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## Economic evaluation of chemotherapy

# Costs of intensive treatment and follow-up of patients with multiple myeloma

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**In a retrospective study, we calculated the treatment and follow-up costs of patients with newly diagnosed multiple myeloma. The total treatment programme consisted of eight phases: VAD or VAMP chemotherapy, follow-up I, high-dose melphalan followed by transplantation of whole blood, follow-up II, collection of peripheral blood progenitor cells by leukapheresis, follow-up III, high-dose chemotherapy (busulfan/cyclophosphamide) followed by reinfusion of peripheral stem cells and follow-up IV (until 3 months from hospital discharge after peripheral stem cell transplantation). For each phase the average costs were calculated for all patients who were on treatment/follow-up in each particular phase. The total average cumulative costs of treatment and follow-up of all patients amounted to US$49 850. Considering only the patients who completed the total treatment programme as it was scheduled, the average total treatment and follow-up costs were US$44 800. The average costs of treatment and follow-up of patients who did not complete the programme as it was scheduled (patients who died, patients who were withdrawn from treatment and patients who received additional treatment) were US$57 025. [© 1998 Lippincott Williams & Wilkins.]**

*Key words*: Costs, multiple myeloma, stem cell transplantation.

## Introduction

Multiple myeloma is a diffuse neoplasm of bone marrow plasma cells in which the malignant cells mingle with the hematopoietic cells throughout the red bone marrow. Most frequent complications of myeloma are painful pathologic fractures, anemia, hypercalcemia, renal failure and recurrent bacterial infections.[1–3]

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For years the standard treatment for newly diagnosed myeloma has been chemotherapy consisting of melphalan and prednison. Response rates to this treatment vary between 50 and 60%, with lower response rates in patients with advanced stages of the disease. Only 5–10% of these responses are complete remissions. Patients responding to conventional chemotherapy have a median survival of approximately 3 years, while non-responding patients have a median survival of less than 1 year.[1–6] Cure from multiple myeloma is unlikely: less than 5% of patients will survive for 10 years or more.[7]

As prognosis after melphalan and prednison treatment is poor, other induction regimens such as vincristine, adriamycin and dexamethason (VAD) and vincristine, adriamycin and methyl prednison (VAMP) have been applied. Higher response rates have been reported for some regimens, but in general survival did not improve as compared to melphalan/prednison treatment.[5–13]

A recent treatment option is the administration of high-dose melphalan (HDM). HDM is associated with higher response rates in multiple myeloma, but the treatment-associated morbidity and mortality is high; about 20%, due to complications of prolonged bone marrow depression.[9,10,14,15] Stem cell transplantations and/or the administration of colony-stimulating factors are performed to hasten hematopoietic recovery.[16,17] Peripheral blood progenitor cell transplantation (PBPCT) is increasingly used in the treatment of malignancies to alleviate bone marrow toxicity resulting from high-dose chemotherapy. It has been introduced as an alternative to autologous bone marrow transplantation (ABMT).

Some cost studies concerning the introduction of stem cell transplantation in multiple myeloma have been performed. In the study of Bredeson *et al.*, 48

patients underwent autologous transplantation: eight patients received bone marrow (BM) alone, 17 patients received BM+PBPC and 23 PBPC alone.[18] Patients in the BM group had a median hospital stay of 27.5 days (range 19-39), patients in the BM+PBPC group had a median stay of 21 days (range 15-25) and patients in the PBPC group also had a median hospital stay of 21 days (range 15-32 days). The median costs in the BM group were higher (Canadian $32 289) compared to the groups receiving either BM+PBPC (median: Canadian $23 179) or PBPC alone (median Canadian $22 089) (1 Canadian$ ≈ 0.74 US$).

The results of another cost study have been presented by Duncan *et al.*[19] In this study, patients received HDM and either marrow ($n$=14) or peripheral blood stem cells ($n$=37). Patients receiving PBPCT had a faster hematopoietic recovery post-transplant, resulting in a reduced need for i.v. antibiotics and platelet transfusions when compared to ABMT. This faster hemaotopoietic recovery resulted in a shorter hospital stay. During the post-transplantation period, patients in the ABMT group had a median hospital stay of 27.5 days (range 21-42) compared to 19 days in the PBPCT group (range 15-28). The overall costs of treatment were significantly lower for the PBPCT group than for the ABMT group, £11 026 sterling (range £8023-21 535) versus £7995 (range £5756-11 443) (1£ ≈ 1.44 US$). However, in this study only costs which were felt that PBPCT could have an impact on were included. For example, the costs of the HDM itself were not taken into account.

Henon *et al.* retrospectively compared survival time, quality of life and therapy costs in 37 patients suffering from newly diagnosed multiple myeloma, divided into three groups.[20] Twelve patients with grade III multiple myeloma (classification of Durie-Salmon) underwent a two-phase therapy: they first received HDM, both as tumor-reducing and blood cell-mobilizing therapy, subsequently followed by blood cell transplantation after a conditioning regimen combining total body irradiation and HDM. Group II, comprising 10 patients also with grade III multiple myeloma, was treated with conventional combination chemotherapy (M2 or VAD regimens). Finally, group III enrolled 15 patients with lower grade disease (grade II), who were also treated with conventional chemotherapy. The median overall survival time and quality of life were significantly lower in group II than in group I and III. Total costs of group I were higher than those of the other two groups. The average costs in group I amounted to US$56 700, in group II to US$46 555 and in group III to US$37 430.

Uyl-de Groot *et al.* performed a cost-minimization analysis in patients with multiple myeloma.[21] The treatment costs of 26 patients, who received either HDM combined with granulocyte colony-stimulating factor (r-met Hu G-CSF) ($n$=7) or without r-met Hu G-CSF ($n$=11) or, alternatively, HDM followed by PBPC reinfusion were compared. In comparison with the control group, a shortening of the pancytopenic period and platelet recovery was noticed in the PBPCT group. This resulted in a reduction in hospital costs, diagnostics, laboratory services, total parenteral nutrition and transfusions. The average costs per treatment in the PBPCT group amounted to about US$ 17 908 as compared to US$32 223 in the control group, implying a cost reduction of 44%.

This article focuses on the costs of a whole treatment programme from the start of first induction chemotherapy (VAD or VAMP) until 3 months of follow-up after peripheral stem cell transplantation (PSCT). The results are based on a retrospective study of detailed patient records. The perspective is the hospital point of view. This means that medical costs outside the hospital (such as visits to general practitioner, medication at home, etc.) and non-medical costs (such as formal or informal homecare, productivity losses, etc.) were not taken into account.

## Patients and methods

The study included 29 patients suffering from newly diagnosed multiple myeloma. The median age at the start of treatment was 52 (mean 52; range 37-65). All patients were treated in the University Hospital, Vrije Universiteit, The Netherlands. The first patient started treatment in February 1994 and the last patient completed his treatment in March 1997. Data on the resource utilization were collected by a retrospective study of detailed records of the 29 patients. Cost-prices, reflecting the real use of resources, were calculated for the main activities. For some diagnostic procedures the Dutch tariff system has been used as an approximation of unit costs.

The total treatment programme consisted of eight phases:

- Two courses of VAD or VAMP chemotherapy.
- Follow-up I.
- HDM followed by transplantation of whole blood.
- Follow-up II.
- Collection of peripheral stem cells by leukapheresis.
- Follow-up III.
- High-dose chemotherapy (busulfan/cyclophosphamide) followed by reinfusion of peripheral stem cells.

- Follow-up IV (until 3 months from hospital discharge after PBPCT).

For each treatment phase the average costs were calculated for all patients who were on treatment/follow-up in that particular phase. Furthermore, costs during each phase were calculated separately for the 13 patients who completed the whole treatment programme as scheduled (i.e. up to 3 months after PBPCT, no death and no re-induction therapy) and for those patients who did not. This distinction was made to explore whether the costs of withdrawals would influence the average total treatment costs. Differences in costs between these subgroups of patients were tested by using the *t*-test when costs were normally distributed and by using the non-parametric Mann–Whitney test when the assumption of a normal distribution did not hold.

From the beginning of 1994, 29 patients started treatment, of whom 13 completed the whole treatment programme as scheduled. Two patients had progressive disease during treatment and were re-induced with VAD after leukapheresis. Their treatment schedule was as follows: VAD–HDM–leukapheresis–VAD –IDM/HDM –leukapheresis–busulfan + cyclophosphamide + PBPCT.

Six patients died during the treatment programme: three patients during follow-up II, one patient during follow-up III and two patients during hospitalization for PBPCT. Six patients were withdrawn from the treatment programme: four patients during follow-up II and two patients during follow-up III. By the time of cost analysis, two patients were still in the programme, but had not yet completed it.

### Cost-prices

Cost-prices were calculated for the following activities: hospital in-patient days for normal hematological care and for care in a protected environment, day-care treatment, out-patient visits, parenteral nutrition, leukapheresis, transfusions, the insertion of a subclavian catheter, X-rays, CT scans, and laboratory procedures. The cost-prices include costs for personnel, materials, medical equipment and overheads. In Appendix 1 the cost-prices used are presented. For all other cost items the Dutch tariff system has been used as an approximation of unit costs. The drug prices used were wholesale prices. The base year for the cost-price study was 1995 (1 US$ ≈ 2.0 Dutch guilders).

## Results

### Costs during phase I: VAD/VAMP chemotherapy

The University Hospital, Vrije Universiteit is an academic hospital and the hematologists have a consultation function for several local hospitals. The policy of the hematologists is to treat these referred patients in the academic hospital when needed, but in the referring hospital when possible. Because VAD/VAMP chemotherapy can be given safely in a non-academic hospital, 15 patients received this part of the treatment programme in a local hospital. The costs per course are based on the 14 patients who were treated at the University Hospital, Vrije Universiteit. These 14 patients received a total of 27 VAD courses and five VAMP courses.

The mean costs of one VAD course were US$3200. The mean costs of one VAMP course were US$3275. Applying the average costs of one course of chemotherapy at the university hospital to the courses given in the other hospitals, the average costs for all 29 patients during this first treatment period were US$8400.

In Table 1 the costs for one VAD/VAMP course and the total costs during this induction phase are presented.

Of the 13 patients who completed treatment as scheduled, 12 patients received two VAD or VAMP courses and one patient received four courses of VAD. Their average costs were US$6975. The other 16 patients received a total of 48 courses with average costs per patient of US$9675. For this treatment phase, the difference in costs between the two subgroups was not tested, because the average costs of the patients who were treated at the university hospital had been applied to the other patients.

### Costs during phase II: follow-up between VAD/VAMP and HDM

The mean duration of this follow-up period was 62 days (median 61; range 14–122). The costs for this phase were calculated for the 14 patients who received the VAD/VAMP chemotherapy at the university hospital. For the other 15 patients (part of) the follow-up took place in the local hospitals. The costs are also presented in Table 1. The average costs during this period were US$425, and mainly consisted of costs for out-patient visits and medication. One patient was hospitalized during 4 days because of fever between the first and second course of VAD.

Of the 14 patients who were treated at the university hospital during this period, five completed the whole treatment programme as scheduled. Their average costs for this period were US$300 compared to US$500 for those patients who failed to pass through the programme as scheduled ($p$=NS).

### Costs during phase III: HDM melphalan followed by whole blood transplantation

All 29 patients were treated at the university hospital for this part of the treatment. One patient who had progressive disease after HDM was re-induced with VAD and received a second course of HDM. Patients were hospitalized during this treatment phase for an average of 19 days (median 17; range 14–36). To mobilize stem cells, r-met Hu G-CSF was administered daily during 5 days, starting 4 days prior to hospital admission. One liter of whole blood was collected by phlebotomy, kept unprocessed at 4°C and re-infused 24 h after HDM. r-met Hu G-CSF was restarted 1 day after re-infusion of whole blood until granulocytes were $0.5 \times 10^9$/l.

The average costs of the 30 courses of HDM given were US$11 000 (median 9950; range 8100–19 225) (Table 2). Costs for hospitalization and r-met Hu G-CSF counted for 49 and 29% of these costs, respectively.

The average costs of this treatment phase for the 13 patients who completed the whole treatment programme as scheduled were significantly lower than the average costs of the other 16 patients: US$10 125 compared to US$12 400 ($p$=0.03). This is mainly due to less in-patients days (17 versus 22) and less costs for medication. By excluding the patient who received two courses of HDM from the analysis, the $p$ value just exceeds the 5% significance level: average costs US$10 125 versus US$12 050 ($p$=0.06).

### Costs during phase IV: follow-up between HDM and leukapheresis

The average duration of this follow-up period was 196 days (median 178; range 17–473). Three patients died during this period: one after 65 days, one after 251 days and one after 410 days. Two patients were hospitalized: one because of fever (8 days) and one because of progressive disease (this patient died after 12 days of hospitalization). In Table 2 the average costs of this treatment phase are presented. These costs amounted to US$1825 (median 950; range 200–9175). The main activities were out-patient visits (21%) and medication (20%).

For this follow-up period, the costs of the 13 patients who completed the treatment programme as scheduled were significantly lower than the costs of the other 16 patients: US$725 compared to US$2725 ($p < 0.001$). This difference is largely due to two in-patient periods in the latter group. Excluding the two patients who were hospitalized from the analysis, the difference in average costs remains significant (US$725 versus US$1925, $p < 0.01$).

**Table 1.** Average costs during induction therapy and follow-up in US$ (median; range)

| | Phase I: induction therapy | | | Phase II |
|---|---|---|---|---|
| | Average costs of one VAD course ($n$=27) | Average costs of one VAMP course ($n$=5) | Average costs per patient ($n$=29) | Average costs of follow-up ($n$=14) |
| Hospital in-patient days | 0 (1725; 1425–6025) | 1725 (1725; 1725–1725) | 5375 | 100 (0; 0–1150) |
| Out-patient visits | 0 | 0 | 0 | 100 (100; 0–225) |
| Medication | 550 (450; 325–2975) | 1050 (1025; 950–1100) | 1675 | 125 (100; 0–375) |
| Medical procedures | 300 (200; 100–1100) | 300 (200; 150–575) | 775 | 25 (0; 0–325) |
| Laboratory | 125 (100; 25–500) | 125 (125; 100–175) | 325 | 50 (25; 0–225) |
| Transfusions | 100 (0; 0–500) | 75 (0; 0–200) | 250 | 25 (0; 0–200) |
| **Total** | **3200 (2575; 1925–10875)** | **3275 (3250; 2925–3525)** | **8400** | **425 (275; 0–2200)** |

**Table 2.** Average costs for HDM and follow-up in US$ (median; range)

| | Phase III | Phase IV |
|---|---|---|
| | Costs of HDM ($n$=30) | Costs of follow-up between HDM and leukapheresis ($n$=29) |
| Hospital in-patient days | 5350 (4875; 4000–10325) | 275 (0; 0–4575) |
| Day-care treatment | 0 | 100 (70; 0–775) |
| Out-patient visits | 0 | 375 (350; 100–1000) |
| Parenteral nutrition | 100 (0; 0–925) | 0 |
| r-met Hu G-CSF (18 days) | 3200 (3150; 2225–10125) | 50 (0; 0–750) |
| Other medication | 900 (625; 375–2700) | 350 (175; 0–2375) |
| Medical procedures | 400 (275; 200–1775) | 175 (75; 0–650) |
| Laboratory | 400 (325; 175–825) | 225 (175; 25–700) |
| Transfusions | 650 (650; 225–1525) | 275 (110; 0–1800) |
| **Total** | **11000 (9950; 8100–19225)** | **1825 (950; 200–9175)** |

### Costs during phase V: stem cell collection by leukapheresis

Of the 29 patients who started the treatment programme, 21 were leukapheresed. Three patients already died before this phase, one patient did not yet reach this phase by the time of analysis, three patients went off the treatment programme because of poor performance status and in one patient it was not possible to mobilize stem cells for collection.

To mobilize stem cells r-met Hu G-CSF was started on day −5 followed by the first leukapheresis procedure on day 0. Leukapheresis was then continued on consecutive days until enough stem cells were harvested. On the last day of leukapheresis no r-met Hu G-CSF was administered. Half of the patients had one period of leukaphereses (consisting of on average 3.4 procedures) and the other patients needed two periods of leukaphereses (on average 7.5 procedures). For all patients, the mean number of leukapheresis procedures performed was 5.6 (median 5; range 2–10). Four patients were hospitalized for leukaphereses, the other 17 patients were treated in day-care.

In Table 3, the costs of stem cell collection are presented. The average costs during this phase were US$9350 (median 9125; range 3950–15 525). The costs for the leukapheresis procedures contribute to 49% of these costs and the costs for r-met Hu G-CSF to 44%.

During this period, there is a 10% difference in costs between the patients who completed the whole treatment programme as scheduled and those who did not: US$9000 versus US$9900 ($p$=NS).

### Costs during phase VI: follow-up between leukapheresis and stem cell transplantation

The mean duration of this period was 129 days (median 106; range 7–547). During this phase one patient died after 79 days and two patients left the treatment programme because of progressive disease. One of these latter patients was hospitalized for 17 days. The mean costs during this period were US$1250 (median 475; range 0–14 725) (see Table 3).

For this follow-up period, the average costs of the 13 patients who completed the treatment programme as scheduled were significantly lower than the costs of the other eight patients: US$325 compared to US$2 750 ($p<0.05$). One patient who left the treatment programme had very high costs. Excluding this patient from the analysis, the difference in average costs remains significant: US$325 versus US$1050 ($p<0.05$).

**Table 3.** Average costs for stem cell collection and follow-up in US$ (median; range)

| | Phase V | Phase VI |
|---|---|---|
| | Stem cell collection ($n$=21) | Follow-up ($n$=21) |
| Hospital in-patient days | 150 (0; 0–850) | 225 (0; 0–4875) |
| Day-care treatments | 350 (275; 150–700) | 25 (0; 0–350) |
| Out-patient visits | 0 | 225 (125; 0–1225) |
| Leukapheresis procedures | 4550 (4100; 1650–8125) | 0 |
| r-met Hu G-CSF and other medication | 4125 (4575; 2125–6350) | 475 (50; 0–5550) |
| Medical procedures | 50 (0; 0–375) | 75 (0; 0–775) |
| Laboratory | 100 (100; 50–225) | 125 (75; 0–700) |
| Transfusions | 25 (0; 0–350) | 100 (0; 0–1250) |
| **Total** | **9350 (9125; 3950–15525)** | **1250 (475; 0–14725)** |

### Costs during phase VII: high-dose chemotherapy followed by peripheral stem cell transplantation

All the remaining 17 patients were hospitalized for high-dose chemotherapy with busulfan and cyclophosphamide, followed by reinfusion of the cryopreserved autologous peripheral stem cells harvested by leukapheresis. During hospitalization two patients died: one after 21 days and one after 26 days. The average duration of hospitalization for all 17 patients was 28 days (median 26; range 21–52). Patients were treated in a protected environment for an average of 14 days (median 14; range 8–19). One patient stayed on the intensive care department for 7 days (this is one of the patients who died). Half of the patients got parenteral nutrition for an average of 10 days. In Table 4 the average treatment costs are presented. During this period these costs were US$15 125 (median 12 825; range 11 075–30 950). The costs for hospital in-patient days count for 72% of the costs.

### Costs during phase VIII: follow-up after stem cell transplantation (3 months)

In this last phase there were 15 patients: 13 patients who completed the whole treatment programme as scheduled and two patients who received additional therapy during the programme. The mean costs of these 3 months of follow-up were US$2400 (median 1725; range 275–10 475) (see Table 4). Three patients were hospitalized: one because of nose-bleeding (2 days), one because of fever (14 days) and one because of feeling sick (27 days).

### Total treatment costs

Total average treatment costs were calculated by adding the average costs of all treatment phases for all the patients who were in the programme during each particular phase. Total treatment costs have also been calculated seperately for the 13 patients who completed the whole treatment programme as it was scheduled and for those patients who did not.

The total treatment costs of all patients amounted to US$49 850. Considering only patients who completed the whole programme the total treatment and follow-up costs were US$44 800. The total costs of treatment and follow-up of patients who either did not complete the programme or who received additional treatment were US$57 025.

Cumulative costs were calculated after each phase for all the patients, for the 13 patients who were treated according to the programme and for the patients who did not complete the programme as it was scheduled (see Figure 1).

## Discussion

As new, more intensive treatment modalities for patients with multiple myeloma become available, the treatment of these patients requires a larger share of the available resources. Several cost studies concerning myeloma patients have been performed. These studies are mainly focused on the costs of stem

**Table 4.** Average costs for high-dose chemotherapy+PSCT and follow-up in US$ (median; range)

| | Phase VII | Phase VIII |
|---|---|---|
| | PSCT ($n$=17) | Follow-up ($n$=15) |
| Hospital in-patient days | 10900 (10050; 8150–17800) | 825 (0; 0–7725) |
| Day-care treatment/out-patient visits | 0 | 550 (450; 175–1275) |
| Parenteral nutrition | 225 (0; 0–825) | 0 |
| Medication | 2025 (1625; 850–6400) | 225 (25; 0–850) |
| Medical procedures | 450 (250; 150–1500) | 125 (25; 0–700) |
| Laboratory | 625 (500; 300–2000) | 175 (125; 75–600) |
| Transfusions | 900 (650; 200–3575) | 500 (450; 0–1525) |
| **Total** | **15125 (12825; 11075–30950)** | **2400 (1725; 275–10475)** |

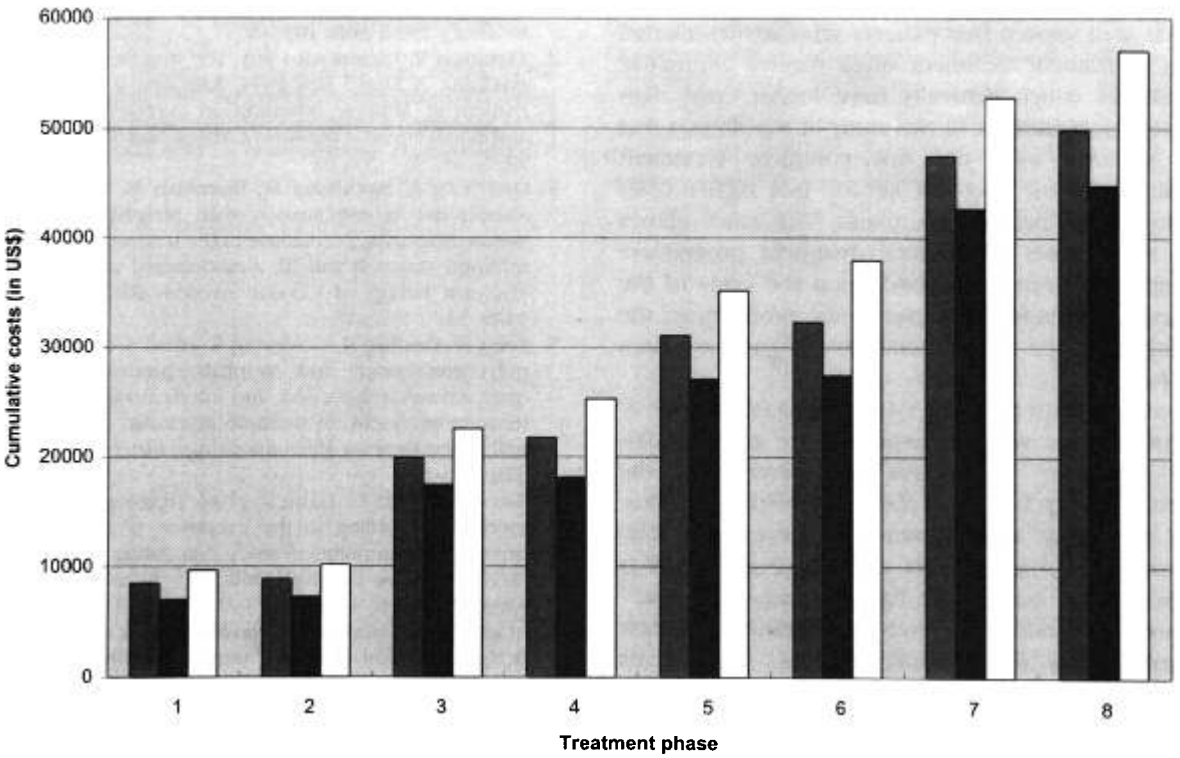


**Figure 1.** Cumulative treatment and follow-up costs. ▭, All patients. ■, Completed programme. ▭, Did not complete programme.

cell transplantations. There are some important differences between these studies which makes a direct comparison of costs or cost-effectiveness difficult. These differences concern, for example, neutrophil level for stopping the administration of hematopoietic growth factors, discharge criteria, the use of parenteral nutrition and the number of in-patient days for graft procurement. However, all studies reported savings when PBPCT was compared with ABMT.

In this study, the whole treatment programme of patients with multiple myeloma has been taken into account. The treatment programme consisted of induction therapy with VAD or VAMP, HDM with whole blood rescue, leukapheresis and busulfan/cyclophosphamide followed by PBPCT. Furthermore, the costs of follow-up between the treatment phases and 3 months following discharge from hospital after PBPCT were considered.

Based on our results, it would be clear that PBPCT, including mobilization of stem cells, is the most important cost component of the treatment programme. The costs of leukapheresis and PBSCT accounted for almost 50% of the total costs. VAD/VAMP treatment and HDM in combination with a full blood procedure were responsible for, respectively, 17 and 22% of the total costs. The costs of follow-up contributed to only 12% of the total costs.

It is well known that patients who are withdrawn from a protocol treatment often receive alternative treatments which generally have higher costs than the regular treatment. In this study, it was shown that the patients who did not complete treatment according to the protocol already had higher costs while still on protocol treatment. This study shows that if the costs of the total treatment programme would have been only based upon the costs of the patients who indeed completed the programme, the estimation of the average total costs would have been too low.

Today, in most hospitals VAD courses (VAD alone or in combination with cyclosporine) are given in day-care treatment. Continuous administration of the cytostatic drugs is then replaced by bolus injections. This will result in a decrease of the cost of VAD treatment. In some centers also ABMT or PBPCT is given on an out-patient base. Jagannath *et al.*[22] reported the results of a study concerning out-patient autotransplants in myeloma patients. All patients received HDM 200 mg/m$^2$ as cytoreductive regimen. A total of 91 (selected) patients received 118 transplants as out-patients and 160 patients received 218 transplants as in-patients. Only 21% of out-patients required admission after transplantation. Charges of providers were used as a proxy of treatment procedure costs. Total average charges for in-patients amounted to US$50 757, while the out-patients charges amounted to US$37 403. The authors state that patient selection criteria for out-patient management and liberal criteria for hospitalization has resulted in a safe conduct of out-patient transplants. However, this approach requires weekend oncology clinic services, including pharmacy, nursing and physician support in the direct neighborhood of the patients. Therefore, out-patient transplantations may not be applicable in many centers.

Currently, additional treatment modalities in this patient group are applied. Use of intermediate doses of melphalan, allogeneic stem cell tranplantation and low-dose interferon-α treatment are treatment options now being studied. Economic evaluations linked to clinical trials provide information about the cost-effectiveness of new treatment modalities. When these new treatment options are implemented in the clinical setting, these studies should provide the necessary information on the economic consequences of introducing such new technologies.

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**Appendix 1.** Cost-prices in US$

| | |
|---|---|
| Bone marrow harvest | 2950 |
| Leukapheresis, per procedure | 804 |
| In-patient day, haematological ward | 286 |
| In-patient day, protected environment | 469 |
| In-patient day, intensive care | 1051 |
| Day-care treatment | 70 |
| Out-patient visit | 45 |
| Parenteral nutrition, per day | 49 |
| X-ray thorax, sinus | 52 |
| Ultrasound | 103 |
| CT scan | 232 |