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A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly diagnosed patients with stage II/III multiple myeloma: a prospective randomised phase III study

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Abstract

A prospective randomised phase III study in patients ⩽65 years old with previously untreated multiple myeloma (MM), intensive chemotherapy followed by myeloablative chemotherapy and autologous stem-cell rescue was compared with intensive chemotherapy alone. This economic evaluation was based on detailed data from patient charts and hospital information systems. In the intention-to-treat analysis, mean total treatment and follow-up costs of the myeloablative treatment arm were €81,643 compared to €68,802 for the chemotherapy arm ($P=0.09$). Costs per quality-adjusted life year were €51,357 versus €37,328. In the clinical study, no significant differences were found in overall survival after a median follow-up of 33 months from randomisation. Intensive chemotherapy is regarded as standard therapy for younger patients with previously untreated MM. Cost-effectiveness of myeloma therapy after 3 years of follow up seems not to be favoured by myeloablative treatment with autologous stem-cell rescue.

Keywords: Costs and cost analysis; Multiple myeloma; Intensive chemotherapy; Melphalan; Myeloablative therapy; Transplantation, autologous; Stem-cell rescue; Interferon

1. Introduction

Melphalan-based chemotherapy regimens have been the standard treatment for multiple myeloma (MM) for more than 30 years [1–3]. With conventional chemotherapy, the median survival is around 30–36 months and the 10-year survival is less than 5% [4–6].

The feasibility of dose escalation with melphalan with the aim of overcoming resistance to conventional-dose alkylating agents has led to the introduction of high-dose chemotherapy and autologous stem-cell rescue [7,8]. At present, two randomised studies have been published showing superiority of myeloablative treatment followed by autologous bone marrow transplantation over conventional chemotherapy [9,10]. Along these lines, the Dutch-Belgian Haemato-Oncology Cooperative Study Group (HOVON) had started a prospective multicentre randomised phase III study in 1995 to evaluate the efficacy of intensive chemotherapy followed by myeloablative therapy with autologous stem-cell rescue as compared to intensive chemotherapy alone (the HOVON 24 MM study). The clinical results of this study have been reported elsewhere [11]. Now, high-dose therapy has become standard treatment for

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MM, while a cost-effectiveness evaluation has never been pursued in a prospective randomised phase III study [12]. We here present the results of this economic evaluation in detail as related to the clinical outcome of the study, and summarise the ultimate results in a cost-utility analysis, given the importance of quality of life as an outcome measure in these patients [13].

2. Patients and methods

2.1. Patients

This cost analysis was part of a prospective multicentre randomised phase III clinical study of the HOVON. Patients $\leqslant$65 years of age with previously untreated MM, and stage II or III A/B disease [14] were eligible for the study. Exclusion criteria were: World Health Organisation (WHO) performance score 4, severe cardiac, pulmonary, neurological or metabolic disease, inadequate liver function (bilirubin $\geqslant$2.5 times normal), prior malignant disease except for non-melanoma skin tumours or stage 0 cervical carcinoma, and prior extensive radiation therapy involving the bone marrow precluding total body irradiation. In this study, 261 patients were eligible for randomisation.

For this cost analysis, 100 patients, matched for age and sex, were included. Response and survival were unknown at the time the participants were selected. The following criteria were consequently applied from the first randomised patient onwards to select the 100 participants: patients from both university and local hospitals, and within each hospital patients in both study groups (to prevent cost differences from being caused by hospital-specific differences). The theoretical follow-up duration from the randomisation date up to the scheduled date of the analysis had to be at least 2 years.

2.2. Treatment

An outline of the clinical study is shown in Fig. 1. The aim was to calculate treatment costs up to maximally 3 years after randomisation. The primary endpoint was a comparison of the costs of both treatment groups based on an intention-to-treat (ITT) analysis. The secondary outcome was a comparison based on per protocol (PP) analysis. The latter was performed to gain insight into the costs for patients who actually received the treatment they were randomised to. For the cost analysis, the time interval of the study was divided into the following phases.

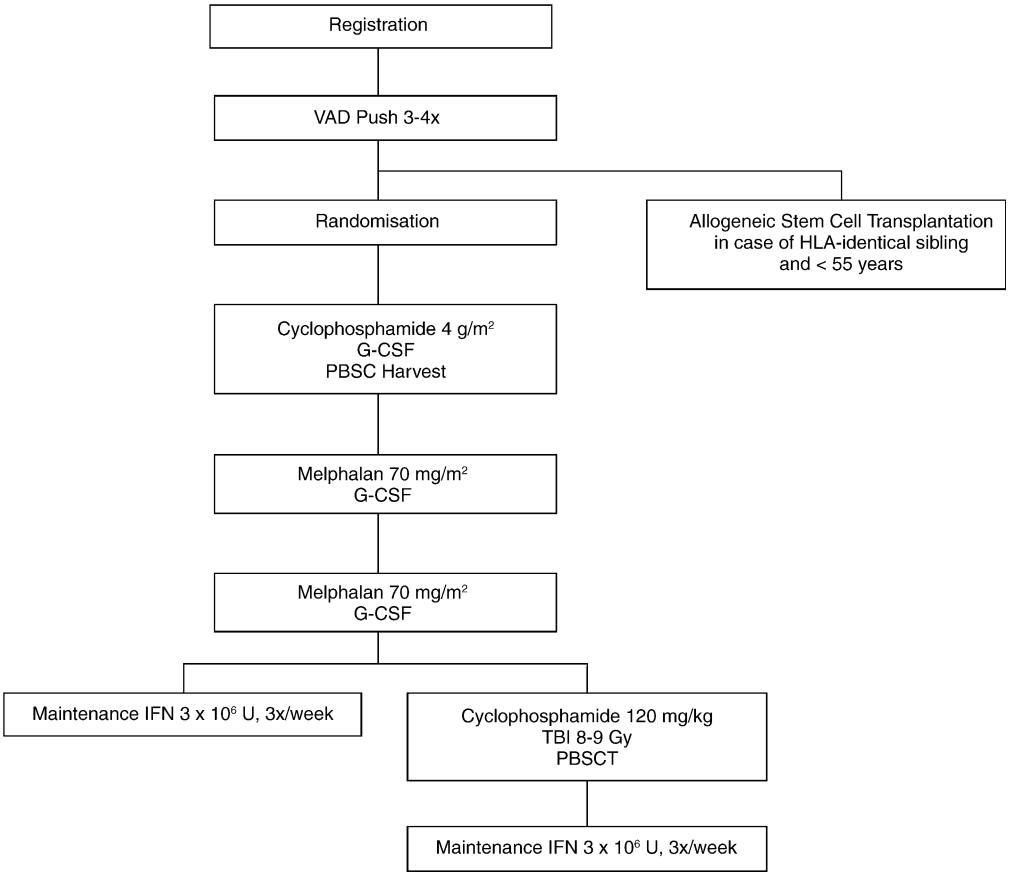

Fig. 1. Outline of the study. See 'Patients and Methods' for an explanation of the abbreviations.

2.3. Phase 1: VAD remission-induction therapy (P1VAD)

The start date of this phase was day 1 of the first VAD cycle. Patients were treated with 3–4 cycles of VAD remission-induction chemotherapy (vincristine intravenously (i.v.) 0.4 mg, days 1–4; doxorubicin i.v. 9 mg/m^2, days 1–4; dexamethasone orally 40 mg, days 1–4, days 9–12 and days 17–20 at cycles 1 and 3, or days 1–4 at cycles 2 and 4)), repeated at 28-day intervals [15]. After VAD, patients were randomised to undergo either intensive chemotherapy only or intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue. Patients $\leqslant$55 years of age with a HLA-identical sibling were candidates for allogeneic stem-cell transplantation and were therefore not randomised.

2.4. Phase 2: Cyclophosphamide and autologous stem-cell collection (P2CYCLO)

The start date of this phase was the date of hospitalisation for cyclophosphamide administration. Four to six weeks after the final VAD cycle, peripheral blood stem cells were collected from all randomised patients (also in the intensive chemotherapy only group, to be used in case of progression or relapse), after they had been given cyclophosphamide (i.v. 4 g/m^2 at day 1; granulocyte colony-stimulating factor (G-CSF) subcutaneously 300–480 μg, starting at day 5 until the last day of leukapheresis). A minimum of 2.5×10^6 CD34+ cells/kg was required to proceed to myeloablative treatment and autologous stem-cell reinfusion.

2.5. Phase 3: Intensive melphalan (P3IM)

The start date of this phase was day 1 of the first intensive melphalan (IM) cycle. Two cycles of intermediate-dose melphalan (70 mg/m^2 i.v. each cycle) were administered as described before [16], at a maximum interval of 8 weeks. G-CSF was started on the fourth day after the melphalan infusion (300–480 μg) until the neutrophil count reached $\geqslant1.0\times10^9$/l.

2.6. Phase 4: Peripheral blood stem-cell transplantation (P4PBSCT)

This phase was only applicable to the patients randomised to the myeloablative treatment group and started at the day of hospitalisation. Patients included in the myeloablative treatment group who had reached at least a partial remission and an adequate stem-cell harvest were given cyclophosphamide 60 mg/kg on two consecutive days, followed by total body irradiation (TBI) 1×9 Gy (lung dose 8 Gy, fractionated TBI 2×5 Gy or 2×6 Gy was allowed) and autologous stem-cell reinfusion ($\geqslant2.5\times10^6$/kg CD34+ cells).

2.7. Phase 5: Maintenance with interferon-α-2a (P5MI)

The start date of this phase was the first date of interferon-α-2a (IFN) administration. IFN maintenance treatment (3×10^6 units thrice weekly) was scheduled to start 60–90 days after the second IM cycle (intensive chemotherapy group) or 60–90 days after stem-cell reinfusion (myeloablative treatment group) until relapse or progression in patients who had at least a partial remission, WHO performance score 0–2, absence of severe organ dysfunction, platelet count $>50\times10^9$/l, and neutrophil count $>1.0\times10^9$/l.

For the cost analysis, this phase ended 3 years after the date of randomisation or death, if earlier. For the intention-to-treat analysis, all follow-up costs of patients who went off protocol treatment before the start of the treatment they were randomised to were also included in P5MI. Costs of relapse or progressive disease were also included.

2.8. Costs

The patients' medical consumption was based on case-registry forms, patient files and records from the hospital information systems. Average unit costs were calculated for the most important items, reflecting full hospital costs, including overhead costs [17,18]. To determine these unit costs (Table 1), we applied the micro-costing method, which is based on a detailed inventory and measurement of resources consumed [19]. Valuation of the resources and overhead costs was based on financial data from two university hospitals and six local hospitals (year 2000 prices) to prevent

Table 1
Unit costs (in Euro). The unit cost of a haematology university hospital day has been applied to all hospitalisations related to treatments that were only performed in university hospitals or specialised cancer centres (cyclophosphamide, leukapheresis, and stem-cell reinfusion). The day-care treatment unit cost was applied to all occasions at which patients had chemotherapy, blood components, or intravenous bisphosphonates administered during a session in the outpatient clinic. Nutrition only included regular meals (costs of parenteral nutrition were calculated separately)

Unit costs	P	E	A	Total
Haematology regular hospital day[a]	212	55	114	**380**
Haematology university hospital day	221	60	129	**411**
Intensive care unit hospital day[a]	663	190	288	**1140**
Haematology dept. outpatient visit[a]	71	10	11	**93**
Haematology dept. day-care treatment[a]	60	41	76	**177**
Stem-cell harvesting (leukapheresis)	234	239	118	**591**
Stem-cell freezing following harvesting	258	511	192	**961**
Stem-cell defrosting preceding reinfusion	133	20	54	**206**
Radiotherapy megavolt session	139	19	56	**214**

P, Personnel, including specialist, nursing, administrative personnel; E, Equipment, materials, nutrition, laundry, cleaning; A, Accommodation and overheads.

[a] Weighting factor 66:34 for university and local hospitals applied.

costs from being different due to hospital type. Some financial data (indicated by the footnote in Table 1) were weighted for their origin: 66% of the final unit costs was based on financial data from the university hospitals, and 34% on financial data from local hospitals, according to the relative distribution of all study participants. These percentages also reflect the distribution of patients among hospitals in Dutch daily practice.

Diagnostic tests and other procedures were multiplied by Dutch charges, as these are proper approximations of the actual unit costs [18]. Costs of medication were based on Dutch wholesale prices [20]. The hospital perspective was applied [13], but costs of medication used by the patient at home as part of the assessed treatments were also calculated.

2.9. Sensitivity analysis

In economic evaluations, total costs are usually determined mainly by the influence of hospital days, but the variation in the unit costs of hospitals days is known to be wide, depending on the hospitals participating in the trial, and therefore they can markedly affect the outcomes of any economic evaluation [21]. For this reason, we analysed the uncertainty in our results by varying the hospital-day unit cost. In a study in which standard hospital-day unit costs were calculated on the basis of unit-cost data from 21 Dutch hospitals, the lowest unit cost was approximately 34% lower than the (mean) standard unit cost, whereas the highest was approximately 34% higher [18]. Therefore, we analysed the influence of varying the hospital-day unit cost with 34% on the total costs. Unit costs other than those of hospital days as used in our analysis were considered to be fairly stable or of less influence and were therefore not subjected to sensitivity analysis.

2.10. Cost-utility analysis

This study also included a quality-of-life (QoL) analysis, of which the results were reported separately [22]. In the QoL questionnaires, the EuroQol-5D instrument was included with the aim of calculating utility values. The EuroQol-5D is a generic QoL instrument that measures health-related QoL in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [23]. Utilities represent preferences for different health states and enable the calculation of quality-adjusted life years (QALYs). QALYs combine two health dimensions (health status and life duration) into one single index. The preference weights used in this study were obtained from a sample of the general population of the United Kingdom [24].

From that QoL analysis, utility values from patients responding to treatment were available up to 24 months. As the time horizon of the cost-utility analysis presented here was 36 months, utility values for these patients were assumed to be stable after 24 months. For patients who were not in remission, the following method was applied to estimate their utility values. First, utility values were obtained from the general public for an age value corresponding to the patients in this study [25]. To this value (0.8), a correction factor for patients with MM was applied [26]. According to this literature study, a correction factor of −19.5% should be applied to the 'general utility value' for patients who were in an undefined state following intentionally curative primary therapy. Therefore, for these patients a utility value of 0.644 (0.8−(0.195*0.8)) was used.

For the cost-utility analysis, both costs and QoL as measured during years occurring after the first year were discounted at a recommended rate of 4% [27]. The number of life years was calculated as the area under the overall survival curve (by using linear interpolation to move from the distinct 6-monthly QoL measurements to a survival curve on which the life years calculation was based). The number of QALYs was calculated as the area under the event-free survival curves to which the utility values for responding patients were applied plus the area between the overall survival curve and the event-free survival curve to which the utility value for non-responding patients was applied, as described by Drummond [13].

2.11. Statistical analysis

Statistical analysis was performed with *SPSS for Windows*, version 10.0. Data are presented as means per patient. Because in general cost data are not normally distributed, firstly the non-parametric Mann–Whitney U-test was applied, using a two-sided significance level $\alpha = 0.05$. Secondly, costs were additionally compared by the non-parametric bootstrap test, as recommended [28], given its independency with regard to the sample size distribution [29]. The bootstrap test is a way of estimating a parameter's distribution by means of a large number of simulations, based on 'drawing with replacement' from the original data. To obtain this, four steps are undertaken: (1) draw with replacement N_A pairs of costs and effects from patients in group A (N_A representing the number of patients in group A); (2) calculate mean costs (and effects) from this new sample; (3) repeat these steps for group B; (4) calculate the difference in mean costs (and effects) between the result of step 2 for group A and the result of step 2 for group B (and, if desired, the incremental cost-effectiveness ratio by dividing the cost difference by the difference in effects). These four steps represent one bootstrap simulation. In total, 1000 simulations were executed. On the basis of these simulations, a confidence interval (CI) was calculated using the so-called percentile method, imply-

ing that the results of the 1000 simulations were consecutively ordered and the borders of the 95% CI were indicated by the 25th and 975th observation [28–31]. Significance levels shown in the tables result from the Mann–Whitney U-test.

3. Results

3.1. Patients

The characteristics and the clinical results of the study participants have been reported elsewhere [11]. A summary of the main findings after a median follow-up of 33 months (range 8–65 months) is presented in Table 2 and an event-free survival curve is shown in Fig. 2. Although intensive chemotherapy followed by myeloablative therapy as first-line treatment for MM resulted in a higher complete remission rate and a longer time to progression when compared to intensive chemotherapy alone, it did not result in a better event-free or overall survival.

From both the intensive chemotherapy group and the group undergoing myeloablative chemotherapy with autologous stem-cell rescue following intensive chemotherapy, 50 randomised patients were originally selected to be included in this cost analysis. However, 2 patients (one from each group) were excluded from the analysis because they finally did not fulfil the study's eligibility criteria. Incomplete patient charts made it infeasible to calculate resource use in 8 patients (5 intensive chemotherapy, 3 myeloablative treatment). Data for the remaining 90 (44 intensive chemotherapy, 46 myeloablative treatment) patients were used to calculate mean costs in ITT analysis. As 18 patients (9 intensive chemotherapy, 9 myeloablative treatment) subsequently did not proceed to the treatment they were randomised for, the costs of the intensive chemotherapy and myeloablative treatment groups in the PP analysis were calculated on the basis of 35 and 37 patients, respectively.

In Table 3, the characteristics of the remaining 90 patients for the ITT cost analysis per treatment arm are presented and compared to all 261 patients described in the clinical study.

There were no differences between both treatment groups with respect to Salmon and Durie stage, and WHO performance status. Also, the distribution of these variables did not differ from those of all patients included in the clinical analysis of the study.

Table 2
Summary of the main clinical findings in the clinical analysis of the study [11]

Outcome measurement	Intensive chemotherapy ($n=129$)	Myeloablative treatment ($n=132$)	P
Complete response	13%	29%	0.002
Median event-free survival (months)	21	22	0.28
Median time to progression (months)	25	31	0.04
Median overall survival (months)	50	47	0.41

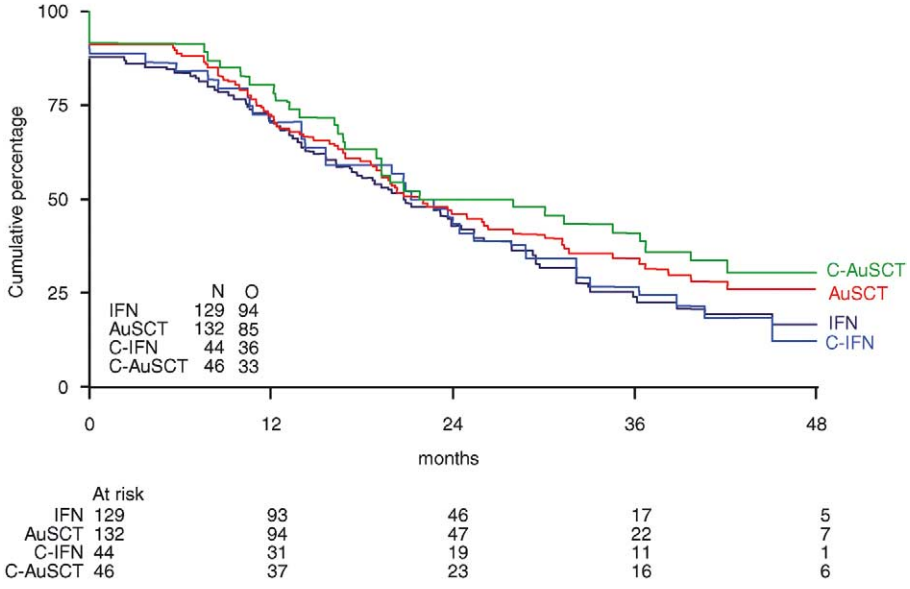

Fig. 2. Event-free survival from randomisation in the clinical study population (AuSCT = myeloablative chemotherapy with autologous stem-cell rescue following intensive chemotherapy, IFN = intensive chemotherapy) and in the subgroup of patients in the cost analysis per treatment group (C-AuSCT, C-IFN).

Table 3
Patient characteristics (intention-to-treat analysis)

	Cost analysis		Clinical study	
	Intensive chemotherapy ($n=44$)	Myeloablative therapy ($n=46$)	Intensive chemotherapy ($n=129$)	Myeloablative therapy ($n=132$)
Mean age (years: median; range)	54 (55; 39–64)	54 (56; 33–65)	55 (55; 38–65)	55 (56; 32–65)
Male	23	28	74	81
Female	21	18	55	51
Stage (Salmon and Durie)				
IIA	10	11	32	26
IIB	–	2	–	3
IIIA	31	32	89	92
IIIB	3	1	8	11
WHO performance				
0–1	33	37	109	107
2–3	10	9	19	25
Not done	1	–	1	–

As mentioned before, an inclusion criterion for the 'cost-analysis patients' was a theoretical follow-up duration from the randomisation date up to the scheduled date of the analysis of at least 2 years. 9 patients (5 intensive chemotherapy, 4 myeloablative treatment) were censored at the date of analysis. In order to complete their follow-up to 3 years after randomisation, they should have been followed for 122 (range 51–272) and 103 (range 5–184) days on average, respectively. This did not result in differences in mean follow-up duration, and therefore no imputation methods were applied to extend artificially the follow-up durations of these patients.

3.2. Costs: ITT analysis

The costs and main indicators of medical-resource use of all phases are presented in Table 4. As expected, no major cost differences between either treatment groups occurred during phases 1, 2 and 3. During P1VAD (lasting 99.49 days on average), the mean hospital stay for all patients was 8.20 days. This number was constituted by some of the patients who received the remission-induction chemotherapy during hospitalisations. Most of the patients had their chemotherapy administered as outpatients (all costs except for cytostatics included in 'day-care treatments'). The P1VAD phase cost €9,799 on average (95% CI 8,499–11,099).

During P2CYCLO patients were hospitalised for 6.91 days, which were virtually all scheduled admissions for administration of the cyclophosphamide chemotherapy and the leukapheresis procedure(s). This phase lasted 49.17 days and cost €9,865 (95% CI 8,974–10,757) on average. Of these costs, 23.1% were on behalf of the stem-cell collection itself.

The P3IM phase lasted 130.71 days on average, during which the patients were hospitalised for 12.20 days. Many of these hospitalisations were scheduled admissions for intensive-dose melphalan administration. Also, unscheduled admissions for neutropenic fever or general malaise occurred frequently. This phase cost €19,967 (95% CI 17,169–22,764) of which the costs of G-CSF and hospitalisation were the main determinants.

In total, the P1VAD, P2CYCLO, and P3IM phases cost €41,455 for patients who were planned to receive intensive chemotherapy and €37,889 for patients who received additional myeloablative treatment. This difference is not related to treatment arm, but is caused by the fact that 2 patients in the intensive chemotherapy only group generated extremely high costs during P3IM. The difference was not statistically significant, either by the Mann–Whitney test or by the bootstrap test.

For the ITT analysis, the costs of the 37 patients who actually underwent myeloablative treatment in phase P4PBSCT (their average costs were €26,593) were divided over 46 patients who were randomised for this treatment. For the entire patient group, this therefore resulted in average P4PBSCT costs of €21,389. Costs for hospitalisation accounted for 55% of the total costs, followed by laboratory diagnostics (10%) and blood components (8%).

During IFN maintenance (P5MI), mean costs were €27,459 for intensive chemotherapy only and €22,366 for intensive chemotherapy followed by myeloablative treatment. Five patients randomised for intensive chemotherapy only were reinfused with their previously collected stem cells at the time of disease progression during follow up. In both groups, hospital days were the main cost driver (23% and 31%, respectively) followed by laboratory diagnostics (14% and 16%). Total treatment and follow-up costs until 3 years from randomi-

Table 4
Results of the intention-to-treat analysis

	P1VAD		P2CYCLO		P3IM		P4PBSCT		P5MI		Total	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
Resource use (numbers)												
Haematology hospital days	8.33	8.07	7.27	6.57	13.25	11.20	–	26.04	16.18	18.02	44.91	69.89
Intensive care unit days	0	0	0.04	0	0.89	0	–	1.04	0.18	0.50	1.11	1.54
Day-care treatments	9.56	8.69	1.09	1.04	6.84	5.54	–	0.26	9.41	5.22	26.70	20.78
Haematology outpatient visits	4.07	3.88	2.61	2.96	8.75	9.59	–	3.78	20.66	17.02	36.02	37.24
Days parenteral nutrition	0.56	0.26	0.08	0	0.75	0.15	–	2.26	1.80	0.22	3.18	2.87
Costs (Euro)												
Haematology hospital days	3175	3079	2938	2667	5058	4272	–	10577	6232	6923	17362	27524
Intensive care unit days	0	0	51	0	1012	0	–	1190	208	571	1271	1762
Day-care treatments	1683	1532	192	184	1206	977	–	46	1659	919	471	3665
Haematology outpatient visits	377	359	242	273	810	888	–	350	1913	1576	334	3448
Outpatient visits, other departments	75	152	45	56	142	155	–	390	194	325	475	1074
Parenteral nutrition	59	28	10	0	79	16	–	240	191	23	338	308
Blood components	230	62	335	302	3448	2592	–	1691	1296	884	5301	5539
Radiotherapy	195	260	0	0	0	37	–	358	750	233	945	886
Leukapheresis	0	0	2116	2429	36	0	–	270	353	0	2505	2699
Stem-cell graft defrosting	0	0	0	0	4	0	–	166	23	0	28	166
Laboratory diagnostics	1468	1422	1152	894	2122	1638	–	2116	3727	349	8422	9565
Radiology diagnostics	309	361	153	152	360	370	–	489	1152	979	2018	2349
Other imaging diagnostics	29	58	28	17	58	91	–	99	118	241	233	506
Microbiology diagnostics	58	52	79	147	134	214	–	628	244	356	549	1399
Pathology diagnostics	52	88	2	37	44	85	–	59	80	199	184	466
Other medical consumption	1	28	58	3	10	73	–	73	80	98	148	274
Cytostatics	113	1150	104	103	215	211		102	648	105	2074	1669
G-CSF	0	0	175	1992	5415	506		42	95	0	7261	7100
Antifungal/antibacterial prophylaxis	347	443	221	273	512	593		430	276	223	1354	1958
Bisphosphonates	90	81	35	33	155	71		56	1702	672	1982	914
Antibiotics	254	106	158	182	698	741		1456	383	503	1494	2993
Interferon-α	0	0	0	0	25	0		54	5212	3221	5237	3274
Other medication	342	457	174	138	192	185		508	923	823	1630	2107
Total costs (Euro)	**9874**	**9718**	**9845**	**9885**	**21735**	**18276**		**21389**	**27459**	**22366**	**68802**	**81643**
Median	*7806*	*7582*	*899*	*9369*	*16550*	*14801*		*18956*	*24769*	*16281*	*68269*	*69418*
Minimum	*414*	*4538*	*4983*	*5463*	*7265*	*7016*		*0*	*6262*	*0*	*26491*	*42340*
Maximum	*44151*	*2268*	*31760*	*27464*	*8404*	*59737*		*135716*	*72437*	*71798*	*140695*	*240521*

G-CSF, granulocyte colony-stimulating factor; P1VAD, phase 1: VAD remission induction chemotherapy; P2CYCLO, phase 2: cyclophosphamide and leukapheresis; P3IM, phase 3: intensive melphalan; P4PBSCT, phase 4: peripheral blood stem-cell transplantation; P5MI, phase 5: maintenance with Interferon-α-2a. Mean values of the most important indicators of medical resource use and mean costs (Euro). Group A = intensive chemotherapy only; group B = intensive chemotherapy followed by myeloablative therapy with stem-cell support.

sation amounted to €68,802 for the intensive chemotherapy and to €81,643 for intensive chemotherapy followed by myeloablative treatment. The cost difference of €12,841 in favour of the former group was not statistically significant ($P = 0.09$ by Mann–Whitney test), and also not by the bootstrap test.

3.3. Costs of intensive chemotherapy and myeloablative treatment: PP analysis

In this analysis, only patients who were actually treated according to the assigned treatment arm were considered. Therefore, in general, costs according to the ITT analysis were somewhat lower than those according to the PP analysis, as the ITT analysis also included patients who did not undergo the treatment they were randomised to. As the treatment during P1, P2 and P3 was similar in both treatment groups, only costs during P4 and P5 were considered. Mean costs (Table 5) of 35 patients who received intensive chemotherapy only were significantly lower (€29,517; 95% CI 24,185–34,847) than the costs of patients who additionally received myeloablative chemotherapy with autologous stem-cell rescue (€48,935; 95% CI 38,203–59,668) (also significant by the bootstrap test). This was mainly due to a difference in the mean number of hospital days (intensive

Table 5
Results of the per protocol analysis (P4PBSCT + P5MI)

	Intensive chemotherapy	Myeloablative treatment	*P*
Resource use indicators			
Mean phase duration (days)	814.06 (865.00; 165–1231)	713.27 (844.00; 37–998)	0.79
Haematology hospital days	14.80 (0; 0–95)	51.57 (38; 22–187)	0.00
Intensive care unit days	0.23 (0.00; 0–8)	1.86 (0.00; 0–33)	0.03
Day-care treatments	10.06 (5.00; 0–45)	4.14 (0.00; 0–30)	0.03
Haematology outpatient visits	22.91 (20.00; 0–62)	21.68 (21.00; 0–44)	0.96
Days parenteral nutrition	2.26 (0.00; 0–54)	2.89 (0.00; 0–26)	0.05
Cost categories			
Haematology hospital days	5720 (0; 0–36246)	20530 (15252; 9032–73958)	0.00
Intensive care unit days	261 (0; 0–9130)	2129 (0; 0–37662)	0.03
Day-care treatments	1773 (881; 0–7932)	728 (0; 0–5288)	0.03
Haematology outpatient visits	2122 (1852; 0–5741)	2007 (1944; 0–4074)	0.10
Outpatient visits, other departments	186 (93; 0–1242)	857 (556; 0–4778)	0.00
Parenteral nutrition	239 (0; 0–5723)	307 (0; 0–2756)	0.05
Blood components	1082 (0; 0–12984)	2603 (1637; 0–21124)	0.00
Radiotherapy	692 (0; 0–4498)	625 (428; 428–3427)	0.01
Leukapheresis	443 (0; 0–3104)	336 (0; 0–1552)	0.64
Stem-cell graft defrosting	29 (0; 0–206)	206 (206; 206–206)	0.00
Laboratory diagnostics	4134 (3427; 544–11621)	6058 (5020; 350–27882)	0.06
Radiology diagnostics	1196 (1065; 0–3744)	1648 (1053; 0–8952)	0.73
Other imaging diagnostics	105 (0; 0–780)	382 (80; 0-3704)	0.00
Microbiology diagnostics	264 (0; 0–2160)	1070 (739; 0–7353)	0.00
Pathology diagnostics	85 (0; 0–633)	261 (0; 0–1446)	0.22
Other medical consumption	73 (0; 0–865)	210 (0; 0–2482)	0.08
Cytostatics	667 (0; 0–2717)	216 (117; 0–2011)	0.42
G-CSF	119 (0; 0–3809)	52 (0; 0–1904)	0.58
Interferon-α-2a	6507 (6464; 521–14028)	3744 (2799; 0–12303)	0.00
Antifungal/antibacterial prophylaxis	337 (0; 0–3244)	754 (499; 0–3259)	0.00
Bisphosphonates	2001 (612; 0–7691)	645 (102; 0–5507)	0.01
Antibiotics	416 (3; 0–3882)	2314 (1514; 125–21614)	0.00
Other medication	1064 (290; 0–10865)	1252 (900; 135–4164)	0.00
Total costs (Euro)	**29517 (26323; 8115–72437)**	**48935 (39330; 22078–201207)**	0.00

G-CSF, granulocyte colony-stimulation factor; P4PBSCT, phase 4: peripheral blood stem-cell transplantation; P5MI, phase 5: maintenance with interferon-α-2a. Mean values (median; range) of the most important indicators of medical resource use and mean costs (Euro) of the intensive chemotherapy group ($n = 35$) and the myeloablative treatment group ($n = 37$).

chemotherapy 14.80; 95% CI 7.36–22.24 versus myeloablative treatment 51.57; 95% CI 38.61–64.53). In the myeloablative treatment group, the hospitalisation for the treatment itself (myeloablative chemotherapy, TBI and autologous stem-cell reinfusion) lasted 28.35 days on average (median 25; range 10–123), implying that these patients also had eight additional unscheduled hospital days as compared to patients who underwent intensive chemotherapy only. Almost all other cost categories, particularly Intensive Care Unit hospital days, blood components, microbiology diagnostics, antifungal and antibacterial prophylaxis, and therapeutic antibiotics showed higher values in the myeloablative treatment group. The costs of IFN during maintenance were higher in the intensive chemotherapy group, as these patients used IFN longer than the myeloablative-treated patients during the assessed time interval. In the intensive chemotherapy group, the costs of day-care treatments and bisphosphonates were also higher.

3.4. Sensitivity analysis

The sensitivity of the total costs to varying the unit costs of hospital days by ±34% was tested, as described before. The influence of this variation appeared to be rather modest: total costs according to the ITT analysis varied by ±9% (intensive chemotherapy) and ±11% (myeloablative treatment), respectively. In the PP analysis, these variations were 7% and 14%, respectively.

3.5. Cost-utility analysis

Table 6 shows the results of the cost-utility analysis. Total costs up to 3 years after randomisation of patients

Table 6
Results of the cost-utility analysis, up to 3 years after randomisation (discounted values in parentheses)

	Intensive chemotherapy	Myeloablative treatment	Incremental results
Costs (up to 3 years):			
Total	€68802 (€67563)	€81643 (€80630)	€12841 (€13067)
Number of (up to 3 years):			
Life years	2.55 (2.46)	2.40 (2.32)	−0.15 (−0.14)
Quality-adjusted life years (QALY)	1.87 (1.81)	1.63 (1.57)	−0.24 (−0.24)
Results:			
Costs per life year	€26981 (€27465)	€34018 (€34754)	−€85607 (−€93336)
Costs per QALY	€36793 (€37328)	€50087 (€51357)	−€53504 (−€54446)

who underwent intensive chemotherapy only were €68,802 as compared to €81,643 for patients who underwent myeloablative treatment (€67,563 versus €80,630, respectively, if discounted). Utility values for patients in response as obtained by the QoL questionnaires of this study were 0.81 (intensive chemotherapy only) versus 0.65 (myeloablative treatment) at 6 months from randomisation, 0.80 versus 0.62 (12 months), 0.81 versus 0.69 (18 months), and 0.77 versus 0.75 (24 months), respectively. After 3 years of randomisation, the total (discounted) number of QALYs was 1.83 (intensive chemotherapy only) versus 1.57 (myeloablative treatment). The lower number of QALYs in the myeloablative arm was particularly caused by the lower utility values during the first year of follow up. Costs per QALY up to 3 years after randomisation were therefore €37,328 versus €51,357, respectively. The incremental analysis shows negative cost-utility ratios, implying that in a 3-year perspective it may be not cost-effective if myeloablative treatment and stem-cell reinfusion is applied after patients have already received intensive chemotherapy.

4. Discussion

Mean costs of MM patients who underwent myeloablative therapy and autologous stem-cell reinfusion followed by IFN maintenance treatment were €81,643 on average (up to 3 years after randomisation), as compared to €68,802 for chemotherapy only. Discounted costs per QALY were €37,328 (intensive chemotherapy only) versus €51,357 (myeloablative treatment), the incremental costs per QALY were – €54,446.

This study provides insight into the cost of treatment and follow up of patients with MM in The Netherlands. In other countries these costs might differ due to different practices or to different costs per unit. From the tables presented, other calculations can easily be performed. For instance, if maintenance treatment with IFN were omitted, total costs would be approximately €63,500 for the intensive chemotherapy only group and €78,000 for the myeloablative treatment group. In addition, if stem cells were not routinely harvested in the intensive chemotherapy only group, this would reduce the average costs to approximately €53,500.

A factor that may have negatively influenced the cost of myeloablative therapy is the application of TBI as part of the conditioning regimen. In most protocols, high-dose melphalan is nowadays used as the conditioning regimen, since TBI has been shown to result in more severe mucositis and treatment-related mortality than high-dose melphalan alone [32,33].

Costs of autologous stem-cell transplantations have already been significantly reduced by harvesting stem cells from the peripheral blood instead of from the bone marrow, which leads to more rapid haematological recovery and early discharge [34,35]. Currently, patients may even receive myeloablative therapy and autologous stem-cell rescue as an outpatient treatment [36,37]. This may further reduce the costs of medication, hospitalisation and diagnostic procedures [36]. However, costs generated by patients using IFN maintenance treatment following intensive chemotherapy can also be further reduced. For example, we observed a more frequent and prolonged use of bisphosphonates in these patients, necessitating a higher occupation of the day-care treatment department. Coyte and colleagues [38] showed that the latter costs can be reduced if the medication is administered at home using a portable and disposable intravenous device. In addition, the adequate duration of bisphosphonate treatment has to be validated in a prospective study.

There have, we believe, been no earlier publications on costs of high-dose chemotherapy followed by stem-cell rescue for MM in the context of a prospective randomised study. Henon and colleagues [39] compared costs of high-dose therapy with stem-cell rescue to conventional treatment in an uncontrolled study [40]. They considered the costs of the high-dose therapy and stem-cell rescue to be acceptable given the treatment's capability of improving survival. Sampson and colleagues [12] have provided cost estimates in one specific university hospital, for which reason they may be not representative of the 'everyday' treatment costs. On the basis of the British study and the French randomised study by Attal and colleagues [9], it has been suggested that the cost-effectiveness ratio of high-dose therapy

and stem-cell rescue is within 'acceptable' limits. Similar conclusions have been drawn by others [41]. However, these conclusions were all drawn from comparisons of myeloablative treatment with conventional chemotherapy.

In the present study, however, the costs of myeloablative treatment supported by stem-cell rescue were investigated in patients who received prior intensive chemotherapy, as is routinely done now. In the ITT analysis it was found that the costs of the latter treatment were 1.2 times higher than the costs of the former treatment.

High-dose chemotherapy is currently offered to all patients up to the age of 70 years who are stable or in objective response following induction chemotherapy [42,43]. Our results show that in the short term it may be not cost-effective if such myeloablative treatment and stem-cell reinfusion is applied after patients have already received intensive chemotherapy. A recent update of the clinical analysis of this study, however, showed that after 5 years of randomisation, a significant difference in favour of the myeloablative treatment occurred with regard to event-free survival (22% versus 8%). Also, time to progression turned out to be in favour of myeloablative treatment (median 32 versus 25 months). The overall survival is still equal between both arms at 5 years from randomisation at 39% (myeloablative treatment) versus 43% (intensive chemotherapy only). Given the results and the above-expressed expectation that the costs of myeloablative treatment will remain higher than those of intensive chemotherapy only, it seems implausible that the costs per QALY will ever become more favourable in the former treatment as compared to the latter. Nevertheless, as pointed out above, it may very well be that society decides to be willing to pay the higher costs per QALY for the myeloablative treatment of these patients. After all, despite the high costs, myeloablative treatment appears to result in improved outcome measures after a longer follow-up duration, and may finally result in a significant higher overall survival, as was shown before [9,10].

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