BSA), each dose of rituximab is personalized and involves work of hospital pharmacist. Finally, spillage may be an issue in preparing the required dosages as rituximab concentrate for solution for infusion is supplied in vials of 100 mg or 500 mg and unused material in a vial is usually discarded.

Recently, rituximab for subcutaneous (SC) administration has been approved for use in common forms of NHL - follicular lymphoma and DLBCL [8,11]. However, the only currently published trial on comparative efficacy of SC and IV rituximab investigates its use in follicular lymphoma (SABRINA trial) [12], while the study that is being conducted for DLBCL patients (MabEase trial) is expected to be completed in August 2016 [13]. The SABRINA trial proved rituximab SC injection as effective and safe as IV infusion of rituximab.

The SC formulation is 12-fold more concentrated then the concentrate used as solution for IV and supplied in ready-to-use vials of 11.7 ml [8]. The content of the vial contains 1400 mg of rituximab, corresponding to a single dose for SC administration. Notably, this dose is uniform for all patients, while the exact IV dose of rituximab needs to be

adjusted according to a patients' BSAs. Rituximab SC is co-formulated with the enzyme recombinant human hyaluronidase. This enzyme transiently degrades interstitial hyaluronan at the injection site, increasing the volume that can be administered and facilitating drug entry into the circulation [14].

It is expected that SC-injections will shorten the treatment time per administration of rituximab in comparison with IV-infusions. The pharmacy preparation time is expected to decrease as well as the administration time in the ward. Additionally, spillage of rituximab during the preparation could be prevented. Similarly, use of a single injection can potentially make disposable items (for example, dedicated infusion line or cannula) as well as (dis)connection of these items, redundant. Logically, the decreases in time investments and absence of spillage should result in lower overall costs for SC as compared to SC rituximab.

The aim of this study is to identify all costs related to the process of preparing and administrating rituximab and explicitly comparing the costs for IV and SC rituximab within a cost-minimization framework. The a-priori assumption is that SC administration will result in lower costs than IV administration. For this purpose, micro-costing analysis was performed to capture all costs in a high level of detail.

Methods

Ethics statment

This study follows clinical study MabEase with respect to costs of individual patients. However, no personal patient data were available to the authors at any point of this study. Therefore, ethics committee approval, or any other specific approval was not needed for the conduct of this study in the context of the national Dutch setting.

Study setting, inclusion, measurements & costing

The design of the study is a prospective, observational, bottom-up, micro-costing study enabling cost-minimization analysis. The study was conducted alongside the MabEase phase IIIB international clinical trial of Hoffmann-La Roche (designated number in EU Clinical Trials Register: EudraCT number 2012-000669-19) [15]. In this trial, previously untreated CD20 positive DLBCL patients were randomized to investigate the efficacy of SC rituximab versus IV rituximab, both in combination with CHOP. Our data were collected from December 2012 until January 2014 in several hospitals in the Netherlands: Isala Clinics in Zwolle, Medical Center Leeuwarden (MCL), AZC Dordrecht, MC Alkmaar, OMC Sittard-Geleen and Maasstad Hospital in Rotterdam. Dutch patients randomized to SC or IV in the MabEase study were eligible for inclusion in this micro-costing study. No additional exclusion criteria were used. Both the MabEase study and this micro-costing study were designed to interfere as little as possible with the daily practice. Consequently the monitored processes realistically reflected the daily hospital procedures.

In the presented study we measured time and respective costs spent by nurse, time and respective costs spent in chemotherapy unit (chair), BSAs and administered doses for 20 administrations of SC rituximab and 33 administrations of IV rituximab. More IV infusions were measured than SC injections, as larger variance in treatment time for the IV infusion was expected. Given the specific nature of the first administration and the fact that the first administration is always IV according to the SmPC [8], only subsequent administrations were included in the micro-costing study. Furthermore, maximally

3 administrations per patient were measured to avoid single patients to become too influential in the overall analysis.

As for pharmaceutical preparation of injections/infusions, we observed 6 and 7 measurements for rituximab SC and rituximab IV, respectively, for analysis of preparation time and costs (related to the time and costs of pharmacist's assistant labor). These numbers of measurements were considered sufficient given the minimal variance in the respective observations.

Variables measured in our study were collected on four case report forms: i) for IV-administration, ii) for SC-administration, (iii) for IV-preparation and iv) for SC-preparation. Two researchers performed the measurements (PB and EvB) and aligned their approach for consistency a-priori and during the study. Case report forms were used to achieve further uniformity in observation.

Costs were categorized into four classes: i) drug costs including spillage, ii) labor costs, iii) daycare treatment costs and iv) material costs. Costing was done in line with the costing guidelines for the Netherlands [16]. All costs were expressed in 2014 €'s; if initially expressed in other price years appropriate adjustment was undertaken using annual deflators [16].

Drug costs including spillage

The drug costs of IV rituximab were retrieved from the list price and amounted to €540.82 for the package of two vials containing 100mg rituximab and €1351.07 for the package of one vial containing 500mg of rituximab (costs as of September 2014). The costs of a 1400 mg fixed dose SC rituximab is €1822.15 (September 2014). In accordance with their official posology [8], rituximab IV was given in doses of 375 mg/m^2, while rituximab SC was given in a unique dose of 1400mg for all patients regardless of their BSA. As explained earlier in the text, we measured time and costs spent for 33 IV administrations and 20 SC administrations. Additionally, we also measured BSAs of patients and recorded administered doses. In order to calculate drug costs, an average dose [mg] for IV and SC administration was multiplied by the cost of 1mg of IV and SC rituximab, respectively.

While SC rituximab consists of a single dose injection given as "one-size-fits-all" equally to each patient, IV rituximab is known to be delivered with potential spillage. However, since 33 measurements for IV administration were not taken with subsequent vials (e.g. the first and the second measurement did not happen with the vial number N and vial number N+1 at the certain clinic), this prevented us from estimating the spillage on the original sample. Thus, data on spillage was retrieved from much bigger samples with subsequent IV rituximab administrations. Included were samples from hospital pharmacies in the Isala Clinics from Zwolle (412 preparations) and MCL from Leeuwarden (517 preparations) for the year 2012 using claims data. Since claims data contained general information on patients, including body weight and body surface area, it was possible to calculate recommended doses from these data. The difference between calculated doses collected from claims data and doses that are actually prescribed and infused was considered spillage. Finally, the total drug costs for IV administration were calculated by adding the average spillage per infusion to the average drug costs per infusion.

Labor costs

Wage costs of the staff involved were specified by distinguishing the tasks performed throughout the whole process of preparation and administration. For example, a nurse

does the health check and a pharmacist's assistant does the pharmacy preparation, with varying hourly wages [16,17]. Total labor costs were calculated by multiplying the hourly wages for each employee and activity by the total time invested in the activity. The reference value for the labor costs per hour of a nurse in the Netherlands is €30.23 [16]. Based on the average monthly wage of a pharmacy assistant with a 36-hour week, the hourly salary is €21.43 [17]. Two pharmacy assistants are required to prepare rituximab. One assistant prepares the administration while the other oversees the process. As mentioned, all these time investments were exactly observed and recorded.

Daycare treatment costs

According to the Dutch costing guideline, standard daycare treatment costs include direct labor costs (medical specialists, residents, nurses, administrative staff), indirect labor costs (for example, laundry and cleaning), hotel, nutrition, overheads (general expenses, maintenance and energy, rent and leasing) and capital (depreciation of inventory and interest) [16]. Standard daycare treatment costs were estimated earlier in the study specifically designed to assess these costs in oncology/hematology departments in the Netherlands [18]. On average, daycare treatment amounted to €305 or €162 when direct labor costs were excluded, given in 2007 prices [18]. To avoid double counting of direct labor, we have taken the latter estimate and inflated it to 2014 prices (inflation rate of 13.88% for period 2007-2013 [19]) to get €184.48. This value was ascribed to the cost of daycare treatment for IV rituximab (current practice). Subsequently, it was divided by the average time [min] spent in the chemotherapy unit during rituximab IV administration to get per minute cost of daycare treatment for rituximab administration. Per minute cost of daycare treatment was then multiplied by the average time of SC administration to obtain the cost of rituximab SC daycare treatment cost. In this way the difference in costs between two administrations correlated with the difference in time observed for these administrations.

Material costs

Non-disposables were already taken into account in the daycare treatment costs' calculus. Remaining disposable materials and corresponding quantities were recorded during the process mapping and during the actual measurements. The prices of the different type of disposables were retrieved from the suppliers' catalogue, obtained from the Isala Clinics' hospital pharmacy [16]. The total costs of disposables were calculated as the sum of quantity times the prices of the various materials.

Statistical analysis

The differences between the costs of IV and SC administrations were estimated using Excel 2013 for Windows. All observed variables and calculated cost items were described with standard statistical parameters, such as standard deviation and 95% confidence intervals (CI), assuming normal distribution. Student's t-test was used for statistical significance, with the level of significance set to 5% (α=0.05). Statistical analysis with t-test could have been performed for comparison of following costs items: drug costs, labor costs (nurse cost), labor costs (preparation cost) and daycare treatment costs as for these items we conducted measurements as explained above. However, spillage costs and material costs were estimated relying on mean values from data other than those from MabEase trial. Therefore, we could not calculate statistical significance parameters for the estimate of difference in total costs. Final estimate was, thus, described with standard deviation and 95% CI.

Results

Drug costs inclusive spillage

Based on measurements of BSA and dose for 33 IV administrations, the mean drug cost of IV rituximab was €1907.49 per administration (95% CI: €1835.19-1979.79), which corresponded to the average BSA od 1.8821 m^2 and the average dose of 705.77 mg (Table 1). On the other side, SC rituximab was always given in unique dose (1400 mg) and had constant cost of €1822.15 regardless of BSA (mean of 1.8858 m^2). Drug costs' difference was estimated at €85.34 with statistical significance (p=0.0273).

The average spillage per pharmacy preparation of the IV infusion based on secondary data from Isala Clinics Zwolle (412 preparations with mean spillage of €100) and MCL (517 preparations with mean spillage of €44.50) was calculated at €69.11. Taking these data into account, difference in drug costs including spillage was €154.45.

Labor costs

The average nursing time was 13.65 minutes (95% CI: 12.33-14.97 min.) and 16.50 minutes (95% CI 15.16-17.84 min.) for the IV and SC administrations of rituximab, respectively. Consequently, the average labor costs of nursing were €6.88 (95% CI: €6.22-7.54) and €8.31 (95% CI: €7.63-8.99) for the IV and SC administration, respectively. The difference of €1.43 was statistically significant (p=0.005). Measurements of time and respective costs spent by nurse are given in Table 2.

The average duration of a pharmacy preparation was 242.57 (95% CI: 224.88-260.26) and 226.5 (95% CI: 197.03-255.97) seconds for the IV infusion and SC injection, respectively. The average labor costs of a pharmacy preparation were €2.89 (95% CI: €2.68-3.10) for the IV infusion and €2.70 (95% CI: €2.35-3.05) for the SC injection. The difference of €0.19 was not statistically significant (p=0.4119). Measurements of preparation time and respective cost for both IV and SC rituximab are shown in Table 3.

The total costs of labor and administration were, therefore, €9.77 and €11.01 for the IV infusion and SC injection, respectively. Consequently, the estimated difference in labor and administration costs between SC and IV rituximab was €1.24.

Daycare treatment costs

The average daycare costs per minute were calculated at €1.26. Since mean time spent in chemotherapy unit by a patient receiving an IV infusion was 139.30 (95% CI: 128.74-149.86) minutes, daycare cost of IV rituximab administration reached €184.48 (95% CI: €170.49-198.47) (Table 2). For SC rituximab, time spent in chemotherapy unit was measured at 57.80 (95% CI: 44.75-70.85) minutes. If transferred in monetary values, this amounted to €76.55 (95% CI: €59.26-93.83) (Table 2). The estimated difference in daycare costs between IV and SC administration of €107.94 was found statistically significant (P<0.00001).

Material costs

The costs of the various disposables used in the pharmacy preparation of the IV and SC rituximab are presented in Table 4. Costs of disposables for the IV infusion were based on one estimate of €5.40, as opposed to €1.38 for the SC-injection. Hence, a difference in material costs was estimated at €4.02.

Table 1: Measurements of BSA, doses and drug costs

IV rituximab				*SC rituximab*			
Measurement number	***BSA (m^2)***	***Dose (mg)***	***Cost (€)***	***Measurement number***	***BSA (m^2)***	***Dose (mg)***	***Cost (€)***
1	1.6520	619.49	1674.18	1	1.6152	1400	1822.15
2	2.1829	818.59	2212.57	2	1.7455	1400	1822.15
3	1.8821	705.77	1907.49	3	1.7695	1400	1822.15
4	1.4277	535.37	1446.72	4	1.7177	1400	1822.15
5	1.8004	675.14	1824.65	5	1.8204	1400	1822.15
6	1.9637	736.40	1990.33	6	1.8473	1400	1822.15
7	1.8661	699.79	1891.32	7	1.6791	1400	1822.15
8	2.1438	803.92	2172.91	8	1.7501	1400	1822.15
9	1.7032	638.71	1726.15	9	1.7921	1400	1822.15
10	1.9994	749.79	2026.53	10	1.8821	1400	1822.15
11	1.6203	607.61	1642.07	11	1.8880	1400	1822.15
12	1.8980	711.75	1923.66	12	1.9740	1400	1822.15
13	2.0186	756.97	2045.93	13	1.9603	1400	1822.15
14	1.7252	646.94	1748.41	14	2.0518	1400	1822.15
15	1.8338	687.68	1858.59	15	2.0289	1400	1822.15
16	2.3364	876.17	2368.26	16	1.9312	1400	1822.15
17	1.5812	592.95	1602.41	17	1.9594	1400	1822.15
18	2.0609	772.83	2088.83	18	2.1735	1400	1822.15
19	1.7455	654.57	1769.04	19	2.0189	1400	1822.15
20	2.0850	781.87	2113.28	20	2.1109	1400	1822.15
21	1.8173	681.49	1841.83				
22	1.9303	723.85	1956.39				
23	1.6791	629.67	1701.70				
24	1.7829	668.58	1806.92				
25	1.9468	730.05	1973.15				
26	2.1121	792.05	2140.80				
27	2.0389	764.60	2066.57				
28	1.5274	572.78	1547.86				
29	1.8501	693.77	1875.05				
30	1.9812	742.96	2008.06				
31	1.9140	717.77	1939.93				
32	1.7647	661.75	1788.45				
33	2.2367	838.76	2267.12				
Mean	***1.8821***	***705.77***	***1907.49***		***1.8858***	***1400.00***	***1822.15***
Lower limit of 95% CI	1.8108	679.03	1835.19		1.8198	1400.00	1822.15
Upper limit of 95% CI	1.9533	732.51	1979.79		1.9518	1400.00	1822.15
Standard deviation	0.2090	78.3649	211.9065		0.1505	0.0000	0.0000

Table 2: Measurements of nurses' and daycare time and costs

IV rituximab					*SC rituximab*				
Measurement number	*Total nurse time (min)*	*Nurse costs (€)*	*Total chair time (min)*	*Daycare costs excl. nurse costs (€)*	*Measurement number*	*Total nurse time (min)*	*Nurse costs (€)*	*Total chair time (min)*	*Daycare costs excl. nurse costs (€)*
1	17.93	9.04	147	194.68	1	15.97	8.04	60	79.46
2	16.85	8.49	150	198.65	2	17.55	8.84	85	112.57
3	12.58	6.34	140	185.41	3	12.85	6.47	17	22.51
4	11.73	5.91	133	176.14	4	15.92	8.02	55	72.84
5	15.65	7.88	125	165.54	5	19.85	10	80	105.95
6	9.37	4.72	105	139.06	6	19.98	10.07	85	112.57
7	8.33	4.2	100	132.43	7	17.22	8.67	95	125.81
8	11.45	5.77	126	166.87	8	15.62	7.87	24	31.78
9	13.57	6.84	109	144.35	9	11.82	5.95	27	35.76
10	8.58	4.32	140	185.41	10	16.25	8.19	60	79.46
11	15.88	8	105	139.06	11	16.22	8.17	29	38.41
12	11.97	6.03	225	297.98	12	21.57	10.87	92	121.84
13	13.67	6.89	126	166.87	13	16.15	8.14	30	39.73
14	7.88	3.97	123	162.89	14	17.77	8.95	48	63.57
15	12.9	6.5	125	165.54	15	19.12	9.63	21	27.81
16	9.25	4.66	160	211.89	16	17.67	8.9	112	148.33
17	13.03	6.57	129	170.84	17	16.92	8.52	73	96.68
18	8.7	4.38	126	166.87	18	11.8	5.84	67	88.73
19	15.22	7.67	179	237.06	19	9.75	4.91	16	21.19
20	17.65	8.89	115	152.30	20	19.95	10.05	80	105.95
21	18.4	9.27	161	213.22					
22	19.78	9.97	138	182.76					
23	7.23	3.64	138	182.76					
24	19.72	9.93	126	166.87					
25	16.58	8.36	124	164.22					
26	10.9	5.49	119	157.60					
27	17.33	8.73	157	207.92					
28	12.97	6.53	103	136.41					
29	12.3	6.2	138	182.76					
30	20.22	10.19	230	304.60					
31	19.7	9.93	196	259.57					
32	11.52	5.8	138	182.76					
33	11.67	5.88	141	186.73					
Mean	***13.65***	***6.88***	***139.3***	***184.48***		***16.50***	***8.31***	***57.80***	***76.55***
Lower limit of 95% CI	12.33	6.22	128.74	170.49		15.16	7.63	44.75	59.26
Upper limit of 95% CI	14.97	7.54	149.86	198.47		17.84	8.99	70.85	93.83
Standard deviation	3.8622	1.9467	30.9521	40.9909		3.0532	1.5478	29.7757	39.4330

Table 3: Measurements of preparation times and costs

IV rituximab			SC rituximab		
Measurement number	Preparation time (sec)	Costs (€)	Measurement number	Preparation time (sec)	Costs (€)
1	230	2.74	1	220	2.62
2	249	2.96	2	225	2.68
3	281	3.34	3	206	2.45
4	260	3.09	4	171	2.04
5	219	2.61	5	289	3.44
6	213	2.54	6	248	2.95
7	246	2.93			
Mean	242.57	2.89		226.5	2.7
Lower limit of 95% CI	224.88	2.68		197.03	2.35
Upper limit of 95% CI	260.26	3.10		255.97	3.05
Standard deviation	23.8807	0.2806		39.7832	0.4722

Table 4: Costs of disposables

IV rituximab		*SC rituximab*	
Disposable item	**Cost (€)**	**Disposable item**	**Cost (€)**
White clamp	0.10	Seal bag	0.10
Connect Z clip	0.25	Injection needle	0.14
Codan spike (2x)	1.82	Syringe LL 20 ml	0.23
Syringe LL 50 ml	0.30	Codan spike	0.91
Seal bag	0.10		
Connect set	2.10		
0,9% NaCl infusion	0.73		
Total costs	***5.40***	***Total costs***	***1.38***

Total costs

All costs and descriptive statistical parameters are summarized in Table 5. When all individual cost items are summed up, total costs of an IV rituximab administration resulted in €2176.26 (95% CI: €2134.77-2217.74) and total costs of a SC rituximab administration in €1911.09 (95% CI: €1901.42-1920.76). Ergo, the difference in total costs between IV and SC administration methods was estimated at €265.17 (95% CI: €231.99-298.35), suggesting that this amount would be saved per each administration of SC rituximab if it replaces IV rituximab.

Table 5: Total costs and difference between intravenous and subcutaneous rituximab administration

Cost item	*Costs for IV rituximab administration*	*Costs of SC rituximab administration*	*Costs' difference*	*p-value**
Drug costs	1907.49	1822.15	85.34	0.0273
Spillage cost	69.11	0.00	69.11	N/A
Material costs	5.40	1.38	4.02	N/A
Labor costs (nurse)	6.88	8.31	-1.43	0.0050
Labour costs (preparation)	2.89	2.70	0.19	0.4119
Daycare costs	184.48	76.55	107.94	<0.0001
Total costs	***2176.26***	***1911.09***	***265.17***	
Lower limit of 95% CI	2134.77	1901.42	231.99	
Upper limit of 95% CI	2217.74	1920.76	298.35	
Standard deviation	107.9218	19.7331	77.5774	

*- p-value could not have been calculated for the estimated costs difference

Discussion

This study shows that SC rituximab has the potential to be cost saving compared to IV injection. Cost savings are primarily related to drug prices, drug spillage and time spent in chemotherapy unit (daycare costs). Drug costs savings derive from the difference in posology, since SC rituximab is given always in the same dose, while IV rituximab adjusts to the BSAs of the patients. With the current price of SC rituximab dose and an average IV rituximab dose referring to the European SmPC (dose 375 mg/m^2, BSA 1.89 m^2), SC rituximab is expected to save costs within Dutch setting. Additionally to the direct drug cost savings, spillage that is inevitable in use of IV rituximab would not occur in administration of SC rituximab contributing to further cost decreases. Time savings achieved in chemotherapy unit, due to significantly faster SC administration as compared to IV, further contribute to the costs difference and notably enhances patients' comfort. Finally, it may also enhance hospital management as, due to time savings, chemotherapy unit becomes available for more patients.

Other cost items, such as material and labor costs, differed only marginally between SC and IV rituximab. Formulation of rituximab for SC administration seems to induce less material, yet, insignificantly more labor costs than IV formulation. For the moment, the novelty of SC rituximab may explain current lack of advantage in labor costs. However, it is expected that preparation time of SC rituximab will shorten through time, thus enabling further cost savings beyond those identified here.

It should be noted that the primary outcome of our study, cost difference between IV and SC rituximab, significantly depends on the administration rate applied for IV infusion of rituximab. The study design of the MabEase clinical trial allowed all administration rates used in clinical practice. For instance, the fastest available technique that requires only one hour of infusion at constant rate (from second cycle onwards) was allowed. All other advised infusion regimens require considerably more time for IV application. For example, the European SmPC of IV rituximab suggests infusion rates that result in

approximately 2.5 hours of infusion time [8]. The recommendation in the USA suggests a rate that would require 1.5 hour for the infusion [20]. It seems that the protocol of the MabEase trial resulted in shorter IV infusion times, and that for hospitals applying administration rates, as specified in the EU SmPC, cost savings for SC rituximab use could appear even higher than these estimated.

Variations in settings were observed among different Dutch hospitals in the MabEase study, for example resulting in differences in time spent in chemotherapy units. Notably, administration of pre-medication differed per hospital, although similar for IV- and SC-administrations within one and the same hospital. Analgesics were administered fifteen to thirty minutes prior to rituximab, orally unless the patient cannot swallow the drug. Antihistaminics were mostly administered by infusion, considering that the patient already has a cannula connected. Still, there were observations of oral administrations fifteen minutes prior to IV rituximab, or even oral antihistaminic intake at home, as suggested by one hospital in order to shorten time in chemotherapy unit. Premedication at home was not observed in the SC-injections, yet this could be done and potentially would lead to further cost savings in our design. Finally, variation in the frequency of medical checks was observed between hospitals, affecting nurses' time investments and chemotherapy unit time.

Cost savings can be extrapolated to hospital levels. An average hospital in the Netherlands can save between €109,250 (based on 412 administrations given yearly in Isala Clinics) and €137,093 (based on 517 administrations given yearly in MCL), annually. In addition, patients treated with SC rituximab will spend less time in the hospital, experience less emotional stress and a more comfortable administration which consequently results in increased patients' convenience [21]. Additionally, potential overnight stays, caused by decreased infusion rates due to infusion related adverse reactions, will be averted for some patients. All the above discussed items into account, SC-treatment can even be further optimized to reach maximum cost savings.

Some comparative data from other countries exist. Samanta et al [22] performed a time motion study on NHL-patients treated with SC-injection and IV-infusion of rituximab in 3 healthcare centers in the United Kingdom. Decreases in time spent by healthcare professionals in preparing and administering rituximab were measured for SC- versus IV-administrations. Additionally, they observed that patients being administered SC-injections stayed 70 minutes (95% CI: 57-87) on the ward, whereas patients with IV-infusions stayed almost 4.5 hours (95% CI: ±4 - ±5 hours). This resulted in a decrease in total mean staff costs of £115. Although the results for the Netherlands cannot be translated to the UK and vice versa, similar trends can be observed, with the SC injection of rituximab reducing time spent in chemotherapy unit and patients' costs. With a similar study design as ours, Burcombe et al [23] analyzed treating HER2- early breast cancer with SC trastuzumab injections instead of IV infusion in four medical centers in the UK. Injections given SC resulted in both time and cost savings. They observed a time saving of approximately half an hour, primarily caused by administering the drug on the ward. Shpilberg et al [24] analyzed both rituximab and trastuzumab and concluded that advantages of SC- over IV administrations exist regarding total costs and patient convenience. It has been argued that savings caused by decreases in pharmacy staff and nursing time should not be counted as no staff reductions may immediately occur [25]. Yet, from the pharmacoeconomic perspective of opportunity costing, we would argue that counting these savings is valid as the staff gets the opportunity to perform alternative productive tasks that otherwise might have been neglected.

Conclusion

We conclude that, the SC injection of rituximab comes with lower costs than the IV infusion of rituximab, mainly due to reduced drug costs, lack of spillage and savings related to reduced times spent in chemotherapy unit. For some middle-sized Dutch hospitals overall savings could amount to up to €140,000 per year. Savings can be optimized by gaining practical experience with the SC administration form and by generalizing protocols that hospitals are currently using, for example regarding pre-medication and health checks.

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