From transplant to novel cellular therapies in multiple myeloma: European Myeloma Network guidelines and future perspectives

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ABSTRACT

Survival of myeloma patients has greatly improved with the use of autologous stem cell transplantation and novel agents, such as proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies. Compared to bortezomib- and lenalidomide-based regimens alone, the addition of high-dose melphalan followed by autologous transplantation significantly improves progression-free survival, although an overall survival benefit was not observed in all trials. Moreover, follow up of recent trials is still too short to show any difference in survival. In the light of these findings, novel agent-based induction followed by autologous transplantation is considered the standard upfront treatment for eligible patients (level of evidence: 1A). Post-transplant consolidation and maintenance treatment can further improve patient outcome (1A). The availability of several novel agents has led to the development of multiple combination regimens such as salvage treatment options. In this context, the role of salvage autologous transplantation and allotransplant has not been extensively evaluated. In the case of prolonged remission after upfront autologous transplantation, another autologous transplantation at relapse can be considered (2B). Patients who experience early relapse and/or have high-risk features have a poor prognosis and may be considered as candidates for clinical trials that, in young and fit patients, may also include an allograft in combination with novel agents (2B). Ongoing studies are evaluating the role of novel cellular therapies, such as inclu-

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sion of antibody-based triplets and quadruplets, and chimeric antigen receptor-T cells. Despite encouraging preliminary results, longer follow up and larger patient numbers are needed before the clinical use of these novel therapies can be widely recommended.

Introduction

The treatment landscape and clinical outcome of multiple myeloma (MM) patients have changed in the last decades,[1] with an improved median survival of 8-10 years. Multiple combinations of proteasome inhibitors (PIs) and immunomodulatory drugs (IMIDs) have been under evaluation in the transplant and non-transplant settings, and studies are still ongoing. Several pre-transplant inductions and post-transplant novel agent-based consolidation and maintenance regimens have been investigated, although direct comparisons between such strategies have rarely been performed. Autologous stem cell transplant (ASCT) is currently considered the standard of care for fit newly diagnosed MM (NDMM) patients, although remarkable results obtained in the non-transplant setting[2,3] with novel agent-based treatment have raised questions as to the role of upfront *versus* delayed ASCT.

The availability of 2nd-generation PIs and IMIDs, monoclonal antibodies, histone deacetylase inhibitors, and, more recently, check-point inhibitors and small molecules, has led to the development of multiple salvage options that include different combinations of these drugs. In this context, the role of salvage ASCT and allotransplant have not been extensively evaluated. These exciting advances require a critical review to delineate the merit of different induction, consolidation and maintenance approaches, as well as to define the role of upfront ASCT, salvage ASCT and allotransplant in the novel agent era. These important considerations prompted the European Myeloma Network (EMN) to provide guidelines to harmonize treatment selection. A brief overview of novel cellular therapies, which can be considered the new frontier for transplant, is also provided.

Methodology

Clinical EMN experts on MM developed these recommendations based on published data through August 2017. Expert consensus was used to suggest recommendations in case of inconclusive data. Grades of recommendations were assigned using the GRADE criteria for grade of recommendation (*Online Supplementary Table S1*). The manuscript underwent revision in 3 rounds until the EMN experts reached mutual consent.

Upfront autologous transplant

The current treatment paradigm for NDMM patients eligible for ASCT consists of 4 phases: pre-transplant induction, transplant, post-transplant consolidation and maintenance.

Pre-transplant induction

Induction treatment generally consists of 3-6 cycles with the goal of achieving rapid disease control, improve symptoms, and allow for subsequent successful stem cell collection. The current standard is a 3-drug bortezomib-based combination. Doxorubicin-bortezomib-dexamethasone (PAD) proved to be superior to standard chemotherapy in a randomized trial,[4] and more recently, bortezomib-cyclophosphamide-dexamethasone (VCD) was found to be non-inferior to PAD.[5] Improved responses were observed with combinations including both PIs and IMIDs. Indeed, complete response (CR) rates were significantly higher with bortezomib-thalidomide-dexamethasone (VTD) compared with thalidomide-dexamethasone (TD) in 2 randomized trials (35% *vs*. 14%, P=0.0001; 31% *vs*. 11%, P<0.001).[6,7] VTD *versus* VCD improved CR rates (13% *vs*. 9%, respectively).[8] Higher CR rates were reported with bortezomib-dexamethasone plus the 2nd-generation IMID lenalidomide (VRD) (23-48%) (Table 1).[9,10] No direct, randomized comparisons of PAD *versus* VTD have been made.

Expected efficacy of a given regimen is one of the main factors to be considered in the treatment choice, the second factor being the expected toxicity. Infections are common events in NDMM, often to the underlying disease itself and to the treatment. The main issue with the use of bortezomib (in particular when combined with thalidomide) is the occurrence of peripheral neuropathy (PNP), which can be decreased substantially with subcutaneous and once-weekly administrations. The main concern with combinations including thalidomide or doxorubicin is the thromboembolic risk. Both PNP and thromboembolism rates seem to be lower when bortezomib is associated with cyclophosphamide (Table 2).

Given that the benefit of bortezomib could be hampered by its neurological side effects, 2nd-generation PIs with minimal neurotoxicity demonstrated that induction treatment with ixazomib-lenalidomide-dexamethasone (IRD) was very well tolerated (no grade 3-4 PNP, cardiac, liver or renal toxicities) and led to a 12% CR rate.[11] Carfilzomib-thalidomide-dexamethasone (KTd)[12] or carfilzomib-lenalidomide-dexamethasone (KRd)[13] lead to a 18-24% CR rate, although cardiovascular toxicities (mainly hypertension) have been reported.

The impact of depth of response on outcome[14] provides the rationale for choosing the most effective induction regimen, provided the toxicity profile is acceptable. Nevertheless, only one randomized trial (Myeloma XI) investigated a response-adapted approach based on the sequential use of chemotherapeutic agents, with different modes of action in patients with a suboptimal response (minimal response/partial response) to thalidomide-based induction. Some 40% of patients upgraded their response with VCD before ASCT and significant improvement in PFS was observed (median 48 *vs*. 38 months; P<0.0001).[15] However, the trial included suboptimal induction regimens (CTD and cyclophosphamide-lenalidomide-dexamethasone) not widely used outside the UK. The current standard of care is bortezomib plus IMIDs or chemotherapy, supported also by the results of two meta-analyses[16,17] that showed the superiority of bortezomib- over non-

bortezomib-induction treatments. Thus, the impact of switching treatment, with currently much more effective induction regimens, still needs to be confirmed.

Autologous transplantation

Several trials compared different chemotherapy regimens to standard high-dose melphalan (200 mg/m^2, MEL200), showing a favorable risk-benefit profile with MEL200 over busulfan/melphalan, idarubicin/melphalan/cyclophosphamide, BCNU/etoposide/melphalan, melphalan 100/140 mg/m^2. Conditioning regimens including novel agents have so far only been evaluated in single arm studies.[18] Given the efficacy and favorable toxicity profile of MEL200, this regimen remains the standard.

Efficacy of novel-agent treatments in the non-transplant setting, together with a manageable safety profile and the advantage of the administration in the outpatient setting, questioned the role of MEL200-ASCT. Four randomized trials compared MEL200-ASCT *versus* novel agent-based triplets. In two trials, patients received Rd induction and were randomized to tandem MEL200-ASCT or oral lenalidomide-based chemotherapy [melphalan-prednisone-lenalidomide (MPR)/cyclophosphamide-lenalidomide-dexamethasone (CRD)]. Median PFS was significantly longer for patients randomized to tandem MEL200-ASCT than for those randomized to MPR (43 *vs*. 22 months; *P*<0.001) or CRD (43 *vs*. 28 months; *P*<0.001). Tandem ASCT also improved the 4-year OS rate *versus* MPR (82% *vs*. 65%; *P*=0.02) or CRD (86% *vs*. 73%; *P*=0.004).[19,20]

Two large studies compared MEL200-ASCT *versus* bortezomib-based regimens. MEL200-ASCT significantly prolonged PFS *versus* bortezomib-lenalidomide-dexamethasone (VRD)[10] (median 50 *vs*. 36 months; *P*<0.001), and *versus* bortezomib-melphalan-prednisone (VMP)[21] (3-year PFS 65% *vs*. 57%; *P*=0.001). Follow up of these two trials is still too short to show any differences in OS.

Indeed, data confirmed that the toxicity profile was better and more manageable in the non-transplant arm, but no increase in toxic deaths was reported with MEL200-ASCT.[10,19,20,21]

Before the introduction of novel agents, several studies showed a prolonged event-free survival (EFS) with double *versus* single ASCT.[22] A subgroup analysis of one of those trials reported an improved OS only in patients achieving less than very good partial response (VGPR) after the first ASCT.[23] A more recent integrated analysis of patient-level data from 4 European trials demonstrated that, in patients receiving bortezomib-based induction, the greatest benefit with double *versus* single ASCT in terms of extended PFS [Hazard Ratio (HR)=0.41] and OS (HR=0.22) was seen in patients with t(4;14) and/or del(17p) who failed CR to induction therapy.[24] Preliminary results of the EMN02 trial confirmed that patients receiving double ASCT have a superior PFS in comparison with patients randomized to a single ASCT (3-year PFS 74% *vs*. 62%; *P*=0.05). The benefit was particularly evident in patients with high-risk cytogenetics (3-year PFS 65% *vs*. 41%; HR 0.49, *P*=0.046).[25]

On the contrary, the STAMINA trial showed no

Table 1. Efficacy of sequential approaches with autologous transplantation: improvement in response rates, progression-free survival and overall survival with sequential induction, transplant, and consolidation-maintenance regimens.

Regimen	N of patients	Median FU (months)	CR (%)	PFS	OS	Study ref
PAD			7			
MEL 200	413	41	21	50% at 35 months	61% at 60 months	4
V maintenance			36			
VTD			23			
MEL 200	236	43	49	60% at 36 months*	90% at 36 months*	28
VTD consolidation			61			
VTD			35			
MEL 200	130	35	46	50% at 56 months	74% at 48 months	6
T/INF/VT maintenance			-			
VRD			-			
MEL 200	350	39	59°	50% at 50 months	81% at 48 months	10
VRD consolidation			-			
R maintenance			-			
VCD			-			
MEL 200	1499	53	32	65% at 36 months	86% at 36 months	21
VRD/no consolidation			-			
R maintenance			-			
KRD			24			
MEL200	46	17	41	91% at 24 months	-	13
KRD consolidation			61			
R maintenance			-			
IRD			12			
MEL200	42	20	17	83% at 20 months	95% at 20 months	11
IRD/IR consolidation			29/44			
I maintenance			-			

CR: complete response; MEL 200: melphalan 200 mg/m^2; PFS: progression-free survival; OS: overall survival; Study ref: references in literature; FU: follow up; R: lenalidomide; RP: lenalidomide-prednisone; N: number; T: thalidomide; V: bortezomib; VTD: bortezomib-thalidomide-dexamethasone; INF: interferon; VT: bortezomib-thalidomide; IR: ixazomib-lenalidomide; I: ixazomib; PAD: bortezomib-adriamycin-dexamethasone; VRD: bortezomib-lenalidomide-dexamethasone; VCD: bortezomib-cyclophosphamide-dexamethasone; KRD: carfilzomib-lenalidomide-dexamethasone; IRD: ixazomib-lenalidomide-dexamethasone; -: data not available. °Response to the overall treatment. *PFS/OS from the start of consolidation.

improvement in PFS in patients receiving double ASCT followed by maintenance *versus* single ASCT followed by VRD consolidation and lenalidomide maintenance. However, different induction regimen, more effective and prolonged therapy with better disease control before ASCT, as well as non-adherence to the double ASCT policy in 30% of patients can prove to be a limitation of this comparative trial.[26]

Consolidation regimens

Consolidation is a commonly adopted approach after transplant to improve depth of response. In "naïve" patients, bortezomib consolidation prolonged PFS *versus* no consolidation (median 27 *vs*. 20 months, respectively; *P*=0.05), but no difference in OS was seen.[27] In another trial, VTD consolidation increased the CR rate from 15% to 49% and the molecular remission rate from 3% to 18%.[14] More recently, post-ASCT consolidation with the same induction regimens was assessed. VTD increased the CR/nCR rate from 63% to 73%.[28] Similarly, CR plus stringent CR rate increased from 47% to 50% after VRD.[9] Preliminary results of the EMN-02 trial suggest that post-transplant VRD consolidation also prolongs PFS *versus* no consolidation (3-year PFS 65% *vs*. 60%, respectively; *P*=0.045).[29] The STAMINA trial did not find any improvement in PFS with single ASCT followed by VRD consolidation and lenalidomide maintenance *versus* single ASCT followed by lenalidomide maintenance. However, the rate of non-compliance to VRD was sizeable at 12%.[26]

Similarly to induction phase, combining 2nd-generation PIs and IMIDs is advantageous also in the consolidation phase, enhancing CR rates from 20% to 32% with IRD, from 31% to 64% with KTD, and from 45% to approximately 70% with KRD.[11-13]

Maintenance regimens

The optimal maintenance regimen should aim at prolonging the remission duration without affecting patients' quality of life. Although meta-analyses showed a reduced risk of progression (HR=0.65) and death (HR=0.84) with thalidomide maintenance, in the IFM and MRC IX studies, patients with unfavorable cytogenetics did not benefit from this approach.[30,31] In addition, grade 3-4 PNP (7-19%) and treatment discontinuation due to PNP limit the long-term use of thalidomide.

Bortezomib maintenance seems to be a better option: a landmark analysis of the HOVON-65/GMMG-HD4 trial showed that bortezomib maintenance significantly reduced the risk of progression (*P*=0.04) and death (*P*=0.05) as compared with thalidomide, with a similar rate of grade 3-4 PNP (5% *vs*. 8%).[4] Results of this trial also suggest that pre-transplant bortezomib induction followed by bortezomib maintenance significantly reduces the high-risk impact of del(17p) and renal impairment on survival.[32] More recently, longer PFS was reported also with the bortezomib-thalidomide combination *versus* thalidomide alone.[33]

Lenalidomide is another valid strategy for long-term treatment, with limited neurotoxicity: 4 trials subsequently evaluated lenalidomide maintenance after ASCT,[19,34–36] showing a consistent PFS benefit for lenalidomide *versus* no maintenance (HR range 0.46-0.50). A meta-analysis of the first three randomized trials reported a significant increase also in OS (7-year OS 62% *vs*. 50%; HR 0.75, *P*=0.001) across all subgroups analyzed with the exception of patients with high-risk cytogenetics. In the MRC trial, a significant PFS benefit was maintained also in patients with high-risk cytogenetics, but no data on OS are currently available. Main grade 3-4 toxicities were neutropenia (23-51%), and infections (6-13%).[19,34,35] Although second primary malignancies (SPMs) were higher with lenalidomide maintenance *versus* control (hematologic SPM 6.1% *vs*. 2.8%; solid tumor SPM 7.3% *vs*. 4.2%),[37] the OS benefit outweighed the SPM risk.

Recommendations in NDMM patients eligible for high-dose therapy and ASCT, sequential treatment including novel agent-based induction, upfront transplant, post-transplant bortezomib plus IMIDs consolidation and maintenance is recommended (1A) (Figure 1). Treatment choice should be based on evidence supporting a specific treatment, and on a thorough evaluation of the patient's characteristics, toxicity of the expected regimens, and availability of drugs in the specific countries (Table 3).

Table 2. Safety (grade >3 adverse events) of selected pre-transplant induction and post-transplant consolidation/maintenance regimens.

Regimen	Neutropenia (%)	Thrombocytopenia (%)	Anemia (%)	Thromboembolism (%)	PNP (%)	Infection (%)	Study ref
Induction							
PAD	3	10	8	4	24	26	4
VTD	10	8	-	12	14	21	6
VCD	35°	4	6	3#	8#	22#	5
KRD	16	2	2	-	-	15	13
Consolidation							
VTD	-	5*	-	1	1	1	28
KRD	26	15	-	-	-	2	13
Maintenance							
V	0	4	1	1	5	24	4
T	1-16	2	1	1	8-14	18	4,33
R	23-51	4-14	2-5	2-3	1	6-8	19,20,34,35
TV	13	10	-	-	15	-	33

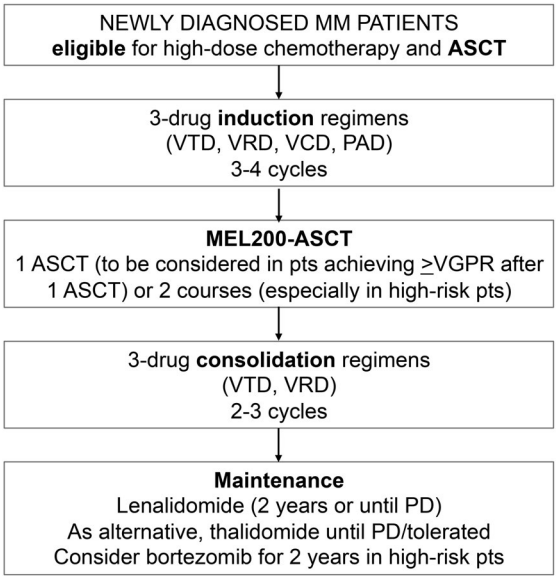
R: lenalidomide; T: thalidomide; V: bortezomib; VTD: bortezomib-thalidomide-dexamethasone; PAD: bortezomib-adryamicin-dexamethasone; VRD: bortezomib-lenalidomide-dexamethasone; VCD: bortezomib-cyclophosfamide-dexamethasone; KRD: carfilzomib-lenalidomide-dexamethasone; IRD: ixazomib-lenalidomide-dexamethasone; Study ref: references in literature; TV: thalidomide-bortezomib; PNP: peripheral neuropathy; -: data not available. °Including leukopenia. #: ≥grade 2. *All grade events.

Special considerations

Currently, selection criteria for high-dose therapy include age and comorbidities. However, a definite age cut off, rather than assessment of patient's biological age, comorbidities, fitness and frailty/comorbidity scores is suboptimal. Besides age, the performance status, and cardiac, pulmonary, hepatic and renal functions should be considered to better evaluate the risk-benefit ratio of transplant for each patient, and specific risk-assessment models, such as the Myeloma Comorbidity Index (MCI) and/or Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) should be used to better modulate the dose of chemotherapy.[38-40] Specific considerations refer to patients with renal failure (RF) and elderly patients.

Renal failure (RF)

Approximately 20% of patients have creatinine more than 2 mg/dL at diagnosis. Bortezomib-based regimens remain the cornerstone of management of renal failure (RF). Indeed, higher response rates were reported with PAD *versus* VAD induction in patients with RF (81% *vs.* 63%; *P*=0.31).[41] In dialysis patients, bortezomib-based induction *versus* conventional chemotherapy significantly increased pre-transplant (83% *vs.* 36%; *P*=0.02) and post-



MM: multiple myeloma; ASCT: autologous stem cell transplantation; VTD: bortezomib-thalidomide-dexamethasone; VRD: bortezomib-lenalidomide-dexamethasone; VCD: bortezomib-cyclophosphamide-dexamethasone; PAD: bortezomib-adriamycin-dexamethasone; MEL 200: melphalan 200 mg/m^2; VGPR: very good partial response; PD: progressive disease; pts: patients.

Figure 1. Recommended sequential treatment.

Table 3. Recommendations for up-front treatment in transplant-eligible patients.

	Regimens	Recommendation	Rationale for recommendation
Induction	VTD (1A) VRD (1B) PAD (1A) VCD (1B) -	Treatment choice: -Non-neurotoxic agents (doxorubicin, lenalidomide, cyclophosphamide) preferred in pts with PNP. Non-thrombotic agents (cyclophosphamide) to be considered in pts with thrombosis. - Lenalidomide use is supported by better toxicity profile than thalidomide, and the advantage of an oral use as compared with doxorubicin. Number of cycles: - Treatment should be continued for at least 3-4 cycles with all regimens. - Patients achieving >PR with VTD can continue for another 2 cycles.	Treatment choice: - Randomized comparisons showing the superiority of one of these regimens over the others are lacking. - Treatment choice should consider patients' characteristics and expected toxicity of the proposed regimens. - VTD showed superiority *vs.* TD, chemotherapy without novel agents and VCD.[6,7,8] - VRD showed promising phase II and III efficacy results, with a good safety profile, but randomized comparisons VRD *vs.* other induction regimens are lacking.[9,10] Number of cycles: - Most of the trials evaluated 3-4 cycles of induction. - Phase III data on efficacy and toxicities of > 4 cycles are lacking, except for VTD.[4,5,6,7,8] - Randomized comparison of prolonged induction until best response and ASCT *vs.* fixed duration of induction and ASCT are lacking.
Transplant	MEL200 (1A)	Treatment choice: MEL200 Number of cycles: 2 MEL200-ASCT are recommended in particular in patients with high-risk disease and <CR. 1 MEL200-ASCT can be considered for standard risk patients achieving >VGPR.	Treatment choice: - Randomized trials showed a favorable efficacy and safety profile of MEL200 *vs.* other regimens (Bu/Mel, Ida/Mel/Cy, BCNU/Etoposide/Mel, Mel100, Mel140).[18] - Novel agents in the conditioning regimens so far evaluated only in single arm studies.[18] Number of cycles: - Data from meta-analysis and 2 phase III trials suggest that the greatest benefit with double *vs.* single ASCT is for patients with high-risk disease.[4,24,25] Phase III data of STAMINA trial showed equal PFS between patients that, after a first ASCT, were randomized to consolidation with a second ASCT plus lenalidomide maintenance, or VRD consolidation followed by maintenance or maintenance only, but these results may be affected by non-adherence to the second transplant policy in 30% of patient maintenance.[4,26] - Integrated patient level meta-analysis in the context of bortezomib induction showed the greatest benefit for double *vs.* single ASCT in patients who failed CR to induction therapy. Before novel agent treatment, the benefit of double ASCT was reported in patients achieving <VGPR after the first ASCT.[23]

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transplant (100% *vs.* 58%; *P*=0.01) overall response rate. Prolonged EFS and a trend towards less time on hemodialysis (6 *vs.* 17 months) was also reported.[42] Combination of bortezomib with high cut-off hemodialysis led to prompt and remarkable responses.[43] RF does not appear to affect the quality of stem cell collection.[44] Persistent RF or dialysis are not contraindications to high-dose therapy and ASCT,[45] since patients may improve renal function after ASCT. Nevertheless, the rate of treatment-related mortality (TRM) ranges from 0 to 29% in different reports and with different melphalan doses.[42,44] Thus, due to the potentially higher toxicity of 200 mg/m^2, dose reductions are mandatory, particularly in dialysis patients. Other suggested reductions in case of impaired organ function are reported in *Online Supplementary Table S2*. Of note, a recent large retrospective analysis showed no significant differences in the 5-year PFS and OS between transplant patients with normal, moderate [glomerular filtration rate (GFR) 30-60 mL/min/1.73 m^2)] and severe RF (GFR<30). For patients with moderate RF, 5-year PFS was 18% with melphalan 140 mg/m^2, and 46% with melphalan 200 mg/m^2 (*P*=0.009); 5-year OS was 67% and 68%, respectively (*P*=0.52). In patients with severe RF (GFR<30), no differences in 5-year PFS and OS were reported between groups. Relapse remained the primary cause of death in all patient subgroups.[46] In this report, 85% patients achieved dialysis independence post ASCT even though, in previous case series, rate of dialysis independence varied from 6% to 25%.[44]

Of interest, around 10% of younger patients may achieve long-lasting responses, which makes them potential candidates for renal transplantation. However, many issues, including donor availability, the immunosuppression risks and the possible disease relapse on the xenograft, need to be considered. Thus, patients with low-risk disease and with negative minimal residual disease (MRD) might be considered eligible for transplantation in the future but currently, due to limited data, no recommendations can be made.[44]

Transplant in the elderly

Aging is associated with reduced organ function and drug metabolism, with potentially increased toxicity and TRM. The potential increase in toxicity has led to the evaluation of reduced doses of melphalan conditioning (100-140 mg/m^2). Many studies, mostly retrospective, observa-

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	Regimens	Recommendation	Rationale for recommendation
Consolidation	VTD (2A) VRD (2A)	Treatment choice: - Lenalidomide use is supported by a better toxicity profile than thalidomide. - Lenalidomide should be preferred in pts with PNP. Duration of therapy: - 2 VTD cycles. - 2 VRD cycles.	Treatment choice: - Randomized comparisons showing the superiority of one of the regimens over the other are lacking. - Treatment choice should consider patient characteristics and expected toxicity of the proposed regimen. Duration of therapy: - A randomized trial showed the superiority of 2 VTD *vs.* 2 TD consolidation in terms of response rate and PFS.[7] - Preliminary data of a randomized trial showed the superiority of 2 VRD cycles *vs.* no consolidation in terms of PFS.[29]
Maintenance	Lenalidomide (1A) Thalidomide (1A) Bortezomib (1B)	Treatment choice: - Lenalidomide use is supported by a better toxicity profile than thalidomide, which favors the long-term administration. - Bortezomib use is supported by a better toxicity profile than thalidomide, and a potentially higher efficacy. - IMIDs alone could be suboptimal in high-risk patients and patients with renal failure, who may benefit from bortezomib. Duration of therapy: - Lenalidomide: at least 2 years or until tolerated. - Thalidomide: until tolerated - Bortezomib: 2 years.	Treatment choice: - Treatment choice should consider patients' characteristics and expected toxicity of the proposed regimen. - Thalidomide and lenalidomide maintenance have been evaluated in several trials.[19,30,31,34,35] - One study showed the superiority of bortezomib over thalidomide maintenance, but results are limited by the fact that patients receiving bortezomib maintenance received bortezomib induction, while patients randomized to thalidomide received VAD.[4] - Randomized comparisons showing the superiority of lenalidomide *vs.* thalidomide/bortezomib are lacking. - Subgroup analyses of randomized trials showed an uncertain benefit of IMIDs in patients with high-risk cytogenetics and renal failure, and a possible benefit with bortezomib.[30,31,4,35,37] Duration of therapy: - There are no randomized trials comparing 2 years of lenalidomide *vs.* lenalidomide until PD, but the median duration of maintenance is approx. 2 years in most of the trials. - Long-term thalidomide use is limited by the poor tolerance (PNP). - Bortezomib maintenance has been administered in clinical trials for up to 2 years.

MEL200: melphalan 200 mg/m^2; ASCT: autologous stem cell transplant; PFS: progression-free survival; OS: overall survival; VTD: bortezomib-thalidomide-dexamethasone; PAD: bortezomib-adriamycin-dexamethasone; VRD: bortezomib-lenalidomide-dexamethasone; VCD: bortezomib-cyclophosphamide-dexamethasone; VAD: vincristine-doxorubicine-dexamethasone; PNP: peripheral neuropathy; IMID: immunomodualtory drugs. TD: thalidomide-dexamethasone; PD: progressive disease; PR: partial response; VGPR: very good partial response; CR: complete response; pts: patients.

tional or registry-based, provided encouraging results with ASCT in patients over 65 years of age, with TRM less than 3-4%.[47] No differences in TRM (1%) were reported with tandem melphalan 140 mg/m^2 in patients aged 60-65 years *versus* 65-70 years in the large DSMM II trial.[48] Interestingly, a recent study found that ASCT-TRM was 0% with either melphalan 140 mg/m^2 or 200 mg/m^2, which may partly be due to improvements in supportive therapy and better patient selection.[49] A recent European Society for Blood and Marrow Transplantation (EBMT) study confirms increased utilization and safety of ASCT with improved post-transplant survival, particularly in elderly MM patients.[50]

Former analysis of non-ASCT treatment *versus* ASCT in the elderly (65-75 years) compared thalidomide-based chemotherapy (MPT) *versus* reduced-intensity (melphalan 100 mg/m^2) ASCT in patients aged 65-75 years in the IFM9906 trial. MPT significantly reduced the risk of progression (HR 0.54, P=0.0002)[51] and death (HR 0.69, P=0.027), but the lack of novel agents in the pre-ASCT induction and the low melphalan dosing could be a limitation to the study. The rate of toxic deaths was also higher (5%) during induction in the ASCT arm. Other prospective trials subsequently evaluated a sequential approach including novel agent based-induction, consolidation and maintenance. One study showed that PAD induction, followed by MEL100-ASCT, lenalidomide-prednisone consolidation and lenalidomide maintenance was highly efficacious (VGPR rate 82%, 5-year OS 63%) and feasible, in particular for patients under 70 years of age who reported a significantly lower rate of TRM in comparison with elderly patients (5% *vs*. 19%).[52] A recent report suggests that bortezomib consolidation after ASCT may determine clinical outcomes in older patients, who may have been less heavily pre-treated, as in younger patients treated with standard doses of melphalan.[53] The phase III DSMM XIII trial compared continuous Rd *versus* Rd induction followed by tandem melphalan 140 mg/m^2-ASCT and lenalidomide maintenance. Results of the planned interim analysis showed a 3-year-survival rate of 75% for all patients. A longer follow up is needed to evaluate the potential advantages and disadvantages of combining lenalidomide with high-dose melphalan-ASCT as compared with continuous RD.[54]

Recommendations: biological age rather than chronological age, PS, and organ function should be considered to better evaluate the risk-benefit ratio of transplant for each patient (1B) (Figure 2). Objective risk-assessment scores, such as the Revised-Myeloma Comorbidity Index (R-MCI) and/or the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) can be used to define the appropriate dose of chemotherapy[38-40] (1B) (Table 4).

Transplant at relapse

Upfront *versus* rescue transplant

In the past, several randomized trials confirmed the PFS benefit with early ASCT as compared with chemotherapy. In 3 randomized studies, OS was similar whether ASCT was performed early or at first relapse. Despite similar OS, early ASCT improved the average time without symptoms and reduced treatment-related toxicities in 1 trial.[55] However, at the time of these trials, most novel agents were not available. Based on the impressive results of novel agent-based treatments in the non-transplant setting, the option of delaying ASCT until first relapse was reconsidered.[2,3,56] In all the recent randomized phase III trials comparing ASCT *versus* novel agent-based therapies, patients who did not receive ASCT upfront were recommended to receive it at first relapse. A pooled analysis including the GIMEMA and the EMN441 trials showed that only 53% of patients eligible for Mel200-ASCT at diagnosis actually received ASCT at first relapse. Upfront MEL200-ASCT significantly improved not only PFS[1], but also PFS[2] (4-year PFS2 71% *vs*. 54%; HR 0.53, P<0.001) and OS (4-year OS 84% *vs*. 70%; HR 0.51, P<0.001) as compared with oral chemotherapy plus lenalidomide.[57]

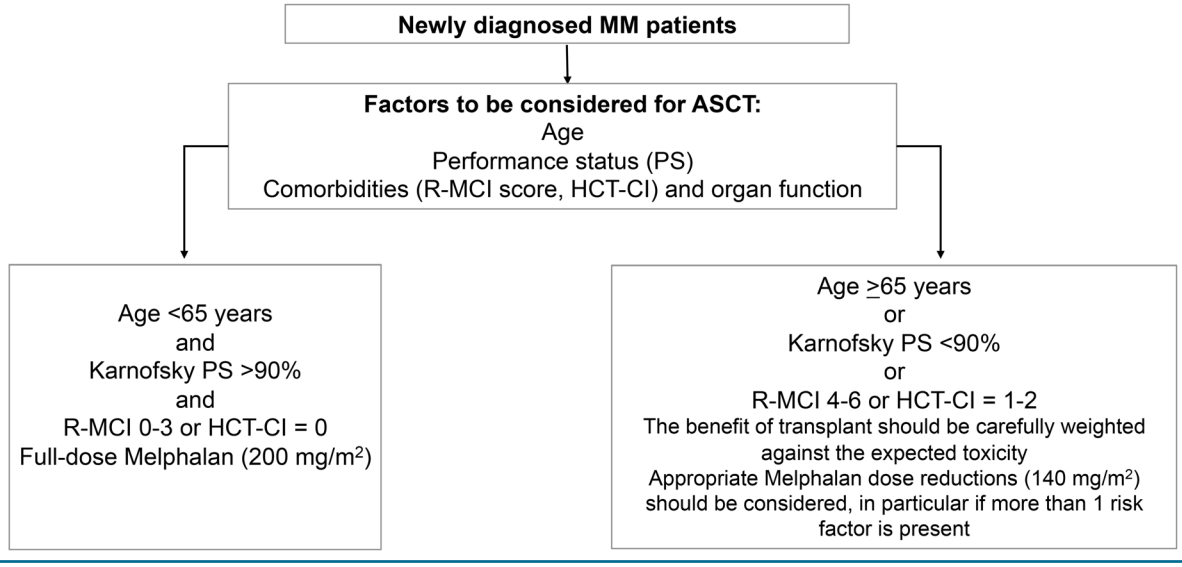

Figure 2. Factors to consider for transplantation. MM: multiple myeloma; ASCT: autologous stem cell transplant; R-MCI: Revised-Myeloma Comorbidity Index; HCT-CI: Hematopoietic Cell Transplantation - Specific Comorbidity Index.

Of note, in the IFM2009 trial, in which up to 79% of patients treated with lenalidomide plus bortezomib upfront were rescued with ASCT at relapse, no differences in OS were noticed.[10]

Transplant in patients relapsing after prior autograft

Multiple retrospective analyses showed that chemo-sensitivity and remission duration after first ASCT are the most important prognostic factors for long-term disease control after salvage ASCT.[58,59] Most reports also highlighted the impact of the number of prior therapies on outcome, suggesting that salvage ASCT should be part of the initial salvage strategies, rather than be offered to patients who have failed multiple therapy lines. A retrospective analysis on 1061 patients showed a significantly longer median survival for patients who received salvage ASCT (4 years) *versus* those who received salvage IMIDs/PIs and no ASCT (3.3 years), and those who received conventional chemotherapy (2.5 years).[60] A limitation of this analysis is a possible selection bias as patients who were treated with ASCT may have been in better clinical condition compared with those who were not. Nevertheless, the phase III multicenter randomized Myeloma X trial showed a significant advantage in time to progression (19 *vs*. 11 months; $P<0.001$) and OS (67 *vs*. 52 months; $P=0.022$) in patients relapsing after a previous ASCT, and then randomized to receive either a second ASCT or oral cyclophosphamide.[61] The limitation of these trials, however, is that, even though all patients were re-induced with PAD prior to randomization, the control arm with cyclophosphamide alone can now be considered suboptimal. A recent retrospective EBMT analysis showed that even a third ASCT at relapse may be feasible, with more than 80% of patients achieving at least a PR, although with increased non-relapse mortality. Particularly in severely cytopenic patients in whom hematologic toxicity of conventional treatment may be prohibitive, ASCT may be a rescue option. The option of a third ASCT mostly followed a previous upfront approach with tandem ASCT; some patients received a first ASCT followed by a second ASCT at second relapse and a third ASCT at subsequent relapse. The first scenario resulted in better results with a median OS of more than four years if the relapse occurred after more than three years after the upfront tandem ASCT.[62]

Recommendations: upfront ASCT remains the standard option for patients eligible for HDT (1A) (Figure 1). A second transplant at relapse should be considered after a minimal duration of remission of 18 months after a first ASCT (1B); this cut off could be extended to 24 months in the context of novel induction/maintenance.[63] A second ASCT should be offered as a first salvage therapy rather than after failing multiple lines (2B). Novel-agent based induction and consolidation-maintenance should be adopted also in the elderly (1A).

Table 4. Recommendations for transplant in elderly patients and patients with co-morbidities. All recommendations are level 2C.

Factor to consider	Cut off for full-dose melphalan	Recommendation	Rationale for recommendation
Age	<65 years	- Age should be considered not as single factor but together with Performance Status and co-morbidities (HCT-CI/MCI). - Biological rather than chronological age should be used in deciding eligibility to ASCT. - In patients between 65-70 years, with Karnofsky PS>90% and HCT-CI = 0 or R-MCI 0-3, it is reasonable to consider full dose melphalan (200 mg/m^2). - Based on biological age, melphalan dose reductions (melphalan 100-140 mg/m^2) can be appropriate.	- Retrospective data showed in recent years no increase in TRM in elderly patients, probably due to better supportive measures and patient selection. These results have been achieved not only with reduced dose of melphalan, but also with full dose.[50–53,55–57]
Performance Status	Karnofsky>90%	- In patients with Karnofsky PS <90% melphalan dose reductions (melphalan 100-140 mg/m^2) should be considered. - Full dose melphalan (200 mg/mq) could be considered in patients with poor PS related to the MM, more than to other co-morbidities.	- Retrospective analysis of registry data showed an inferior OS in patients with Karnofsky PS<90%.[41] - Poor PS can be related to MM (i.e. bone disease, and rib and vertebral fractures that affect respiratory function, suboptimal response of MM to previous therapy can lead to anemia and fatigue). Achieving optimal disease control can improve patient PS.
Co-morbidities	HCT-CI = 0 R-MCI 0-3	- In patients with HCT-CI >1 or R-MCI 4-6 melphalan dose reductions (melphalan 100-140 mg/m^2) need to be considered. Specifically, in case of impaired: a) cardiac function (LVEF 40-50%; NYHA II) b) liver function (bilirubin >1.5 ULN, AST/ALT >2.5 ULN) c) pulmonary function (DLCO/FEV1 40-80%) d) renal function (GFR <60) but, in particular, for c) and d) a careful evaluation of the cause of impaired organ function should be done, and in case of impaired renal function related to MM, the risk benefit of full-dose melphalan should be considered.	- Retrospective analysis of registry data showed an inferior OS in patients with HCT-CI 1-2 or >2, even if TRM at 1 year was equivalent in HCT-CI 0 or >2.41. - Retrospective data showed also inferior OS in patients with R-MCI >4 *vs.* 0-3.[43] - Reduced organ function can be related to MM, in particular in case of renal failure and reduced pulmonary function due to bone fractures (thoracic cage). Achieving optimal disease control can improve organ function, in particular in patients with renal failure, as shown in retrospective studies.[49]

Study ref: references in literature. HCT-CI/MCI: Hematopoietic Cell Transplantation - Specific Comorbidity Index/Myeloma Comorbidity Index; ASCT: autologous stem cell transplant; PS: Performance Score; R-MCI: Revised-Myeloma Comorbidity Index; MM: multiple myeloma; LVEF: left ventricular ejection fraction; ULN: upper limit normal; AST: aspartate transaminase; ALT: alanine transaminase; DLCO/FEVI: diffusion lung capacity for carbon monoxide/forced expiratory volume; GFR: glomerular filtration rate; TRM: treatment-related mortality; OS: overall survival.

Allotransplant

When and in which patients

A review of approximately 3000 ASCTs and allo-SCTs, performed in the USA between 2007 and 2009 showed that, overall, 47.1% of ASCTs and only 3.6% of allo-SCTs were performed in MM patients.[64] However, the number of allo-SCTs for MM in Europe steadily increased from 1990 to 2012.[65] Before new drugs became readily available almost 20 years ago, in a series of "biologically" randomized prospective studies, the concept of splitting myeloablation and graft-*versus*-myeloma (GvM) by a tandem approach with a standard ASCT followed by a non-myeloablative allo-SCT from a matched sibling or an unrelated donor was explored in NDMM (Table 5).[66-76] Results were discordant, and this was likely due to differences in study design, target population and post-transplant immunosuppression (Table 3). Moreover, only at long-term follow up were differences in clinical outcomes between arms observed.[73,74] Of note, at that time, most studies could not include new drugs either at induction or as post allo-SCT maintenance/consolidation.

Partly due to the conflicting results and to the introduction of new drugs, in recent years used allo-SCT has tended to be used as a salvage strategy at relapse, often not in the context of clinical trials. Most reports were single institution or registry analyses. Only a few comparative studies have been conducted, and these are limited by their retrospective nature and/or small patient cohorts (Table 6). In a recent EBMT report[65] on 7333 MM patients who underwent allo-SCT between 1990 and 2012, 3405 had received allo-SCT as a second line or beyond regimen; this report showed that 25% of the patient cohort who received allo-SCT more than eight months from the first ASCT survived at ten years, suggesting that cure may have been reached through a GvM mechanism in some patients. Another retrospective EBMT analysis identified patient and donor cytomegalovirus (CMV) seronegativity as the key prognostic factor for better outcome after allo-SCT in relapsed patients.[77] One prospective study[78] concluded that, with well-matched donors, the non-relapse mortality was 10%, and approximately 20% of patients achieved long-term disease-free survival. The high response rates seen after donor lymphocyte infusions (DLI) administration provide additional evidence for the GvM effect.

Taken together, these studies have showed the feasibility of allo-SCT in relapsed MM; however, given the heterogeneous patient cohorts and differences in conditioning regimens and supportive care, its real role and curative potential has not been clearly established. Both reduced-intensity and myeloablative conditionings have been successfully used and, so far, the choice should be based on center policy and patients' comorbidities.

Considering the lack of effective therapy for high-risk patients carrying del(17p), gain(1q), t(4;14) and t(14;16) abnormalities, new treatment modalities should be sought in this patient subset. The negative prognostic impact of high-risk cytogenetics appeared to be partly neutralized by GvM in two recent studies. Kröger *et al.* did not observe significant differences in PFS between patients harboring del17p13 and/or t(4;14) and those without these genetic abnormalities after a median follow up of six years (24% *vs.* 30%; *P*=0.70). Depth of remission had a remarkable impact on 5-year PFS: 17% for PR, 41% for CR, 57% for molecular CR, and 85% for sustained molecular CR.[79] A French trial also showed no differences in clinical outcomes between t(4;14) and non-t(4;14) patients. Moreover, the 3-year progression rate did not exceed 45% in patients with del(17p).[80] Taken together, these findings raise the question as to whether high-risk patients who usually experience poor outcomes and easily develop resistance to novel agents would benefit from allo-SCT earlier in the course of the disease.

Table 5. Allogeneic stem cell transplant upfront, donor *versus* no-donor prospective trials.

Study design	Patients	Median FU	PFS	OS	Study ref
High-risk patients					
BU-FLU-ATG allo-SCT	65		Median 19%	Median 34%	
Auto-SCT		4.8 years	*vs.*	*vs.*	67,68
2nd auto-SCT	219		22% (*vs.*=0.58)	48% (*P*=0.07)	
FLU-MEL allo-SCT	25		Median not reached	Median not reached	
Auto-SCT <CR		5.2 years	*vs.*	*vs.*	69
2nd auto-SCT	85		31 months (*P*=0.08)	58 months (*P*=0.9)	
2Gy TBI allo-SCT	80		Median 2.8 years	Median not reached	
Auto-SCT		7 years	*vs.*	*vs.*	66,73
2nd auto-SCT	82		2.4 years (*P*=0.005)	4.25 years (*P*=0.001)	
2Gy TBI allo-SCT	185		At 3 years 43%	At 3 years 77%	
Auto-SCT		3.3 years	*vs.*	*vs.*	70
Auto-SCT +/-maintenance	397		46% (*P*=0.67)	80% (*P*=0.191)	
2Gy TBI allo-SCT	122		At 6 years 28%	At 6 years 55%	
Auto-SCT		6.4 years	*vs.*	*vs.*	71
Maintenance T/IFN	138		22% (*P*=0.19)	55% (*P*=0.68)	
FLU-TBI allo-SCT	91		At 8 years 22%	At 8 years 49%	
Auto-SCT		8 years	*vs.*	*vs.*	72,74
+/- 2nd auto-SCT	249		12% (*P*=0.027)	36% (*P*=0.030)	

FU: follow up; PFS: progression-free survival; OS: overall survival; Study ref: references in literature; SCT: stem cell transplant; BU: busulfan; FLU: fludarabine; ATG: anti-thymocyte globuline; MEL: melphalan; TBI: total body irradiation; Gy: Gray; T: thalidomide; IFN: interferon.

Evidence of graft-*versus*-myeloma effect

Response to DLIs is often seen as proof of GvM effect. However, the prolonged post-relapse survival reported after tandem auto-allo-SCT upfront suggests an important synergy between novel agents and GvM.[73,74] In several reports, DLIs have been used as salvage treatment. Beitinjaneh *et al.*[81] reported on 23 of 162 patients with MM receiving DLI post allo-SCT for residual or relapsed disease: 22% achieved VGPR or better with a median duration of 21.8 months. Similarly, an analysis of EBMT registry data reported a response rate of 63% in 70 patients when DLI was given pre-emptively and 52% when given at relapse.[82] Ladetto *et al.* reported a gradual reduction of residual disease with longer follow up. Minimal residual disease negativity, detected by molecular methods, remained low up to three months post alloSCT, then increased up to 44% at six and 47% at 12 months.[83] Importantly, these patients did not receive any maintenance/consolidation treatment. These findings also compared favorably with the molecular analysis conducted by the same group in patients undergoing autografting and VTD consolidation.[14] Finally, although not univocal, many trials reported a favorable association between development of chronic graft-*versus*-host disease (GvHD) and prolonged PFS and OS,[84,85] again supporting a GvM effect.

Novel agents and graft-*versus*-myeloma effect

Although the introduction of 'new drugs' has made allografting a less attractive treatment option because of its toxicity, the mechanisms of action of new drugs and immune-mediated GvM effects are by no means mutually exclusive.[73,74] Given that one of the most important predictors of survival is the response at the time of transplant, and the major limitation remains disease recurrence as for all other treatments, the new anti-MM drugs may strongly improve outcomes of allo-SCT. Moreover, the concept of maintenance treatment was also recently introduced in the setting of allografting. Bortezomib has been used before allo-SCT and early after allo-SCT to eliminate residual disease and to decrease GvHD incidence and severity based on its presumed immunomodulatory potency in at least two prospective studies[86,87] on 16 and 12 high-risk MM patients, respectively. Both trials proved feasible and safe and, based on these results, the expert panel agree that larger confirmatory studies should be designed.

Lenalidomide is also of interest in the allo-SCT setting, although this should be considered with caution because of the risk of GvHD flares if given too soon after transplant. Three trials[86,88,89] demonstrated that post allo-SCT lenalidomide maintenance was feasible and contributed to further reduce MM tumor burden with PFS rates of 52% at three years;[88] 63% at three years,[89] and 60% at two years.[90] GvHD flares were observed in 28- 47% of cases.

Update on current studies

At the 2016 American Society of Hematology meeting (December 2016), reports on myeloma and allo-SCT mainly focused on interactions of new drugs and GvM effect, and three groups unanimously reported remarkable responses to new drugs used as post-allo-SCT salvage, clearly showing a synergism with GvM effect. A retro-

Table 6. Allogeneic stem cell transplant at relapse

Study design	Patients	Median FU	PFS	OS	Study ref
Tandem auto-allo-SCT at first relapse, retrospective	23	27 months	Median 36.8 months	61% at 2 years	111
Allo-SCT RIC and MAC, retrospective	149 (121 RIC)	28.5 months	15% at 5 years	21% at 5 years	112
Donor *vs.* no doner, retrospective	75 donor (68 allo-SCT) 94 no donor	19 months	Donor 51% at 2 years No donor 53% at 2 years *P*=0.32	Donor 42% at 2 years No donor 18% at 2 years *P*<0.0001	113
First relapse post auto-SCT: allo-SCT *vs.* 2nd auto-SCT, retrospective	19 allo-SCT 27 auto-SCT	57 months from diagnosis	Median 6 months Median 19 months *P*=0.56	Median 19 months Median 27 months *P*=0.255	114
First relapse: MAC + lenalidomide maintenance	33	19 months	52% at 3 years	79% at 3 years	88
RIC in relapse post auto-SCT, retrospective	413	-	Median 9.6 months	Median 24 months	77
First relapse post auto: allo-SCT *vs.* auto-SCT, retrospective	152 allo-SCT 137 auto-SCT	30 months	6% at 3 years 12% at 3 years *P*=0.038	20% at 3 years 46% at 3 years *P*<0.001	115
Allo-SCT at relapse, retrospective	639 before 2004 2766 after 2004	36 months	25% at 5 years 33% at 5 years *P*<0.0001	10% at 5 years 15% at 5 years *P*<0.0001	65
Allo-SCT at first relapse post auto-SCT, retrospective	89	48 months	28% at 5 years	57% at 5 years	116

FU: follow up; Study ref.: references in literature; auto-SCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant; BU: busulfan; FLU: fludarabine; ATG: anti-thymocyte globuline; MEL: melphalan; TBI: total body irradiation; T: thalidomide; IFN: interferon. SCT: stem cell transplant; RIC: reduced intensity conditioning; MAC: myeloablative conditioning; EBMT: European Group for Blood and Marrow Transplantation; CIBMTR: Center for International Blood and Marrow Transplant Research. *In 99 patients completing allo-SCT program there was a prolonged progression-free survival (PFS) compared to 155 completing the other arm (*P*=0.04).

spective study comparing OS after relapse from upfront auto-allo (n=178) *versus* double auto-SCT (n=404) was conducted through the registry of the Center for International Blood and Marrow Transplant Research (CIBMTR).[91] Despite a higher risk population (46% of early relapse from 2nd SCT *vs*. 26%) in the allo-SCT group, long-term reduction in post-relapse mortality (HR for death in auto-auto-SCT=1.55; *P*=0.0052) was observed. This was clearly attributable to improved response to salvage therapy due to the donor-derived immunological milieu that potentiated the immune effects of new agents. Similarly, Giaccone *et al.* showed prolonged OS from 1st relapse post tandem auto-allo-SCT compared to double auto-SCT (89.8 months *vs*. 23.5 months; *P*=0.009).[92] López-Corral *et al*. reported similar pre-transplant and post-transplant response rates and durability of response achieved with new drugs before and after allo-SCT; responses post allo-SCT were at least similar in proportion and durability to those observed in the pre-transplant setting, which is in contrast to the usual course of the disease outside the allo-SCT setting.[93] Another study reported on 18 high-risk MM patients who received upfront auto-SCT followed by RIC allo-SCT and bortezomib as maintenance, which was overall well tolerated, although 4 of 18 had asymptomatic Epstein Barr virus (EBV) reactivation. Depth of response improved after bortezomib, with 67% of patients in CR or stringent CR.[94]

Daratumumab has also demonstrated encouraging efficacy in 10 heavily pre-treated relapsed/refractory patients after allo-SCT. The safety profile was good with, in the majority of cases, non-severe adverse effects (AEs) mostly after the first infusion; 5 of 9 evaluable patients responded and all responding patients maintained their responses 7, 14, 35, 54 and 84 days after the first administration.[95] Cook *et al.* monitored immune biomarkers with the use of lenalidomide after T-cell-depleted reduced intensity conditioning (RIC)-alloSCT, showing that the agent allowed sustained quantitative and functional reconstitution of donor immune homeostasis.[96] McKiernan *et al.*[97] reported a long-term comparison in patients receiving allo-SCT as upfront consolidation (n=75) or as salvage therapy (n=43). The 10-year OS for patients who received allo-SCT as salvage was 36% *versus* 68% for the consolidation group (*P*=0.0007). Of note, having undergone 2 or more prior auto-SCTs predicted for a higher risk of mortality (*P*=0.05). Chronic GvHD was favorable, associated with a 36% improvement in OS (*P*=0.0008).

Recommendations: previous studies that did not include novel agents reported long-term molecular remissions, and possibly cure, in patient subsets. Well-designed prospective trials combining GvM and new drugs may become urgent in young high-risk/ultra high-risk patients whose treatment remains an unmet clinical need. However, there are no current data supporting an upfront allograft. A clinical indication or recommendation may also become "early relapse" after first-line treatment (including the new PI and IMIDs) which identifies patients at very poor prognosis independent of other prognostic factors (Table 7). Re-induction to obtain tumor shrinking using novel drugs as a bridge to transplant is highly recommended/mandatory in this setting.[98] Novel agent-based combinations should be considered also in association with DLI in case of relapse after allogeneic transplant.

Future developments

Treatment for MM has undergone a dramatic improvement in the past decade given the considerable advances in the understanding of the disease pathogenesis and the approval of numerous novel drugs and combinations for the disease. However, despite the development of novel agents which target not only MM cells but also the microenvironment,[99] the prognosis of patients with early relapsed/refractory MM remains poor. Thus, new therapeutic modalities are urgently needed to overcome resistance to current therapies. Several immunotherapies have recently been proposed which, among others, include monoclonal antibodies, antibody-drug conjugates, chimeric antigen receptor T-cell therapy (CAR-T cells), tumor vaccines and immune checkpoint inhibitors.[100] Preliminary results observed in patients with B-cell hematologic malignancies with infusion of T cells genetically modified to express synthetic CARs against the lineage-specific surface antigen CD19 were impressive. T cells engineered with an anti-CD19 CAR induced CR also in a patient with MM.[101] Recently, a number of other CAR-T cells have been designed to target surface antigens expressed by MM cells and include CD38,[102] CD138,[103] CD269, the B-cell maturation antigen (BCMA),[104] κ light chains,[105] CS1 (CD319)[106] and CD44v6.[107] However, despite their efficacy, CAR-T cells have raised many concerns on their short- and long-term toxicities, in particular, the development of life-threatening cytokine release syn-

Table 7. Recommendations for allografting in transplant eligible patients.

	Level of evidence	Practical considerations	Rationale for considerations
At diagnosis	-	Clinical trial in young ultra high-risk/high-risk patients.	Though results were discordant, prospective randomized studies (designed in the late '90s – early 2000s) showed long-term disease control in subsets of patients who were not treated with new drugs; the combination of new drugs and graft-*versus*-myeloma may be of benefit in patients where prognosis remains currently very poor.
At relapse	2C	Young patients with early relapse (18 months) from first-line treatment with/without high-risk features.	Regardless of prognostic features, early relapse is overall associated with poor diagnosis. Retrospective studies support the existence of a potential benefit of graft-*versus*-myeloma in this setting. The inclusion in control trials would be recommended.
Maintenance	-	Clinical trial.	Maintenance therapy is currently part of prospective trials open to accrual. post allografting. Results are eagerly awaited.

drome (CRS) and prolonged aplasia of the healthy counterparts.[108] Genetic modifications of cells belonging to the innate immune system, such as natural killer (NK) cells, are also being explored, and modification of the human NK-cell lines NKL and NK-92 with a lentiviral vector encoding for CS1 and CD138 CARs has proven to be feasible.[109] However, several steps to optimize and validate CAR-modified NK cells have to be undertaken before their wider clinical use can be considered.

Conclusions

Over the last two decades, changes in the treatment paradigm for MM patients have dramatically improved survival. Clearly, results of the most recently published trials confirm the role of ASCT in the era of novel agents, with new drugs administered both in the pre-transplant and post-transplant phases. The expert panel emphasizes that current clinical research should maintain a balance between treatment efficacy and quality of life, identify the optimal sequencing of treatment, the appropriate tools for patient selection, evaluate costs of prolonged novel-agent application *versus* transplant remission efficacy, and treatment-free intervals, and it should identify how to best induce long-term remission.[110] In the future, objective, prospective and proficiently performed fitness tools may prove to be of benefit before intensive treatment is started, especially since fitness assessments made by patients and physicians are not as objective as fitness evaluations derived from well-defined tests and scores. Future randomized studies will also need to evaluate the role of ASCT as salvage treatment in the context of the novel combinations currently available as salvage options.

The trend in survival improvement is likely to continue in the future with new classes of drugs [such as monoclonal antibodies (MoAbs)] and 2nd-generation PIs and IMIDs moving in the upfront setting. If most patients can now expect long-term disease control, the optimal definition of high-risk disease and the specific treatment for these patients remains a major challenge. Based on the available data, the opinion of the expert committee is that allotransplant in combination with novel agents might be considered in the context of clinical trials for high-risk patients who are willing to accept the TRM for a chance of a better long-term survival. Moreover, cellular therapies, that for the moment are still highly experimental, should be optimized and made more widely available and cost approved so they can be included in our treatment armamentarium.

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