A cost of illness and quality of life study in patients with B-cell chronic lymphocytic leukemia (CLL) in the Netherlands

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Summary

Objective

During the last decade the management of CLL was subject to progressive changes in diagnostic and prognostic procedures as well as to the development of new alternative treatments. The aim of this study was to assess management, costs, quality of life and survival of CLL patients in daily practice. This information is becoming more important for reimbursement decisions, as new expensive drugs are only reimbursed when the incremental cost-effectiveness ratio lies within existing thresholds. Cost-effectiveness ratios are preferably calculated both in a daily practice (or real world) setting and a clinical trial setting.

Methods

An observational multicentre (n=19) study was performed in the Netherlands using data collected from hospital medical records of patients diagnosed with CLL between June 1999 and 2003 (group 1). Due to the developments in the management of CLL, these patients did not completely reflect the first and second line management of CLL in 2008 anymore. Therefore, we included additional patients who were diagnosed from 2003 to 2008 and were treated with FC, FCA, FCR, or alemtuzumab monotherapy in the first or second line (group 2). Since we focused on certain therapies for the selection of patients in group 2, this group did not represent the complete CLL population. Those patients will therefore be analyzed separately from the patients diagnosed before 1 June 2003.
Quality of life was measured using the EQ-5D and the EORTC QLQ-C30 at the start, halfway through and at the end of each treatment line. Additionally, quality of life was measured every six months during periods without treatment. Patients in group 2 completed only one quality of life questionnaire at inclusion. The costs were calculated using 2007 prices. Kaplan-Meier analyses were performed to assess survival rates.

Results

The 160 patients included in Group 1 were followed during a period of 6.4 years on average. The mean follow-up duration for Group 2 (16 patients) was 2.4 years. The mean age at diagnosis was 63 years (SD: 11; range: 30-86) and 57 years (SD: 8; range: 40-72) respectively for patients in group 1 and 2. The percentage of male patients was 63% vs. 75%. In Group 1 most patients were diagnosed with a Binet stage A (71%), as most patients in Group 2 were diagnosed with a Binet B stage (50%).
In group 1, 39% of the patients stayed on watchful waiting during follow-up, 20% received one treatment line, 12% two treatment lines and 24% received three or more lines. First line

treatment of most patients (87%) was chlorambucil. Second line treatment was dominated by fludarabine (46%). As from the third line, extensive variation was found in alternative treatment types. Six patients received allogeneic stem cell transplantation (of which 1 MUD). The CLL transformed into diffuse large B-cell lymphoma in five patients and in Hodgkin Lymphoma in two patients. Overall 5-year survival was 89% and CLL-specific 5-year survival was 91%.
In group 2, all 16 patients received upfront therapy of: chlorambucil, FC, FCA or FCR and 5 patients also received a second therapy existing of FC or FCR. None of the patients experienced a transformation or death. As the number of patient was limited and the follow-up was relatively short, we did not estimate the overall survival for this group of patients.
The mean total costs per patient per year were on average € 5,898 in group 1 and €13,996 in group 2. The total costs per year increased with consecutive treatment lines; ranging from €1,273 (wait & see) to €63,084 (5^{th} line) for patients in group 1.
Based on the patients in group 1, quality of life decreased with increasing number of treatment lines, and was lower during the treatment compared to the episode after treatment. The patients experienced most problems with fatigue, dyspnea and insomnia.

Conclusions

The management of CLL after the second line treatment varied strongly. Consequently, comparison of cost and effects between alternative treatments was not feasible. The costs per therapy line increased as the disease progressed. The costs of the first years after diagnosis were higher for patients in group 2 (treated with FC, FCR or FCA) than for patients in group 1. The quality of life of patients during watchful waiting was in line with the quality of life in the general population, but it decreased with an increasing number of treatment lines.

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1. Introduction

1.1 CLL

Chronic lymphocytic leukemia is the most common adult leukemia occurring in the Western world, affecting between around 3 to 6 people per 100,000 population (www.ikcnet.nl; SEER, 2009). As with many malignancies, the incidence increases with age, peaking between 60 and 80 years, and twice as many males as females are affected (SEER 2009, Sant et al., 2003). However, CLL also affects younger people and, in the 6% of cases occurring below the age of 50, the disease tends to be more aggressive (Catovsky 1998). CLL can have a T-cell and a B-cell origin. The B-cell origin occurs most (95%) and is subject of this study.

Early symptoms of CLL are often minimal and diagnosis may follow the chance finding of a high lymphocyte count in the blood or a lymph node swelling. However, as the disease advances, patients may experience fatigue, shortness of breath, weight loss, bleeding or bruising and recurrent or persistent infections (Anaissie et al., 1998; Morrison et al., 1998).

The clinical course of CLL is highly variable (Binet et al., 1981). Survival from the time of initial diagnosis can range from several months to 20 or more years, depending on prognostic markers (Rozman et al., 1995, Keating et al., 2003). Stages of the disease, as defined by Rai (Rai et al., 1975) and Binet (Binet et al., 1981) have been the first prognostic factors for CLL patients (Hallek et al., 1997). In addition to the stage of the disease at time of presentation, the prognostic markers: chromosomal abnormalities (Byrd et al., 2004) and mutational status of the immunoglobuline (Ig) genes (Hamblin et al., 1999) have been defined more recently.

For many years chlorambucil has been the most important therapeutic drug for previously untreated CLL. With the introduction of fludarabine in first line treatment (Rai et al., 1990) a higher response rate was observed, which however did not result in a prolonged overall survival when compared to the use of chlorambucil in primary treatment. For this reason, in combination with the lower costs, chlorambucil has been treatment of choice for CLL patients in the Netherlands at the time of the present study.
The first Dutch (HOVON/CBO) guideline for CLL (2004) was in accordance with this policy and advised first line therapy with chlorambucil in CLL, with fludarabine as second line treatment in chlorambucil-resistant patients.

From 2005 the introduction of fludarabine combinations with cyclophosphamide (FC) and the monoclonal antibodies alemtuzumab (FCA) or rituximab (FCR) resulted in more powerful treatment options. Although not proven to prolong overall survival at that time, these therapeutic modalities have been used more often in the recent years at the start of treatment, especially in younger patients. Recent results show that FCR may improve the life expectancy of CLL patients (Hallek et al., 2010).

In the past decade, healthcare costs, also in CLL, have increased remarkably in most Western countries (Meltzer 2001). As new treatment modalities like fludarabine and monoclonal antibodies tend to be more expensive, economic evaluations are becoming an integral and inevitable part of healthcare decision-making. Increasingly pharmaceutical companies and healthcare workers are or will be obliged to provide calculations on the expected cost-effectiveness of new drugs, if these drugs are to be considered for reimbursement (Garrison et al., 2003).
To be able to make a priori calculations of the economic impact that new treatments will have, structured information about the costs of those currently available is urgently needed.

This report describes the costs of CLL from a hospital perspective, i.e. all hospital costs were taken into account. Furthermore it describes the quality of life of CLL patients during (the treatment of) their CLL.

1.2 Aim of study

The management of CLL has changed a lot in the last 20 years because of the changes described above. In this multi-center, single country burden-of-illness study of patients with B-cell chronic lymphocytic leukemia, the objectives were:

1. To assess the medical resources consumed in the management of patients with CLL at various “episodes” of the disease and the main outcomes associated, with the aim of estimating the incidence-based lifetime cost for:
    - The patient cohort overall diagnosed before June 2003 (Group 1)
    - The patient cohort overall diagnosed from June 2003 (Group 2)
2. To investigate the HRQL impacts of the CLL disease and the current management strategies.

1.3 Study design

This is a multi-centre observational study in patients with CLL. The patients enrolled in this study have been managed according to daily clinical practice in the Netherlands. This study was not intended to encourage any particular treatment strategy. As stated above, the objective was to review the regular clinical management of patients with CLL and to assess the accompanying cost and relevant outcomes. Therefore patients could be included regardless of whether or not they received any active treatment. Patients who were treated in the context of a clinical trial could participate as well.

2. Methods

2.1 Patient selection

In 2004 and 2005, four university hospitals and 15 general hospitals in the Netherlands invited CLL patients to participate when they presented in daily clinical practice. All patients older than 17 years with a CLL diagnosis between 1 June 1999 and 1 June 2003 (Group 1) could enter the study when the patient did not suffer from another serious malignant disease or previous malignancy, had a complete record and gave informed consent. The mean follow-up duration in Group 1 was 2,329 days (6.4 years).

Due to the developments in the management of CLL, the data of the patients enrolled in 2004 and 2005 did not completely reflect the current management of CLL in the first and second line anymore. In 2008, we therefore adjusted the inclusion criteria to be able to analyze more recent treatments of CLL as well. Additional patients diagnosed from 2003 to 2008 treated with FC, FCA, FCR, and alemtuzumab monotherapy were enrolled (Group 2). The mean follow-up duration for Group 2 was 880 days (2.4 years). Since we focused on the FC, FCA, FCR and alemtuzumab treatment for the selection of patients in group 2, this group did not represent the complete CLL population. Those patients will therefore be analyzed separately from the patients diagnosed before 1 June 2003.

2.2 Data collection and monitoring

In 16 of the 19 participating centers, all relevant outcomes and medical resource use data from a hospital perspective was derived from patient records and hospital databases by trained study nurses under the supervision of the treating hematologists. In the three remaining hospitals these data were collected by experienced data managers from our institute. Any information missing from the case notes but considered necessary for the data-analysis was discussed with the treating hematologist by the study nurse or the data manager to ensure a complete data set.

This data entered in the electronic data files was monitored regularly – approximately every year - through access to patient files. The monitor from our institute checked the basis characteristics (like age, stage at diagnosis and WHO score) and resource related to the chemotherapy treatment for all patients. The remaining information like monitoring visits, adverse events and diagnostic procedures were monitored in at least 25% of the patients.

In all treatments except of chlorambucil a treatment line exists of 1 to 5-day cycles. A cycle of chlorambucil was defined as a period of treatment without long breaks (of more than a month) and a line as the period of chlorambucil treatment as long as it was not interrupted by another treatment.

2.3 Clinical Outcomes

The clinical outcomes used were: time to next treatment and response to the treatment.
The time to next treatment was defined as the time between the start of a therapy line to the start of the next therapy line. For the calculation of the time to next treatment patients who died due to non-CLL related causes were censored.
The response at the end of each treatment line has been determined retrospectively. It was based on the documentation of physicians in the patient file, on the judgment of the physician at the time of data collection or on the judgment of the data monitor using the results of laboratory tests and diagnostic procedures.

2.4 Cost calculation

Resource use was derived directly from patient records and hospital databases.
The following components were distinguished:

- Chemo(immuno)therapy, including other medication (e.g. prophylactic medication), administration setting, diagnostic and other procedures (e.g. X-rays, scans).
- Monitoring visits, including medication, laboratory tests, diagnostic procedures, blood transfusions and hospital contacts.
- Adverse events, including hospital contacts, medication, diagnostic procedures and blood transfusions.
- Stem cell transplantations, including costs of conditioning therapy, prophylactic medication, diagnostic procedures, and hospital stay.

Different sources were used to derive unit costs in Euros (see below). Costs were calculated by multiplying the resource use and unit costs. The cost year was 2007.

Costs of hospital days, outpatient visits and day care treatment

Unit costs of inpatient hospital days, outpatient visits and daycare treatments were derived from a micro-costing study among patients treated in the hematological departments in a sample of hospitals representative of practice setting and treatment patterns in the Netherlands. (Tan et al., 2010) Unit costs for university and general hospitals were

determined separately. Cost components included direct labor of medical specialists and residents, nurses and administrative staff and indirect labor of clinical and non-clinical departments (e.g. laundry and cleaning), hotel and nutrition, overheads and capital. Additionally, information from this study was used to calculate cost of visits to the emergency room in patients with hematologic diseases. Cost of intensive care unit (ICU) stay was derived from a micro-costing study performed in one university and two general hospitals in the Netherlands. (Tan et al., 2008) For the calculation of these unit costs the type of hospital where the patient was treated was taken into account (see Table 2.1).

Table2.1. Unit costs of hospital days, outpatient visits and day care treatment (in €, year 2007)

Unit	General hospital	University hospital	Source
Inpatient hospital day	400	680	Tan et al. 2010
Outpatient visit	86	142	Tan et al. 2010
Day care treatment	176	305	Tan et al. 2010
ICU per day	1,940	1,940	Tan et al. 2008
Emergency room visit	206	206	Tan et al. 2010
Inpatient hospital isolation day*	n.a.	890	van Agthoven et al. 2002

* see stem cell transplantation

Stem cell transplantation

Costs of stem cell transplantation (SCT) were reported separately (Table 3.9). However, not all components of stem cell transplantation could be identified in the patient file. We therefore combined the data from the patient file with the cost calculation from another study (van Agthoven et al., 2002).

Our study provided information about the conditioning chemotherapy, prophylactic medication, blood transfusions, diagnostic procedures, hospital stay and other contacts during SCT. The

unit costs of an inpatient hospital stay during SCT is relatively high compared to the costs of a standard inpatient hospital day, which is mainly the result of the high nursing intensity in order to comply with isolation protocols that are related to these interventions (see table 2.1).

The following components of stem cell transplantation were valued using the previous cost-calculation: HLA typing of the patient, HLA typing of the donor, stem cell harvesting, stem cell selection, DLI, and personnel costs. We adjusted costs to 2007 using general price index figures from the Netherlands (CBS) and distinguished allogeneic SCT from related donors and from matched unrelated donors. For the donor costs of unrelated donor transplants the average costs of a transplant in the Netherlands was derived. We assumed that four HLA-typing procedures were performed preceding the SCT. Finally, we assumed

that 50% of the patients received a donor lymphocyte infusion (DLI) following the stem cell infusion (van Agthoven et al., 2002).

Chemotherapy and other medication
Cost of medication was based on Dutch retail prices derived from the Farmacotherapeutisch Kompas (www.fk.cvz.nl, Dutch). For the calculation of the cost of medication that was administered via injections wasting was taken into account.

Laboratory test and other diagnostic procedures
Cost of laboratory tests and other diagnostic procedures were based on national tariffs derived from the Dutch Healthcare Authority (NZa) which are assumed to reflect the actual cost reasonably (www.nza.nl). During standard follow-up (monitoring visits), various laboratory tests were performed. We recorded the number of days per line on which laboratory test were performed and assumed that only one withdrawal was performed per day. An exception was made for hospitalizations during which we assumed one additional withdrawal per day. The unit costs of laboratory tests per withdrawal were based on a research in multiple myeloma patients (Franken et al., 2011). In that study all laboratory tests that were performed were listed during the follow-up of 3 consecutive treatment lines, resulting in a total of 500 laboratory days. The weighted cost per laboratory day was €52.97.

2.5 Quality of life

Two distinct types of instruments were used for the health related quality of life (HRQL) assessment: the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) questionnaire, including CLL specific attachment and an experimental version of the EQ-5D self-report questionnaire. The EORTC QLQ-C30, including CLL specific attachment provided a descriptive profile of the HRQL of a cohort of patients with CLL. The experimental EQ-5D comprised the same 2 options as the current standard version: a descriptive classification and a visual analogue scale. However, in this study, the experimental five level (rather than 3 level) descriptive EQ-5D was used as this classification may provide a more sensitive measure of change in health status than the current 3 level instrument. The VAS component included is the same as that included in the current standard instrument and provided a single overall summary score of HRQL.

All patients were asked to fill in quality of life questionnaires. If informed consent was obtained, the patient filled in a form with some basic characteristics regarding smoking,

education, and employment. The patient also received a questionnaire at the time of enrollment. This provided us with cross-sectional information about quality of life in CLL patients at least one year after diagnosis. After enrollment, patients received a questionnaire every six months during periods without treatment. During treatment, the patient received a questionnaire around the start, halfway through and after a treatment line. Patients treated with chlorambucil however, received a questionnaire around the start of treatment and subsequently every six months, because this treatment often was not given according a predetermined schedule and could last for over a year. The questionnaires during follow-up were sent to the patient by the researchers, whereas questionnaires during treatment were given or sent to the patient by hospital staff.

As hospital staff sometimes forgot to hand out the questionnaire during the treatment period, data about quality of life during the treatments was limited. To enable analysis of the quality of life per treatment line, we distinguished the following groups:

- Patients who were not treated at all;
- Patients during vs. after treatment in the first line
- Patients during vs. after treatment in the second line;
- Patients during vs. after treatment in the third line;
- Patients during vs. after treatment in the fourth or later line.

"During treatment" was defined as the period from 2 months before treatment until 90 days after the end of treatment.

2.6 Data and statistical analysis

This report contains a descriptive analysis of the treatments used for the management of CLL. The mean and standard deviation are presented for the chemotherapy costs of the various treatments, the mean costs per treatment line and the mean costs per CLL patient per year for the two patient groups. Furthermore the mean and standard deviation are presented for the quality of life of the two patient groups at time of enrollment, in time and per treatment line.

If one line is dominated by multiple treatment regimens, the treatments with more than 30 patients were statistically tested with regard to response rate (CR and PR), progression free survival, time to next treatment, disease-specific mortality, overall survival, and quality of life at the 2-sided 5% level. In the second (or later) line, we will not take into account the influence of previous treatments on the clinical outcomes.

No utility values for the two additional levels of the experimental EQ-5D were available. We therefore estimated the utility values for these levels based on the Dutch tariffs using three different imputation methods:

- Method 1 (3 level): Utility values were generated based only on questionnaires where patients had selected the standard 3 options of response; all other questionnaires where patients had scored either of the additional boxes were eliminated from the analysis.
- Method 2 (5 level, middle): Based on the total data set, and where respondents had used either of the additional 2 levels provided, these were valued based on the same tariff value as the current level 2 score.
- Method 3 (5 level, midpoint): Based on the total data set, utility values were generated for either of the additional 2 levels assuming the midpoint value between the standard 2 tariff values.

3. Results

3.1 Baseline

In 2004 and 2005, 19 hospitals through the Netherlands selected CLL patients who fulfilled the inclusion criteria and invited them to participate. Informed consent for participation was given by 173 patients (Group 1). Of these patients, 13 patients (6%) were excluded from the analysis for the following reasons: One hospital refused further participation during follow-up, resulting in three patients with incomplete follow-up data. Another ten patients were excluded for different reasons: eight patients did not meet the inclusion criteria after all; one patient chart was missing; and the chart of the other patient was such sizeable that it was not possible to collect all data within a reasonable time span. Subsequently, 144 patients participated in the quality of life study as well.

In 2008, 6 hospitals identified 16 patients receiving FC, FCA, FCR or alemtuzumab monotherapy in first or second line. They gave informed consent and were enrolled in the second part of the study. Nine of them filled in a quality of life questionnaire at the time of enrollment. The results for this group of patients (Group 2) will be reported separately. The patients' characteristics of both groups are presented in Table 1.

Table 3.1. Patients' characteristics at diagnosis

		All patients (n=176)	Group 1 (n=160)	Group 2 (n=16)
Age at diagnosis:	Mean (SD)	62.8 (10.5)	63.4 (10.6)	57.4 (8.7)
	Median	63	63	58
	Range	30-86	30-86	40-72
Gender (% male)		63.6	62.5	75
Patients (%) with first or second degree relatives with leukemia or lymphoma		8.5	8.1	12.5
Binet Stage (%):				
A		67.6	71.9	25
A progressive		1.7	1.9	-
B		18.2	15.0	50
C		12.5	11.3	25
% of patients with 1 or more extranodal sites		87.5	88.1	81.3
B-symptoms (yes %)		14.2	12.5	31.3
Involvement of bone marrow (yes %)		66.5	66.3	68.8
Involvement of spleen (yes %)		29	27.5	43.8
WHO-performance score (%):				
0		77.3	78.1	68.8
1		19.3	19.4	18.8
2		1.1	0.6	6.3
n.a.		2.3	1.9	6.3

N.a.: not available

Patients included after 2003 (Group 2) were younger, had a Binet B stage at diagnosis more often and had relatively more severe symptoms at baseline compared to the patients in Group 1. Additionally, these patients reported more frequently to have relatives with leukemia or lymphoma. Furthermore, the majority of patients in Group 2 are high risk patients participating in the HOVON 68 trial. In group 1 the number of high risk patients is probably lower, but we are not sure about this, since the risk category has not been registered in this study.

3.2 Management of CLL

Time to first treatment

During follow-up 39% (63) of the patients in Group 1 remained in the episode of watchful waiting. One of these patients died during the study due to a non-CLL related cause after 1523 days of follow-up. The follow-up of the remaining 62 patients was on average 2485 days (SD 421).

Sixty one percent (97) of the patients in Group 1 proceeded to a first treatment line (see Table 3.2). Of these patients receiving first line, 22% (34) started therapy immediately or shortly after (e.g. within 28 days) they were diagnosed with CLL, and 39% (63) patients started first line treatment after an average time of watchful waiting of 926 days (SD 713). Then, 36% patients continued to receive a second line therapy and 24% received 3 or more lines.

In Group 2, all patients started therapy during follow-up. Two patients (13%) started immediately after the diagnosis CLL with first line treatment. The remaining patients started after on average 338 days (SD 381) with first line therapy. Then, 31% received a second therapy line, but no patients received a third line of treatment before the end of our study (, but might receive it later on). The different pattern in number of lines between Group 1 and 2 cannot be interpreted easily, because of the shorter follow-up in the second group of patients and the differences in disease stage at diagnosis.

Table 3.2. Therapy lines during follow-up

	Group 1 (n)	Group 2 (n)
First line therapy	61% (97)	100% (16)
Second line therapy	36% (57)	31% (5)
Third line therapy	24% (39)	n.a.
Fourth line therapy	18% (28)	n.a.
Fifth line therapy	7% (11)	n.a.
Sixth line therapy	6% (9)	n.a.
Seventh line therapy	1% (2)	n.a.

n.a.: Not applicable

Treatments per line

The treatment sequence of Group 1 gives information about the clinical practice in the period 1999 – 2007 for patients diagnosed until mid 2003. The treatments are presented schematically in the Appendix I.

Most of the patients who received first line therapy were treated with chlorambucil (87%). Fludarabine monotherapy was applied as second line treatment in almost 50% of the patients. No treatment line was dominated by multiple treatment regimens with each more than 30 patients. Statistical comparison of treatments per line was therefore not performed. In the second group of patients either chlorambucil, FC and FCA were administered to about a third of the patients each in the first line. However, as stated before, this does not reflect the current clinical practice in the Netherlands, as the FC, FCA and FCR treatment was the criterion to invite these patients for participation.

3.3 Clinical outcomes

Response rates

The following table shows the consecutive treatment therapies. To simplify the presentation of the CLL management, we used treatment categories in the table below, which are explained in Appendix III. The clinical outcomes have been presented when 4 or more patients received the treatment. That clinical outcome should be used with cautiousness, because of the following reasons: 1) In most cases, the number of patients who received the treatment is small, 2) the differences in time to first treatment are large and therefore the prognosis is highly variable, 3) the outcomes depend on the treatments in the past and the outcomes of different treatments are therefore not comparable.

Table 3.3. Treatment lines and results in patients in Group 1

Treat-ment line		% (n)	Mean number of cycles (SD)	Time to next treatment in days (SD)	PR %	CR %	PD %	SD %	Tox %	Death %
1	**Total**	**100 (97)**								
	Chlorambucil	86.6 (84)	2.4 (1.8)	894 (690)	48.8		32.2	13.1	5	
	Fludarabine (oral/i.v.)	2.1 (2)	5.0 (4.2)	796 (631)						
	FC	2.1 (2)	4.0 (2.8)	n.a.						
	Other rituximab combi	1.0 (1)	14 (n.a.)	n.a.						
	Other chemo therapy	7.2 (7)	7.0 (3.4)	674 (256)	85.7				14.3	
	Transformation therapy	1.0 (1)	9.0 (n.a)	n.a.						
2	**Total**	**100 (57)**								
	Chlorambucil	5.3 (3)	3.3 (2.3)	1188 (533)						
	Fludarabine (oral/i.v.)	45.6 (26)	4.2 (2.6)	521 (513)	38.5	3.8	19.2	34.6	3.8	
	FC	7.0 (4)	4.0 (2.5))	192 (n.a.)	25			25	25	25
	FCR	8.8 (5)	6.2 (2.5)	345 (372)	60		20			20
	Other rituximab combi	8.8 (5)	5.2 (3.2)	588 (439)	80			20		
	Other chemo therapy	19.3 (11)	5.6 (2.0)	497 (236)	81.8		9.1	9.1		
	Rituximab mono	3.5 (2)	4.0 (0.0)	349 (n.a.)	50			50		
	Transformation therapy	1.8 (1)								
3	**Total**	**100 (39)**								
	Chlorambucil	17.9 (7)	1.6 (0.8)	358 (285)	14.3		71.4		14.3	
	Fludarabine (oral/i.v.)	15.4 (6)	5.0 (1.3)	471 (360)	83.3		16.7			
	FC	15.4 (6)	3.3 (1.8)	230 (166)	16.7	16.7	33.3		33.3	
	FCR	5.1 (2)	5.0 (1.4)	189 (n.a.)						
	Other rituximab combi	5.1 (2)	7.0 (2.8)	753 (n.a.)						
	Other chemo therapy	23.1 (9)	6.0 (1.4)	397 (243)	44.4			44.4	11.1	
	Rituximab mono	5.1 (2)	6.0 (2.8)	n.a.						
	Alemtuzumab mono	2.6 (1)	2.0 (n.a.)	539 (n.a.)						
	Induction therapy	7.7 (3)	4.0 (2.6)	436 (576)						
	Transformation therapy	2.6 (1)								
4	**Total**	**100 (28)**								
	Chlorambucil	3.6 (1)	1.0 (n.a.)	n.a.						
	Fludarabine (oral/i.v.)	17.9 (5)	2.6 (1.8)	241 (200)	60		20		20	
	FC	10.7 (3)	3.0 (1.0)	n.a.						
	FCR	7.1 (2)	3.0 (0.0)	252 (n.a.)						
	Other rituximab combi	7.1 (2)	4.0 (2.8)	n.a.						
	Other chemo therapy	14.3 (4)	2.0 (1.4)	34 (11)	50		25	25		
	Alemtuzumab mono	10.7 (3)	1.0 (n.a.)	454 (n.a.)						
	Alemtuzumab combi	3.6 (1)	1.0 (n.a.)	n.a.						
	Induction therapy	7.1 (2)	5.0 (1.4)	68 (58)						
	Condit therapy + SCT	10.7 (3)	1.0 (0.0)							
	Transformation therapy	7.1 (2)								

Treat-ment line		% (n)	Mean number of cycles (SD)	Time to next treatment in days (SD)	PR %	CR %	PD %	SD %	Tox %	Death %
5	**Total**	**100 (11)**								
	Chlorambucil	9.1 (1)	1.0 (n.a.)	232 (n.a.)						
	Fludarabine (oral/i.v.)	9.1 (1)	6.0 (n.a.)	512 (n.a.)						
	FC	9.1 (1)	3.0 (n.a.)	83 (n.a.)						
	FCR	9.1 (1)	2.0 (n.a.)	65 (n.a.)						
	Other rituximab combi	18.2 (2)	2.5 (0.7)	47 (n.a.)						
	Other chemo therapy	9.1 (1)	6.0 (n.a.)	158 (n.a.)						
	Rituximab mono	9.1 (1)	1.0 (n.a.)	n.a.						
	Induction therapy	9.1 (1)	6.0 (n.a.)	136 (n.a.)						
	Condit therapy + SCT	18.2 (2)	1.0 (0.0)	420 (163)						
6	**Total**	**100 (9)**								
	Fludarabine (oral/i.v.)	11.1 (1)	1.0 (n.a.)							
	Other chemo therapy	22.2 (2)	1.5(0.7)							
	Rituximab mono	44.4 (4)	3.3(1.5)	75 (n.a.)	50	25	25			
	Induction therapy	11.1 (1)	1.0 (n.a.)	n.a.						
	Condit therapy + SCT	11.1 (1)	1.0 (n.a.)	250 (n.a.)						
7	**Total**	**100 (2)**								
	Other chemo therapy	50.0 (1)	6.0 (n.a.)	n.a.					100	
	Transformation therapy	50.0 (1)								

A total of six patients received allogeneic stem cell transplantation and in five patients, the disease transformed into the Richter syndrome. Additionally, the disease transformed into Hodgkin lymphoma during follow-up in two patients. The follow-up of these two patients was censored at the time of the transformation as these transformations were considered not to be related to CLL. All these patients were included in Group 1. Treatment outcomes of transformation therapies are not included in this Table. The treatment characteristics and the results of the transformation therapies are presented in table 3.4. One patient received two transformation therapies during the second and third treatment line. Four out of five patients with the Richter syndrome died during follow-up.

Table 3.4. Transformation therapies and results

Patient	Treatment line	Type of treatment	Number of cycles	Time to next treatment in days	Outcome
1	Line 1	CHVm/BV	9	n.a.	CR
2	Line 2	R-CHOP	2	37	PD
2	Line 3	R-VIM/R/DHAP	2	72*	-
3	Line 4	R-CHOP	2	892 *	PR
4	Line 7	R-CHOP	3	126*	PR
5	Line 4	R-CHOP	2	51*	PD

* Patient died due to CLL during follow-up

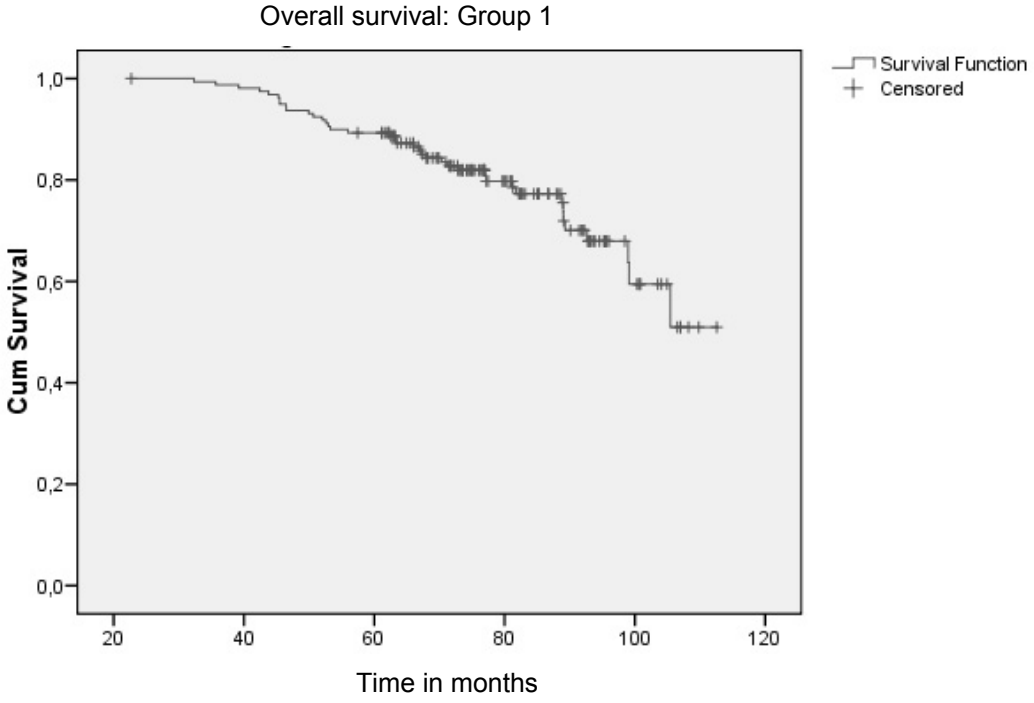
Table 3.5 presents the consecutive treatment therapies and the results for the patients in Group 2.

Table 3.5 Therapy lines and results in patients in Group 2

Treatment line		% (n)	Mean number of cycles (SD)	Time to next treatment in days (SD)	PR %	CR %	PD %	SD %	Tox %
Line 1	**Total**	**100 (16)**							
	Chlorambucil	31.3 (5)	2 (1.2)	426 (212)	20		20	40	20
	FC	31.3 (5)	5.4 (1.3)	n.a.	20	60	20		
	FCR	6.3 (1)	5 (n.a.)	n.a.					
	FCA	31.3 (5)	6 (0.0)	n.a.	60	20		20	
Line 2	**Total**	**100 (5)**							
	FC	40.0 (2)	6 (0.0)	n.a.					
	FCR	60.0 (3)	5.3 (0.6)	n.a.					

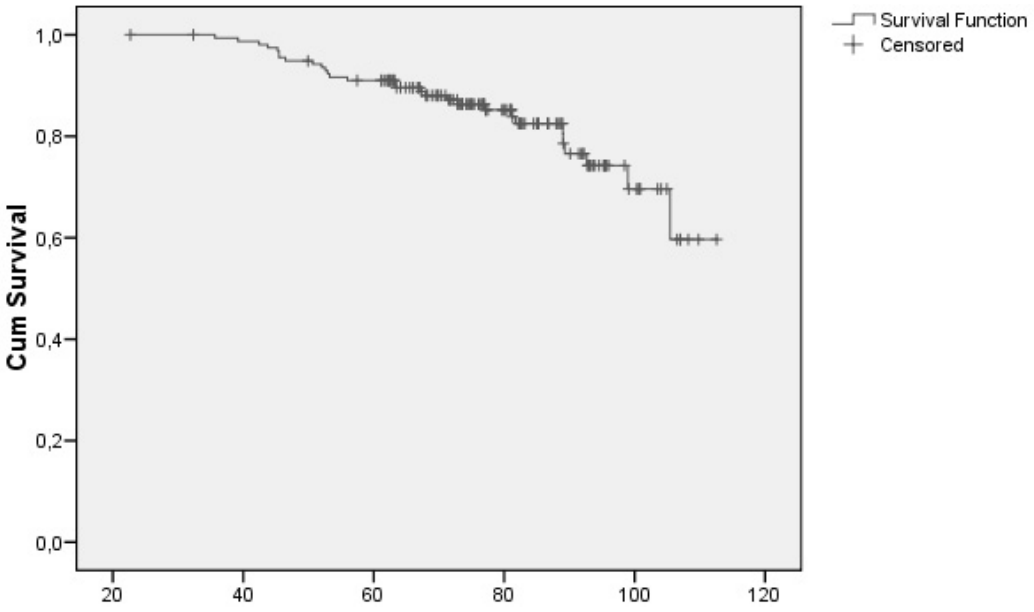
Survival

The two-year overall survival in Group 1 was 100% and the five-year overall survival was 89%. A total of 39 patients died during follow-up, 29 due to CLL and 8 due to other causes. In two patients the cause of death was unknown.



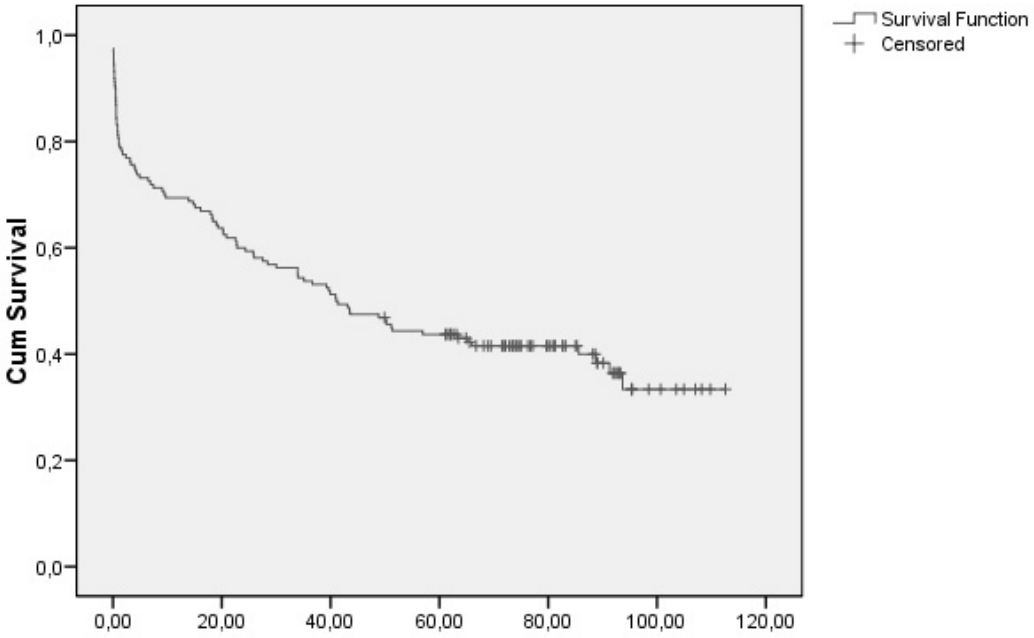
The second Kaplan Meier curve presents the CLL specific survival of the patients in Group 1. The two-year CLL specific survival was 100% and the five-year CLL specific survival was 91%.

CLL specific survival: Group 1

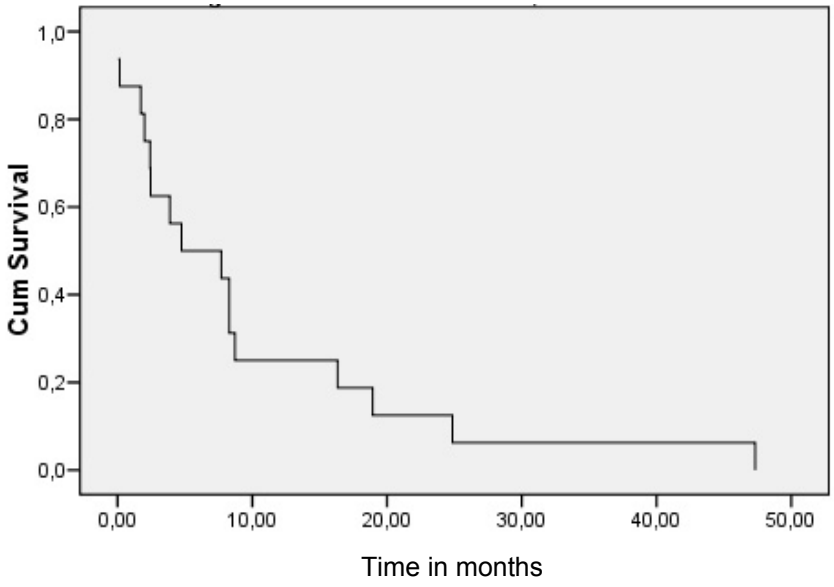


No deaths were reported in Group 2. We therefore do not present the Kaplan Meier Curve for Group 2. The median time to first treatment for Group 1 and 2 is 41 and 4 months respectively. Patients in Group 2 received treatment much earlier than the patients in Group 1. This illustrates that both groups were not comparable with each other in terms of severity of the disease.

Time to first treatment in months: Group 1



Time to first treatment: Group 2



3.4 Costs

In this section we present the costs of the alternative chemotherapies and the costs per treatment line. In Appendix II detailed tables are presented including resource use and cost per treatment line of chemotherapy (chemotherapy costs only) in Table 7.1 en 7.5, monitoring visits (MV) in Table 7.2, and 7.6, adverse events (AE) in Table 7.3 and 7.7 and Stem cell transplantations in Table 7.4.

Table 3.6 presents the average cost of the alternative chemotherapy lines. In these figures costs of prophylactic medication and other resource use are excluded.

Table 3.6. Average cost of chemotherapy of the alternative chemotherapy lines

Group 1					**Group 2**			
	n	Mean number of cycles (SD)	Mean cost per line (SD)	Cost range	n	Mean number of cycles (SD)	Mean cost per line (SD)	Cost range
Chlorambucil	96	2.3 (1.8)	414 (834)	21-7,835	5	2.0 (1.2)	268 (205)	142-631
Fludarabine (oral/i.v.)	41	4.1 (2.4)	4,224 (3,405)	452-15,501	-	-	-	-
FC	16	3.5 (1.8)	2,896 (2,463)	440-10,576	7	5.6 (1.1)	7,478 (3,891)	3,620-14,333
FCR	10	4.9 (2.4)	13,930 (7,273)	2,157-24,181	4	5.3 (0.5)	20,584 (4,348)	15,259-25,899
Rituximab combi	12	5.6 (3.8)	12,479 (9,105)	1,911-33,993	-	-	-	-
Rituximab mono	9	3.8 (2.0)	11,559 (10,869)	2,032-39,809	-	-	-	-
Alemtuzumab mono	4	6.5 (5.8)	12,505 (8,880)	2,966-22,970	-	-	-	-
Alemtuzumab combi	1	1 (n.a.)	2,684 * (n.a.)	2,684	-	-	-	-
Other chemotherapy	35	5.4 (2.6)	645 (507)	35-2,737	-	-	-	-
FCA	-	-	-	-	5	6 (n.a.)	8,204 (732)	6,929-8,724

n.a.= Not applicable * Note that this concerns only one patient.

Overall, monoclonal antibodies were the most expensive treatment regimens.

Table 3.7. Average total costs (including chemotherapy, other medication, monitoring visits, adverse events, stem cell transplantation and tests) per patient per treatment line (in €) in patients in Group 1

	N	Total cost per line (all patients)	Mean follow-up in days (SD)	Mean cost per patient	SD
Period preceding first line treatment	160	746,407	1,339 (1,106)	4,665	11,080
First treatment line	97	1,454,682	1,050 (797)	14,997	21,983
Second treatment line	57	1,355,843	555 (466)	23,787	27,504
Third treatment line	39	981,072	367 (273)	25,156	22,089
Fourth treatment line	28	817,792	219 (278)	29,207	31,307
Fifth treatment line	11	378,070	199 (182)	34,370	40,886
Sixth treatment line	9	198,530	162 (162)	22,059	24,161
Seventh treatment line	2	84,706	412 (405)	42,353	40,602
Total per patient	**160**		**2,329 (527)**	**37,607**	59,914

In table 3.7 the costs include the total costs during chemotherapy, costs of monitoring visits, adverse events, prophylactic medication, tests and stem cell transplantations. More details are presented in Appendix II.
The total costs per patient during the 2,329 days of follow-up of the study were on average € 37,607. The mean costs *per study year* were € 5,898.
The mean costs per patient were lowest during the episode preceding first line treatment. Additionally, cost increased with consecutive treatment line until the sixth treatment line.

In Table 3.8 the average costs per patient per treatment line of patients in Group 2 are presented. The total costs per patient during the 880 days of follow-up were on average € 33,720. This is lower than in Group 1 because of the shorter follow up duration. However, the costs *per study year* were € 13,996, which are higher than the costs per follow-up year in Group 1 because of the more expensive treatments and a higher mean number of cycles per treatment line. This might be (partly) caused by the more advanced disease stage at diagnosis.

Table 3.8. Average costs per patient per treatment line (in €) in patients in Group 2

	N	Total cost per line (all patients)	Mean follow-up in days (SD)	Mean cost per patient	SD
Period preceding first line treatment	16	33,985	296 (373)	2,124	1,615
First treatment line	16	339,904	448 (253)	21,244	17,762
Second treatment line	5	165,634	437 (346)	33,127	16,203
Total per patient	**16**		**880 (369)**	**33,720**	**17,773**

The costs of stem cell transplantation are presented in Table 3.9. The components marked with *** were directly derived from our study. The other components could not be extracted from the patient files in most cases. We used the data from another study (Van Agthoven, 2002) to calculate these costs. In the tables in Appendix II, the costs of stem cell transplantations are integrated in the costs of chemotherapy (conditioning therapy) and adverse events (hospitalization).

Table 3.9. Cost of Allogeneic SCT (excluding laboratory costs).

	SCT of related donor	SCT of unrelated donor
HLA typing patient	1,258	1,258
HLA typing donor	3,606*	52,916**
Stem cell harvesting	1,486	n.a.
Stem cell selection	5,721	5,721
DLI	1,260	4,238
Personnel cost	14,551	14,551
Conditioning therapy	3,228***	3,228***
Prophylactic medication	1,342***	1,342***
Blood transfusions	894***	894***
Diagnostic procedures	1,697***	1,697***
Inpatient stay	15,723***	15,723***
Other contacts during SCT (day ward, outpatient visits)	52***	52***
Total cost	50,818	101,619

* On average HLA-typings of four relatives will be performed in order to choose one donor

** Including stem cell harvesting, transport and mediation of Europdonor

*** Mean costs of all STC (5 related, 1 unrelated) based on the data collected during this study (Table 7.4).

In a recent study the costs of different types of stem cell transplantations were calculated for a combination of multiple myeloma, leukemia and lymphoma patients. When we made both cost calculations comparable by excluding the laboratory costs and costs during the 1 year follow-up of that study, the costs were comparable (€ 50,306 for a SCT of a related donor and € 88,944 for an unrelated donor SCT). (Blommestein et al., 2010)

3.5 Health Related Quality of Life

3.5.1 Initial assessment

The health related quality of life at the time of enrollment has been presented in Table 3.9.

Table 3.9. Mean (SD) quality of life for all patients, Group 1 and Group 2.

	All patients	Group 1 (N=144)	Group 2 (N=9)
EQ-5D: utility			
Method 1: Dutch, 3 level	0.90 (0.1)	0.90 (0.1)	0.91 (0.1)
Method 2: Dutch, 5 level middle	0.87 (0.1)	0.87 (0.1)	0.91 (0.1)
Method 3: Dutch, 5 level midpoint	0.88 (0.1)	0.88 (0.1)	0.91 (0.1)
EQ-5D: VAS score	76.14 (14.4)	75.94 (14.4)	79.22 (15.2)
EORTC QLQ-C30: functioning scales			
Role functioning	79.17 (24.3)	79.14 (23.9)	79.63 (30.1)
Emotional functioning	87.30 (15.4)	87.45 (15.0)	84.88 (21.6)
Cognitive functioning	87.31 (17.4)	87.79 (17.07)	79.63 (21.7)*
Social functioning	88.93 (17.7)	89.63 (16.8)	77.78 (27.6)*
Physical functioning	83.44 (16.8)	83.19 (16.7)	87.41 (18.4)
Global health status	76.64 (17.0)	76.57 (17.13)	77.78 (16.7)
EORTC QLQ-C30: symptoms			
Fatigue	17.18 (15.1)	16.94 (14.7)	20.99 (21.8)
Nausea and Vomiting	2.21 (6.6)	2.35 (6.8)	0.00 (0.00)
Pain	12.69 (20.2)	13.50 (20.6)	0.00 (0.00)*
Dyspnea	18.22 (25.5)	18.91 (25.9)	7.41 (14.7)*
Insomnia	22.30 (27.4)	22.54 (27.1)	18.52 (33.8)
Appetite loss	7.28 (18.0)	7.28 (18.2)	7.41 (14.7)
Constipation	3.11 (10.5)	3.31 (10.8)	0.00 (0.00)
Diarrhea	5.86 (14.4)	6.24 (14.8)	0.00 (0.00)*
Financial difficulties	5.74 (16.7)	4.93 (15.3)	18.52 (29.4)*
EORTC CLL module (last week):			
Losing weight	1.26 (0.5)	1.27 (0.5)	1.11 (0.3)
Dry mouth	1.52 (0.8)	1.52 (0.7)	1.44 (0.9)
Bruises	1.10 (0.4)	1.10 (0.4)	1.00 (0.0)
Unpleasant feeling in stomach	1.34 (0.6)	1.36 (0.6)	1.11 (0.3)
Temperature up and down	1.17 (0.5)	1.17 (0.5)	1.11 (0.3)
Night sweating	1.65 (0.8)	1.65 (0.8)	1.67 (0.9)
Feeling sick / ill	1.25 (0.5)	1.25 (0.5)	1.11 (0.3)
Listless	1.52 (0.7)	1.52 (0.7)	1.56 (0.7)
Lifeless	1.59 (0.7)	1.58 (0.7)	1.78 (1.0)
Limited in planning activities	1.47 (0.8)	1.46 (0.8)	1.67 (1.0)
Worries about future health status	1.79 (0.8)	1.80 (0.8)	1.67 (0.7)
EORTC CLL module (last 4 weeks):			
Pneumonia	1.64 (0.9)	1.64 (0.9)	1.56 (1.1)
Other infections	1.31 (0.7)	1.33 (0.7)	1.11 (0.3)
Need for antibiotics repeatedly	1.39 (0.8)	1.38 (0.7)	1.56 (1.1)
Worries for infections	1.45 (0.7)	1.45 (0.7)	1.44 (1.0)

* More than 5 points difference between Group 1 and Group 2

The initial quality of life for both groups is comparable with regard to the utilities of the EQ-5D regardless of the imputation method used. Group 2 scores better on the VAS, which

might be explained by the lower age of this group of patients. Their physical functioning is better compared to the patients in Group 1 as well. However, they have more financial difficulties. This might also be because they are younger and will have more loss of income. Compared to Group 1, Group 2 experiences more problems with fatigue, emotional functioning, cognitive functioning and social functioning, but less problems with dyspnea, pain and diarrhea.

3.5.2 Assessment per line

The patients in Group 1 filled in multiple quality of life questionnaires from enrollment till the end of the study. This group of patients can therefore be used to get an impression of the changes in quality of life over time. The patients of Group 2 were not included in this analysis, because of the small patient number and because of the fact that they (related to their retrospective identification at the end of the follow-up) only completed one questionnaire (at the time of enrollment).

Figure 3.1 shows that the EQ VAS score (0-100) slightly decreases as the line number increases, and is lower during the treatment compared to after the treatment. The VAS as used in the study is shown in Appendix IV (Dutch).

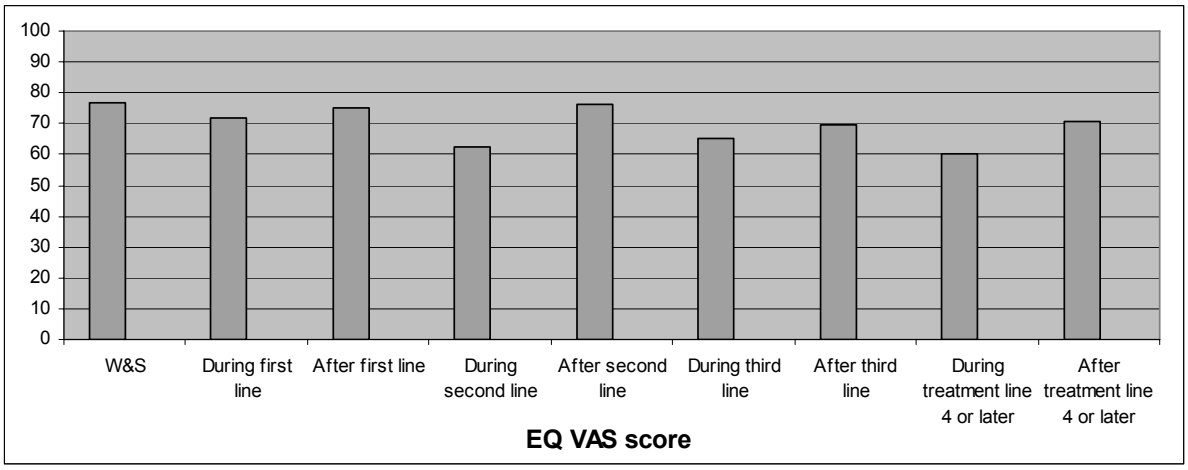


Figure 3.1. Mean EQ Vas score: Group 1

We saw a similar pattern in Figure 3.2 for the utilities, using 3 imputation methods.

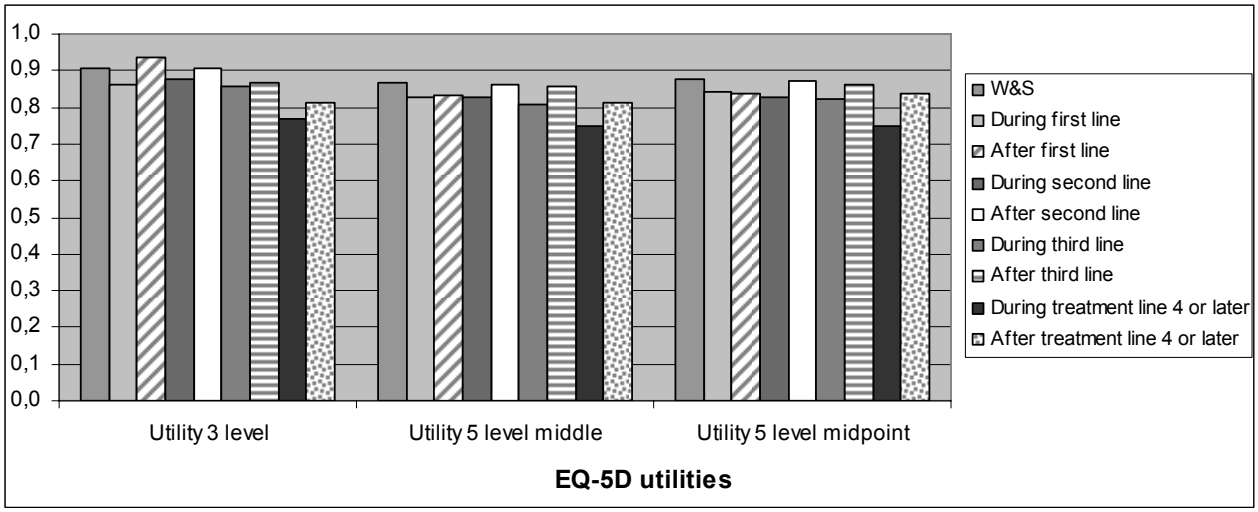


Figure 3.2. Mean EQ-5D utilities: Group 1

The EORTC QLQ-C30 questionnaire distinguishes 6 functioning scales. The CLL patients in Group 1 scored worst on the role functioning scale and the global health, followed by physical functioning. For the most scales, the pattern in scores is comparable with the utilities and VAS: the score decreases in time, being better during the time after treatment in comparison with the time during treatment (Figure 3.3.).

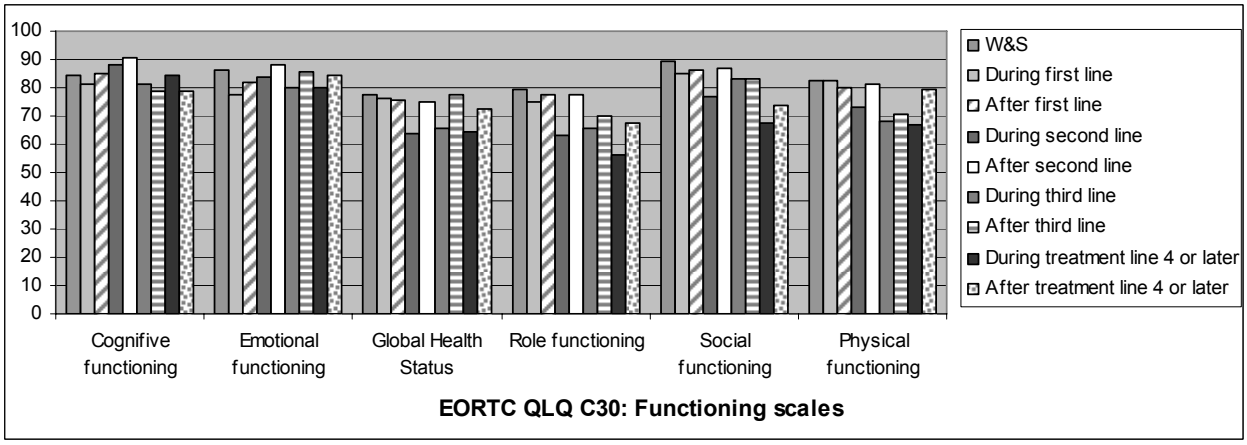


Figure 3.3. Mean scores on the functioning scales of the EORTC QLQ-C30: Group 1

In contrary to the functioning scales of the EORTC QLQ-C30, a higher score on the symptoms scales means more symptoms and thus a worse quality of life. The CLL patients experience most problems with fatigue, dyspnea and insomnia. In general, they experience more problems during treatment than after treatment.

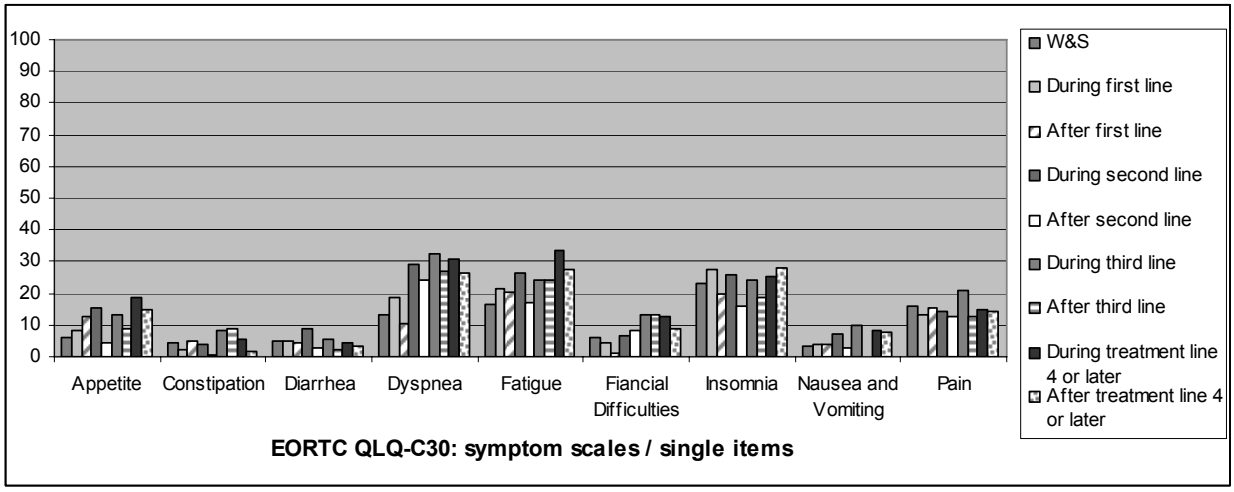


Figure 3.4. Mean scores on the symptoms scales and single items of the EORTC QLQL-C30: Group 1

4. Discussion and conclusion

In this study we followed patients with CLL in order to assess the costs and Quality of Life of the patients during current daily clinical practice.
The study cohort consisted of two groups of patients: the first group included patients diagnosed between 1999 and 2003. Group 2 included patients who were diagnosed after 2003 and who received a therapy with FC, FCA, FCR and alemtuzumab monotherapy as a first or second line treatment.

The first cohort was assumed to be representative of patients with CLL and current clinical daily practice. However, due to the developments in the management of CLL during our study, current clinical practice may have changed. Therefore Group 2 was added to the study later.
The Dutch guideline changed accordingly, recommending a first line treatment within a trial with FC or FCA (HOVON 68 study) or outside a trial with chlorambucil or FC(R) in the period from 2005 until 2011 (www.hovon.nl).

Based on the patients' characteristics and the time to first treatment, it appeared that the two cohorts were significantly different. Patients in Group 2 were relatively younger and had more severe symptoms at the time of the diagnosis. Consequently, the management of this group may represent current daily practice in patients diagnosed with more severe CLL. However, valid conclusions are hardly to make due to the relatively low number of patients in this group. Additionally, the follow-up period of this group was much shorter.

In Group 1 almost 40% of the patients remained in watchful waiting after CLL was diagnosed. The follow-up duration in this group was not significantly different compared to the overall follow-up duration of all patients in Group 1 (respectively 2485 and 2329 days). A first line treatment was given to over 60% of the patients during the follow-up. Chlorambucil was applied mostly as first line therapy (>85%). Almost half of the patients receiving a second line therapy were treated with fludarabine.
In Group 2 only one third of the patients received chlorambucil as first line treatment.

Costs were lowest during watchful waiting in patients of Group 1 as well as in patients of Group 2. Generally, cost increased in patients with raising number of treatment lines. The mean total cost per patient in Group 1 was € 37,607 during follow-up or € 5,898 per year. The mean total cost per year of patients after starting therapy were ten-fold compared

to the cost of patients who were not treated actively (€ 12,057 versus €1,273). The corresponding costs were relatively high in Group 2, as well as after the start of therapy as during watchful waiting. The mean total costs per year in this group were € 19,757 and € 2620 respectively. Cost of chemotherapy was lowest in patients treated with chlorambucil (mean cost per line € 414). The highest costs related to therapies with rituximab and alemtuzumab (> €10,000 per line). Since currently disease management strategies can be better adapted to the risk profile of the patient, these higher costs might be justified when the survival improves – resulting in a so-called preferable cost-effectiveness ratio. Whether this is the case, should be determined in larger (clinical) trials. Overall, we can conclude that the costs per patient varied considerably.

The quality of life was measured at pre-determined times. The general heath related quality of life measured by the EQ-5D self-report questionnaire decreased in time and was lower during treatment compared to the period after treatment. The disease specific quality of life measured by the EORTC QLQ-C30 showed a similar pattern. CLL patients experienced most problems with fatigue, dyspnea and insomnia. From the six functioning scales, the role functioning was limited most. However, the quality of life of CLL patients did not seem to differ much from the general population (Else et al., 2008; Schwarz et al., 2001).

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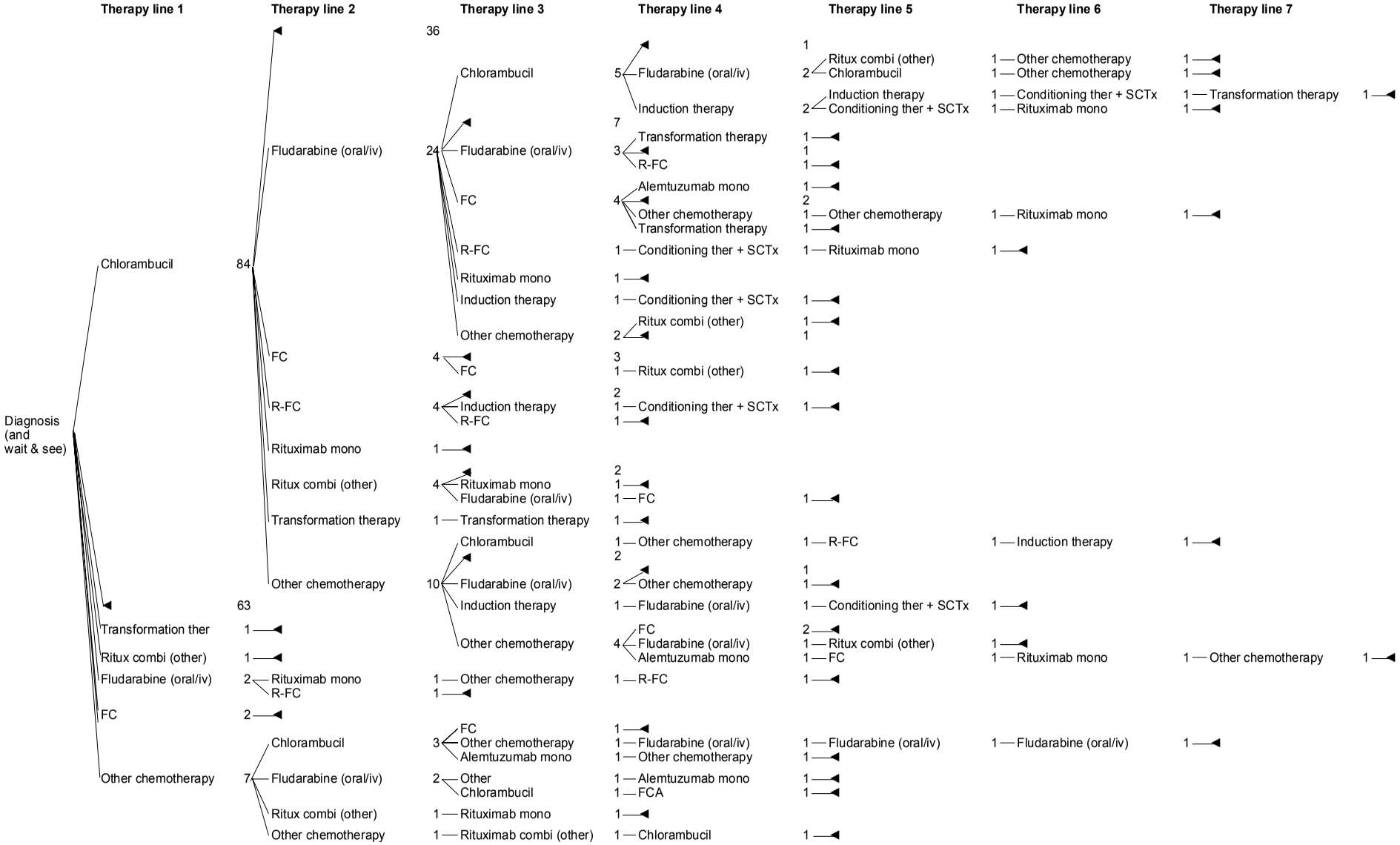
6. Appendix I: flowchart treatments CLL



7. Appendix II: cost tables

Table 7.1 Costs and resource use of chemotherapy** (mean cost per patient per line in Euros) Group 1

	Treatment line 1 (n=97)		Treatment line 2 (n=57)		Treatment line 3 (n=39)		Treatment line 4 (n=25)		Treatment line 5 (n=9)		Treatment line 6 (n=8)		Treatment line 7 (n=2)	
Costs chemotherapy	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Chemotherapy	1119	3783	4960	5802	4437	7499	6551	6835	4758	4530	4886	4733	3968	5465
Prophylactic medication	1129	6707	572	1908	1557	3610	764	1524	468	1036	47	81	89	126
Procedures and blood products	203	1102	565	2522	376	783	419	955	45	134	322	650	802	n.a.
Hospital contacts related to chemotherapy	178	441	1173	1713	1117	1266	1564	2736	1135	1465	678	608	716	282
Day wards related to blood transfusions	79	412	171	678	94	209	80	187	19	56	84	155	472	195
Total costs chemotherapy	**2708**	8256	**7441**	9232	**7581**	8718	**9378**	9397	**6425**	5732	**6016**	5664	**6047**	6068
Resource use chemotherapy	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Outpatient visits	0.6	1.3	1.1	2.4	1.2	2.6	0.2	0.5	0.1	0.3	0.1	0.4	3.0	4,2
Day wards	0.7	2.5	4.6	10.2	3.1	4.1	4.5	7.6	1.7	2.5	1.4	1.8	1.5	2.1
Inpatient days	0.0	0.1	0.6	1.5	1.1	2.8	2.0	5.1	1,9	3,8	0,8	1,4	n.a.	
Day wards related to blood transfusions	0.4	2.4	0.9	3.9	0.6	1.3	0.5	1.1	0.1	0.3	0.5	0.9	2.0	0.0

** Conditioning therapy excluded. These costs are included in the stem cell transplantations (See table 7.4).

Table 7.2 Costs in Euros and resource use during monitoring visits (MV) in Group 1

Monitoring visits (MV)	W&S (n=160)		Treatment line 1 (n=97)		Treatment line 2 (n=57)		Treatment line 3 (n=39)		Treatment line 4 (n=28)		Treatment line 5 (n=11)		Treatment line 6 (n=9)		Treatment line 7 (n=2)	
Costs	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Outpatient contacts	1209	1092	2018	1926	1508	1145	1068	832	974	1453	1406	1456	1356	1379	1998	215
Day wards	25	111	169	443	457	1192	218	679	293	556	228	437	321	508	236	98
Procedures (including blood transfusions)	1274	6317	1248	1615	2341	4229	2577	5355	1209	1806	2567	5629	1642	1607	4498	4425
Medication	188	1212	2256	14422	1963	4525	2625	9206	3621	9392	1323	3206	1805	2610	201	284
Laboratory cost	690	762	2487	1825	2641	3910	2441	2235	2109	2063	2851	2273	1301	779	2966	1199
Total cost MV	**3386**	6922	**8178**	15923	**8910**	9469	**8929**	11938	**8207**	12287	**8375**	10024	**6425**	5475	**9899**	2825
Resource use MV	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Outpatient contacts	12.2	9.5	20.1	16.6	15.2	11.2	11.1	8.3	9.1	10.8	13.5	14.6	12.3	13.4	19.0	8.5
Day wards	0.1	0.7	1.0	2.7	2.7	7.1	1.3	4.1	1.8	3.3	1.4	2.6	1.9	3.0	1.4	0.6
Telephone contacts	0.4	1.1	1.1	2.5	0.7	1.5	0.7	1.7	0.1	0.3	0.4	0.9	0.2	0.4	n.a.	
Nurse contacts	n.a.		n.a		0.1	0.7	0.1	0.2	0.6	3.2	n.a.		n.a.		n.a.	

Table 7.3 Costs in Euros and resource use of adverse events (AE) in Group 1

Adverse events (AE)	W&S (n=160)		Treatment line 1 (n=97)		Treatment line 2 (n=57)		Treatment line 3 (n=39)		Treatment line 4 (n=28)		Treatment line 5 (n=11)		Treatment line 6 (n=9)		Treatment line 7 (n=2)	
Costs Adverse Event	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Inpatient days	543	1803	2500	5300	5124	14794	6124	10098	4233	8776	8873	10862	3067	3695	3160	622
Intensive Care Unit	461	5828	60	591	34	257	n.a.		n.a.		n.a.		431	1293	21340	30179
Other hospital contacts (outpatient visits, SEH, ICC, dietician)	11	49	151	498	342	1021	190	354	106	282	184	299	25	52	0	0
Medication	34	389	107	519	285	940	751	2255	226	655	838	1297	10	31	165	233
Procedures (incl blood transfusions)	231	1361	1293	4459	1651	3204	1580	2683	1157	2538	1293	1919	384	713	1742	1918
Total cost AEs	**1279**	8669	**4111**	8291	**7435**	18011	**8646**	13690	**5722**	10322	**11188**	13956	**3918**	4563	**26407**	31709
Resource use AE	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Inpatient days	1.2	3.9	5.8	12.9	12.6	37.0	14.4	24.7	9.9	21.6	20.9	27.6	6.1	7.1	6.5	3.5
Days ICU	0.24	3.0	0.03	0.30	0.02	0.13	n.a.		n.a.		n.a.		0.22	0.67	11.0	15.56
SEH admittance	0.03	0.16	0.10	0.39	0.18	0.50	0.23	0.74	0.04	0.19	0.27	0.65	n.a.		n.a.	
Day wards	0.01	0.08	0.46	1.94	0.98	3.47	0.36	0.99	0.29	0.85	0.09	0.30	n.a.		n.a.	
Outpatient visits	0.03	0.17	0.29	1.03	0.61	1.42	0.74	1.90	0.07	0.26	0.27	0.65	0.22	0.44	n.a.	
ICC	0.01	0.16	0.04	0.32	0.04	0.19	n.a.		0.11	0.57	0.27	0.65	n.a.		n.a.	
Dietician contacts	n.a.		0.01	0.10	0.04	0.19	n.a.		n.a.		1.18	3.92	n.a.		n.a.	

Table 7.4 Cost in Euros and resource use allogeneic stem cell transplantations (N=6*)

Cost SCT	Mean	SD
Conditioning therapy	3,228	2,306
Prophylactic medication	1,342	753
Blood transfusions	894	1,388
Diagnostic procedures	1,697	1,675
Inpatient stay	15,723	6,508
Other contacts during SCT (day ward, outpatient visits)	52	126
Procedures patient + donor**	36,349	20,739

Resource use SCT	Mean	SD
Total inpatient days	17.7	7.3
Other hospital contacts	0.3	0.8

* all patients were included in Group 1
** mean costs based on 5 related donor and 1 unrelated donor transplantations (see for more information Table 3.9)

Table 7.5 Costs in Euros and resource use during chemotherapy in Group 2

	Treatment line 1 (n=16)		Treatment line 2 (n=5)	
Costs chemotherapy	Mean	SD	Mean	SD
Chemotherapy	6676	5706	14046	9814
Prophylactic medication	1458	1993	2721	2363
Procedures and blood transfusions	108	269	241	359
Hospital contacts related to chemotherapy	1247	1594	1336	1451
Day wards related to blood transfusions	31	91	100	149
Total costs chemotherapy	**9519**	7313	**18443**	12236
Resource use chemotherapy	Mean	SD	Mean	SD
Outpatient visits	0.4	1.3	n.a.	
Day wards	3.6	5.1	8.0	8.7
Inpatient days	0,6	1,7	n.a.	
Day wards related to blood transfusions during chemotherapy	0.2	0.5	0.6	0.9

Table 7.6 Cost in Euros and resource use during monitoring visits (MV) in Group 2

Monitoring visits (MV)	W&S (n=16)		Treatment line 1 (n=16)		Treatment line 2 (n=5)	
Costs	Mean	SD	Mean	SD	Mean	SD
Outpatient contacts	605	660	1888	1487	1222	905
Daywards	21	84	195	550	100	224
Procedures (incl bloodtransfusions)	1020	962	2774	3126	901	1029
Medication	27	100	1498	3686	9462	15832
Laboratory tests	209	319	2063	1912	1218	807
Total cost MV	**1881**	1556	**8418**	7807	**12904**	16049
Resource use MV	Mean	SD	Mean	SD	Mean	SD
Outpatient contacts	5.8	6.7	16.4	10.5	14.0	10.6
Daywards	0.1	0.5	1.2	3.3	0.6	1.3
Telephone contacts	0.2	0.5	1.8	2.6	1.4	2.6

Table 7.7 Costs in Euros and resource use of adverse events (AE) in Group 2.

	W&S (n=16)		Treatment line 1 (n=16)		Treatment line 2 (n=5)	
Costs adverse events	Mean	SD	Mean	SD	Mean	SD
Inpatient days	200	800	2605	6527	1680	2945
Intensive Care Unit	n.a.		n.a.		n.a.	
Other hospital contacts (outpatient visits, SEH, ICC, dietician)	5	22	59	237	52	77
Medication	n.a.	0	55	220	n.a.	
Procedures (incl blood transfusions)	38	150	588	1154	48	107
Total costs adverse events	**243**	972	**3307**	7816	**1780**	3123
Resource use adverse events	Mean	SD	Mean	SD	Mean	SD
Inpatient days	0.5	2.0	5.8	15.6	4.2	7.4
Days ICU	n.a.		n.a.		n.a.	
SEH admittance	n.a.		0.13	0.50	n.a.	
Day wards	n.a.		n.a.		n.a.	
Outpatient visits	0.06	0.25	0.31	1.25	0.60	0.89
ICC	n.a.		0.06	0.25	n.a.	
Dietician contacts	n.a.		n.a.		n.a.	

8. Appendix III: classification of chemotherapies

Classification of different chemo therapies

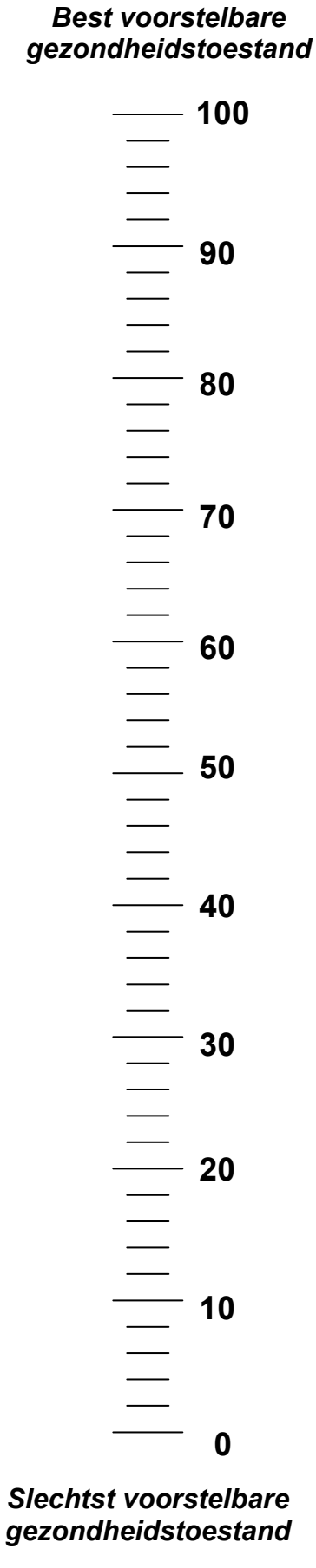
1. Chlorambucil	Chlorambucil; Chlorambucil + prednison
2. Fludarabine	Oral/ i.v.
3. FC	Fludarabine + Cyclophosphamide
4. FCR	FC + Rituximab / Rituximab + Fludarabine
5. Other Rituximab combi	Other combination with rituximab (R-CHOP; R-CVP)
6. Other chemotherapy	Endoxan/cyclophosphamide; cyclophos + pred; CHOP; CVP; CVPP (cyclop.+ vinblast+ pred + procarbazine)
7. Rituximab mono	Rituximab mono therapy
8. Alemtuzumab mono	Alemtuzumab mono therapy
9. FCA	Alemtuzumab combination therapy

9. Appendix IV: experimental EQ-5D

Om mensen te helpen bij het aangeven hoe goed of hoe slecht een gezondheidstoestand is, hebben we een meetschaal (te vergelijken met een thermometer) gemaakt. Op de meetschaal hiernaast betekent “100” de beste gezondheidstoestand die u zich kunt voorstellen, en “0” de slechtste gezondheidstoestand die u zich kunt voorstellen.

We willen u vragen op deze meetschaal aan te geven hoe goed of hoe slecht volgens u uw eigen gezondheidstoestand de afgelopen week was. Trek een lijn van het hokje hieronder naar het punt op de meetschaal dat volgens u aangeeft hoe goed of hoe slecht uw gezondheidstoestand de afgelopen week was. Vul bovendien het door u gekozen punt op de meetschaal in in het kleine vakje hieronder.

Uw gezondheidstoestand in de afgelopen week



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