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Autologous hematopoietic progenitor cell transplantation for multiple myeloma through an outpatient program

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1. Introduction

Multiple Myeloma (MM) is a clonal plasma cell neoplasma sensitive to several antineoplastic agents including alkylating agents, anthracyclines, corticosteroids, radiation therapy, immunomodulators and proteasome inhibitors. It accounts for approximately 10% of all hematologic malignancies [1]. In recent years, major progress has been made in its treatment, thanks to the introduction of novel agents, such as bortezomib and lenalidomide used in combination with conventional drugs, including dexamethasone [2-7], and to the improvement of transplant procedures [8,9].

2. Autologous hematopoietic progenitor cell transplantation for multiple myeloma

Over the last decade, autologous hematopoietic progenitor cell transplantation (AHPCT) has been considered the standard of care for younger patients with newly diagnosed MM [10,11], based on the increased rate of complete response (CR), prolonged disease free (DFS) and overall survival (OS), compared with conventional chemotherapy (CC) in several randomized studies [12,13]. However, not all the studies published have clearly demonstrated the superiority of AHPCT [14-16] and a systematic review and meta-analysis has shown a significant benefit with single AHPCT in terms of prolonged progression-free survival (PFS), but not of OS [17]. More recently, to further reduce residual disease, some studies evaluated the efficacy of additional therapies after AHPCT either based on a second autograft (‘tandem autologous transplant') or on a reduced-intensity/non-myeloablative conditioning followed by allogeneic hemopoietic progenitor cell transplantation (allo-HPCT). The tandem AHPCT approach achieved improvement in OS [18,19] even though a survival benefit was mainly seen in patients who failed to achieve at least very good partial remission as defined by the European Group for Blood and Marrow Transplantation [20,21]. An alternative to autotransplantation up-front is to delay high-dose chemotherapy (HDC) with AHPCT at the time of relapse. Although in a study the length of OS for patients receiving early or late AHPCT after CC was equivalent, early AHPCT was associated with a longer event-free survival (EFS) and better quality of life [22].
In patients eligible to receive HDC, the role of AHPCT continues to evolve in the novel agent era [23-25] and the new drugs have been incorporated into the therapeutic algorithm along with AHPCT [26-28]. Autotransplantation, applied after novel-agent-based induction regimens, provides further improvement in the depth of response, a gain that translates into extended disease control [29] and, however, the International Myeloma Working Group (IMWG) recommends that AHPCT should be offered at some point in the course of the treatment program for a medically fit patient [29].

Based on these studies, high-dose melphalan (HDM) (dose range 140 – 220 mg/m^2) followed by AHPCT has become an integral treatment modality [30-32] and MM remains the leading indication for AHPCT in Europe and in the United States [33,34]. High-dose melphalan rarely causes severe toxicity to major organs with the exception of the gastrointestinal tract where mucositis still represents a frequently observed extra-hematological toxicity [35].
Moreover, better supportive care, the extensive use of peripheral blood progenitor cells (PBPCs) and post-transplant growth factors have gradually made HDM less toxic and it should now be considered a safe procedure [25,31,33,36,37] with a transplant-related mortality (TRM) down to 1 – 5% [38-43]. In Europe, virtually all autologous transplants are performed using G-CSF-mobilized PBPCs [33] and their use results in a rapid and durable full hematopoietic recovery [38-40]. Improvement in oral antibiotic prophylaxis [41-43] and the use of once-daily dosing i.v. parenteral antibiotics [44-47] have clearly simplified the management of infectious complications, major cause of morbidity in this setting.

2. Outpatient care programs

Patients who undergo AHPCT are commonly admitted to bone marrow transplant units on a wholly inpatient program. In this setting, central venous catheter (CVC) insertion, HDC administration, hemopoietic progenitor cell infusion and supportive care during neutropenia are carried out in positive-pressure reverse isolation rooms with a hospital stay of approximately 3 – 4 weeks [48]. The growing demand for AHPCT significantly increases waiting lists and generate concerns about the appropriate use of health care resources and patient's quality of life. Over the past years, a number of studies have investigated safety, efficacy and potential cost-advantages of reducing hospital stay for patients undergoing AHPCT [49-60]. Thus, outpatient transplant programs have been proposed for various hematological and non-hematological malignancies [61,62].
The most representative clinical trials of AHPCT as an outpatient procedure are summarized in Table 1. Studies usually conclude that HDC is feasible and safe in the outpatient setting given the availability of hematopoietic growth factors, myeloablative drugs that do not induce severe mucositis and efficacious antimicrobial prophylaxis, which lowers neutropenia-related complication rates [57]. The easy administration of HDM and the relatively low extra-medullary toxicity, including nausea and vomiting, and the short period of neutropenia [63-65] make MM patients ideal candidates for outpatient transplant programs.

Table 1. Autologous hemopoietic progenitor cell transplantation through an outpatient program. Results of clinical trials.

Author, Year	Diagnosis	Regimen	Model	No. of Transplants	No readmission %	TRM	Comments
Peters, 1994	MBC	Cy/CDPP/BCNU	EDM	110	70%	Unknown	Febrile neutropenic patients were admitted to the hospital for evaluation and initiation of parenteral antibiotics
Jagannath, 1997	MM	HDM	TOM	118	79%	unknown	Post-transplant febrile neutropenia was successfully managed in most outpatients by prompt self-administration of antibiotics via infusers connected to central venous catheters without re-admission. The model is associated with the shortest duration of hospital stay
Weaver, 1997	NHL	BEAC	DAM	83	100%	7.2%	High-risk patients Patients were hospitalized only during the aplastic phase and median duration of hospital stay was reduced to 2 weeks This outpatient model was not associated with a significant reduction of hospital stay
Meisenberg, 1997	NHL/HL MM AML ST	Cy/TT/ETOP/CBDCA/ CDDP/Mitox/BCNU containing regimen HDM; BU/Cy; TBI/HDM	STOT TOM	165	70%	1.5%	The study shows that different treatments for several malignant diseases can successfully be delivered on the outpatient service Fever and mucositis were major reasons for re-admission. The use of drugs inducing severe mucositis are associated with higher risk of re-admission The model is associated with the shortest duration of hospital stay
Gluck, 1997	MBC	Cy + Mitox based	Mixed	53	54.7%	0%	Three-step approach to outpatient follow up after transplant. The authors have identified the most important reasons for re-admission
Westermann, 1999	NHL/HL ST	BEAM, CTC	EDM HC	40 (EDM) 24 (HC)	27.5% (EDM) 29.1% (HC)	0%	Outpatient management of the aplastic phase after high-dose chemotherapy and transplantation by community-based professionals is feasible without increased toxicity or infections
Morabito, 2002	MM	HDM	MIOM	60	56.7%	0%	Patients received HDM and then were admitted for HPC infusion for 2 days for reimbursement purposes Mucositis was the only independent predictor of break-through fever
Gertz, 2008	MM	HDM	TOM	716	39%	1.1%	Younger patients and those with serum creatinine levels less than 1.5 mg/dL were more likely to complete the transplant program as outpatients. Disease status at the time of transplant did not appear to affect the duration of hospital stay

AML: Acute myeloid leukemia; BCNU: Carmustine; BEAC: Carmustine, Etoposide, Cytarabine, Cyclophosphamide; BEAM: Carmustine, Etoposide, Cytarabine, Melphalan; BU: Busulfan; CBDCA: Carboplatin; CDPP: Cisplatin; CLL: Chronic lymphocytic leukemia; CTC: Carboplatin, thiotepa and cydophosphamide; Cy: Cyclophosphamide; DAM: Delayed admission model; ETOP: Etoposide; HC: Home Care; HDM: High-dose melphalan; HL: Hodgkin lymphoma; MBC: Metastatic breast cancer; MIOM: Mix impatient–outpatient model; Mitox: Mitoxantrone; MM: Multiple myeloma; NHL: Non-Hodgkin lymphoma; ST: Solid tumor; STOT: Subtotal outpatient program; TBI: Total-body irradiation; TOM: Total outpatient clinic; TRM: Transplant-related mortality; TT: Thiotepa.

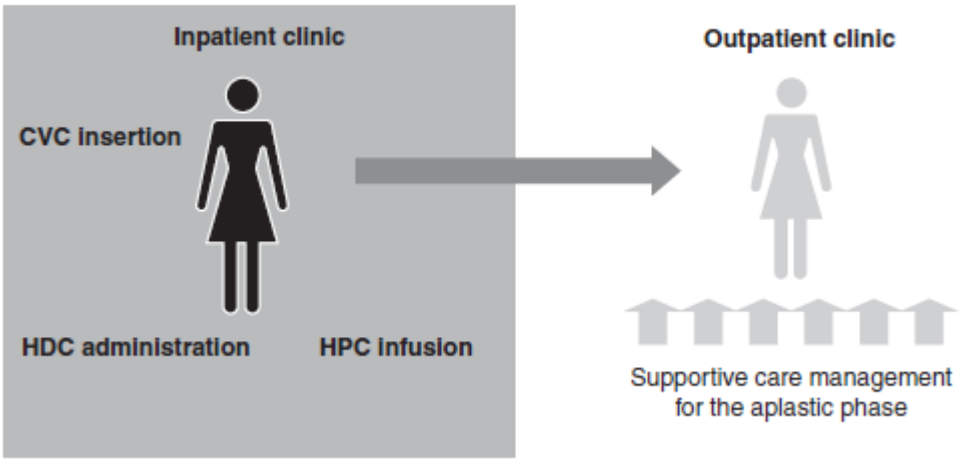
Author, Year	Diagnosis	Regimen	Model	No. of Transplants	No readmission %	TRM	Comments
							The model is associated with the shortest duration of hospital stay
Anastasia, 2009	MM NHL/HL ST	HDM	DAM	123	95%	0%	Discharge on day 1 after HDM followed by AHPCT and re-admission on day 5 The model is not associated with a significant reduction of hospital stay
Kassar, 2007	MM	HDM	TOM	90	42%	0%	The study showed that the duration of neutropenia was short. Eighty per cent of the patients remained neutropenic for 5 days or less, and no patient had a neutropenic period longer than 7 days
Ferrara, 2011	MM	HDM	EDM	48 (PEG) 113 (G-CSF)	88% 74%	0% 0.8%	Febrile neutropenia and severe mucositis were the most frequent causes of re-admission. The administration of single-dose PEG-Filgrastim resulted in no different outcome in terms of safety and efficacy as compared to 8 days of daily G-CSF
Montanari, 2011	MM HL NHL	HDM; BEAM	EDM	172	89% (MM) 73% (HL/NHL)	1.7% (MM) 0% (HL/NHL)	Authors used amifostine as mucosal cytoprotective agent In univariate analysis, the only significant factor affecting re-admission was disease status at transplant other than CR and VGPR
Martino, 2011	MM	HDM	HC	11	81.9%	0%	Small study No unexpected emergencies were encountered
Faucher, 2012	MM NHL/HL ST CLL	BU/TBI; HDM; Other	EDM	66	20% (only 30 patients dis-charged on day 0)	0%	First randomized study comparing EDM with standard inpatient AHPCT. A total of 131 patients were enrolled, 66 of whom were randomized to the EDM arm and 65 to the traditional inpatient program. A total of 39% on the EDM arm were not discharged for social or psychological reasons This study showed a mean cost per patient 6% inferior to that seen in the conventional inpatient group

AML: Acute myeloid leukemia; BCNU: Carmustine; BEAC: Carmustine, Etoposide, Cytarabine, Cydophosphamide; BEAM: Carmustine, Etoposide, Cytarabine, Melphalan; BU: Busulfan; CBDCA: Carboplatin; CDPP: Cisplatin; CLL: Chronic lymphocytic leukemia; CTC: Carboplatin, thiotepa and cyclophosphamide; Cy: Cydophosphamide; DAM: Delayed admission model; ETOP: Etoposide; HC: Home Care; HDM: High-dose melphalan; HL: Hodgkin lymphoma; MBC: Metastatic breast cancer; MIOM: Mix impatient-outpatient model; Mitox: Mitoxantrone; MM: Multiple myeloma; NHL: Non-Hodgkin lymphoma; ST: Solid tumor; STOT: Subtotal outpatient program; TBI: Total-body irradiation; TOM: Total outpatient clinic; TRM: Transplant-related mortality; TT: Thiotepa.

3.1 Early-discharge model (EDM)

In this model (Figure 1), CVC insertion, fluid infusion, HDC administration and HPC infusion are carried out in positive-pressure reverse isolation rooms, whereas supportive care of the aplastic phase is carried out on the outpatient service. During the past decade, several experiences have been published. Historically, one of the first studies was published by Peters *et al.* in a cohort of patients with primary metastatic breast cancer (MBC). The authors [59] reported a 28.5% reduction in days of hospitalization in 110 women who underwent HDC with cyclophosphamide, cisplatin and carmustine followed by HPC support. Approximately 70% of these patients required no re-admission or only a brief hospital stay of 1 – 4 days. Overall, charges related to the transplant procedure were reduced by 50% over the following 2 – 5 years after the implementation of the outpatient transplant program.

Figure 1. Hemopoietic Progenitor Cell Transplantation. Outpatients Early Discharge model.



One EDM approach was reported by Ferrara *et al.* Preliminary findings on 28 MM patients showed feasibility and safety of the procedure without early TRM and a 36% rate of re-admission [51]. Another study from the same group reported on a series of MM patients who underwent an autograft on an outpatient program using either post-transplant single-dose PEG-Filgrastim or conventional daily G-CSF. The conditioning was HDM (140 – 200 mg/m^2). Overall, the re-admission rate was 32% (36 out of 161 procedures). There was no statistically significant difference in re-admissions between the two cohorts: 12% (6/48) in the PEG-Filgrastim group versus 26% (30/113) [66].

Montanari *et al.* [64] have recently reported on an outpatient transplant program in MM and lymphoma patients consisting of the inpatient administration of HDC and stem cell infusion followed by early discharge on day 1. High-dose chemotherapy regimens were HDM (200 mg/m^2) for MM and carmustine, etoposide, cytarabine and melphalan (BEAM regimen) [67] for Hodgkin lymphoma and non-Hodgkin lymphoma (NHL) patients. Amifostine was administered before melphalan infusion. Re-admission rates were 11% for MM patients and 27% for lymphoma patients, respectively. Amifostine is a cytoprotector that detoxifies reactive metabolites of platinum and alkylating agents [68,69]. Its potential role in preventing extra-hematological toxicity after HDM has been investigated in a retrospective study that suggested that the drug could reduce severe mucositis and, consequently, the use of analgesic drugs [70,71].

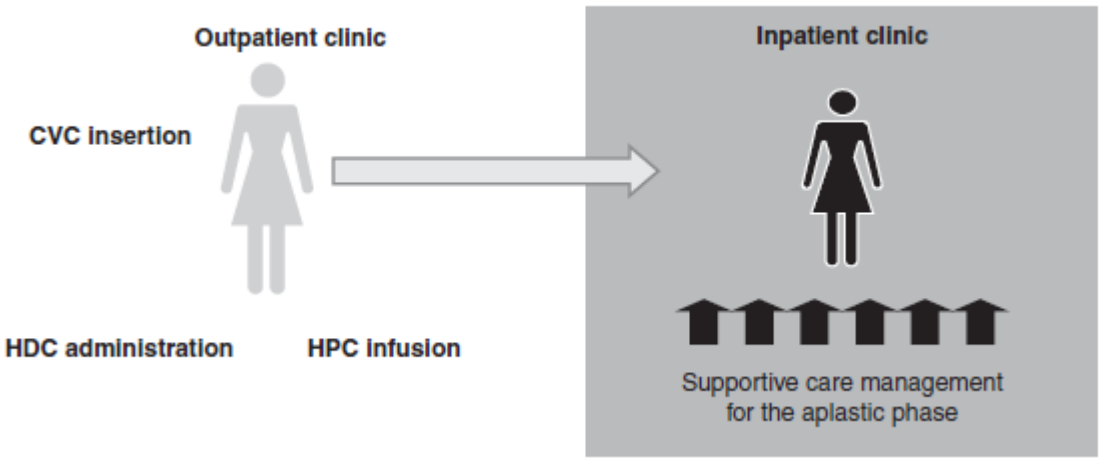
In the same outpatient setting, Olivieri *et al.* [72] evaluated the post-transplant combined administration of erythropoietin with filgrastim. Not only was this combination associated with shorter duration of neutropenia, but also with significantly improved clinical outcomes after HDC. Importantly, this procedure translated into significant cost savings and, in the future, may be

extended to elderly medically fit patients. Nevertheless, currently the use of erythorpietin or amifostine remains unclear whether in the inpatient or outpatient setting.
Recently, Faucher *et al.* [73] reported the first randomized study comparing EDM with standard inpatient AHPCT on a cohort of 131 patients with non-leukemic malignant diseases. In both arms A and B, HDC and stem cell infusion occurred during the hospital stay. Early-discharge model in arm A allowed discharge on day 0, home stay with a caregiver and outpatient follow-up. Patients on arm B were followed up as inpatients. The study reported an 86% rate of re-admission which usually occurred during the first week (87% of re-admitted patients) and mainly before hematological recovery (for 93%). The EDM within the French health system, while safe and feasible, was highly dependent on economic–social factors. In fact, 39% of patients with an indication for HDC could not be discharged early because of social or psychological reasons (lack of a caregiver, living far away from the transplant center or patient will). In particular, lack of a caregiver was a major limitation to outpatient transplant programs [74].

3.2 Delayed admission model (DAM)

In this model (Figure 2), HDC and HPC infusion are performed on the outpatient service, whereas the supportive care of the aplastic phase is given in positive-pressure reverse isolation rooms.

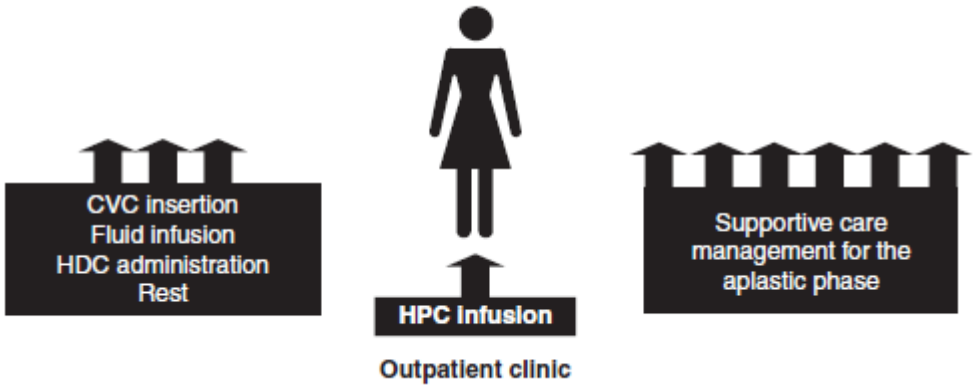
Figure 2. Hemopoietic Progenitor Cell Transplantation. Outpatients Delayed Admission Model.



Weaver *et al.* [75] reported on the outcome of 83 NHL patients who had failed first-line chemotherapy and received HDC with carmustine, etoposide, cytarabine and cyclophosphamide (BEAC regimen) [76] followed by AHPCT as outpatients. The outpatient treatment facility was designed ‘ad hoc' with daily follow up for complications such as febrile neutropenia or inadequate oral intake. Patients were hospitalized only during the aplastic phase and their median duration of hospital stay was two weeks.
Another DAM approach was proposed by Anastasia *et al.* [49]. Discharge was scheduled on day 1 and re-admission on day 5. One hundred forty-four patients with various hematological and non-hematological malignancies entered the program. Early discharge was feasible in 86% (123/144 procedures) and only a small proportion (5%) of discharged patients was re-admitted before day 5, mainly due to severe mucositis or fever. These findings, however, do not strongly support that the DAM model may significantly reduce the duration of hospitalization and its costs when compared to other models.
3.3 Total outpatient model (TOM)
This approach (Figure 3) is associated with the shortest duration of hospitalization [58,77,78]. High-dose chemotherapy and HPC infusion are performed as outpatients. After HPC infusion, patients

are followed daily on the outpatient service where they receive supportive care: growth factor injections, red blood cell and platelet transfusions, and prophylactic therapy with oral antibiotics, antiviral and antifungal medications.

Figure 3. Hemopoietic Progenitor Cell Transplantation. Total Outpatient Model.



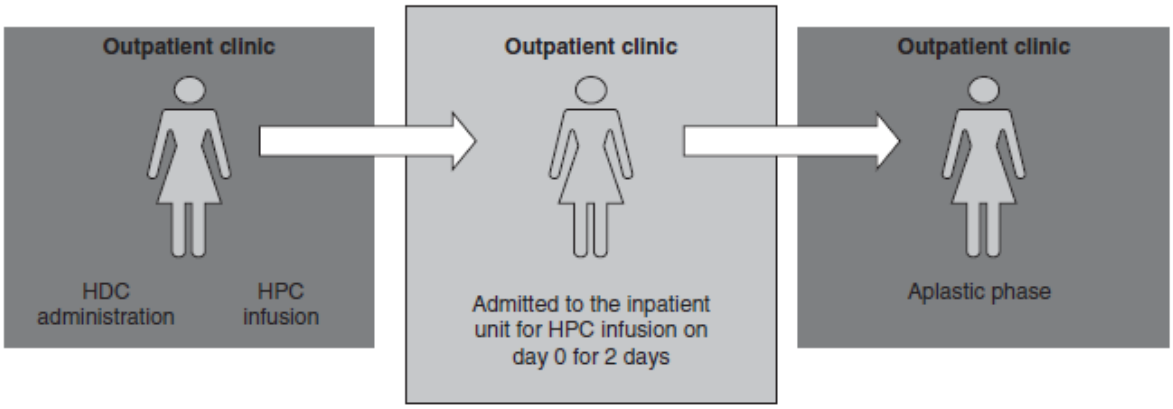
Gerzt *et al.* [78] reported on the feasibility of the TOM model in 716 MM patients who underwent AHPCT at the Mayo Clinic in Rochester, MN (USA). The study showed that 278 (39%) out of the 716 patients completed the entire procedure without requiring admission. The median duration of hospitalization for all patients was 4 days. This experience showed that outpatient transplant was feasible for all patients with MM and resulted in shorter hospital stays and low TRM rates in both high-risk and low-risk patients. However, it should be observed that most patients, who lived far from the Center, had to temporarily find lodging in local hotels to allow prompt access to the outpatient care unit. This policy may not negligibly increase the out-of-pocket cost burden to the patients.

Using a TOM model, Kassar *et al.* [65] stressed the remarkable consistency in the time to neutropenia (from the HPC infusion day to the day with ANC $< 0.5 \times 10^9$/L) and its duration in 89 MM patients treated with HDM (140 – 200 mg/m^2). Nearly two-thirds of patients became neutropenic on day 5 and the remaining developed neutropenia one day earlier or later. Duration of neutropenia was ≤ 5 days in 80% of the patients and ≤ 7 days in all.

3.4 Mixed inpatient–outpatient model (MIOM)

This program has primarily been designed and employed in Italy [63]. Central venous catheter insertion, fluid infusion, HDM, as well as supportive care during the aplastic phase were carried out on the outpatient service (Figure 4). Multiple myeloma patients were admitted for only two days during which HPC were infused. The inpatient HPC infusion is mandatory to obtain the optimal reimbursement according to the Italian diagnosis-related group (DRG) system (Ministry Decree, April 15, 1994 and Gazzetta Ufficiale n. 107, May 10, 1994). A prerequisite for this program was the availability of dedicated specialized staff and an outpatient service operating 12 h/day including week-ends. The patients who did not live within easy reach from the Center (expected time from home to hospital by car or by public transportation not exceeding 45 min) were temporarily staying in nearby hotels free-of-charge and could easily reach emergency phone numbers at all times. Clinical outcomes of this program were compared with those of MM patients traditionally transplanted according to a wholly inpatient procedure. Patients on the MIOM program had a significant reduction of the hospital stay without increased toxicity. Overall, 6.7% were not discharged after the HPC infusion, and among those discharged as planned, 43% were re-admitted for a median hospital stay of 9 days, significantly shorter than the median of 20 days observed with conventional inpatient AHPCT. These data are consistent with Jagannath's report [55] where only 21% of the outpatient population required re-admission after AHPCT.

Figure 4. Hemopoietic Progenitor Cell Transplantation. Mixed Inpatient–Outpatient Model.



3.5 At-home management of the aplastic phase following HDC and AHPCT for hematological and non-hematological malignancies

Westermann *et al.* [79] developed a home care program for patients undergoing HDC with AHPCT for malignant lymphomas conditioned with BEAM, and breast cancer or germ-cell cancer treated with three courses of high-dose cyclophosphamide, thiotepa and carboplatin [80]. Patients were discharged on the day of HPC infusion if they resided in the surrounding areas. All supportive care, which included blood draws from CVC, transfusion of blood products, and infusion of parenteral antibiotics, was delivered at home by highly specialized nursing staff. No increased toxicity was observed and most patients appreciated the opportunity to stay with their families right after HPC reinfusion without increasing patient's anxiety. For most patients and their families major advantage was the opportunity to be together in a non-medical environment. No unexpected emergencies occurred and toxicity was similar to that of the traditional inpatient transplant program without any transplant-related death. A similar multi-center experience has recently been proposed in Italy for MM patients [81].

3.6 Outpatient programs in the setting of allografting

Allo-HPCT after reduced-intensity conditionings (RIC) has been associated with decreased early toxicity [82]. This suggested that the procedure could be performed on an outpatient basis. In particular, trials which employed non-myeloablative TBI-based conditionings showed that the procedure could fully and safely be administered as outpatient [83-85]. One study showed a median reduction from 27 days to 9 days of hospital stay using an outpatient approach [84]. These findings form the basis for larger outpatient transplant programs after RIC conditionings.

3. Outpatient management: reasons for hospitalization

Gluck *et al.* [54] identified five reasons for hospitalization during an outpatient program: i) unexpected severe complications, related to the administration of the preparative regimens, such as nausea and vomiting leading to severe side effects (i.e., dehydration); ii) need of large volumes of iv fluids; iii) dimethylsulphoxide (DMSO)-related toxicity; iv) neutropenic fever; and v) severe extra-hematological toxicities such as mucositis, diarrhea or significant hemorrhage.

However, after introducing the technique of DMSO depletion, toxicities have consistently been reduced [63,86,87] and hydration fluids, electrolytes administration and antiemetic therapy can easily be administered on an outpatient basis. Post-transplant neutropenic fever can successfully be managed in the ambulatory setting [88] with several antibiotics that require once-daily i.v. administration [47-50], and only infections that result in hemodynamic instability require admission. Severe mucositis is an important complication that often predicts the onset of fever suggesting that the outpatient approach *per se* is not a major risk factor for fever [63]. Progressive

mucositis that prevents appropriate oral intake or causes severe pain intractable with oral or transdermal narcotics requires admission [78]. Some authors reported the results of studies of cryotherapy for the prevention of HDM-induced oral mucositits in patients undergoing AHPCT [89,90]. They showed that oral cryotherapy contributes significantly to a decrease in the incidence and duration of grades 3 – 4 oral mucositis, as do the uses of narcotics and total parenteral nutrition. A Cochrane review of this area was most recently published [91]. There were 10 interventions, where there was more than one trial in the meta-analysis, that showed some statistically significant evidence of a benefit (albeit sometimes weak) for either preventing or reducing the severity of mucositis, compared to either a placebo or no treatment. These ten interventions were: aloe vera, amifostine, cryotherapy, granulocyte-colony stimulating factor (G-CSF), intravenous glutamine, honey, keratinocyte growth factor, laser, polymixin/tobramycin/amphotericin (PTA) antibiotic pastille/paste and sucralfate. Two interventions, cryotherapy (ice chips) and keratinocyte growth factor (palifermin®) showed some benefit in preventing mucositis. Sucralfate is effective in reducing the severity of mucositis, and a further seven interventions, aloe vera, amifostine, intravenous glutamine, G-CSF, honey, laser and antibiotic lozenges containing PTA showed weaker evidence of benefit. By contrast, transfusion of blood products can properly be planned on an outpatient basis.

Overall, the success of the program also depends upon a proper patient selection. Younger myeloma patients and those with serum creatinine levels less than 1.5 mg/dL were more likely to complete transplant programs as outpatients [78]. It is controversial whether the disease status affects the efficacy of the program. Montanari [64] showed that disease status may be correlated with the risk of re-admission after early discharge. In another study, disease status at the time of transplant did not appear to affect length of hospitalization if patients underwent transplant within 12 months from diagnosis [78].

4. Outpatient transplant programs: cost analysis

Outpatient programs have mainly been urged by the growing demand for autografting in hematological malignancies and by continuous cost-containment pressures.

Barosi *et al.* [92] reported that the length of hospitalization accounted for most of the costs of an autograft at a single Italian institution. The authors applied a Markov model [93] to simulate the entire procedure by the probabilities of key events and costs. The number of days spent in hospital was the major cost factor accounting for 80% of the total cost of the procedure.

One study reported a statistically significant correlation between the length of hospital stay and total costs, which were primarily associated with nursing care personnel's salaries [94]. In another study, the costs of a mean duration of hospitalization of 31 days (range, 27 – 37 days) during the autograft far exceeded reimbursement [95].

In the United States, the management of autografting for myeloma in the outpatient setting has allowed for remarkable financial savings, mainly due to a shorter length of hospitalization and lower drug and laboratory costs [55]. Cost savings associated with outpatient autografting have been estimated up to 25% [96]. Moreover, given that most outpatients did not receive parenteral nutrition or antibiotics, differences in costs between inpatient and outpatient treatments may probably have been underestimated.

Rizzo *et al.* [60] confirmed that both outpatient-based allogeneic and autologous HPCT are feasible with regard to conditioning regimen delivery and management of clinical complications. Importantly, the study also shows that significant reductions in unadjusted total medical charges to payers may not result from simply shifting care to the outpatient setting for all transplant patients. Of note, the results suggested that a select group of patients, in particular, those with standard risk of disease recurrence, may derive substantial cost savings from an outpatient-based transplant program.

In the Italian study by Anastasia *et al.* [49], the authors did not report a formal cost analysis. However the job-order system of their institution is 418 Euros daily for inpatient care, which includes a summary of all costs such as room, meals, nursing care. The introduction of their mixed inpatient–outpatient transplant program allowed cost savings up to 1672 Euros/patient without any negative impact on patient's outcome.
In a French randomized study [73], shifting from inpatient care to early discharge programs allowed cost savings up to 19% in a group of patients who were actually discharged early. However, considering all randomized patients, the program showed a mean cost per patient only 6% inferior as compared with that of the traditional inpatient group.
Overall, though it is difficult to compare cost analyses among different countries, all studies conclude that outpatient programs lead to cost savings from 7 up to 47% [50,55,58,73].

5. Outpatient transplant programs: quality of life

The most of outpatient studies did not perform a formal study dealing with quality of life. However, this aspect should be explored, because the feeling is that outpatient patients might have a better perception of well-being than do those transplanted in the inpatient context. This sensation is in line with a report dealing with a comparison between the psychosocial impact of inpatient–outpatient autologous transplants [97]. In this study, Summers *et al.* found that outpatients had significantly higher scores for emotional well-being and global quality of life than did inpatients.

6. Expert opinion

The role of HDM followed by AHPCT in the treatment of MM continues to evolve in the novel agent era and the IMWG recommends that AHPCT should be offered at some point in the course of the treatment program for a medically fit patient. Various models have shown that the AHPCT programs may be performed in the outpatient setting and may highly contribute to shorten waiting lists and to considerably cut health costs [98]. The easy administration of HDM and the relatively short neutropenia and the limited extra-marrow toxicity make MM patients ideal candidates for outpatient transplant programs. The recommendations for the different models are summarized in Table 2.

Table 2. Potential indications for the different outpatient models.

	TOM/MIOM/EDM/	DAM	HCM	TIM
Psychosocial evaluation	Good social status Good functional capacity	Good social status Good functional capacity	Good social status Good functional capacity	Poor social status Poor functional capacity
Compliance of patients and caregivers	Patients and Caregivers Correctly follows medical advice	Patients and Caregivers Correctly follows medical advice	Patients and Caregivers Correctly follows medical advice	Non-compliance
Availability of a caregiver on a 24-h basis	Available	Not available	Available	Not available
Housing in close proximity to the transplant center	Yes	No	Yes	No
Competency and commitment of patients	Yes	Yes	Yes	No
Competency and commitment of caregivers	Yes	No	Yes	No
Concordance (patient and clinician make decisions together about treatment)	Concordance	Concordance	Concordance	No Concordance
ECOG status (The day of discharge)	< 2	< 2	< 2	≥ 2
Patient desire to stay as an inpatient	No	Yes	No	Yes
Could phone unit physicians directly 24/24-h	Yes	Yes	Yes	No
First step in emergency department by a preferential way	Yes	Yes	Yes	No
Dedicated specialized staff	Yes	No	Yes	No
Outpatient Clinic operating 12 h/day and during week-ends	Yes	No	N.A.	No
Physicians and nurses operating 24 h/day and during week-ends	No	No	Yes	No

DAM: Delayed admission model; EDM: Early discharge model; HCM: Home care model; MIOM: Mix impatient outpatient model; N.A.: Not applicable; TIM: Total impatient model; TOM: Total outpatient model.

The key findings and weaknesses in the research done in this field so far are:

- a positive-pressure reverse isolation room during the neutropenic period is not mandatory in MM patients. This finding should offset the reconstruction of the global outpatient care model, requiring extensive coordination and implementation of resources;
- reduced length of hospitalization results in remarkable cost containments [55,92] and reduced exposure to hospital micro-organisms may have a favorable effect on complication rates [63,99];
- neutropenic fever can be managed with single daily dose broad-spectrum antibiotics as first-line treatment in the majority of cases and only few cases require combination antibiotic therapy [44,100];
- mucositis appears the most serious side-effect in the setting of outpatient transplant programs. The administration of cytoprotectors may reduce its severity and ameliorate symptoms [64,89-91,101];
- successful outpatient care requires the availability of a permanent outpatient service where medications and supportive care can rapidly and efficiently be provided by highly trained personnel [50,63];
- patient concerns and anxiety about quality of care, the lack of a caregiver and financial constraints may represent important limitations to the large application of outpatient transplant programs. However, there is evidence that patients prefer being treated as outpatients and that their quality of life is thereby improved [97];
- outpatient transplant programs cannot be offered to all patients. Ideal candidates may be those who are asymptomatic and fully active, who have a full-time caregiver and who can reside within easy reach from the transplant center.

In the future, it is crucial to establish largely accepted guidelines for early discharge after stem cell infusion and re-admission. Major medical conditions that could require prompt hospitalization include declining performance status not compatible with outpatient care, progressive mucositis that precludes oral intake, intractable pain from mucositis that cannot be controlled with oral or transdermal narcotics and infections that lead to hemodynamic instability. Moreover, the number of studies that compare inpatient and outpatient transplant programs are limited and essentially compare retrospective or prospective patient cohorts with historical groups or case control groups. Future trials should focus on the analysis of large prospective multi-center outpatient programs, which may identify patient subgroups who may most benefit from this innovative approach.

Article highlights.

- The role of high-dose melphalan (HDM) followed by autologous hemopoietic progenitor cell transplantation (AHPCT) in the treatment of multiple myeloma continues to evolve in the novel agent era.
- The International Myeloma Working Group recommends that AHPCT should be offered at some point in the course of the treatment program for a patient eligible to receive HDM.
- There are considerable concerns regarding the appropriate use of health care resources to reduce costs and waiting lists associated with AHPCT.
- One of the strategies to reach this goal is outpatient-based (OpB) AHPCT.
- Various models have shown that the procedure is feasible and safe and associated with an improvement of quality of life.
- Ideal candidates may be those who are asymptomatic and fully active, who have a full-time caregiver and who can reside within easy reach from the transplant center.

This box summarizes key points contained in the article.

Declaration of interest

The authors state no conflict of interest and have received no payment for preparation of this manuscript.

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