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Guideline

ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Multiple Myeloma

Binod Dhakal[1], Nina Shah[2], Ankit Kansagra[3], Ambuj Kumar[4], Sagar Lonial[5], Alfred Garfall[6], Andrew Cowan[7], Bishesh Sharma Poudyal[8], Caitlin Costello[9], Francesca Gay[10], Gordon Cook[11], Hang Quach[12], Herman Einsele[13], Jeff Schriber[14], Jian Hou[15], Luciano Costa[16], Mahmoud Aljurf[17], Maria Chaudhry[18], Meral Beksac[19], Miles Prince[20], Mohamad Mohty[21], Murali Janakiram[22], Natalie Callander[23], Noa Biran[24], Pankaj Malhotra[25], Paula Rodriguez Otero[26], Philippe Moreau[27], Rafat Abonour[28], Raheel Iftikhar[29], Rebecca Silberman[30], Sham Mailankody[31], Tara Gregory[32], Yi Lin[33], Paul Carpenter[34], Mehdi Hamadani[1,*], Saad Usmani[31], Shaji Kumar[33]

[1] *Blood and Marrow Transplant and Cellular Therapy Program, Medical College of Wisconsin, Milwaukee, Wisconsin*
[2] *Division of Hematology-Oncology, University of California, San Francisco, California*
[3] *Department of Hematology and Oncology, University of Texas Southwestern Medical Center, Dallas, Texas*
[4] *Program for Comparative Effectiveness Research, University of South Florida Morsani College of Medicine, Tampa, Florida*
[5] *Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, Georgia*
[6] *Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania*
[7] *University of Washington, Seattle WA, and Fred Hutch, Seattle, Washington*
[8] *Department of Clinical Hematology and Bone Marrow Transplant, Civil Service Hospital, Kathmandu, Nepal*
[9] *UCSD/Sharp Healthcare Transplant Program, Blood & Marrow Transplant Services, Moore's Cancer Center, San-Diego, California*
[10] *Division of Hematology 1 Clinical Trial Unit, AOU CIttà della salute e della Scienza, University of Torino, Turin, Italy*
[11] *Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trial Research, University of Leeds, Leeds, United Kingdom*
[12] *University of Melbourne, St. Vincent's Hospital, Melbourne, Australia*
[13] *Universitätsklinikum Würzburg, Department of Internal Medicine II, Würzburg, Germany*
[14] *Cancer Treatment Centers of America, Phoenix, Arizona*
[15] *Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China*
[16] *Division of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, Alabama*
[17] *Oncology Center, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia*
[18] *Department of hematology/Oncology, George Washington University and Cancer Center, Washington, District of Columbia*
[19] *Department of Hematology, Ankara University, Ankara, Turkey*
[20] *Epworth Healthcare and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia*
[21] *Department of Clinical Hematology and Cellular Therapy, Saint-Antoine Hospital, AP-HP, Sorbonne University, Paris, France*
[22] *Division of Myeloma, Department of Hematology & Hematopoietic Cell Transplantation, City of Hope, California*
[23] *University of Wisconsin Carbone Cancer Center, Madison, Wisconsin*
[24] *Hackensack Meridian Health, John Theurer Cancer Center, Multiple Myeloma Division, Hackensack, New Jersey*
[25] *Department of Clinical Hematology & Medical Oncology, Postgraduate Institute of Medical Education and Research, Chandigarh, India*
[26] *Clinica Universidad de Navarra, University of Navarra, Pamplona, Spain*
[27] *Department of Hematology, University Hospital Hôtel-Dieu, Nantes, France*
[28] *Indiana University School of Medicine, Indianapolis, Indiana*
[29] *Armed Forces Bone Marrow Transplant Centre, Rawalpindi, Pakistan*
[30] *Department of Medicine, Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon*
[31] *Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New, York, New York*
[32] *Colorado Blood Cancer Institute, Sarah Cannon Cancer Network, Denver, Colorado*
[33] *Mayo Clinic, Rochester, Minnesota*
[34] *Division of Clinical Research, Fred Hutchinson Cancer Research Center and Department of Pediatrics, University of Washington, Seattle, Washington*

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A B S T R A C T

Over the past decade, therapeutic options in multiple myeloma (MM) have changed dramatically. Given the unprecedented efficacy of novel agents, the role of hematopoietic cell transplantation (HCT) in MM remains under scrutiny. Rapid advances in myeloma immunotherapy including the recent approval of chimeric antigen receptor (CAR) T-cell therapy will impact the MM therapeutic landscape. The American Society for Transplantation and

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*Corresponding author. Mehdi Hamadani, Blood and Marrow Transplant and Cellular Therapy Program, Medical College of Wisconsin, Milwaukee
E-mail address: mhamadani@mcw.edu (M. Hamadani).

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Cellular Therapy convened an expert panel to formulate clinical practice recommendations for role, timing, and sequencing of autologous (auto-HCT), allogeneic (allo-HCT) and CAR T-cell therapy for patients with newly diagnosed (NDMM) and relapsed/refractory MM (RRMM). The RAND-modified Delphi method was used to generate consensus statements. Twenty consensus statements were generated. The panel endorsed continued use of auto-HCT consolidation for patients with NDMM as a standard-of-care option, whereas in the front line allo-HCT and CAR-T were not recommended outside the setting of clinical trial. For patients not undergoing auto-HCT upfront, the panel recommended its use in first relapse. Lenalidomide as a single agent was recommended for maintenance especially for standard risk patients. In the RRMM setting, the panel recommended the use of CAR-T in patients with 4 or more prior lines of therapy. The panel encouraged allo-HCT in RRMM setting only in the context of clinical trial. The panel found RAND-modified Delphi methodology effective in providing a formal framework for developing consensus recommendations for the timing and sequence of cellular therapies for MM.

The treatment landscape of multiple myeloma (MM), a cancer of antibody-producing plasma cells, has been dramatically transformed by the introduction of several novel therapeutic agents [1,2]. For the past 20 years, high-dose therapy followed by autologous hematopoietic cell transplantation (auto-HCT) has been the standard treatment for eligible patients [3–5]. Prospective studies performed in the context of modern induction have consistently shown an improved depth of response and progression-free survival (PFS) benefit with auto-HCT [3,5-7]. In particular, the long-term follow-up of IFM 2009 trial [8] and large retrospective studies [9] have confirmed the continued benefit of auto-HCT in the modern era. The role of allogeneic (allo-) HCT despite its curative potential, remains controversial given the inconsistent benefit seen across trials when compared to auto-HCT approach [10,11]. Important recent advances in MM therapy include the benefit observed with quadruplet induction [12], the reconfirmation of continued benefit of auto-HCT [12,13] and regulatory approvals of several novel agents in relapsed or refractory (RRMM) setting including the first approval of B-cell maturation antigen (BCMA)–directed chimeric antigen T-cell therapy (CAR-T) cell therapy [14]. Furthermore, early results seen with bispecific antibodies [15] and maturing data from CAR-T cell therapy [14,16] are likely to impact the MM treatment landscape. Despite these advances, multiple questions remain: the timing of upfront auto-HCT, the role of post-HCT consolidation/maintenance, timing of CAR-T therapy, and finally the role of allo-HCT, if any, in the present context. A wide variation of clinical practice pattern exists on choosing therapeutic modalities in MM, and thus guidance on the contemporary role, optimal timing, and sequencing of cellular therapies in MM is warranted. Clinical practice recommendations addressing areas of clinical ambiguity not only can aid the treating transplant and cellular therapy physicians but also can inform MM experts' and community hematologists' practice for timely referral of appropriate patients to transplant and cell therapy programs. The American Society of Transplantation and Cellular Therapy's (ASTCT) Committee on Practice Guidelines therefore undertook this project to formulate consensus clinical practice recommendations regarding the role, timing, and sequencing of auto- and allo-HCT and CAR T-cell therapy for patients with newly diagnosed (NDMM) and relapsed MM.

METHODS

Panel composition

The development of clinical practice recommendations was approved by the ASTCT Committee on Practice Guidelines. As an initial step, a steering committee was formed comprising of 7 members, including a project coordinator, representatives of the ASTCT Committee of Practice Guidelines, and an independent methodologist with expertise in systematic reviews, meta-analysis, and the RAND-modified Delphi method. The steering committee was responsible for drafting the protocol, initial draft of consensus statements based on review of the literature and clinical practice considerations, and setting up the expert panel [17]. The aim was to put together a panel with a balanced distribution of "MM" and "cellular therapy and transplant" experts, to have broad expertise and to cover a wide spectrum of views, while keeping administrative efforts manageable as previously recommended [18,19]. The panel of experts consisted of physicians with diverse geographical representation and expertise in the field, as demonstrated by their track record of peer-reviewed publications, leadership on clinical trials relevant to the consensus project and by their involvement in national and international MM or transplant organizations. Additionally, 2 physicians representing a community-based practice were included in the panel, as previously recommended [17]. The final consensus panel consisted of 35 physicians and investigators, including members of the steering committee (N = 6), except the (nonclinical) independent methodologist, who did not vote on the recommendations.

Consensus Methodology

The RAND-modified Delphi method was used to generate consensus statements addressing the role of HCT and CAR-T cell therapies in patients with NDMM and RRMM. In the Delphi method, the participants rate the statements anonymously in at least two rounds of evaluations. In the modified version of the method, a face-to-face meeting with presentation of the results precedes the second rounds of rating [17–19]. Because of the ongoing COVID-19 pandemic, a virtual (ZOOM, San Jose, CA) platform was used in lieu of a face-to-face meeting. Details regarding the systematic step-by-step approach used in this project are illustrated in Table 1.

After the panel selection, a Baseline Demographics and Scope survey was developed to determine the scope of the project. Participants were invited to submit their suggestions regarding the scope of the consensus project and provide input about the clinical issues relevant to clinical practice (details in Supplemental Appendix). After finalization of the scope of the consensus project, the steering committee formulated preliminary consensus statements based on expert opinion for first round of voting (details in Supplemental Appendix; Tables).

The First Voting Survey included 20 consensus statements. Panel members rated each statement electronically. The steering committee methodologist analyzed and summarized the results, while keeping the individual ratings anonymous. A specific statement was defined as having achieved formal consensus, if ≥75% of the panel members voted to agree with the proposed statement. The results of First Voting Survey, along with the statements not reaching the threshold of consensus were presented at the virtual teleconference of the panel members. Consensus statements that met the predefined criteria for formal consensus were recommended for approval. Statements that failed to achieve predefined criteria for consensus were discussed during the virtual meeting and based on the discussions the statements were modified for revoting. The Second Voting Survey was sent to all the panel members for rating of the reformulated statements.

All surveys were administered online using www.Qualitrics.com (Qualtrics LLC, Provo, UT), and results were reviewed and collated independently by the methodological expert. At each step of the process, the electronic survey also allowed the participating members to provide written feedback and comments about each statement. Collated results were shared via email with the consensus panel members in real time after each step was completed to ensure transparency of the process. The final consensus statements were graded based on the strength and level of supporting evidence, according to the Agency of Healthcare Research and Quality grading [20].

RESULTS

Member participation

Table 2 describes the baseline characteristics of consensus panel members. The panel included transplant and cell therapy physicians and non-cell therapy physicians from both teaching and community-based practitioners. The panelists'

Table 1
Steps Involved in RAND-Modified Delphi Methodology

Step	Representation*	Description	Method
Concept development and approval	Steering Committee	Approved and endorsed by ASTCT CoPG,	Teleconference
Protocol development	Steering Committee	Protocol development according to the modified Delphi method Identify and invite potential members of Consensus Panel including academic experts plus community practice representatives	Email & electronic communication
BD&S survey	Consensus Panel	(i) Obtain demographic details of the participants and (ii) Determine the clinical scope of the project ratings along with written feedback, March 2021	Online survey (100% panel response rate)
Review of results of BD&S	Steering Committee	(i) Results complied by steering committee and shared with the Consensus Panel	Email
	Consensus Panel	(ii) questions pertaining to cellular therapy (including auto-HCT, allo-HCT and CAR T-cell) and practice scenarios generated for First Voting Survey (SC)	Email
First Voting Survey	Consensus Panel	(i) Rate clinical practice recommendation statements on a Likert score, May 2021	Online survey (100% panel response rate)
Review of results of First Voting Survey	Steering Committee	(i) Results complied and reviewed by the Steering Committee	Email
	Consensus Panel	(ii) Results shared with the Consensus Panel, September 2021	Email
Discussion and revision of recommendations	Consensus Panel	(i) Presentation of results of First Voting Survey by Steering Committee (ii) Group discussion on the ranking of clinical practice recommendation statements and modification of statements not achieving consensus threshold, October 2021	Virtual (video) conference†
Second Voting Survey	Consensus Panel	Revised clinical practice recommendation statements sent to Consensus Panel for voting, November	Online survey (100% panel response rate)
Final evaluation of consensus and manuscript	Steering Committee/ Consensus Panel	Ratings are accepted if consensus is reached based on predefined threshold. If no consensus reached, statements were noted as "consensus could not be reached." Results compiled as manuscript and first draft written by S.C. and shared with Consensus Panel for review and editing	Email

ASTCT CoPG indicates American Society of Transplantation and Cellular Therapy Committee on Practice Guidelines; allo, allogeneic.

* Steering committee comprised of 6 members including 3 project leaders/coordinators, 1 statistical expert (independent non-voting member). Consensus Panel (n = 35) comprised of the 6 Steering Committee members (except the statistical expert) plus 27 academic experts and 2 community representative.

† Attended by 18 members (persons provided their recommendation via review of survey questions, review of video recording of the meeting and were not present during the meeting) of the Consensus Panel via teleconference held on October 13, 2021.

participation and response rates were excellent with 100% (N = 35) participation noted for the Baseline Demographics and Scope, *First Voting and Second Voting Surveys*. The virtual meeting was attended by 20 members including 15 members who provided the absentee vote following the meeting, after reviewing the video recordings of the teleconference.

First Voting Survey

The First Voting Survey consisted of 20 statements specific to the role of auto-HCT in NDMM patients (9 statements, 1 statement for plasma cell leukemia) and RRMM patients (3 statements), allo-HCT for NDMM patients (2 statements) and RRMM patients (1 statement), CAR-T cell therapy for RRMM patients (4 statements). Only 2 out of 20 statements did not achieve consensus by predefined criteria (Supplementary Table S1). The results of the *First Voting Survey* were electronically shared with all panel members. The 2 statements not achieving consensus (<75% agreement) during the prior voting process were reviewed by the steering committee and presented to the panel members at the virtual video conference. The ensuing discussion resulted in revising the 2 statements. The statements were modified for the *Second Voting Survey*. Supplementary Table S2 shows the outcomes of the virtual video conference.

Second Voting Survey

All statements included in the *Second Voting Survey* met the prespecified criteria for consensus (Supplementary Table S2). The final consensus recommendations on auto-HCT, allo-HCT, and CAR-T cell therapy for NDMM and RRMM consisting of 20 statements are shown in Tables 3 and 4.

Table 2
Demographic Information of Members of Consensus Panel

Member Demographics	N = 35
Gender	
Male	23 (66%)
Female	12 (34%)
Setting of practice	
Academic	31 (89%)
Community	4 (11%)
Years of clinical experience in MM or HCT practice	
>10	21 (60%)
6-10	11 (31%)
≤5	3 (9%)
Description of clinical practice	
Non-transplant myeloma practice	1 (3%)
Primarily HCT or cell therapy practice	2 (6%)
Combined myeloma and HCT/cell therapy practice	32 (91%)
Region of practice	
North America	21 (60%)
Europe	6 (17%)
Asia	6 (17%)
Australia	2 (6%)
Estimated number of NDMM patients seen by individual member annually	
>76	20 (57%)
51-75	4 (11%)
26-50	8 (23%)
≤25	3 (9%)
Estimated number of MM patients seen by individual member annually	
>40	33 (94%)
31-40	0
21-30	0
≤20	2 (6%)
Estimated annual transplant volume at respective programs (number of autologous plus allogeneic HCT)	
>300	10 (29%)
201-300	8 (23%)
101-200	7 (20%)
51-100	5 (14%)
≤50	4 (11%)
Unsure	1 (3%)
Estimated annual autologous HCT performed at respective centers	
>250	4 (11%)
201-250	1 (3%)
151-200	8 (23%)
101-150	10 (29%)
51-100	5 (14%)
≤50	7 (20%)
Estimated annual autologous HCT performed at respective centers for myeloma	
>200	4 (11%)
151-200	1 (3%)
101-150	9 (26%)
51-100	11 (31%)
26-50	6 (17%)
≤25	4 (11%)
Estimated annual CAR T-cell therapies performed at respective centers for myeloma (on or off clinical trial)	
>20	8 (23%)
16-20	4 (11%)
11-15	8 (23%)
≤10	15 (43%)
Estimated allogeneic HCT performed at respective centers for myeloma (on or off clinical trial)	
>20	0
16-20	1 (3%)
11-15	1 (3%)
≤10	33 (94%)

(*continued*)

Table 2 (*Continued*)

DISCUSSION

Formulation of expert recommendations using established approaches, such as the RAND-modified Delphi method provides, a formal, reproducible, and systematic process [17,21]. Using the same method, in this project, a broadly representative panel of myeloma, transplant, and cellular therapy experts with diverse practice experience and geographical representation, endorsed by ASTCT Committee on Practice Guidelines, was formed to generate clinical practice recommendations on the role of auto-HCT, allo-HCT, and CAR-T cell therapy for NDMM and RRMM. Given the rapidly expanding repertoire of therapeutic options in MM since the last publication of ASTCT guidelines in MM (2015), this undertaking was conceived to address gaps in literature and provide clinical guidance. Here we reported 20 practice recommendations addressing the role of auto-HCT, allo-HCT, and CAR-T cell therapy in MM.

Treatment recommendations for Newly Diagnosed Multiple Myeloma

Thirteen consensus statements were generated for transplantation and CAR-T cell treatments in the front-line setting for NDMM including one statement for plasma cell leukemia (Table 3).

Upfront auto-HCT

Before the advent of novel therapy, several prospective studies had demonstrated PFS benefit of auto-HCT. Some studies have also demonstrated overall survival (OS) with auto-HCT when compared to standard conventional therapy [22–25]. Despite the unprecedented efficacy associated with novel agents, a number of trials have re-evaluated the role of auto-HCT with modern induction and have shown a consistent PFS benefit [3,5-7,26], and OS benefit in 2 studies [5,7]. Considering the evidence from these trials, the panel recommended early auto-HCT as a consolidation therapy in eligible, NDMM patients after 4 to 6 cycles of induction therapy (Table 3). Since the publication of 2015 guidelines, the question of early (upfront) versus delayed (at first relapse) transplant was reevaluated in the IFM 2009 study in the context of modern triplet induction therapy [3]. Although the OS was similar between the 2 arms at a median follow-up of 44 months and at 93 months, early ASCT was associated with higher minimal residual disease (MRD) negativity rates and superior PFS benefit [3,8]. The consensus panel does acknowledge that, in select patients, delayed ASCT is a reasonable option given the similar OS benefit between the 2 approaches. However, the fact that only 79% of patents at first relapse were able to proceed to

Table 3
Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T-Cell Treatments in the Front-Line Setting for MM

Consensus Statements	Grading of Recommendations*	Percentage of Panelists in Agreement
1. The panel recommends early autologous transplantation as a consolidation therapy in eligible, newly diagnosed myeloma patients after 4-6 cycles of induction	A	94.2%
2. The panel recommends mobilization and storage of peripheral blood stem cells in newly diagnosed myeloma patients not undergoing autologous transplantation after first line of therapy for future use as a treatment at first relapse	B	100%
3. The panel does not recommend using MRD testing to guide use of autologous transplantation after induction therapy in myeloma, outside the setting of a clinical trial	C	94.2%
4. The panel does not recommend age as the only selection factor when considering autologous transplantation in myeloma	B	100%
5. In the absence of clinical trial, the panel recommends early autologous transplantation in myeloma patients with high-risk cytogenetics [t (4;14); t (14;16); t (14;20)], 1p deletion, 1q gain/amplification and 17p deletion	B	97.1%
6. The panel does not recommend tandem autologous transplantation in standard risk myeloma patients after induction, outside in the setting of a clinical trial	B	94.2%
7. The panel does not recommend routine multiagent consolidation therapy in patients in very good partial response or better after autologous transplantation outside the setting of clinical trial	B	85.7%
8. The panel does not recommend consolidation with CAR-T cell therapy in patients after first line therapy outside the setting of clinical trial	C	100%
9. The panel recommends lenalidomide maintenance after autologous transplantation in standard risk patients unless contraindicated	A	94.2%
10. The panel recommends bortezomib and lenalidomide maintenance or clinical trial after autologous transplantation in high-risk patients	B	82.8%
11. The panel does not recommend allogeneic transplantation except in the context of clinical trial	C	91.4%
12. The panel does not recommend tandem autologous-allogeneic transplantation except in the context of clinical trial	C	88.5%
13. The panel recommends dose adjusted melphalan in patients with renal impairment including on dialysis, >70 years and KPS<80	B	82.8%
14. The panel recommends treating primary plasma cell leukemia similar to high-risk myeloma in the absence of clinical trial	B	97.1%

KPS indicates Karnofsky performance status.

* Agency of Healthcare Research and Quality grading of recommendations based on level of evidence: A = There is good research-based evidence to support the recommendation; B = There is fair research-based evidence to support the recommendation; C = The recommendation is based on expert opinion and panel consensus; X = There is evidence of harm from this intervention.

delayed ASCT in the IFM study largely because of disease refractoriness, it is important to have a shared discussion between the oncologists and the patients on delayed auto-HCT approach. Furthermore, the continued improvement in PFS with frontline approaches may delay the first relapse and potential transplant such that it may no longer be a consideration due to age and other comorbidities. With the emergence of MRD as an important prognostic marker for both PFS and OS in MM [27,28], future randomized studies will determine whether the MRD status can be used to decide the timing of ASCT for both standard and high risks and define its role more definitely in the context of anti-CD38 antibodies

Table 4
Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T-Cell Treatments for RRMM

Consensus Statements	Grading of Recommendations*	Percentage of Panelists in Agreement
1. The panel recommends autologous transplantation in first relapse in patients who have not received transplant as a first-line therapy	A	94.2%
2. The panel recommends consideration of autologous transplantation in patients with primary refractory disease	C	85.7%
3. The panel recommends salvage second autologous transplantation in patients who were in remission for (at least) 36 months with maintenance and 18 months in the absence of maintenance	B	85.7%
4. The panel recommends CAR-T cell therapy after 4 or more prior lines of therapy	A	85.7%
5. The panel recommends clinical trial, if possible after CAR failures	B	97.1%
6. The panel encourages allogeneic transplantation in relapsed and/or refractory setting only in the context of clinical trial	B	77.1%

* Agency of Healthcare Research and Quality grading of recommendations based on level of evidence: A = There is good research-based evidence to support the recommendation; B = There is fair research-based evidence to support the recommendation; C = The recommendation is based on expert opinion and panel consensus; X = There is evidence of harm from this intervention.

therapies upfront. However, for the time being, the panel did not recommend using MRD as a guide to decide the timing of auto-HCT outside clinical trial setting (Table 3). As an undetectable MRD has been shown to overcome the poor prognosis in high-risk MM [27,29], and upfront auto-HCT has been shown to confer a higher rate of MRD negativity, as well as sustained MRD negativity in recent trials [6], the panel recommends early auto-HCT in patients with high-risk cytogenetics after initial induction (Table 3). Regardless of the timing of the transplantation, the panel recommends mobilization and storage of peripheral blood stem cells for HCT eligible patients (Table 3). None of the pivotal, paradigm-defining auto-HCT trials have included patients ≥70 years of age and randomized studies comparing auto-HCT versus conventional chemotherapy are lacking in this age group [3,7]. However, multiple retrospective studies have described the feasibility and comparable safety and efficacy profile of auto-HCT to younger patients [30,31]. The panel recommends against using age as an only selection criterion for auto-HCT (Table 3), and additional consideration of performance status and frailty index should be incorporated when deciding on eligibility for auto-HCT. In patients with renal impairment (including in dialysis), Karnofsky performance status <80 and in those >70 years of age or determined to be less than fit the panel recommends consideration of dose adjusted melphalan (Table 3). The dosage of melphalan conditioning is an important decision point, and studies have shown the safety of melphalan (200 mg/m^2) in patients with renal impairment and more than 70 years of age [31,32]; thus additional consideration of Karnofsky performance status, frailty, and clinical judgement are warranted when adjusting melphalan dose [33].

Post- auto-HCT (tandem auto-HCT/consolidation)

The role of the post-HCT approach, particularly in the role of preplanned tandem auto-HCT, continues to remain an area of debate in the era of novel agents. However, for patients with standard-risk cytogenetics, the panel did not recommend the tandem auto-HCT in patients with standard risk cytogenetics based on the results of 2 large, randomized studies that showed no benefit of tandem auto-HCT in patients with standard risk cytogenetics (Table 3) [26,34].The magnitude of the benefit of tandem auto-HCT was higher in patients with high-risk cytogenetics in EMN02/HO95 trial [26], whereas no such benefit was observed in the STaMINA trial [34]. Given these conflicting results and with the emergence of quadruplet induction with CD38 antibodies, a prospective trial would be needed to understand the role of tandem auto-HCT in abrogating high-risk cytogenetics. Another post-HCT intervention, consolidation with multiagent therapies has been shown to improve the responses; however, only a few randomized studies have addressed this question [26,35-37]. In the STaMINA trials 4 cycles of VRD (bortezomib, lenalidomide, dexamethasone) consolidation did not improve PFS when compared to tandem auto-HCT or no consolidation; whereas EMN02/HO95 trial did show that VRD consolidation (all patients lenalidomide naïve before consolidation) did improve PFS and quality of responses. Several recent trials in transplant-eligible NDMM used standard consolidation [38,39] but to what extent consolidation has contributed to the outcome of these trials is unknown. The panel did not recommend routine multiagent consolidation therapy in patients with very good partial response or better after auto-HCT outside the setting of clinical trial (Table 3). Several trials are investigating the role of CAR-T therapy as either upfront or consolidative strategies after auto-HCT (NCT05032820; NCT04923893), and, hence, currently the panel does not recommend consolidative CAR-T therapy outside the setting of clinical trial (Table 3).

Post-auto-HCT (Maintenance)

Lenalidomide maintenance is considered a standard post auto-HCT given the remarkable improvement in PFS in several large phase III randomized studies [7,40-42]. These individual trials were not powered to demonstrate OS benefit; however, a patient level metanalysis did demonstrate the improvement in OS with lenalidomide maintenance [43]. The benefit of lenalidomide maintenance was observed in all sub-groups except in those with International Staging System III or those with high-risk cytogenetics [43]. For standard risk patients, the panel recommends lenalidomide maintenance after auto-HCT (Table 3). The panel also acknowledges the fact that since the ideal duration of lenalidomide maintenance is lacking and being investigated in clinical trials, considerations of cost, toxicities, and monitoring for therapy-related second malignancies should be included in the discussion in the context of indefinite maintenance. For patients with high-risk cytogenetics, the panel recommends clinical trial or consideration of bortezomib and lenalidomide maintenance (Table 3). The safety and efficacy of proteasome inhibitor and immunomodulator (ImiD) maintenance in high-risk cytogenetics has been demonstrated in several studies [6,9,44,45] including a recently published randomized controlled trial [44], however maintenance with ImiD/proteasome inhibitor combination has not been compared in a randomized, controlled trial to maintenance with ImiD monotherapy. This heterogenous patient population, however, is underrepresented in nearly all clinical trials, and high-quality evidence in this patient population is lacking, underscoring the need for innovative clinical trials in high-risk enriched cohorts.

Upfront allo-HCT (including tandem auto-allo HCT)

The role of allo-HCT remains controversial and poorly defined in MM despite it being a potentially curative option because of tumor-free graft and graft-versus-myeloma effects [46,47]. The higher rates of non-relapse mortality (NRM) associated with traditional myeloablative conditioning [48] has led to the emergence of reduced intensity conditioning regimen that is performed after cytoreduction with auto-HCT. Several trials have used the biologic assignment (assignment to allo-HCT based on the availability of HLA-matched sibling donor) of MM patients to upfront tandem auto-HCT versus reduced intensity allo-HCT after auto-HCT [49–52]. Two trials with longest follow-up [50,53] did show PFS and OS benefit with allo-HCT, but a consistent benefit could not be observed across all studies. Meta-analysis of the published studies showed the potential benefit of allo-HCT in terms of response and survival are offset by the high rates of treatment-related mortality [11,54]. Given this, the panel does not recommend allo-HCT (upfront/tandem after auto) in MM except in the context of clinical trial in select young high risk MM patients who could benefit from this modality (Table 3). Of note, the trial exploring the role of ixazomib maintenance after allo-HCT in high-risk MM (BTM CTN 1302) was prematurely closed after enrolling 57 patients (of 110 planned patients). The study showed 24-month PFS and OS of 52% and 85%, respectively, with TRM of 11% among all allo-HCT recipients [55].

Primary plasma cell leukemia

The prognosis of patients with primary plasma cell leukemia (PCL) remains poor despite the availability of newer and rapidly effective plasma cell directed therapies [56]. Large

scale randomized studies reporting the outcomes of transplant in PCL are lacking; however, 2 retrospective studies from CIBMTR showed no significant benefit of allo-HCT compared to auto-HCT [56,57]. Currently, the panel recommends treating patients with PCL similar to high-risk MM, while acknowledging the need for novel clinical trials using combined immune and nonimmune approaches in patients with PCL (Table 3).

Recommendations in the relapsed or refractory setting

The treatment landscape of RRMM is constantly evolving with the availability of new drugs and combinations, thus broadening the options and giving way to a more individualized approach [58].

Auto-HCT for relapsed disease

The contemporary utility and clinical benefits of transplant-based approach in this patient population is continuously being interrogated. However, even in the context of modern induction, the evidence suggests the benefit of auto-HCT at first relapse in patients randomized to a non-transplant-based approach [3,5-7]. The rates of auto-HCT at first relapse vary across these studies, but in a study specifically designed as an early versus delayed transplant study by IFM, 79% patients received transplant at first relapse [3]. In the long-term follow-up of IFM 2009 study, the survival benefit was similar between the early versus delayed transplant group and confirms the benefit of auto-HCT in patients at first relapse as well [8]. The panel thus recommends auto-HCT at first relapse in patients who did not receive early auto-HCT as a part of first-line therapy (Table 4).

Auto-HCT for primary refractory disease

The management of patients with primary refractory disease (<partial response to induction) is not well established in the context of triplet or quadruplet induction as the proportion of patients not responding to these highly effective regimens is low. Data before the novel agents, limited to retrospective studies, suggested that patients with refractory disease can benefit from auto-HCT [59–63], although that may not be the case with actively progressing disease [61]. Retrospective analysis suggests that additional "salvage" therapy to improve depth of response pretransplantation in patients with <partial response does not affect outcomes [64]. Intensification of treatment in patients with sub-optimal response to induction was shown to benefit PFS but not OS in a prospective study [65]. Hence, the panel recommends consideration of auto-HCT in patients with primary refractory disease (Table 4). Patients with progressive disease to modern induction therapy may represent a biologically aggressive disease that may benefit from clinical trials or alternative induction regimens before auto-HCT.

Salvage auto-HCT

Because choosing therapy in the RRMM space is becoming increasingly complex [58], the specific patient population that would benefit from salvage second auto-HCT (AHCT2) is not clearly defined. The role of AHCT2 is derived mainly from retrospective studies [66–68], and 2 prospective studies showed that AHCT2, when compared to standard of care options, was associated with superior PFS and OS [69–71]. In terms of timing, the duration of remission of first auto-HCT has consistently been predictive of PFS after AHCT2 in these studies. The panel recommends consideration of AHCT2 in patients who have remission of at least 36 months after the first transplant with maintenance and 18 months in absence of maintenance (Table 4). Given the lack of randomized data of comparing AHCT2 to more contemporary regimens, and with the emergence of CAR-T and BsAs in this space, the role of AHCT2 may decline in coming years. However, in situations with limited access to novel combinations, AHCT2 can serve as a cost-effective alternative and could be considered in the setting. In particular, AHCT2 should be a consideration as a form of bridging therapy for patients with rapidly progressive myeloma and severe cytopenias and who may stabilize sufficiently to go on to other interventions.

CAR-T in RRMM

CAR-T targeting BCMA has emerged as the most promising immune approach against MM with unprecedented results in heavily treated patients [14,16]. The Food and Drug Administration has approved a BCMA CAR-T product, idecabtagene vicleucel, for MM that has failed four or more prior lines of therapy based on the results of a pivotal study (KarMMa). This study demonstrated an overall response rate of 73% and a median PFS of 8.8 months in patients with a median 6 prior lines of treatment [14]. Another BCMA CAR-T product, ciltacabtagene autoleucel has been recently approved by the Food and Drug Administration and shows a response rate of 97% with a median PFS not reached in heavily treated patients (CARTITUDE-1) [16]. The panel recommends CAR-T cell therapy as a treatment option for patients who have received 4 or more prior lines of treatment (Table 4). Several studies are underway investigating the role of CAR-T in earlier lines of treatment (NCT 0418127; NCT 03651128) that will help define the role of CAR-T therapy before 4 lines of therapy. In patients whose MM relapse after CAR-T, the panel recommends consideration of clinical trial given the limited approved treatment options available (Table 4).

Allo-HCT in RRMM

The role of allo-HCT in relapsed/refractory setting is less well defined as studies are limited to retrospective studies [72–74] and one prospective study [75]. The conclusion from these studies is that the allo-HCT has lower relapse rates in the salvage setting; however, the survival when compared to other modalities (particularly to AHCT2) was comparable or inferior, likely because of higher NRM after allo-HCT. With the emergence of other highly effective therapies in this setting, the role of allo-HCT remains unclear. For patients with RRMM, the panel encourages allo-HCT consideration only in the context of a clinical trial (Table 4). For younger patients with high-risk disease and early relapse and in the absence of clinical trial, this modality could be of benefit, but the panel acknowledges limited data supporting this practice.

CONCLUSION

In clinical situations where data from prospective studies are rapidly evolving, or in situations where therapeutic advances make patient populations included in published trials less relevant to contemporary clinical practice, formal consensus recommendations can be an invaluable resource in informing clinical decision making [76]. Expert opinions and recommendations in the form of review articles and treatment guidelines, while useful, lack methodological clarity and may be subject to bias. Formulation of expert recommendations using established approaches, such as RAND-modified Delphi method [17], provides a formal, reproducible, and systematic process.

The therapeutic landscape of MM is constantly changing with the emergence of promising cellular immunotherapies. The exact timing and sequencing of therapies like CAR-T in the

context of stem cell transplantation and other therapies is not yet established. However, because several clinical trials are evaluating the role of CAR-T in earlier lines, we envision that cellular therapies will be used earlier in the treatment course of MM in the future. We hope these clinical practice recommendations will serve as a tool when managing patients with both NDMM and RRMM.

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SUPPLEMENTARY MATERIALS

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