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Multiple myeloma: Role of autologous transplantation

Ioannis Ntanasis-Stathopoulos[1], Maria Gavriatopoulou[1], Efstathios Kastritis, Evangelos Terpos, Meletios A. Dimopoulos*

Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

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ABSTRACT

Autologous stem cell transplantation (ASCT) has been the mainstay of multiple myeloma (MM) treatment for approximately 30 years. Although the continuous introduction of novel agents in the armamentarium against MM has questioned its value, ASCT remains a backbone treatment for fit MM patients. However, there is no unanimous approach for several aspects including the positioning of ASCT in the therapeutic algorithm either upfront or following the first relapse, the need for single or tandem ASCT, as well as the role of ASCT as salvage therapy. Furthermore, the anti-CD38 monoclonal antibodies along with the next generation proteasome inhibitors and immunomodulatory drugs provide a platform for optimizing the induction and consolidation/maintenance regimens. In this review, we present current data pertaining to all aspects of ASCT in MM, whereas we highlight the open issues that should be addressed in the design of future clinical trials in the field.

Introduction

Multiple myeloma (MM) is an incurable plasma cell dyscrasia characterized by the uncontrollable proliferation of clonal plasma cells resulting in myeloma-defining events (end-organ damage and/or biomarkers of malignancy) [1]. MM constitutes a significant contributor to the global burden of hematological malignancy causing 2.1 million disability-adjusted life-years (DALYs) worldwide according to the Global Burden of Disease 2016 study [2]. During the last decades, an increase in the disease incidence has been clearly demonstrated, especially in North America, Western Europe and Australasia [2]. However, the constantly evolving therapeutic landscape has contributed to the continuous improvement in survival rates and the consideration of MM as a chronic disease [3,4].

Historically, the introduction of autologous stem cell transplantation (ASCT) has been the foremost improvement in MM therapeutics. It was initially introduced in 80s [5,6], but it was not until the 90s when the Intergroupe Français du Myélome (IFM) provided substantial evidence for its superiority over conventional chemotherapy [7]. Currently, upfront high dose therapy (HDT) followed by ASCT is considered the standard of care for all medically fit, newly diagnosed MM (NDMM) patients [8]. The pivotal role of ASCT in MM treatment is reflected on the inferior outcomes of patients living in countries with restricted health resources and limited availability of ASCT [2].

Furthermore, the introduction of novel anti-myeloma agents, including proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs) combinations, in the pre- and post-transplant setting have resulted in deep and durable remissions and potentiate the value of ASCT [9]. Interestingly though, the highly effective modern therapies challenge the position of ASCT in the therapeutic algorithm of MM and provide the rationale for a critical overview of the current evidence in the field.

The importance of ASCT in MM treatment

The cardinal randomised clinical trials by the IFM and the United Kingdom Medical Research Council (MRC) provided a strong rationale for the universal incorporation of ASCT in MM therapeutics in late 90s and early 00s [7,10]. Both studies clearly demonstrated the superiority of ASCT compared with conventional chemotherapy in terms of overall response rates (ORR), progression-free survival (PFS) and overall survival (OS) (Table 1). However, three subsequent randomised studies did not show any survival benefit beyond improvement in response rates (Table 1) [11–13]. At the same time, the addition of highly effective PI and IMiDs in the therapeutic armamentarium further reinforced the scepticism on the value of ASCT. To address this issue, four large randomised phase 3 studies have been conducted in the era of novel agents with triplet induction regimens; all of them pledge for a PFS benefit

* Corresponding author at: Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital, 80 Vas. Sofias Avenue, 11528 Athens, Greece.
E-mail address: mdimop@med.uoa.gr (M.A. Dimopoulos).
[1] Equal contribution.

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Table 1
Overview of studies comparing ASCT and non-transplant regimens.

Author, year	Patient no	Study design	Response (ASCT vs no ASCT)	PFS (ASCT vs no ASCT)	OS (ASCT vs no ASCT)
Attal et al. [7]	200	VMCP/BVAP × 18 vs VMCP/BVAP × 4–6 + (Mel140 + TBI)	ORR: 81% vs 57%, P < 0.001	5y: 28% vs 10%, P = 0.01	5y: 52% vs 12%, P = 0.03
Child et al. [10]	401	ABCM × 4–12 vs AEP × 3 + (Mel140 + TBI)	CR rates: 44% vs 8%, P < 0.01	Median 31.6 vs 19.6 mo, P < 0.001	Median 54.1 vs 42.3 mo, P = 0.04
Blade et al. [12]	216	VBMCP/VBAD + VBMCP/VBAD × 8 vs (Mel200 or Mel140 + TBI)	CR rates: 30% vs 11%, P = 0.002	Median 42 vs 33 mo, P = NS	Median 61 vs 66 mo, P = NS
Fermand et al. [13]	190	VMCP till plateau vs VAMP × 3–4 and ASCT	CR rates: 36% vs 20%	Median 25 vs 19 mo, P = 0.07	Median 47.8 vs 47.6 mo, P = NS
Barlogie et al. [11]	516	VAD × 4 plus (VBMCP) vs (Mel140 + TBI) +/- IFNmain	CR rates: 17% vs 15%	7y: 17% vs 16% (p = NS)	7y: 37% vs 42% (p = NS)
Palumbo et al. [14]	402	Rd × 4 plus (MPR × 6 +/- Rmain) vs (Mel200 × 2 +/- Rmain)	CR rates 23% vs 18%	Median 43 vs 22 mo, P < 0.001	4y: 82% vs 65%, P = 0.02
Gay et al. [15]	389	Rd × 4 plus (CRd × 6 + R or Rp main) vs (Mel200 × 2 + R or Rp main)	CR rates 33–37% vs 23–27%	Median 43 vs 29 mo, P < 0.001	4y: 86% vs 73%, P = 0.004
Cavo et al. [17]	1503	VCd × 3–4 plus (VMP +/− VRd + Rmain) vs (Mel200 × 1 or 2 +/− VRd + R-main)	≥ VGPR: 84% vs 75%, P < 0.001	3y: 64% vs 57%, P = 0.002	3y from randomisation: 85% in both arms
Attal et al. [16]	700	VRd × 3 plus (VRd × 5 + Rmain) vs (Mel200 + VRd × 2 + Rmain)	CR: 59% vs 48%, P = 0.03 MRDneg: 79% vs 65%, P < 0.001	Median 50 vs 36 mo, P < 0.001	4y: 81% vs 82%, P = NS

PFS: progression-free survival; OS: overall survival; NS: non-significant; TBI: total body irradiation; CRd: cyclophosphamide-lenalidomide-dexamethasone; R-main: lenalidomide maintenance; Rp-main: lenalidomide-prednisone maintenance; Rd: lenalidomide-dexamethasone; VRd: bortezomib-lenalidomide-dexamethasone; MPR: melphalan-prednisone-lenalidomide; VCd: bortezomib-cyclophosphamide-dexamethasone; ORR: overall response rate; CR: complete remission; VGPR: very good partial response; MRDneg: minimal residual disease negativity; VMP: bortezomib-melphalan-prednisone; Mel200: melphalan 200 mg/m^2; Mel140: melphalan 140 mg/m^2; ABCM: Adriamycin-BCNU-cyclophosphamide-melphalan; BVAP: BCNU-vincristine-adriamycin-prednisone; IFN: interferon; AEP: doxorubicin-cyclophosphamide-prednisone; VAD: vincristine-adriamycin-dexamethasone; VAMP: vincristine-adriamycin-melphalan-prednisolone; VBAD: vincristine-BCNU- adriamycin-dexamethasone; VMCP: vincristine-melphalan-cyclophosphamide-prednisone; VBMCP: vincristine-BCNU-melphalan-cyclophosphamide-prednisone.

with the ASCT-based strategies [14–17], whereas an OS advantage emerged in two of them [14,15], as well (Table 1). In the IFM 2009 study, 700 NDMM patients received induction with bortezomib-lenalidomide-dexamethasone (VRD) and they were randomized to receive high-dose melphalan (HDM)/ASCT followed by two cycles of VRD consolidation and lenalidomide maintenance or five cycles of VRD consolidation and lenalidomide maintenance without ASCT [16]. Significantly higher CR (p = 0.03) and minimal residual disease (MRD) negativity rates (p < 0.001) along with a prolonged PFS (50 vs 36 months, respectively, p < 0.001) were shown in the ASCT group compared to the VRD-only group. In a recent *meta*-analysis of the abovementioned clinical trials, HDM/ASCT had a minimal treatment-related mortality rate (< 1%) and it was significantly superior to standard-dose therapy with novel agents in terms of PFS [hazard ratio (HR) = 0.55, 95% confidence interval (CI): 0.41–0.74, p < 0.001], but not for OS (p = 0.20) [18]. Confounding factors such as the subsequent administration of ASCT and other effective anti-myeloma therapies in the relapse setting along with the need for longer follow-up may be implicated in the lack of OS benefit [18].

Assessment of eligibility for ASCT

Traditionally, young patient age has been considered as a principal criterion for proceeding to HDT and ASCT. The cut-off of 65 years has been widely used in pertinent clinical trials for patient enrolment and has been subsequently adopted in the clinical practice. In the recent years, however, there is accumulating data providing evidence for the feasibility of performing ASCT in older patients with no other severe comorbidities. Gay et al conducted a phase 2 study including 102 NDMM patients aged 65–75 years who received bortezomib-based induction followed by reduced-intensity ASCT with melphalan at 100 mg/m^2 and lenalidomide-based consolidation and maintenance [19]. Complete response (CR) rates reached 33% after ASCT and improved to 53% after consolidation and maintenance, whereas median PFS was 48 months and 5-year OS was 63%. Importantly, treatment-related death rate during induction-ASCT was lower among patients younger than 70 years (3/76 versus 5/26, p = 0.024). Another prospective study showed that higher melphalan dose at 200 mg/m^2 resulted in improved survival rates compared with melphalan at 140 mg/m^2 among patients 65 years and older receiving bortezomib-based induction and ASCT, whereas no treatment-related mortality was reported [20]. Interestingly, the Deutsche Studiengruppe Multiples Myelom conducted a randomised trial including 434 NDMM patients aged 60–70 years who were assigned to undergo tandem ASCT with melphalan at 140 mg/m^2 with or without induction treatment [21]. Adverse events were manageable and treatment-related mortality was 1% with no difference among age subgroups. Median PFS was not different between the two study arms, which highlighted the independent value of ASCT in older patients. A recent large retrospective study from Japan also showed no difference in terms of ASCT efficacy and safety between patients < 65 years and those aged 65 years or more [22].

The presence of renal failure is a common matter of debate in terms of optimal melphalan dosing. Although standard dose was initially considered to increase toxicity [23], more recent studies have demonstrated both the safety and the superiority of melphalan at 200 mg/m^2 compared with a reduced dose [24]. Survival outcomes following ASCT do not differ significantly between NDMM patients with or without renal impairment [24,25]. Interestingly, ASCT improves renal function and may result in dialysis independence for a subset of patients [24,26]. Induction treatment with novel agents [27] followed by HDM and ASCT should be the standard of care for otherwise fit NDMM patients with renal failure.

Optimal timing of ASCT

Although ASCT is being considered as an integral part of the upfront treatment among fit MM patients, the necessity of an early ASCT has been challenged on the grounds of the modern highly effective anti-myeloma therapies. In fact, this issue was originally addressed by Fermand et al who conducted a randomized trial including 185 patients that were assigned to receive ASCT either in the first or in the second line treatment in the era of conventional chemotherapy [28]. Early ASCT resulted in a significantly higher response rate, PFS and average time without symptoms, treatment, and treatment toxicity compared with late ASCT; nevertheless, no OS benefit was observed. Subsequent retrospective studies also did not show any significant survival advantage according to the timing of ASCT [29,30]. Furthermore, the establishment of lenalidomide maintenance after ASCT ruled out the argument of a prolonged treatment-free interval in favor of an early ASCT [31,32]. However, a pooled analysis of the phase 3 trials RV-MM-209 and EMN-441 conducted by Gay et al indicated that early ASCT conferred a significantly prolonged PFS and PFS2, as well as OS, irrespectively of the prognostic group [33]. Importantly, in the era of novel agents upfront ASCT has confirmed its superiority over delayed ASCT in terms of ORR and PFS both in the prospective IFM 2009 clinical trial and in a retrospective study; nevertheless, OS rates were similar with both approaches [16,34]. Confounding factors in the retrospective studies and a limited follow-up period in the prospective studies render the interpretation of the OS outcomes cautious. Moreover, the concept of introducing the most effective combination in the first line aiming at MRD negativity and subsequently prolonged PFS and OS favors the use of upfront ASCT, especially among patients with high-risk disease [35]. In addition to the above, an important aspect is the estimated future eligibility of a patient to receive a delayed ASCT. Both patient-related characteristics, such as advanced age, comorbidities and frailty, as well as myeloma-related variables, such as the response to second line treatment, may be implicated. The percentage of relapsed MM patients being unable to proceed to a delayed ASCT range from 11% to 46% in the literature [16,33,36]. Overall, available data support the administration of ASCT in the first-line setting; however, delayed ASCT remains a feasible option and should be discussed during the treatment-decision process with each patient.

Salvage repeating of ASCT

The concept of salvage ASCT includes the administration of a second ASCT at the time of relapse following a re-induction regimen. Usually the stem cells have been previously collected from the initial mobilization and cryopreserved. The randomized Myeloma X clinical trial showed that salvage ASCT was superior to standard chemotherapy with cyclophosphamide after re-induction in terms of PFS ($p < 0.0001$), PFS2 ($p < 0.0001$) and OS ($p = 0.017$); however, the benefit is rather questionable for the poor cytogenetic subgroup [37,38]. More recently, the prospective phase 3 study ReLApsE randomized relapsed MM patients to receive either re-induction with lenalidomide-dexamethasone (Rd) followed by salvage ASCT and lenalidomide maintenance or Rd continuously, which may be considered more representative of the regimens used in the current clinical practice. The landmark analysis suggested a survival benefit among patients undergoing salvage ASCT [39]. Low-risk patients derived the largest benefit [40]. Retrospective studies have also confirmed the efficacy and safety of salvage ASCT [41]. Furthermore, salvage ASCT may restore the integrity and function of the bone marrow and compensate for drug-related hematological toxicity [42]. Taking into consideration that NDMM patients who achieved MRD negativity in the IFM 2009 trial showed similar OS rates irrespective of the administration of upfront ASCT [16], MRD status with salvage re-induction may guide the decision for proceeding to a salvage ASCT. Therefore, salvage ASCT should be considered among patients who have been in remission after the initial ASCT for at least 36 or 18 months with or without maintenance, respectively [41], especially those with favorable disease characteristics.

Single versus tandem ASCT

Tandem ASCT refers to a second ASCT within 6 months after the first ASCT in the upfront setting. This concept was initially introduced in 90s in order to further improve the depth of response and long-term outcomes in the era of conventional chemotherapy [43]. In the contemporary era of novel agents, though, the additive value of a tandem ASCT is rather debatable. The phase 3 EMN02/HO95 clinical trial randomized 415 patients to receive either single or tandem ASCT following bortezomib-based induction [44]. Tandem transplantation resulted in improved response depth by 25%, whereas more than half of the patients achieved CR or better. The tandem ASCT group significantly prolonged the 3-year PFS (HR = 0.70, 95%CI: 0.50–0.98, $p = 0.04$) and 3-year OS (HR = 0.52, 95%CI: 0.31–0.86, $p = 0.011$). Interestingly, tandem ASCT neutralized the adverse cytogenetic and high R-ISS prognosis. More recently, patient-level data (n = 909) from three randomized phase 3 trials including bortezomib-based induction and consolidation/maintenance regimens in the context of single or tandem ASCT were collectively analyzed [45]. Following a long-term follow up of 10 years, tandem ASCT group demonstrated a significantly prolonged median PFS ($p = 0.0008$) and higher 10-year OS rates ($p = 0.0002$) compared with single ASCT. It has to be noted that high-risk patients derived the greatest benefit from tandem ASCT in terms of survival rates. Furthermore, the phase 3 BMT-CTN 0702 STAMINA trial randomized 758 NDMM patients to receive induction followed by tandem ASCT and lenalidomide maintenance or ASCT and consolidation with four cycles of VRD and lenalidomide maintenance or ASCT and lenalidomide maintenance [46]. In contrast to the previous European studies, STAMINA study failed to show any improvement in terms of PFS or OS for the tandem ASCT compared with the single ASCT. Tandem ASCT did not have a benefit over single ASCT among high risk patients. These discrepancies may be attributed to the different study designs, differences in induction regimens and duration of induction treatment, variable depth of response following induction, as well as the fact that approximately two thirds of the patients aligned to received tandem ASCT in the STAMINA trial eventually proceeded to second ASCT. Therefore, tandem ASCT should be considered among NDMM with high-risk disease characteristics, whereas a carefully planned randomized trial with modern induction regimens is eagerly awaited.

Optimizing induction regimens

Upfront induction treatment in MM has two main goals; as early as possible response in order to achieve rapid disease control and as deep as possible response in order to proceed to ASCT safely and improve outcomes [47]. MRD negativity following induction may be considered as the optimal depth of response, which is associated with improved survival outcomes [16,35,48]. The common practice consists of four to six cycles of induction before proceeding to HDT/ASCT and depends on several factors including the presence of response and its depth, patient tolerability to the induction regimen and the availability of ASCT infrastructure. Three-drug combinations incorporating a PI with an IMiD and dexamethasone are currently considered the gold standard regimens [9].

Induction with the triple combination of first-in-class PI, bortezomib, and IMiD, thalidomide, with dexamethasone (VTD) has shown superiority compared with the two-drug combinations thalidomide-dexamethasone (TD) and bortezomib-dexamethasone (VD) in terms of response rates and long-term outcomes [49–52]. Both a meta-analysis of single-arm studies and a phase 3 clinical trial have also demonstrated the superiority of VTD over the combination of bortezomib-cyclophosphamide-dexamethasone (VCD) regarding the depth of response

(VGPR or better rate 66% vs 56%, respectively, p = 0.05), whereas VTD showed a better toxicity profile except for a higher rate of peripheral neuropathy [53,54]. Furthermore, the second generation IMiD, lenalidomide, in combination with bortezomib and dexamethasone (VRD) is superior to lenalidomide-dexamethasone (RD) and it is associated with deeper and durable responses as well as prolonged survival [55]. VRD has been also associated with improved OS compared with VCD and VD [56]. Induction with VRD has demonstrated high rates of deep responses [16,56,57]; in a phase 3 clinical trial more than one third of transplant-eligible NDMM patients achieved MRD negativity and almost half of the patients with high-risk cytogenetics achieved CR or better [58]. Although lenalidomide-based may be superior to bortezomib- and thalidomide-based regimens [49] and VRD has become the prevalent induction regimen in the United States, VTD or even VCD may be viable options depending on the setting and drug availability [59].

Recently, the introduction of the next-generation PI, carfilzomib, in the induction regimens has been evaluated [60]. The combination of carfilzomib-lenalidomide-dexamethasone (KRD) has shown early responses and ORR rates reaching 95%, including a more than 20% CR or better rate [61,62]. Interestingly, KRD has also resulted in highly pure stem cell grafts as defined by MRD negative status [63]. KRD administration both pre- and post- ASCT as induction and consolidation, respectively, is superior to the combination of carfilzomib-cyclophosphamide-dexamethasone (KCD) in terms of depth of response and MRD negativity rates [64]. Carfilzomib has been also evaluated in combination with thalidomide and dexamethasone (KTD) as induction regimen in the phase 2 Carthadex trial resulting in 65% and 18% VGPR or better and CR or better rates, respectively [65].

Furthermore, the addition of anti-CD38 monoclonal antibody, daratumumab (Dara), in triple combinations in the induction setting has showed promising results. Dara-VCD resulted in 81% and 56% ORR and VGPR or better rates, respectively, among NDMM patients participating in the LYRA study [66]. The safety run-in cohort of the phase 2 Griffin trial showed the safety and the efficacy of Dara-VRD, with 50% of the patients achieving MRD negativity following consolidation [67]. Furthermore, the phase 3 Cassiopeia trial has met its primary endpoint by demonstrating a sCR rate of 28.9% with Dara-VTD compared with 20.3% with VTD induction and consolidation ($p \leq 0.001$) [68]. Dara-KRD induction has resulted in impressive response rates with 100% ORR including a 43% CR or better rate with no emergence of new safety signals [69]. Final results of the abovementioned studies are eagerly anticipated.

Mobilization and conditioning regimens

Mobilization of CD34+ stem cells from the bone marrow to the peripheral blood is a prerequisite for harvesting adequate number of haematopoietic stem cells and proceeding to a successful ASCT. The minimum number of CD34+ stem cells should be approximately 5×10^6 CD34+ cells/kg, whereas the lowest cutoff has been set at 2×10^6 CD34+ cells/kg [70]. A higher target should be set for those who will undergo a tandem ASCT. Cryopreservation is an option for those considered potentially eligible for a salvage ASCT in the future. The most widely used regimen for chemo-mobilization is high-dose cyclophosphamide at 2–4 g/m^2 followed by granulocyte colony-stimulating factors (G-CSF) at 5 μg/kg/day administered one to five days after chemo-mobilization until the last apheresis day [70,71]. Another approach is the steady state mobilization with G-CSF consisting of filgrastim or lenograstim at 10 μg/kg/day for 4–6 consecutive days and apheresis on days 5–7 [70,71]. In cases of inadequate mobilization, the addition of plerixafor may improve the counts of harvested stem cells [72]. Plerixafor is a chemokine receptor 4 (CXCR4) antagonist that impairs CXCR4 binding with the stromal derived factor 1 [72]. Therefore, plerixafor is able to counteract the effect of prolonged lenalidomide exposure that upregulates CXCR4 and jeopardizes stem cell mobilization [73,74].

Traditionally, melphalan at 200 mg/m^2 is being considered the gold standard conditioning regimen worldwide following the results of the IFM 9502 study demonstrating its superiority over melphalan at 140 mg/m^2 with total body irradiation [75]. Recent data have also supported the superiority and safety of full dose melphalan among elderly patients and those with renal insufficiency [20,24]. Furthermore, the addition of bortezomib to the high dose melphalan conditioning regimen did not improve outcomes [76]. However, a recent phase 3 clinical trial evaluating the addition of busulfan in the conditioning setting showed that busulfan followed by melphalan at 140 mg/m^2 resulted in a prolonged PFS of 64.7 months compared with 43.5 months with melphalan at 200 mg/m^2 alone (p = 0.022) [77]. Therefore, this combination regimen may become the new standard of care in the near future.

The role of consolidation following ASCT

Consolidation therapy refers to a short intensified course of therapy immediately after day 100 following an ASCT in order to further deepen the response and improve long-term outcomes. Regimens combining a PI (bortezomib or carfilzomib) and an IMiD (thalidomide or lenalidomide) with or without dexamethasone have demonstrated enhanced response rates [16,62,65,78,79]; however, the effect on PFS has been debatable since randomized trials have shown contradictory results. More specifically, although the EMN02 study has demonstrated a PFS advantage with VRD consolidation, the STAMINA trial did not support the superiority of VRD consolidation over no consolidation in terms of survival [46,80]. Thus, the additional benefit and the necessity of consolidation has not been determined yet and it remains under investigation. However, taking into consideration that MRD negativity following induction and ASCT is a strong predictor of long-term survival [35,48], it may be supported that MRD status post ASCT may guide the therapeutic decisions in terms of administration of consolidation, as well as type and duration of maintenance therapy.

Maintenance treatment: is lenalidomide monotherapy the only option?

Since MM remains an incurable disease, the role of maintenance lies in the long-term administration of a low-intensity therapy with minimal toxicity aiming at preventing relapse and prolonging survival. Lenalidomide maintenance has been established as the standard of care worldwide. Two recent meta-analyses of prospective studies have confirmed the survival advantage since lenalidomide maintenance reduces the risk of progression by 52% and the risk of death by 25%, whereas it has been proven superior to other bortezomib- or thalidomide- based regimens [81,82]. Although the optimal duration of maintenance has not been elucidated yet, two to three years or until disease progression are the commonest approaches in the clinical practice [42]. The occurrence of second primary malignancies should be considered, although it is rather unlikely that they may influence survival [83]. The depth of response including MRD status, cytogenetic risk, patient tolerance, patient wish may guide treatment individualization. More intensified bortezomib-based regimens may be considered among high-risk patients [84,85]. Furthermore, the recent results of the randomized, placebo-controlled, phase 3 TOURMALINE-MM3 trial showed a reduction in the risk of death or progression by 28% with ixazomib maintenance compared with placebo, whereas the PFS benefit was also evident among high-risk MM patients [86]. Interestingly, quality of life indices did not differ significantly between the ixazomib and placebo groups, whereas ixazomib showed low incidence of peripheral neuropathy and no additive risk of secondary malignancies [86]. Thus, ixazomib constitutes a novel alternative agent for maintenance following ASCT; however, data from a head-to-head comparison with lenalidomide are not currently available.

Conclusions

Following its introduction approximately 30 years ago, ASCT currently remains the cornerstone of MM therapeutics for fit patients. Although it is usually implemented in the upfront treatment, ASCT is multifaceted; early or delayed, single or tandem, or even salvage. Furthermore, as novel agents are coming in the foreground, there is a constant effort of ameliorating induction treatments, mobilization and conditioning regimens, consolidation and maintenance approaches. Among all, the introduction of carfilzomib and daratumumab in the first line, the addition of busulfan to melphalan and the ixazomib maintenance seem to be incorporated in the clinical practice in the near future. Tailoring of maintenance therapy based on the MRD status is another challenge that is being addressed in ongoing studies, such as the PERSEUS clinical trial [87]. Apart from highly effective therapies resulting in "functional cure", the optimization of the abovementioned ASCT components also lies in the establishment of a favourable safety profile by further minimizing morbidity and mortality and, ideally, performing ASCT in an outpatient setting [88].

Declaration of Competing Interest

INS declares no competing financial interests for this paper. MG declares consultancy and honoraria from Amgen, Karyopharm, Genesis Pharma, Janssen and Takeda. EK declares consultancy, boards and honoraria from Genesis Pharma, Takeda, Janssen and Amgen. ET declares consultancy and honoraria from BMS, Janssen, Celgene, Takeda, Genesis Pharma, Amgen and Novartis. MAD declares consultancy and honoraria from Novartis, Janssen, Celgene, Takeda, Amgen and BMS.

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