Transplantation and Cellular Therapy 27 (2021) 720–728

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Guideline

American Society of Transplantation and Cellular Therapy, Center of International Blood and Marrow Transplant Research, and European Society for Blood and Marrow Transplantation Clinical Practice Recommendations for Transplantation and Cellular Therapies in Mantle Cell Lymphoma

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Financial disclosure: See Acknowledgments on page 726.
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** This article is co-published in the journals Bone Marrow Transplantation and Transplantation and Cellular Therapy https://doi.org/10.1038/s41409021-01288-9 or https://doi.org/10.1016/j.jtct.2021.03.001

https://doi.org/10.1016/j.jtct.2021.03.001

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Article history:
Received 1 March 2021
Accepted 1 March 2021

Key Words:
Mantle cell lymphoma
Autologous transplantation
Allogeneic transplantation
Cellular therapy
CAR T cell
Consensus

A B S T R A C T

Autologous (auto-) and allogeneic (allo-) hematopoietic cell transplantation (HCT) are accepted treatment modalities in contemporary treatment algorithms for mantle cell lymphoma (MCL). Chimeric antigen receptor (CAR) T cell therapy recently received approval for MCL; however, its exact place and sequence in relation to HCT remain unclear. The American Society of Transplantation and Cellular Therapy, Center of International Blood and Marrow Transplant Research, and the European Society for Blood and Marrow Transplantation jointly convened an expert panel to formulate consensus recommendations for role, timing, and sequencing of auto-HCT, allo-HCT, and CAR T cell therapy for patients with newly diagnosed and relapsed/refractory (R/R) MCL. The RAND-modified Delphi method was used to generate consensus statements. Seventeen consensus statements were generated, with a few key statements as follows: in the first line setting, auto-HCT consolidation represents standard of care in eligible patients, whereas there is no clear role of allo-HCT or CAR T cell therapy outside of clinical trials. In the R/R setting, the preferential option is CAR T cell therapy, especially in patients with MCL failing or intolerant to at least one Bruton's tyrosine kinase inhibitor, while allo-HCT is recommended if CAR T cell therapy fails or is infeasible. Several recommendations were based on expert opinion, where the panel developed consensus statements for important real-world clinical scenarios to guide clinical practice. In the absence of contemporary evidence-based data, 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 MCL.

INTRODUCTION

Mantle cell lymphoma (MCL) is a B cell lymphoma that displays significant clinical and molecular heterogeneity [1]. In most cases, it follows an aggressive clinical course; however, a subset of patients can have indolent disease [2]. Similarly, the management of MCL varies greatly in clinical practice in the United States and worldwide [3,4]. This variability applies to both the frontline and relapsed/refractory (R/R) settings [5]. Pertaining to frontline therapy, some advocate induction chemoimmunotherapy followed by high-dose therapy (HDT) and then autologous hematopoietic cell transplantation (auto-HCT) consolidation, whereas others prefer combination chemoimmunotherapy regimens alone without subsequent HDT consolidation. Treatment strategies are even more discordant in the presence of high-risk features, such as TP53 alterations and a high proliferation index [6-8]. In the R/R setting, there is also variability in practice, which is made even more complex by the advent of newer treatment modalities, such as Bruton's tyrosine kinase (BTK) inhibitors [9], lenalidomide, and chimeric antigen receptor (CAR) T cell therapy [10].

Auto-HCT consolidation has been used for over 20 years in the management of MCL patients [11,12], and is associated with improved progression-free survival (PFS) and potentially overall survival (OS) following conventional chemoimmunotherapy in both prospective and retrospective studies [11-14]. However, it is less clear whether auto-HCT has a benefit following more intensive chemoimmunotherapy, such as rituximab-hyper-CVAD/cytarabine/methotrexate [15]. Allo-HCT is a potentially curative modality for MCL [12,16]; however, with a 1-year treatment-related mortality ranging from 10% to 20% and the additional risk of chronic graft-versus-host disease (GVHD), allo-HCT generally has been reserved for the R/R setting [3,17].

There have been recent important advances in MCL therapy, including the demonstration of a survival benefit with rituximab maintenance following auto-HCT [18], the advent of first- and second-generation BTK inhibitors for R/R MCL [19], and the recent approval of the first commercially available CAR T cell therapy (brexucabtagene autoleucel) for MCL [10]. For brexucabtagene autoleucel, the reported objective and complete response rates were 93% and 67%, respectively, with durable remission seen in >50% of patients. Importantly, although this registration trial exclusively studied MCL patients who had been previously treated with BTK inhibitor therapy, US regulatory approval provides an indication for all patients with R/R MCL regardless of previous exposure to a BTK inhibitor.

Given these novel treatment options, guidance on the contemporary role, optimal timing, and sequencing of cellular therapies in MCL is warranted. Clinical practice recommendations addressing areas of clinical ambiguity not only can aid the treating transplantation and cellular therapy physicians, but also can inform lymphoma experts' and community hematologists' practice for referring these patients to transplantation and cellular therapy programs. The American Society of Transplantation and Cellular Therapy (ASTCT), Center of International Blood and Marrow Transplant Research (CIBMTR), and European Society for Blood and Marrow Transplantation (EBMT) undertook a joint project to formulate consensus recommendations regarding the role, timing, and sequencing of auto-HCT, allo-HCT, and CAR T cell therapy for patients with newly diagnosed and R/R MCL.

METHODS

Panel Composition

The development of practice recommendations was approved by the ASTCT, CIBMTR, and EBMT, the 3 leading international organizations in the field of HCT and cellular therapies. As an initial step, a Steering Committee was formed comprising 6 members including 2 project leaders/coordinators; 1 representative each from the ASTCT, EBMT, and CIBMTR; 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, producing the initial draft of the consensus statements based on clinical expertise and clinical practice considerations, and setting up the expert panel [20]. The aim was to put together an expert panel with a balanced distribution of MCL 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 [21,22]. The panel of experts consisted of physicians with a diverse

Table 1
Steps Involved in the RAND-modified Delphi Methodology

Step	Representation	Description	Method
Concept development and approval	Steering Committee	Approved and endorsed by the CIBMTR LYWC in February 2020, the EBMT LWP in March 2020, and the ASTCT CoPG in March 2020	In-person meeting/ teleconference
Protocol development	Steering Committee	Protocol development according to the modified Delphi method; identify and invite potential members of the Consensus Panel, including academic experts plus a community practice representative	Email and electronic communication
BD&S survey	Consensus Panel	Obtain demographic details of the participants and determine the clinical scope of the project, with ratings along with written feedback, June 2020*	Online survey (100% panel response rate)
Review of results of BD&S survey	Steering Committee	Results complied by the Steering Committee and shared with the Consensus Panel	Email
	Consensus Panel	questions pertaining to sequence of cellular therapy (including auto HCT, allo HCT and CAR T cell) and practice scenarios generated for the first voting survey (Steering Committee)	Email
First voting survey	Consensus Panel	Rate clinical practice recommendation statements on a Likert scale, August 2020	Online survey (100% panel response rate)
Review of results of first voting survey	Steering Committee	Results complied and reviewed by the Steering Committee	Email
	Consensus Panel	Results shared with the Consensus Panel in September 2020	Email
Discussion and revision of recommendations	Consensus Panel	Presentation of results of the first voting survey by the Steering Committee	Virtual (video) conference†
		Group discussion on the ranking of clinical practice recommendation statements and modification of statements not achieving consensus threshold, October 2020	
Second voting survey	Consensus Panel	Revised clinical practice recommendation statements sent to the Consensus Panel for voting, November 2020	Online survey (100% panel response rate)
Final evaluation of consensus and manuscript	Steering Committee/ Consensus Panel	Ratings are accepted if a consensus is reached based on predefined threshold. If a consensus is not reached, statements were noted as "consensus could not be reached." Results compiled in a first-draft manuscript written by the Steering Committee and shared with the Consensus Panel for review and editing.	Email

CIBMTR LYWC indicates Center for International Blood and Marrow Transplant Registry Lymphoma Working Committee; EBMT LWP, European Group of Blood and Marrow Transplantation Lymphoma Working Party; ASTCT CoPG , American Society of Transplantation and Cellular Therapy Committee on Practice Guidelines.

* The Steering Committee comprised 6 members, including 2 project leaders/coordinators, 1 statistical expert (independent nonvoting member), and 1 member each representing the CIBMTR, EBMT, and ASTCT. The Consensus Panel (n = 33) comprised 5 Steering Committee members (all but the statistical expert), 27 academic experts, and 1 community representative.

† Attended by 26 members (4 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 10/30/20.

geographical representation and expertise in the field, as demonstrated by their track records of peer-reviewed publications, leadership on clinical trials relevant to the consensus project, and involvement in national and international lymphoma or transplantation organizations. In addition, the panel included a physician representing a community-based practice (N.G.), as previously recommended [20]. The final Consensus Panel consisted of 33 physicians and investigators, including all members of the Steering Committee except the (nonclinical) independent methodologist (A.K.), who did not vote on the recommendations.

Consensus Methodology

The RAND-modified Delphi method was used to generate consensus statements addressing the role, timing, and sequence of HCT and CAR T cell therapies in patients with newly diagnosed and R/R MCL. In the Delphi method, the participants rate the statements anonymously in at least 2 rounds of evaluations. In the modified version of the Delphi method, a face-to-face meeting with presentation of the results precedes the second round of rating [20-22]. Owing to the ongoing COVID-19 pandemic, a virtual platform (Zoom, San Jose, CA) was used in lieu of a face-to-face meeting. Details of the systematic step-by-step approach used in this project are provided in Table 1.

After Consensus Panel selection, a baseline demographics and scope (BD&S) 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 Supplementary Material). Once the scope of the consensus project was finalized, the Steering Committee formulated preliminary consensus statements based on expert opinion for the first round of voting (details in Supplementary Tables S1 and S2).

The first voting survey included 19 consensus statements. Consensus Panel members rated each statement electronically. The Steering Committee methodologist analyzed and summarized the results while keeping the individual ratings anonymous. A specific proposed statement was defined as having achieved formal consensus if $\geq$75% of the panel members voted to agree with it. The results of the 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, were modified for revoting or dropped. The second voting survey was sent to all Consensus Panel members for rating the reformulated or newly added statements.

All surveys were administered online using Qualtrics software (Qualtrics, 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

Table 2
Demographic Information of Consensus Panel Members (N = 33)

Member Demographics		No. (%)
Male sex		24 (72.7)
Female sex		9 (27.3)
Practice setting	Academic	31 (93.9)
	Community	2 (6.1)
Years of clinical experience in lymphoma and/or HCT practice	>10	22 (66.7)
	6-10	9 (27.3)
	≤5	2 (6.0)
Description of clinical practice	Nontransplantation lymphoma practice	3 (9.0)
	Primarily HCT and/or cell therapy practice	5 (15.2)
	Combined lymphoma and HCT/cell therapy practice	25 (75.8)
Region of practice*	North America	26 (78.8)
	Europe	6 (18.2)
	Middle East	1 (3.0)
Estimated number of newly diagnosed lymphoma patients seen by individual member annually	>75	23 (69.7)
	51-75	6 (18.2)
	26-50	3 (9.1)
	≤25	1 (3.0)
Estimated number of mantle cell lymphoma patients seen by individual member annually	>40	6 (18.2)
	31-40	3 (9.1)
	21-30	14 (42.4)
	≤20	10 (30.3)
Estimated annual transplant volume at respective programs (number of autologous plus allogeneic HCT)	>300	13 (39.4)
	201-300	7 (21.2)
	101-200	9 (27.3)
	51-100	3 (9.1)
	≤50	1 (3.0)
Estimated annual autologous HCT performed at respective centers	>250	7 (21.2)
	201-250	3 (9.1)
	151-200	5 (15.2)
	101-150	8 (24.2)
	51-100	8 (24.2)
	≤50	2 (6.1)
Estimated annual autologous HCT performed at respective centers for lymphoma (Hodgkin plus non-Hodgkin)	>200	1 (3.0)
	151-200	3 (9.1)
	101-150	2 (6.1)
	51-100	10 (30.3)
	26-50	13 (39.4)
	≤25	4 (12.1)
Estimated annual CAR T cell therapies performed at respective centers for lymphoma (on or off clinical trial)	>20	21 (63.6)
	16-20	3 (9.1)
	11-15	5 (15.2)
	≤10	4 (12.1)

Statistical expert A.K. did not participate in the voting process.
* Countries represented include: United States, n = 26; Germany, n = 2; United Kingdom, n = 1; Spain, n = 1; Italy, n = 1; Sweden, n = 1; Saudi Arabia, n = 1.

graded based on the strength and level of the supporting evidence, according to the Agency of Healthcare Research and Quality grading system [23].

RESULTS

Member Participation

Table 2 summarizes the baseline characteristics of Consensus Panel members. Included were transplantation and cellular therapy physicians (>75% of practice time in HCT), non-cellular therapy academic physicians, mixed practitioners, and a community-based practitioner. A mixed practice was defined as practitioners devoting approximately 50% of their clinical time to HCT and the other 50% to non-cellular therapy-related lymphoma treatment. In general, panelist participation and response rates were excellent. During the voting process, 100% (n = 33) panel member participation was noted for the BD&S, first voting, and second voting surveys. The virtual meeting was attended by 26 members, including 4 members who provided their absentee vote by providing written feedback in advance of (n = 1) or after the meeting, after reviewing the video recordings of the teleconference (n = 3).

First Voting Survey

The first voting survey consisted of 19 statements specific to the role of auto-HCT in eligible newly diagnosed MCL patients (6 statements) and R/R MCL patients (2 statements), allo-HCT for newly diagnosed MCL patients (3 statements),

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

Consensus Statement	Grading of Recommendations*	Panelists in Agreement, %
1. The panel recommends autologous HCT as consolidation therapy in eligible, newly diagnosed MCL patients (without TP53 mutation or biallelic deletion) in complete remission or partial remission after first-line therapies.	A	87.9
2. The panel does not recommend autologous transplantation as consolidation therapy in MCL patients with disease not responsive to most recent antilymphoma therapy.	B	100
3. The panel does not recommend using measurable residual disease (MRD) testing to guide use of autologous transplantation consolidation after first-line therapies in MCL outside the setting of a clinical trial.	C	100
4. The panel does not recommend using MIPI or MIPI-c prognostic score as a criterion determining use of autologous transplantation as consolidation therapy in eligible newly diagnosed MCL patients in first complete remission or partial remission after first-line therapies.	C	100
5. The panel does not recommend allogeneic transplantation consolidation in MCL patients (without TP53 mutation or biallelic deletion), achieving a complete or partial remission after first-line therapies.	B	97
6. The panel does not recommend consolidation with CAR T cell therapy in MCL patients achieving a complete or partial remission after first-line therapies outside the setting of a clinical trial.	C	100
7. If a TP53 mutation (or biallelic deletion) is present, the panel recognizes that outcomes are poor for MCL patients in complete or partial remission after first-line therapies who then undergo autologous transplantation. However, no specific alternative strategy has yet been shown to improve outcomes in such patients. Therefore, the panel recommends considering autologous transplantation consolidation as well as alternative consolidation strategies (eg, CAR T cell therapy or allogeneic transplantation), ideally in the context of a clinical trial, for such patients.	C	100

PET/CT indicates positron emission tomography/computed tomography.
* Agency of Healthcare Research and Quality grading of recommendations based on level of evidence [15]:
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.

and allo-HCT and/or CAR T cell therapy for R/R MCL patients (8 statements). All but 5 statements achieved consensus by predefined criteria (Supplementary Table S1). The results of the first voting survey were shared electronically with all panel members. The 5 statements not achieving consensus (<75% agreement) during the previous voting process were reviewed by the Steering Committee and presented to the Consensus Panel members at the virtual video conference. The ensuing discussion resulted in one statement regarding auto-HCT being abandoned and all other statements being revised. A total of 3 statements were proposed (2 reformulated statements and 1 merged statement) for the second voting survey. Supplementary Table S2 presents the outcomes of the virtual video conference.

Second Voting Survey

All statements included in the second voting survey (2 reformulated statements and 1 merged statement) met the predefined criteria for consensus (Supplementary Table S2). The final consensus recommendations on auto-HCT, allo-HCT, and CAR T cell therapy for upfront and relapsed MCL consisting of 17 consensus statements are provided in Tables 3 and 4.

DISCUSSION

In this project, a broadly representative panel of lymphoma, transplantation, and cellular therapy experts with diverse practice experience and geographical representation, endorsed by the ASTCT, EBMT, and CIBMTR, was formed to provide consensus recommendations on the roles of auto-HCT, allo-HCT, and CAR T cell therapy in treating newly diagnosed and R/R MCL. Considering the limitations of existing data on treatments with cellular immunotherapy for MCL and the recently approved CAR T cell therapy (brexucabtagene autoleucel) for R/R MCL [10], the optimal sequencing of these treatments in the era of other novel therapies like BTK inhibitors is unknown. Therefore, this undertaking was conceived to provide a rational basis for clinical guidance where evidence is limited, and it resulted in 17 consensus recommendations.

Recommendations in the Front-Line Setting without TP53 Aberrations

Seven consensus statements were generated for transplantation and CAR T cell treatments in the frontline setting for MCL (Table 3). Taking into account the European MCL Network randomized study for upfront auto-HCT consolidation in MCL [4,13] and several other historical prospective trials [18,24-26], the panel recommended auto-HCT as consolidation therapy in eligible, newly diagnosed MCL patients (without TP53 mutation or biallelic deletion) in complete remission or partial remission after first-line therapies (grade A recommendation; Table 3, recommendation 1). Although this is in keeping with current guidelines [3], the Consensus Panel did acknowledge that, owing to the lack of evidence of a survival benefit with upfront auto-HCT consolidation, some experts and centers do not routinely recommend this modality after front-line intensive induction regimens. In addition, the panel did not recommend auto-HCT as consolidative therapy in MCL patients with disease refractory (or unresponsive) to the most recent line of therapy (grade B recommendation; Table 3, recommendation 2). Finally, given the lack of prospective data to guide consolidative auto-HCT based on the presence (or absence) of measurable residual disease (MRD), the panel did not recommend using MRD testing to determine whether auto-HCT consolidation should be applied, outside of a clinical trial (grade C recommendation;

Table 4
Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T Cell Treatments for R/R MCL

Consensus Statement	Grading of Recommendation*	Panelists in Agreement, %
1. If a TP53 mutation (or biallelic deletion) is present, the panel does not recommend autologous transplantation in relapsed MCL patients achieving a complete or partial remission after second or subsequent lines of therapy.	B	100
2. The panel recommends both CAR T cell therapy or allogeneic transplant consolidation as acceptable options, in relapsed MCL patients with TP53 mutation (or biallelic deletion) in a complete or partial remission after second or subsequent lines of therapy.	C	84.9
3. If a TP53 mutation (or biallelic deletion) is present, the panel recommends treatment with CAR T cells in relapsed MCL patients, with disease unresponsive to last antilymphoma therapy.	B	97
4. In relapsed MCL patients, the panel recommends offering CAR T cell therapy before proceeding with allogeneic transplantation.	C	81.8
5. Regarding timing of CAR T cell application in relapsed MCL patients (without TP53 mutation or biallelic deletion), the panel recommends offering CAR T cell therapy to patients relapsing after (or who are intolerant to) at least one BTK inhibitor.	B	93.9
6. The panel does not recommend allogeneic transplantation in relapsed MCL patients with disease refractory to most recent antilymphoma treatment.	B	93.9
7 The panel recommends allogeneic transplantation for eligible relapsed MCL patients who have achieved only a partial remission with a BTK inhibitor in second or subsequent treatment line, particularly in regions without access to CAR T cell therapy or in subjects where such therapy is not feasible.	B	84.9
8. The panel recommends allogeneic transplantation in eligible MCL patients relapsing/progressing after CAR T cell therapy, if they achieve a complete or partial remission or if they have stable disease with subsequent antilymphoma therapies.	C	84.9
9. Among eligible MCL patients lacking a TP53 mutation (or biallelic deletion) not undergoing autologous transplant consolidation following first-line therapies, the panel recommends considering autologous transplantation consolidation therapy in patients who have achieved a complete remission after second-line chemoimmunotherapies.	B	97
10. The panel recommends considering allogeneic transplant consolidation in eligible MCL patients who still have detectable disease at 3 or more months following CAR T cell therapy.	C	100

* Agency of Healthcare Research and Quality grading of recommendations based on level of evidence [15]:
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.

Table 3, recommendation 3). In an effort to bridge this knowledge gap, the ongoing US Intergroup phase III study (ECOG-ACRIN 4151; NCT03267433) is randomizing MRD-negative MCL patients to undergo auto-HCT, followed by maintenance rituximab or maintenance rituximab alone.

The Consensus Panel was not able to reach a consensus on recommending the collection and storage of peripheral blood hematopoietic progenitor cells (HPCs) for patients not undergoing upfront auto-HCT (Supplementary Tables S2 and S3). The costs of collecting and storing HPCs for future use [27], as well as ambiguity about the role of auto-HCT in the R/R setting in the CAR T cell therapy era, were among the major concerns raised by the panel. In addition, it was felt that if necessary, peripheral blood HPC collection is feasible at a later point in the disease process. Although a number of prognostic factors can be used to predict outcomes for MCL, including the MCL International Prognostic Index (MIPI) score [24,28,29], owing to a lack of supporting data, the Consensus Panel did not recommend using the MIPI prognostic score as a criterion for selecting patients for auto-HCT as consolidation therapy (grade C recommendation; Table 3, recommendation 4).

Although the Consensus Panel anticipates that future trials will investigate the role of CAR T cell therapies as consolidation following frontline treatment, it does not recommend this approach outside the setting of a clinical trial (grade C recommendation; Table 3, recommendation 6).

Recommendations in the Front-Line Setting with TP53 Aberrations

The Consensus Panel recognized that that outcomes of MCL patients with a *TP53* mutation (or biallelic deletion) who are in complete or partial remission after first-line treatments are poor following auto-HCT consolidation [6]. Although there is preliminary evidence that both allo-HCT and CAR T cell therapies may overcome any treatment resistance conferred by *TP53* aberrations [10,30], no alternative strategies have been shown to improve the outcomes of first-line therapy in such patients in a randomized trial. Therefore, the panel cautiously recommended considering auto-HCT consolidation as well as other alternative consolidation strategies (eg, CAR T cell therapy, allo-HCT) for such patients, ideally in the context of a clinical trial (grade C recommendation; Table 3, recommendation 7).

Recommendations in the R/R Setting

The Consensus Panel acknowledges that in the modern era of novel immunotherapies, auto-HCT likely will have a limited role in the management of R/R MCL, particularly in the presence of *TP53* aberrations, where the panel does not recommend auto-HCT (grade B recommendation; Table 4, recommendation 1). However, among standard-risk MCL patients (eg, those lacking a *TP53* mutation or biallelic deletion) not having undergone auto-HCT in first remission, the panel felt that considering HDT consolidation therapy in the subset of patients who have achieved complete remission after second-line chemoimmunotherapy, particularly after a long first remission, is reasonable and supported by observations in more recent registry and other retrospective studies (grade B recommendation; Table 4, recommendation 9) [12].

Brexucabtagene autoleucel was approved by the US Food and Drug Administration (FDA) for treating R/R MCL on July 24, 2020, before the first voting survey. The Consensus Panel felt that the FDA label did not identify the optimal timing of

CAR T cell therapy in R/R MCL. Considering the cost of this modality and the availability of other active targeted therapy options, the panel recommended that CAR T cell therapy is best applied in R/R MCL patients who are intolerant to or relapsed after treatment with at least one BTK inhibitor (grade B recommendation; Table 4, recommendation 5). This appears to be in accordance with the European label for brexucabtagene autoleucel granted by the European Medicines Agency (EMA) in December 2020 (after completion of this consensus project) approving this CAR T cell therapy for R/R MCL after 2 lines of systemic therapy including a BTK inhibitor. However, owing to the preliminary evidence of activity of CAR T cell therapy in patients with a *TP53* mutation [10], the use of CAR T cell therapy as a second-line therapy (ie, even without prior BTK inhibitor exposure) may be considered for such patients (grade B recommendation; Table 4, recommendation 3).

With the approval of CAR T cell therapy for R/R MCL, the role of allo-HCT merits reevaluation. The Consensus Panel recognizes the increased toxicities and life-threatening complications of allo-HCT and thus recommends considering CAR T cell treatments before allo-HCT. In practical terms and taking into account recommendation 5 (Table 4) for R/R disease, this means that the treatment sequence would be to treat with BTK inhibitors until failure or intolerance, then move to CAR T cell therapy, and reserve allo-HCT for CAR T cell therapy failure. However, given the lack of comparative data of CAR T cell therapy versus allo-HCT, the panel acknowledges that this recommendation represents an expert opinion for clinicians to consider (grade C recommendation, Table 4, recommendation 4). Thus, allo-HCT remains an option as part of second-line treatment in eligible patients who achieve only a partial response to BTK inhibitors (ie, the majority of BTK inhibitor responders [9,31]), particularly in areas where CAR T cell therapies are not available (grade B recommendation; Table 4, recommendation 7).

In addition, the Consensus Panel considered allo-HCT to be a reasonable treatment option in R/R MCL patients who have relapsed after CAR T cell therapy, particularly if the disease remains sensitive to subsequent treatment attempts (grade C recommendation; Table 4, recommendation 8) [16,17,32-34]. This recommendation also can be considered for those patients with persistent yet not progressive disease detectable beyond 3 months after CAR T cell administration (grade C recommendation; Table 4, recommendation 10), taking into account the low probability of durable disease control in this subset [10].

CONCLUSIONS

In clinical scenarios in which data from prospective studies are either scarce or unavailable, or in situations where therapeutic advances or new drug indications 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 [35]. Expert opinions and recommendations in the form of review articles and treatment guidelines, although useful, lack methodological clarity and may be subject to bias [35]. In contrast, the formulation of expert recommendations using established approaches, such as the RAND-modified Delphi method [20], provides a formal, reproducible, and systematic process.

With the rapidly changing landscape of therapeutic advances in cellular immunotherapies for MCL, the timing, sequence, and feasibility of these novel therapies represent challenges. We envision that clinical trials using CAR T cell therapies potentially in earlier lines of treatment or in combination with BTK inhibitors, may emerge. As a result, treatment algorithms for this disease are likely to continue to evolve. We hope that these clinical practice recommendations will serve as a tool to guide clinicians managing patients with newly diagnosed and R/R MCL.

ACKNOWLEDGMENTS

Financial disclosure: The CIBMTR is supported primarily by Public Health Service Grant U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases (NIAID); Grant U24HL138660 from the NHLBI and NCI; Grants OT3HL147741 and U01HL128568 from the NHLBI; Grants HHSH250201700006C and HHSH250201700007C from the Health Resources and Services Administration (HRSA); and Awards N00014-20-1-2705 and N00014-20-1-2832 from the Office of Naval Research. Additional federal support is provided by National Institutes of Health (NIH) Grants P01CA111412, R01CA152108, R01CA215134, R01CA218285, R01CA231141, R01AI128775, R01HL126589, R01HL129472, R01HL130388, R01HL131731, U01AI069197, U01AI126612, and UG1HL06924, and the Biomedical Advanced Research and Development Authority. Support is also provided by the Be the Match Foundation, Boston Children's Hospital, Dana-Farber Cancer Institute, St Baldrick's Foundation, Stanford University, Medical College of Wisconsin, National Marrow Donor Program, and the following commercial entities: Actinium Pharmaceuticals, Adienne, AlloVir, Amgen, Angiocrine Bioscience, Astellas Pharma US, bluebird bio, Bristol Myers Squibb, Celgene, CSL Behring, CytoSen Therapeutics, Daiichi Sankyo, ExcellThera, Fate Therapeutics, Gamida Cell, Genentech, Incyte; Janssen/Johnson & Johnson, Jazz Pharmaceuticals, Kiadis Pharma, Kite Pharma, Kyowa Kirin, Legend Biotech, Magenta Therapeutics, Merck Sharp & Dohme, Millennium, Miltenyi Biotec, Novartis Pharmaceuticals, Omeros, OncoImmune, Orca Biosystems, Pfizer, Pharmacyclics, Sanofi Genzyme, StemCyte, Takeda Pharma, Vor Biopharma, and Xenikos. The views expressed in this article do not reflect the official policy or position of the NIH, Department of the Navy, Department of Defense, HRSA, or any other agency of the US Government.

Conflict of interest statement: M.H. reports receiving research support/funding from Takeda Pharmaceutical, Spectrum Pharmaceuticals, and Astellas Pharma; serving as a consultant for Janssen, Incyte, ADC Therapeutics, Celgene, Omeros, Verastem, and MorphoSys; and serving on speakers bureaus for Sanofi Genzyme, AstraZeneca, and BeiGene. T.S.F. reports receiving research support/funding from Novartis, Portola, Curis; serving as a consultant to Adaptive Biotechnologies, AbbVie, KaryoPharm, Kite Pharma, MorphoSys, Pharmacyclics, and Sanofi; and serving on speakers bureaus for Sanofi, Seattle Genetics, AstraZeneca, Celgene/Bristol-Myers Squibb, and Adaptive Biotechnologies. P.N.M. reports serving on speakers bureaus for Kite Pharma and Incyte. J.V.C. reports serving on consulting/advisory boards for Janssen, Adicet, BeiGene, Cellectar, Kite Pharma/Gilead, Adaptive, Aptitude Health, AstraZeneca, and Loxo and receiving research support/funding from Novartis, BMS/Celgene, Takeda, Genentech, AstraZeneca, Loxo, LAM, Atara, and BeiGene. N.G. reports serving on speakers bureau for Kite Pharma, AstraZeneca, AbbVie, Janssen, BMS, and Epizyme; serving on consulting/advisory boards for Kite Pharma, AstraZeneca, AbbVie, Janssen, BMS, Incyte, Epizyme, Karyopharma, Genmab, Adaptive Biotech, TG Therapeutics, ADC Therapeutics, and BeiGene; and receiving research funding from Genentech/Roche, BMS, TG Therapeutics, Pharmacyclics, and Kite Pharma. M.K. reports receiving research support/funding from TG Therapeutics and Genentech; serving as a consultant for AbbVie, KaryoPharm, Kite Pharma,

AstraZeneca, Celgene/Bristol-Myers Squibb, Adaptive Biotechnologies, and Curio Science; and serving on the speakers bureau for SeaGen. M.J. reports receiving research support/funding from Janssen, Celgene, Abbvie, Gilead, and Roche, and serving as a consultant for Janssen, Incyte, Gilead, Roche, Bristol-Myers Squibb, Acerta, and BioInvent. J.W.F. served on data safety and monitoring boards for Bayer, Ascerta, and Novartis. C.C.-S. reports receiving research support/funding from ADC Therapeutics, Sanofi, and Roche; serving on consultant/advisory boards for Sanofi, ADC Therapeutics, Roche, Karyopharm Therapeutics, Celgene/Bristol-Myers Squibb, and Incyte; receiving honoraria from Bristol-Myers Squibb, Janssen Oncology, and AstraZeneca; and receiving travel grants from Roche, Janssen, Takeda, and ADC Therapeutics. V.B. reports serving on advisory boards for Kite Pharma and Gamida Cell and receiving research support/funding from Incyte, Gamida Cell, and GT Biopharma. T.P. reports receiving research support/funding from Incyte, BMS/Celgene, Bayer, Abbvie, and Genentech; serving as a consultant for BMS, Bayer, AbbVie, Genentech, Gilead, Gilead/Kite TG Therapeutics, ADC Therapeutics, Incyte, MorphoSys, BeiGene, AstraZenca, and Epizyme. F.L.L. reports receiving research support/funding from Kite Pharma; serving as a scientific advisor for Allogene, Amgen, bluebird bio, BMS/Celgene, Calibr, Celgene, GammaDelta Therapeutics, Iovance, Kite Pharma/Gilead, Legend Biotech, Novartis, and Wugen; and serving as a consultant for Cellular Biomedicine Group, Cowen Consulting, Gerson Lehrman Group, EcoR1, and Emerging Therapies. B.K. reports receiving research support/funding from AbbVie, Acerta, AstraZeneca, Beigene, Celgene, and Genentech and serving as a consultant for AbbVie, Acerta, AstraZeneca, Beigene, Celgene, Kite Pharma, Genentech, Pharmacyclics, and Janssen. M.A.K-D. reports serving as a consultant for Pharmacyclics and Daiichi Sankyo. A.F.H. reports serving as a consulting/advisor for Bristol-Myers Squibb, Merck, Seattle Genetics, Karyopharm, Genentech/Roche; receiving institutional research funding from Bristol-Myers Squibb, Genentech/Roche, Merck, Seattle Genetics, ADC Therapeutics, and Gilead/Kite Pharma; and receiving travel, accommodations, and expenses from Bristol-Myers Squibb. K.J.M. reports receiving research funding from Pharmacyclics, BMS, Merck, and Novartis and serving as a consultant for Pharmacyclics, Janssen, Morphosys, Celgene, Beigene, Kite Pharma, Karyopharm, ADC Therapeutics, and Seattle Genetics. V.P.K. reports research funding from Novartis. D.I. reports research funding from Acerta Pharma. C.S.S. reports serving on consultancy/advisory boards for Juno Therapeutics, Sanofi-Genzyme, Spectrum Pharmaceuticals, Novartis, Genmab, Precision Biosciences, Kite Pharma, Celgene/BMS, Gaqmida Cell, Karyopharm Therapeutics, and GSK and receiving research funding from Juno Therapeutics, Celgene/BMS, Bristol-Myers Squibb, Precision Biosciences, and Sanofi-Genzyme. P.D. reports serving as a consultant for AbbVie, AstraZeneca, bluebird bio, Gilead, Janssen, Novartis, Riemser, and Roche; serving on speakers bureaus for AbbVie, AstraZeneca, Gilead, Novartis, Riemser, and Roche; and receiving research support from Riemser. J.P.L. reports receiving research support from the Leukemia & Lymphoma Society and the Genentech Foundation and serving as a consultant for Sutro, Miltenyi Biotech, AstraZeneca, Epizyme, BMS/Celgene, Regeneron, Bayer, Gilead/Kite Pharma, Karyopharm, Genmab, Genentech/Roche, AbbVie, and Incyte. M.D. reports receiving institutional research funding from AbbVie, Bayer, Celgene, Janssen, and Roche; serving on advisory boards for AstraZeneca, Bayer, BeiGene, Celgene, Genmab, Gilead, Incyte, Janssen, Novartis, and Roche; and receiving speaker's honoraria from Amgen, AstraZeneca, Bayer, Celgene, Gilead, Janssen, and Roche. B.T.H. reports receiving research funding from Kite Pharma/Gilead, Celgene/BMS, Genentech, Pharmacyclics, and AbbVie and serving as a consultant for Kite Pharma/Gilead, Celgene/BMS, Novartis, Beigene, AstraZeneca, Genentech, and AbbVie. The other authors have no conflicts of interest to report.

Authorship statement: Conception and design: P.N.M., T.S.F. B.N.S., S.R, and M.H. Collection and assembly of data: P.N.M., T.S.F., A.K., and M.H. Data analysis: A.K. Data interpretation: All authors. Manuscript writing: first draft prepared by P.N.M., T.S. F., and M.H.; revisions done by all authors. Final approval of manuscript: all authors.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2021.03.001.

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