Cost analysis of common treatment options for indolent follicular non-Hodgkin's lymphoma

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Background and Objectives. We assessed direct health care costs associated with the most commonly prescribed treatments for indolent follicular non-Hodgkin's lymphoma (FL).

Design and Methods. New and previously diagnosed FL patients (≥18 years) known during 1997-1998 to 15 Dutch hospitals were selected for inclusion. Each patient was followed for 3 years, and resource use associated with each of the treatments, including *watchful waiting*, was recorded. The hospital perspective was adopted. Unit costs were based on 2003 price levels.

Results. Two hundred patients were included of whom 75% underwent one or more treatments during the 3-year data collection period [25% were not treated because of a watchful waiting strategy (10%) or complete remission (15%)]. Allogeneic and autologous stem cell transplantations were the most expensive treatments, with a mean (median) per patient cost of €45,326 (44,237; n=7) and €18,866 (16,532; n=9), respectively (up to discharge only). Intravenous fludarabine cost €10,651 (9,995; n=33), rituximab (€10,628; 10,124; n=7), and CHOP €7,547 (5,833; n=42). *Classical* FL treatments were found to be the least expensive treatments used with an estimated cost for cylophosphamide, vincristine and prednisone of €5,268 (2,644; n=58), for radiotherapy of €4,218 (4,313; n=52), and for chlorambucil of €2,476 (1,098; n=53).

Interpretations and Conclusions. This study presents information on resource use and costs associated with the most commonly prescribed FL treatments. In addition to differences in effectiveness, commonly used treatments vary considerably in terms of resource use and overall cost. This information is of value for resource planning, given the high costs of new treatment modalities.

Key words: non-Hodgkin's lymphoma, follicular lymphoma, cost and cost analysis, economics, antineoplastic combined chemotherapy protocols

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Indolent follicular lymphoma (FL) is the second most frequent lymphoid malignancy after diffuse large B-cell lymphoma.[1,2] The disease course is characterized by a pattern of treatment, response and relapse, with shortening disease-free periods after each treatment.[3] The median survival is relatively long (8-10 years).[1] FL patients often ultimately die of progressive, resistant disease or following transformation to aggressive lymphoma.[4]

The appropriate therapy depends on the disease stage.[5] One fifth to one third of patients present with localized disease,[6,7] involving a single lymph node region (stage I) or >2 lymph node regions on the same side of the diaphragm (stage II). The initial treatment for stage I disease is generally radiotherapy at diagnosis, as this induces complete remissions in nearly all patients, resulting in 10-year disease-free survival rates of 40-50%.[8-11] The combination of radiotherapy with chemotherapy is being explored in clinical trials.[12-14] At relapse, subsequent treatment is comparable to that used for patients with disseminated FL.[5]

More typically, FL patients present with disseminated disease,[6,7] involving lymph node regions on both sides of the diaphragm (stage III) or possibly ≥1 extralymphatic organs or tissues (stage IV). For asymptomatic patients, a *watchful waiting* approach is usually adopted,[5,15] with a median time-to-first-treatment of 31 months.[16] Treatment is only initiated in the case of clinical progression, involvement of vital organs, or histological transformation.[15,17]

Oral chlorambucil is widely recommended as first-line therapy.[4,5,9,10] Alternative treatments, as initial therapy or at relapse, include cyclophosphamide, the CVP regimen (cyclophosphamide, vin-

cristine, prednisolone), and CHOP (cyclophosphamide, adriamycin, vincristine, prednisone).[4,9,10,18,19] Fludarabine monotherapy has been shown to be effective in FL treatment and fludarabine combinations (with chemotherapy or monoclonal antibodies) have produced superior response and progression-free survival rates.[20] Monoclonal antibodies (with or without radiolabeling) have more recently been added to the list of treatment options, alone or combined with chemotherapy, and have resulted in even higher response rates and longer disease free periods.[21-24] Although individual studies suggest interferon-α may prolong time to relapse without improving overall survival[19] a recent meta-analysis indicates that overall survival may be prolonged when this cytokine is given in conjunction with intensive initial chemotherapy.[25]

Both autologous and allogeneic stem cell transplantations (SCT) are promising treatments options for good-prognosis FL patients, but so far there is no clear criterion for choosing between these types of SCT.[26] Autologous and allogeneic SCT in first remissions are being explored in investigational settings,[26,27] as well as autologous SCT as first-line therapy.[28] Transplant approaches such as reduced intensity allogeneic transplantations that limit treatment-related mortality are also being investigated.[26,29,30]

Despite the wide array of treatment alternatives, only two studies thus far have focused on the costs of a limited number of treatments.[31,32] A recent review on economic evaluations in non-Hodgkin's lymphoma underscored the need for more information regarding costs of FL, given allocation issues arising from the scarcity of health care resources.[33] As new treatment approaches are rapidly entering the scene, *real-life* cost data are urgently needed in order to calculate the expected cost-effectiveness of these new approaches. Therefore, the objective of this study was to provide information about the cost of the most commonly used FL treatments, according to the methodological requirements that should be met by economic evaluations for lymphoma.[33]

Design and Methods

This retrospective study was performed in 15 of the main Dutch hospitals (4 university hospitals and 11 general hospitals) treating patients with hematologic malignancies.

Patients were identified by the ICD code. A search in the databases of the participating hospitals or the regional cancer centers was performed to identify patients known during 1997-1998, irrespective of whether they were newly diagnosed or had previously been treated. Treatment data were included in the case of patients aged ≥18 years with grade I or II FL,[34] or (if unspecified) *low-grade FL*. All Ann Arbor stages[35] were allowed. Demographic and other baseline characteristics recorded were those indicated at the time of initial diagnosis.

Patients were followed from a distinct treatment event (start of treatment or start of watchful waiting strategy) during the disease course onwards, nearest to 01-01-1998 and between 01-01-1997 and 12-31-1998. If no such event occurred during this period (patients who were in remission or who were in a peirod of watchful waiting), 01-01-1998 was chosen as the starting date. From this point onwards, each patient was followed for three years (or until death or the last follow-up date available, whichever occurred first) for all resource use related to treatment or watchful waiting. When a treatment was initiated immediately prior to the end of the three-year data collection period, these data were also included even if this prolonged the data collection period. The start of a treatment episode was marked by the first day of therapy administration, or in the case of transplantation the first day of the conditioning regimen. For radiotherapy and transplantations, costs of preparation activities that had been performed before the starting date were also added to the treatment episode (simulation sessions, and harvesting and donor costs, respectively). Treatment episodes were considered complete after the final radiotherapy session, at the day of discharge from hospital (in the case of transplantations), or after the tenth day measured from the final day of therapy administration (if a complication following therapy was still present at this day, the last day of the complication was considered to be the concluding date of the treatment episode).

All hospital resource use related to FL (treatment and watchful waiting) during the data collection period was recorded, as well as medication used at home. Resource use for co-morbidity could be easily excluded, because for all resource use items, the requesting department and the reason for performing them were known. Information was collected manually and stored anonymously in a Microsoft® Access database.

In this cost analysis, the hospital perspective was adopted.[36] Average unit costs [euros (€), price level 2003] were calculated for the most important resource use items, on the basis of financial data from five of the participating hospitals. For each unit cost, personnel costs, material costs and overhead costs were included. Personnel costs included wages, social premiums, and fees for irregular working hours of hematologists, registrars, nursing staff and administrators. The costs of nursing staff and administrators were calculated by dividing their total annual costs

by the total annual number of hospital days. Material costs comprised costs of disposables, equipment, regular nutrition, laundry services and cleaning services. Overhead costs contained bare hotel costs and the costs of non-medical departments, such as general management. Overhead costs were calculated on the basis of the hospital's total annual overhead costs, from which a part was allocated to the hematology department on the basis of the percentage square meters of this department.

In order to avoid any cost differences due to the specific hospitals in which patients were treated, we applied the same unit costs resulting from the above mentioned calculation to all patients (we only calculated separate unit costs for university hospitals and general hospitals). The main unit costs calculated were: inpatient hospital day €322 (general hospital) and €434 (university hospital) of which 57% were personnel costs (P), 14% material costs (M), and 29% overhead costs (O); hematology outpatient visit €56 (general hospital) and €95 (university hospital; P80%, M4%, O16%); other outpatient visit €50 (general hospital) and €87 (university hospital; P80%, M4%, O16%); day care treatment €148 (general hospital) and €185 (university hospital; P44%, M18%, O38%); lymph node biopsy under general anesthesia €621 (P46%, M31%, O23%); procedural costs of peripheral blood stem cell transplantation (harvesting, freezing, and defrosting transplant) €2495 (P36%, M44%, O20%). For items with low costs or less influence (due to low average numbers), Dutch tariffs were used as approximations. Drug costs were based on wholesale prices.[37] Data were analyzed by using SPSS® for Windows, version 10.0. Discounting[36] was not applied, as the aim of the analysis was to calculate costs of treatments without a relationship to a specific time frame per patient. Given the aim of the analysis, only descriptive statistics were calculated.

Results

Patients' characteristics

Data were collected on 200 FL patients, of whom 99 were males (49.5%). At initial diagnosis, the mean age was 57 years (median 56, range 19-90); 123 patients (61.5%) were <60 years of age, and 77 (38.5%) were >60 years of age. Stage distribution was: stage I - 50 patients (25.0%), stage II - 22 (11.0%), stage III - 38 (19.0%), stage IV - 86 (43.0%), unknown - 4 (2.0%). Sixty-seven patients (33.5%) had grade I FL, 62 (31.0%) had grade II FL, and 71 (35.5%) were described in the records as having *low-grade FL*.

Of the 200 patients enrolled, 144 patients (72.0%) were followed for the entire three-year observation period. Thirty-seven patients (18.5%) died before the scheduled end of follow-up (at an average of 503 days after data collection began), and the data available for 19 patients ended before the scheduled completion of follow-up (they were followed for 526 days on average).

Eighty-five patients (42.5%) were followed from the start of their first-line treatment, 26 patients (13.0%) were followed from their second-line treatment and 11 (5.5%) from their third-line treatment. Four patients (2.0%), four patients (2.0%), and one patient (0.5%) were followed from their fourth, fifth and sixth treatment lines, respectively. Thirty-five patients (17.5%) were in the watchful waiting stage of their disease at study entry. In 20 of them the watchful waiting strategy was maintained throughout the entire data collection period. In addition, 34 patients (17.0%) were in remission at study entry, of whom 30 remained in remission during the data collection period. Therefore, 50 of the 200 patients followed did not undergo any treatment during the data collection period.

Treatment characteristics

Table 1 shows the characteristics of the treatments administered to the 150 of 200 patients who underwent at least one treatment during the data collection period. Thirty-nine treatments (13.5%) were administered as part of a clinical trial: CVP (12, 30.8%), interferon-α (12, 30.8%), fludarabine (8, 20.5%), autologous stem cell transplantation (6, 15.4%), and CHOP (1, 2.6%).

Resource use and costs of treatment regimens

Tables 2 and 3 indicate mean resource use and costs of the nine different treatments observed, including interferon-α maintenance therapy. It should be noted that only numbers during treatment episodes as defined above were calculated, which clarifies why some figures (such as number of outpatient visits) may appear to be low. Figure 1 shows the overall cost impact of the treatments and Figure 2 shows the breakdown of the total mean costs of the main cost categories.

Mean costs of allogeneic SCT were €45,326 (median €44,237; 95%CI 29,479-61,173), and include donor searching costs (all potential donors were siblings) and all costs from the start of the conditioning regimen until the day patients were discharged from the hospital. The mean duration of hospitalization was 6.2 weeks (up to discharge only). Donor identification and harvesting expenses and procedural costs were responsible for almost one third of the total costs, and the costs of hospital days were 43% of the total treatment costs. Blood components were a major accompanying treatment, accounting for

Table 1. Numbers of treatments in the 54 patients with localized disease (stage I/II), the 93 patients with disseminated disease (stage III/IV) and the 3 patients with unknown disease stage who underwent at least one treatment during the three-year data collection period.

	Total		*Treatment line*								
	n	*%*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*> 8*	*C*
Localized											
Allogeneic SCT	0	0.0%	-	-	-	-	-	-	-	-	-
Autologous SCT	0	0.0%	–	–	–	–	–	–	–	–	–
Chlorambucil	11	14.3%	4	5	1	1	–	–	–	–	–
CVP	13	16.9%	4	7	1	1	–	–	–	–	–
CHOP(-like)	11	14.3%	4	1	3	1	2	–	–	–	–
Fludarabine i.v.	5	6.5%	–	–	3	1	–	1	–	–	–
Radiotherapy	32	41.6%	28	2	1	1	–	–	–	–	–
Rituximab	1	1.3%	–	1	–	–	–	–	–	–	–
IFN-α maintenance	3	3.9%	–	–	–	–	–	–	–	–	3
Other	1	1.3%	–	–	–	1	–	–	–	–	–
Total	**77**	**100.0**	**40**	**16**	**9**	**6**	**2**	**1**	**–**	**–**	**3**
Disseminated	*n*	*%*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*> 8*	*C*
Allogeneic SCT	7	3.4%	–	1	4	1	–	–	–	1	
Autologous SCT	9	4.4%	–	-	1	–	1	–	1	–	6
Chlorambucil	40	19.7%	16	16	5	2	1	–	–	–	–
CVP	42	20.7%	22	11	5	2	1	–	1	–	–
CHOP(-like)	30	14.8%	4	13	10	2	1	–	–	–	–
Fludarabine i.v.	26	12.8%	10	6	4	3	1	1	1	–	–
Radiotherapy	20	9.9%	4	4	4	4	2	1	–	1	–
Rituximab	6	3.0%	–	–	1	2	–	1	–	2	–
IFN-α maintenance	13	6.4%	–	–	–	–	–	–	–	–	13
Other	10	4.9%	–	–	4	4	2	–	–	–	–
Total	**203**	**100.0**	**56**	**51**	**38**	**20**	**9**	**3**	**3**	**4**	**19**
Stage unknown	*n*	*%*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*> 8*	*C*
Chlorambucil	2	25.0%	1	1	–	–	–	–	–	–	–
CVP	3	37.5%	1	1	–	1	–	–	–	–	–
CHOP(-like)	1	12.5%	–	–	1	–	–	–	–	–	–
Fludarabine i.v.	2	25.0%	1	1	–	–	–	–	–	–	
Total	**8**	**100.0**	**2**	**3**	**2**	**1**	**–**	**–**	**–**	**–**	**–**

SCT: stem cell transplantation; C: consolidation treatment; IFN: interferon-α.

approximately 11% of costs.

The mean cost of autologous SCT was €18,866 (median €16,532; 95%CI 12,621-25,110). The mean treatment duration (from the start of the conditioning regimen until discharge after stem cell reinfusion) was 5.4 weeks. More than half of the costs were due to hospital stay. All patients were offered blood transfusions as accompanying treatments, which resulted in a 15% contribution of this item to the total treatment costs.

The mean per patient cost for a treatment with chlorambucil was €2,476 (median €1,098; 95%CI 1,384-3,568). The mean treatment duration was 35.2 weeks in case of a low-dose continuous daily scheme, and 41.8 weeks in case of a high-dose *pulse* regimen (higher doses during two weeks a month). Accompanying treatments were relatively rare, and the majority of costs were due to inpatient days (32%), diagnostic procedures (26%), and the cost associated with the chemotherapy itself (17%).

The CVP regimen was associated with mean per patient costs of €5,268 (median €2,644; 95%CI 3,199-7,337). The mean treatment duration was 22.4 weeks during which 6.2 chemotherapy cycles were administered on average. The treatment was mainly administered on an outpatient basis. Hospital admissions comprised a significant component of the total treatment cost for CVP, due mainly to the fact that the other cost items were relatively low. This was also true for the CHOP scheme, with the exception that the drug acquisition costs for CHOP were much higher. A treatment with CHOP cost €7,547 on average (median €5,833; 95%CI 5,915-9,180) and the mean duration was 16.2 weeks, during which an average of 5.2 cycles were administered.

The mean cost of treatment with intravenous fludarabine was €10,651 (median €9,995; 95%CI 8,795-12,507) for an average of 4.8 cycles of therapy. The use of the day care ward facility was relatively high for intravenous fludarabine as compared with other regimens (22.0 days on average), as each cycle is administered over 5 consecutive days.

Table 2. Mean per-patient resource use numbers of the nine different treatment regimens. BM: bone marrow; PB: peripheral blood. Clinical visits relate to visits during hospitalization of all other specialties than Hematology. Standard radiotherapy outpatient visits during radiotherapy sessions have not been recorded, this variable therefore only indicates additional visits.

	Allogeneic SCT (n=7)	*Autologous SCT (n=9)*	*Chlorambucil (n=53)*	*CVP (n=58)*	*CHOP (n=42)*	*Fludarabine iv (n=33)*	*Radiotherapy (n=52)*	*Rituximab (n=7)*	*IFN-α maint. (n=16)*
Day care treatments									
Total number of days	–	0.3	0.4	7.3	6.6	22.0	–	2.7	0.1
for blood transfusions	–	0.3	0.4	0.1	0.7	0.2	–	–	–
for therapy	–	–	–	7.2	4.7	21.8	–	2.7	–
for diagnostic purposes	–	–	–	–	–	–	–	–	–
for side-effects	–	–	–	–	–	–	–	–	–
for other purposes	–	–	–	–	1.2	–	–	–	–
Hematology inpatient days									
Total number of days	43.1	24.0	1.9	6.4	8.2	5.1	1.8	3.1	2.1
for blood transfusions	–	–	–	–	–	–	–	–	–
for therapy	39.0	24.0	0.3	3.1	3.8	3.4	0.5	3.1	–
for diagnostic purposes	–	–	0.4	0.2	0.7	0.2	0.6	–	0.3
for side-effects	4.1	–	1.2	3.0	3.5	1.1	0.4	–	–
for other purposes	–	–	–	0.1	0.1	0.4	0.2	–	1.8
Other inpatient days									
Intensive Care Unit (days)	–	0.2	–	–	–	–	–	0.1	–
Other departments (days)	–	–	0.4	0.5	–	–	0.2	–	0.7
Outpatient visits									
Hematology (visits)	2.3	0.6	4.9	3.2	3.5	3.7	0.2	1.1	10.0
Radiotherapy (visits)	0.1	–	–	–	–	–	–	–	–
Other departments (visits)	2.4	–	0.6	0.5	0.5	0.3	–	–	0.8
Clinical visits									
Other than Hematology	9.0	0.4	–	0.2	0.2	–	–	–	0.1
Parenteral nutrition (days)	15.6	–	–	–	–	–	–	–	–
Blood products									
Full blood units	34.9	14.2	–	0.2	1.4	–	–	–	–
Platelet units	15.7	10.0	1.0	0.6	2.0	0.4	0.1	–	–
Bacteria cultures	14.1	11.3	0.4	1.8	1.5	0.6	0.2	0.1	0.8
Histology									
BM histology	1.0	0.2	0.1	0.3	0.2	–	–	0.6	0.9
BM immunophenotyping	0.3	0.1	–	0.1	0.1	–	–	–	0.4
Lymph node histology	0.4	–	0.1	0.1	–	–	–	–	0.1
PB immunophenotyping	0.3	0.1	–	–	–	–	–	–	–
Other biopsy	0.6	0.1	0.1	0.2	0.2	–	–	–	–
Radiology									
CT-scans	0.3	0.4	0.6	1.1	0.9	1.2	0.1	–	2.9
Ultrasounds	1.6	–	0.5	0.8	0.5	0.5	–	0.1	0.9
X-rays	4.6	2.2	0.9	1.5	1.4	1.4	0.2	0.6	1.2
MRI-scans	–	–	–	–	–	–	–	–	0.1
Nuclear medicine									
Bone scan	–	0.1	–	–	–	–	–	–	–
Left ventricular ejection fraction	0.1	–	–	–	–	–	–	–	0.2
PET-scan	–	–	–	–	–	–	–	–	–
Internal imaging techniques									
Gastroscopy	0.1	–	–	0.2	–	–	–	–	–
Other									
ECG	0.7	0.9	–	0.2	0.3	0.3	–	0.3	0.9

SCT: stem cell transplantation; IV: intravenously; IFN-α maint.: interferon-α maintenance treatment.

Table 3. Mean costs (euros) of the nine different treatment regimens. SCT: stem cell transplantation. *Treatment* indicates donor/harvesting costs and procedural costs (including conditioning regimen) in the case of SCT, costs of the megavolt sessions in the case of radiotherapy, or costs of cytostatics (chlorambucil, CVP, CHOP), purine analogs (fludarabine IV), interferon-α, or monoclonal antibodies (rituximab).

	Allogeneic SCT (n=7)	*Autologous SCT (n=9)*	*Chlorambucil (n=53)*	*CVP (n=58)*	*CHOP (n=42)*	*Fludarabine iv (n=33)*	*Radiotherapy (n=52)*	*Rituximab (n=7)*	*IIFN-α maint. (n=16)*
Day care treatments									
Total costs	–	57	66	1 133	1 011	3 396	3	464	19
for blood transfusions	–	57	53	18	114	22	–	–	–
for therapy	–	–	–	1 102	717	3 351	3	464	–
for diagnostic purposes	–	–	13	10	–	9	–	–	9
for side-effects	–	–	–	–	3	4	–	–	–
for other purposes	–	–	–	2	176	9	–	–	9
Hematology inpatient days									
Total costs	18 723	9 346	669	2 153	2 719	1 669	608	1 012	923
for blood transfusions	–	–	–	11	16	–	–	–	–
for therapy	16 925	9 346	85	1 011	1 315	1 103	168	1 012	–
for diagnostic purposes	–	–	134	62	230	68	198	–	135
for side-effects	1 797	–	444	1 031	1 112	361	176	–	-
for other purposes	–	–	6	39	46	136	68	–	786
Other inpatient days									
Intensive Care Unit	–	263	–	–	–	–	–	169	–
Other departments	–	–	120	140	19	9	67	–	198
Outpatient visits									
Hematology	217	44	311	192	227	230	11	97	766
Radiotherapy	8	–	2	1	1	-	2	–	-
Other departments	135	–	36	29	29	16	4	–	41
Clinical visits	211	10	1	4	6	2	2	–	3
Parenteral nutrition	838	–	–	–	–	–	–	–	–
Blood products	5 012	2 793	205	145	482	92	25	–	–
Treatment	13 444	2 495	425	247	2 142	4 287	3 366	8 560	9 491
Medication									
Analgesics	12	1	–	4	2	–	3	–	9
Antibiotics	860	306	–	58	44	62	–	1	15
Antiemetics	112	111	3	4	10	–	–	–	–
Antifungals	1 290	98	–	4	6	2	–	–	–
Antihistamines	3	3	–	1	–	–	–	1	–
Antivirals	142	15	–	1	1	–	–	–	–
Growth factors	–	1 499	–	110	–	28	–	–	–
Other drugs	393	126	3	21	51	2	4	7	50
Laboratory services	2 427	828	246	284	296	327	37	160	438
Bacteria cultures	431	346	13	55	47	19	4	4	22
Histology									
Bone marrow/lymph node	447	57	100	126	54	43	21	48	242
Other	58	11	13	25	21	9	–	–	7
Radiology	440	226	228	398	292	381	39	38	853
Nuclear medicine	34	20	20	18	10	39	–	–	55
Internal imaging/other tests	89	210	15	112	76	39	19	86	263
Total costs	**45 326**	**18 866**	**2 476**	**5 268**	**7 547**	**10 651**	**4 218**	**10 648**	**13 396**

SCT: stem cell transplantation; IV: intravenously; IFN-α maint.: interferon-α maintenance treatment.

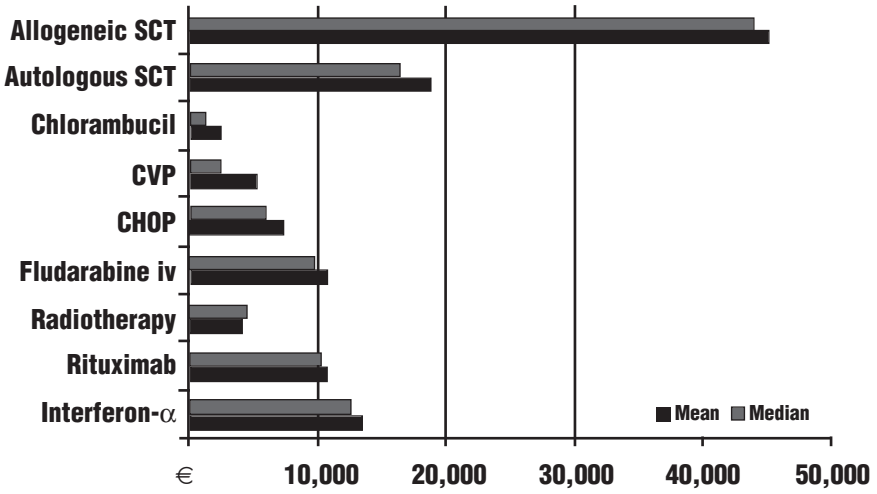

Figure 1. Overall cost impact of follicular lymphoma treatments.

For radiotherapy, mean per-patient costs were €4,218 (median €4,313; 95%CI 3,202-5,235). Apart from the resource use associated with the radiotherapy procedure itself, the additional resource use was remarkably low. Additional outpatient visits were uncommon. Radiotherapy was applied over 3.3 weeks on average, with the mean number of sessions being 15.8.

The mean cost of the rituximab regimen was €10,648 (median €10,124; 95%CI 9,377-11,918). Four doses were administered in all cases. Of the total treatment cost, 81% was associated with the cost of the antibodies. Additional resource use was low.

Interferon-α was applied as maintenance treatment. The mean cost was €13,396 (median €12,690; 95%CI 9,299-17,491), and the mean duration of this treatment was 87.7 weeks. Seventy-one percent of the total treatment cost was due to the drug itself. Again, additional resource use associated with this treatment was relatively low.

From the available data, we were also able to calculate the mean monthly costs of the watchful waiting strategy. These amounted to €279 (inpatient days 35%, outpatient visits 14%, diagnostics 51%), but were mainly constituted by a few hospital admissions (the median monthly cost was €85).

Discussion

This study presents costs of FL treatments in detail, in order to be of value in healthcare decision-making. Allogeneic and autologous stem cell transplantations (SCT) had mean per patient costs of €45,326 and €18,866, respectively (up to first discharge only). These were followed by intravenous fludarabine (€10,651), rituximab (€10,648), and CHOP (€7,547). Classical FL treatments were found to be the least expensive treatments with costs of €5,268 (CVP), €4,218 (radiotherapy), and €2,476 (chlorambucil). In all cases, different median costs as compared to the mean costs were caused by a few patients who were hospitalized more often and/or for longer than the other patients in the group. Medians therefore represent the costs of *ideal* uncomplicated treatments.

Resource use and costs of the most common FL treatments applied during the 1997-2001 period were calculated in a sample of 200 Dutch FL patients. Our male-to-female ratio, age and stage distributions were highly comparable to the Dutch indolent lymphoma population, in which 38% have stage I/II disease and 62% stage III/IV disease.[38] This percentage of patients with disseminated disease may appear low when compared with percentages reported in the literature. For example, 78% of the patients in the FLIPI study had stage III/IV disease.[7] However, as in the FLIPI study, percentages of patients with localized and disseminated disease reported in the literature are often derived from clinical trials, which are likely to include more patients with advanced disease.

The target number of 200 patients for this study appeared just enough for basic descriptive statistics. Although sufficient given the aim of the analysis, the numbers of patients were small for allogeneic and autologous SCT, interferon-α, and rituximab. The study design was a pragmatic one given the nature of the disease. A study on FL costs in which all patients are followed from their initial diagnosis until the end of therapy would take many years, due to the long median survival. We therefore decided to collect data over a recent three-year interval, in order to calculate resource use and costs associated with the most commonly applied treatment regimens. A small proportion of the treatments considered (13.5%) were administered in the context of a clinical trial. We do not expect this to

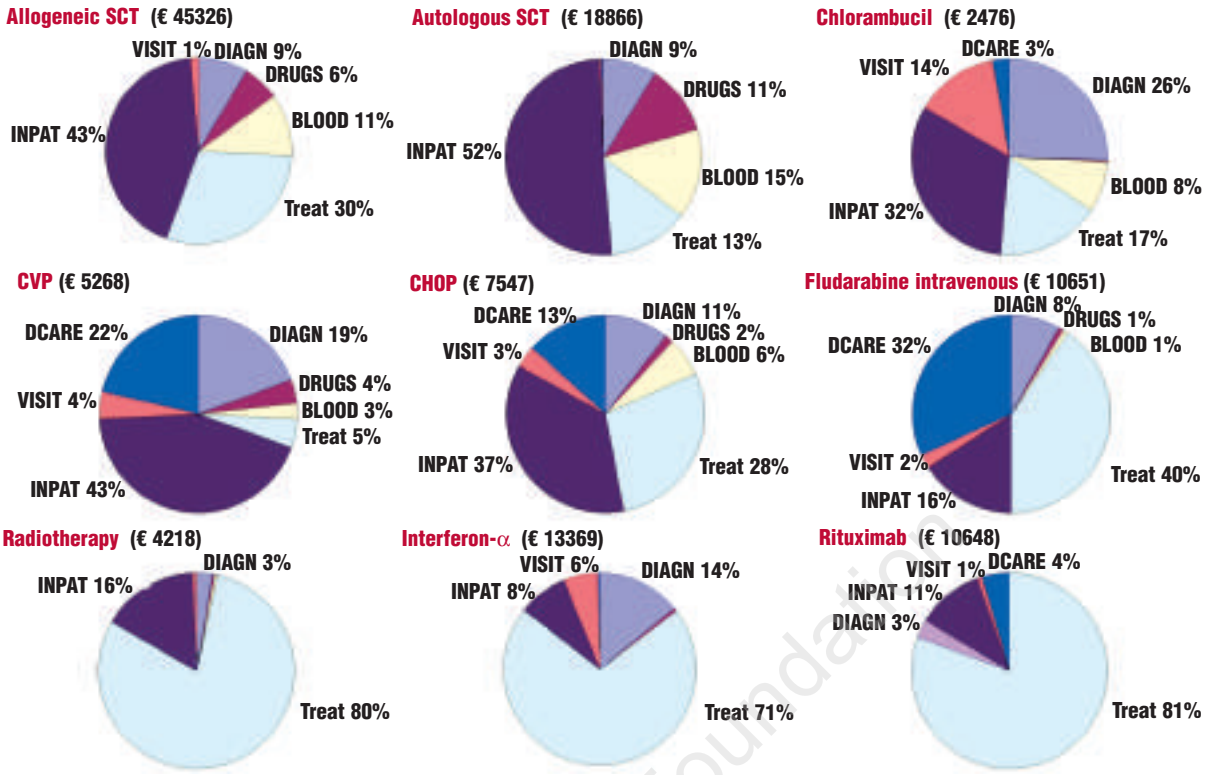

Figure 2. Breakdown of total mean costs to main cost categories. SCT: stem cell transplantation; DIAGN: diagnostics; DRUGS: drugs other than those of the treatment itself; BLOOD: blood products; DCARE: use of day care center; NPAT: hospital inpatient days; VISIT: outpatient visit; TREAT (treatment): donor/harvesting costs and procedural costs (including conditioning regimen) in the case of SCT, costs of megavolt sessions in the case of radiotherapy, or costs of cytostatics (chlorambucil, CVP, CHOP), purine analogs (fludarabine iv), interferon-α, or monoclonal antibodies (rituximab).

have led to significant additional costs, as the protocols of the studies actually reflected care as recommended for these patients in The Netherlands.[39] This assumption is supported by the data, in which we could not demonstrate cost differences between the trial and non-trial settings (not reported therefore) and by earlier work of our own group.[40]

The estimated costs of allogeneic SCT need to be interpreted with caution as they include costs only up to the first discharge. Allogeneic SCT is however not *completed* after discharge. Monitoring by post-discharge outpatient visits remains intensive and often additional hospital admissions are required for the treatment of (late) complications, such as infections or graft-versus-host disease. For a detailed overview of the costs associated with allogeneic SCT, we refer to an earlier analysis in acute leukemia.[41] In that study, costs in the first 6 months after follow-up were approximately €19,500 (when updated to the 2003 price level). Moreover, costs were much higher in the case of an unrelated donor. The total mean costs for up to two years in that study were approximately €116,000 (related donor) and €178,000 (unrelated donor). In summary, it is important to recognize that after allogeneic SCT, high costs are also incurred during the follow-up period. For autologous SCT this is similarly the case, although the absolute amount of money involved is lower. Earlier studies have focused specifically on these costs, such as the study by Barosi *et al.*,[42] and a study by our own group performed using the same methodology as applied in the current analysis.[43]

With regard to the costs of rituximab, it should be kept in mind that our cost estimates were based on 4 weekly doses. However, the use of 6 and 8 doses has also been proposed,[44,45] as well as rituximab maintenance therapy.[46] Since Figure 2 shows that 81% of the costs of the rituximab 4-dose scheme were constituted by costs of the drug itself, our calculation easily allows for an estimation of the costs of schemes with more than 4 doses. On the basis of the presented costs of the drugs themselves and the costs of the administration setting as reported here, readers are able to perform exploratory calculations regarding the cost of schemes containing both rituximab and fludarabine, which have been developed in the meantime.[23] However, one should be aware of costs being different for the use of therapies in combination due to different toxicity profiles relative to those with monotherapy regimens.

In general, the costs reported in this study apply to both localized disease as well as to disseminated disease. We analyzed our data according to disease stage, but with a few exceptions, no major differences in the costs of treatment regimens were found. This is due to the fact that the total costs of most of the regimens are driven by the number of cycles, with the acquisition cost of the active (chemo)therapy usually being the major cost driver (Figure 2). The only exception to this rule is with the cost of CVP, which showed a major difference between stage I/II (€3,049) and stage III/IV (€6,148). This difference was not due to a difference in the mean number of cycles (6.2 in both groups), but to the finding that in the advanced stage patients, the regimen was more often administered on an inpatient basis. A small difference was also seen for chlorambucil and radiotherapy, for which the longer periods of treatment administration caused the costs to be slightly higher in stage I/II patients (€2,942 vs. €2,193 and €4,698 and €3,526, respectively). Finally, we analyzed the costs of treatment regimens according to the lines in which they were administered. However, no differences were found in this analysis, which implies that the cost estimates as reported can be used for any FL cost calculation, irrespective of the order of treatments.

With regard to supportive care, our data may not apply to other countries, as they showed that autologous SCT and CVP were the only treatments for which the use of hematopoietic growth factors comprised a significant part of the medication costs (69% and 54%, respectively).

Only two studies to date have focused on costs of indolent lymphomas. The first study, by Sweetenham *et al.*, compared CHOP, intravenous fludarabine, and rituximab.[31] Like our study, this study focused on direct medical costs within the hospital for clearly defined treatment episodes that were broadly comparable to the period definitions we applied. However, the methods applied by Sweetenham regarding data collection were much less robust than ours, since for both fludarabine and CHOP they used a questionnaire designed to capture resources used during a single cycle of therapy. Sweetenham reported total costs of €7,210 (CHOP), €10,022 (intravenous fludarabine), and €6,080 (rituximab), based on the price level of 1998. The average number of fludarabine cycles on which their cost assessments were made differed between their study (6 cycles) and ours (4.8 cycles). Even if this difference is taken into consideration, in addition to differences in the time period, the costs reported by Sweetenham for both fludarabine and CHOP are higher than ours. The costs of 4 doses of rituximab, however, are comparable in both studies. Therefore, and for the fact that the majority of the cost of rituximab treatment was constituted by drug and administration costs, we assume we have calculated an accurate estimation of these costs in the monotherapy indication, although it was based on only 7 patients. The more recent study, by Herold *et al.*, reported treatment costs for CHOP, CVP and intravenous fludarabine.[32] Although the study was performed on more patients than was ours, the results were not presented in a way that allows for a legitimate comparison. Like our study, that study concluded that not simply drug acquisition costs, but also costs of administration and adverse event management are major contributors to the cost of FL treatment.

A limitation of any cost analysis regarding comparisons to other publications is that unit costs might differ between institutions and that they are known to vary between countries.[47] In particular, European costs often differ from those reported in the United States, which might be caused, in part, by different practice patterns.[48,49] We have accounted for this difference by reporting unit costs and resource use separately, as this enables users to perform calculations using their local unit costs or alternative assumptions regarding the resource use.[33]

It can be questioned whether the treatments applied in our study sample will be typical for the near future. After more than 30 years of clinical studies, no standard has been defined in the order of therapies for indolent FL. Chlorambucil, CVP, CHOP, and radiotherapy have all been applied for several decades and their place in the treatment of FL in the forthcoming years seems to be established. Moreover, the cost profiles of these schemes were the most favorable. We expect that anti-CD20 antibodies combined with chemotherapeutic options will increasingly be used as initial therapy. Rituximab, with its low level of side effects, either used alone or in combination, has contributed significantly to existing chemotherapeutic regimens for FL,[19] and was recently shown to lead to significantly higher response rates and longer disease-free periods when combined to existing chemotherapy regimens.[22,23] This will have a major economic impact, in particular since combining rituximab with chemotherapy means that the 4 doses originally recommended are now more likely to be 6 or even 8.

Costs of intravenous fludarabine therapy were relatively high due to the frequent use of the day care ward for 5 consecutive days of intravenous fludarabine administration within each cycle. The cost profile for fludarabine would therefore be favored significantly in case of a cheaper route of administration, which is now available in the form of an oral preparation. Assuming all other cost items remain comparable, if the intravenous administration costs are excluded, the

costs of an oral fludarabine treatment is estimated to be approximately €7,250 in the Dutch situation.

Interferon-α maintenance treatment may prolong time to relapse and it has been suggested that it may also add to overall survival.[25] However, as this treatment is associated with high costs and a significant side-effect profile, its widespread application in the forthcoming years seems unlikely.

For the future, the role of autologous SCT for patients with FL is still being investigated in trials.[26,27,30] Allogeneic SCT is currently the only possibly curative treatment for patients with indolent FL. In particular, if applied early (e.g. second remission), the outcomes seem favorable with approximately 50% long-term disease-free survival.[50,51] Its application among younger patients with FL in the future may, therefore, increase. Allogeneic SCT is now possible for elderly patients, because of the introduction of non-marrow ablative conditioning, which is associated with less treatment-related mortality.

While there are multiple treatment options for patients with FL, most patients eventually relapse and require a second or third therapy. Emerging treatments such as antibody therapy and allogeneic SCT are increasingly being used in an attempt to lengthen response duration and possibly even improve survival outcomes. There is currently significant interest in the use of (chemo)-immunotherapy in the initial lines of treatment.[52] However, given the major financial consequences, their widespread application requires that adequate resources be available and that these resources be used in an efficient manner, targeting those patients who have the most to gain from the use of more expensive therapies.

The information presented in this paper is of value to health care decision-makers who need to address resourcing issues for the treatment and care of patients with FL, particularly because the calculations were based mainly on *real-life* data instead of data from the *ideal* clinical trial settings. The finding that the costs of the treatment regimens were stable across different disease stages and treatment lines offers the possibility of using these cost estimates also in an era in which the order of therapies for FL is changing rapidly. In particular, it opens the way to modeling studies on the question of whether applying more intensive and more expensive treatments early on might lead to savings in later stages.

MvA managed the data collection process, integrated all data from the participating hospitals, performed the analyses and wrote the manuscript and is therefore the first author. AH as a professor of hematology was the overall clinical supervisor of the project. Given his contribution to the design of the study and the interpretation of the data, he is the last author. CU is the manager of the health economics program in the context of which this study was performed and is therefore the second last author. Fifteen hematologists participated in the research group; as much as possible are included as co-authors, based on the number of patients on whom they delivered data for the analysis, their contributions to the study design and to the manuscript (MK, PS, KvdH, PH, PW, HK, MS, DB, VM).

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References

1. Gupta RK, Lister TA. Current management of follicular lymphoma. Curr Opin Oncol 1996;8:360-5.
2. The Non-Hodkgin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood 1997; 89:3909-18.
3. Johnson PW, Rohatiner AZ, Whelan JS, Price CG, Love S, Lim J, et al. Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single center. J Clin Oncol 1995; 13:140-7.
4. Rohatiner A. Follicle centre cell lymphoma: optimal use of therapeutic options. Ann Oncol 2000;11:111-5.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology - version 1.2005: Non-Hodgkin's Lymphoma. 2005. http://www.nccn.org, Accessed: July 18, 2005.
6. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998;16:2780-95.
7. Solal-Celigny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258-65.
8. Mac Manus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol 1996;14:1282-90.
9. Soubeyran P, Debled M, Tchen N, Richaud P, Monnereau A, Bonichon F, et al. Follicular lymphomas - a review of treatment modalities. Crit Rev Oncol Hematol 2000;35:12-32.
10. Linch D. Current treatment of follicular and low-grade non-Hodgkin's lymphoma. Anticancer Drugs 2001; 12 Suppl 2:S5-9.
11. Coffey J, Hodgson DC, Gospodarowicz MK. Therapy of non-Hodgkin's lymphoma. Eur J Nucl Med Mol Imaging 2003;30 Suppl 1:S28-36.
12. MacManus MP, Seymour JF. Management of localized low-grade follicular lymphomas. Australas Radiol 2001; 45: 326-34.
13. Seymour JF, Pro B, Fuller LM, Manning JT, Hagemeister FB, Romaguera J, et al. Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. J Clin Oncol 2003; 21: 2115-22.
14. Ganti AK, Bociek RG, Bierman PJ, Enke CA, Vose JM, Armitage JO. Follicular lymphoma: expanding therapeutic options. Oncology (Williston Park) 2005;19:213-28.
15. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. N Engl J Med 1984;311:1471-5.
16. Ardeshna KM, Smith P, Norton A, Hancock BW, Hoskin PJ, MacLennan

KA, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet 2003;62:516-22.
17. Rohatiner AZ, Lister TA. The clinical course of follicular lymphoma. Best Pract Res Clin Haematol 2005;18:1-10.
18. Brandt L, Kimby E, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in indolent non-Hodgkin's lymphoma. Acta Oncol 2001; 40:213-23.
19. Archuleta TD, Armitage JO. Advances in follicular lymphoma. Semin Oncol 2004;31:66-71.
20. Lenz G, Hiddemann W, Dreyling M. The role of fludarabine in the treatment of follicular and mantle cell lymphoma. Cancer 2004;101:883-93.
21. Hagenbeek A. Radioimmunotherapy for NHL: experience of 90Y-ibritumomab tiuxetan in clinical practice. Leuk Lymphoma 2003;44 Suppl 4:S37-47.
22. Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105:1417-23.
23. Forstpointner R, Dreyling M, Repp R, Hermann S, Hanel A, Metzner B, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2004;104:3064-71.
24. Lemieux B, Coiffier B. Radio-immunotherapy in low-grade non-Hodgkin's lymphoma. Best Pract Res Clin Haematol 2005;18:81-95.
25. Rohatiner AZ, Gregory WM, Peterson B, Borden E, Solal-Celigny P, Hagenbeek A, et al. Meta-analysis to evaluate the role of interferon in follicular lymphoma. J Clin Oncol 2005; 23: 2215-23.
26. Tse WW, Lazarus HM, Van Besien K. Stem cell transplantation in follicular lymphoma: progress at last? Bone Marrow Transplant 2004;34:929-38.
27. Finke J. The role of stem cell transplantation in the treatment of follicular lymphoma. Semin Cancer Biol 2003; 13:233-9.
28. Deconinck E, Foussard C, Milpied N, Bertrand P, Michenet P, Cornillet-LeFebvre P, et al. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. Blood 2005;105:3817-23.
29. Peggs KS, Mackinnon S, Linch DC. The role of allogeneic transplantation in non-Hodgkin's lymphoma. Br J Haematol 2005;128:153-68.
30. Mounier N, Socie G, Gisselbrecht C. High-dose therapy for indolent lymphoma. Crit Rev Oncol Hematol 2002; 41:225-39.
31. Sweetenham J, Hieke K, Kerrigan M, Howard P, Smartt PF, McIntyre AM, et al. Cost-minimization analysis of CHOP, fludarabine and rituximab for the treatment of relapsed indolent B-cell non-Hodgkin's lymphoma in the U.K. Br J Haematol 1999;106:47-54.
32. Herold M, Sacchi S, Hieke K. The cost of treating relapsed indolent non-Hodgkin's lymphoma in an international setting: retrospective analysis of resource use. Haematologica 2002; 87: 719-29.
33. van Agthoven M, Uyl-de Groot CA, Sonneveld P, Hagenbeek A. Economic assessment in the management of non-Hodgkin's lymphoma. Expert Opin Pharmacother 2004;5:2529-2548.
34. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. The World Health Organization classification of neoplasms of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting--Airlie House, Virginia, November, 1997. Hematol J 2000;1:53-66.
35. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31:1860-1.
36. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. New York/Oxford: Oxford University Press; 1997.
37. van Loenen AC. Pharmaceutical Compass 2003. Amstelveen: Health Care Board; 2003.
38. Snijder S, Coebergh JWW, Otter R, Visser O, Schouten LJ. Hematological malignancies in the Netherlands 1989-1995. Utrecht: Association of Comprehensive Cancer Centres. 1999.
39. HOVON, iMTA, CBO. Guideline Non-Hodgkin's Lymphoma (in Dutch). Alphen aan den Rijn: Van Zuiden Communications BV. 2004.
40. van Agthoven M. Economic evaluations in aggressive non-Hodgkin's lymphoma (Thesis). Rotterdam: Optima Grafische Communicatie BV. 2004.
41. van Agthoven M, Groot MT, Verdonck LF, Lowenberg B, Schattenberg AV, Oudshoorn M, et al. Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia. Bone Marrow Transplant 2002;30:243-51.
42. Barosi G, Marchetti M, Alessandrino P, Locatelli F, Casula S, Lunghi M, et al. A model for analysing the cost of autologous peripheral blood progenitor cell (PBPC) transplantation. Bone Marrow Transplant 1999;23:719-25.
43. van Agthoven M, Vellenga E, Fibbe WE, Kingma T, Uyl-de Groot CA. Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease. a prospective randomised trial. Eur J Cancer 2001; 37: 1781-9.
44. Bremer K. Semi-extended, six weekly rituximab infusions in pre-treated advanced low-grade B cell non-Hodgkin's lymphoma: a phase II study. Anticancer Drugs 2003;14:809-15.
45. Piro LD, White CA, Grillo-Lopez AJ, Janakiraman N, Saven A, Beck TM, et al. Extended Rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol 1999;10:655-61.
46. Hainsworth JD, Litchy S, Burris HA 3rd, Scullin DC Jr, Corso SW, Yardley DA, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-hodgkin's lymphoma. J Clin Oncol 2002;20:4261-7.
47. Schulman K, Burke J, Drummond M, Davies L, Carlsson P, Gruger J, et al. Resource costing for multinational neurologic clinical trials: methods and results. Health Econ 1998;7:629-38.
48. Smith DH, Adams JR, Johnston SR, Gordon A, Drummond MF, Bennett CL. A comparative economic analysis of pegylated liposomal doxorubicin versus topotecan in ovarian cancer in the USA and the UK. Ann Oncol 2002; 13:1590-7.
49. Bennett CL, Armitage JL, LeSage S, Gulati SC, Armitage JO, Gorin NC. Economic analyses of clinical trials in cancer: are they helpful to policy makers? Stem Cells 1994;12:424-9.
50. Verdonck LF, Dekker AW, Lokhorst HM, Petersen EJ, Nieuwenhuis HK. Allogeneic versus autologous bone marrow transplantation for refractory and recurrent low-grade non-Hodgkin's lymphoma. Blood 1997; 90: 4201-5.
51. Verdonck LF. Allogeneic versus autologous bone marrow transplantation for refractory and recurrent low-grade non-Hodgkin's lymphoma: updated results of the Utrecht experience. Leuk Lymphoma 1999;34:129-36.
52. Gandhi MK, Marcus RE. Follicular lymphoma: time for a re-think? Blood Rev 2005;19:165-78.