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Maintenance Therapies for Hodgkin and Non-Hodgkin Lymphomas After Autologous Transplantation

A Consensus Project of ASBMT, CIBMTR, and the Lymphoma Working Party of EBMT

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IMPORTANCE Maintenance therapies are often considered as a therapeutic strategy in patients with lymphoma following autologous hematopoietic cell transplantation (auto-HCT) to mitigate the risk of disease relapse. With an evolving therapeutic landscape, where novel drugs are moving earlier in therapy lines, evidence relevant to contemporary practice is increasingly limited. The American Society for Blood and Marrow Transplantation (ASBMT), Center for International Blood and Marrow Transplant Research (CIBMTR), and European Society for Blood and Marrow Transplantation (EBMT) jointly convened an expert panel with diverse expertise and geographical representation to formulate consensus recommendations regarding the use of maintenance and/or consolidation therapies after auto-HCT in patients with lymphoma.

OBSERVATIONS The RAND-modified Delphi method was used to generate consensus statements where at least 75% vote in favor of a recommendation was considered as consensus. The process included 3 online surveys moderated by an independent methodological expert to ensure anonymity and an in-person meeting. The panel recommended restricting the histologic categories covered in this project to Hodgkin lymphoma (HL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma. On completion of the voting process, the panel generated 22 consensus statements regarding post auto-HCT maintenance and/or consolidation therapies. The grade A recommendations included endorsement of: (1) brentuximab vedotin (BV) maintenance and/or consolidation in BV-naïve high-risk HL, (2) rituximab maintenance in MCL undergoing auto-HCT after first-line therapy, (3) rituximab maintenance in rituximab-naïve FL, and (4) No post auto-HCT maintenance was recommended in DLBCL. The panel also developed consensus statements for important real-world clinical scenarios, where randomized data are lacking to guide clinical practice.

CONCLUSIONS AND RELEVANCE In the absence of contemporary evidence-based data, the panel found RAND-modified Delphi methodology effective in providing a rigorous framework for developing consensus recommendations for post auto-HCT maintenance and/or consolidation therapies in lymphoma.

Supplemental content

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High-dose therapy (HDT) and autologous hematopoietic cell transplantation (auto-HCT) is considered standard treatment for defined indications in classic Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma (NHL).[1,2] According to the Center for International Blood and Marrow Transplant Registry (CIBMTR) and European Society for Blood and Marrow Transplantation (EBMT), in 2016 approximately 14 000 patients with lymphoma received auto-HCT across North America and Europe.[3,4] Auto-HCT can provide durable disease control in a subset of patients. Disease relapse remains the most common cause of death in patients with lymphoma after undergoing HDT. Most relapse events occur within the first 1 to 3 years following auto-HCT, providing a rationale for post-HCT maintenance and/or consolidative strategies to mitigate relapse risk.[5-8]

In recent years, the lymphoma therapeutic landscape has been in flux, with the development of several novel therapies such as monoclonal antibodies (naked, conjugated with drugs, bi-specific T-cell engagers, etc), targeted agents (immunomodulators, proteasome inhibitors, Bruton's tyrosine kinase inhibitors, etc), and immune therapies (checkpoint inhibitors, immune effector cells etc.) that are rapidly finding their way from the relapsed or refractory to the frontline setting. Considering the time involved in designing and executing clinical trials and procuring regulatory approvals, it is not surprising that studies evaluating maintenance and/or consolidation strategies after auto-HCT have not been able to keep pace with drug development in lymphomas. This unfortunately means that some trials evaluating post-HCT maintenance strategies in lymphomas enrolled patient populations that are increasingly less relevant to current practice (eg, rituximab- or brentuximab vedotin [BV]-naïve patients prior to auto-HCT).[5,6] Moreover, the off-label, off-protocol use of approved antilymphoma drugs after auto-HCT as maintenance and/or consolidation therapies is an increasingly common practice. Clinical practice recommendations or consensus statements addressing the contemporary role of maintenance and/or consolidation therapies after auto-HCT in patients with lymphomas are not available. Therefore, the American Society of Blood and Marrow Transplantation (ASBMT), CIBMTR, and EBMT undertook a joint project to formulate consensus recommendations regarding the use of post–auto-HCT maintenance and/or consolidation therapies in cHL and NHL. In addition to providing recommendations for postautologous transplant maintenance and/or consolidation in lymphoma on scenarios where prospective data are available, the panel also developed consensus statements for a number of important clinical scenarios where randomized data are lacking.

Methods

Panel Composition

The development of practice recommendations was approved by ASBMT, CIBMTR, and EBMT, the 3 leading international organizations in the field of HCT. As an initial step, a steering committee was formed comprising 6 members including a project coordinator, representatives of ASBMT, EBMT, 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, initial draft of consensus statements based on systematic review of the literature and clinical practice considerations, and setting up of the expert panel.[9] The aim was to put together a panel with a balanced distribution of lymphoma and transplant experts, to have broad expertise and to cover a wide spectrum of views, while keeping administrative efforts manageable as previously recommended.[10,11] 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 of clinical trials relevant to the consensus project, and by their involvement in national and international lymphoma or transplant organizations. In addition, a physician representing a community practice was included in the panel as previously recommended (S.A.A.).[9] The final consensus panel consisted of 26 physicians and investigators, including members of the steering committee, except the (nonclinical) independent methodologist, who did not vote on the recommendations (A.K.).

Consensus Methodology

The RAND-modified Delphi method was used to generate consensus statements addressing the role of maintenance and/or consolidation therapies after auto-HCT in lymphoma patients, as recommended by the American Society of Clinical Oncology (ASCO).[9-12] In the Delphi method, the participants rate the statements anonymously in at least 2 rounds of evaluations. In the modified version of the method, a face-to-face meeting with presentation of the results precedes the second round of rating.[9-11] Details regarding the systematic step-by-step approach that was involved in this project, are illustrated in eTable 1 in the Supplement.

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 practice (eAppendix in the Supplement). After finalization of the scope of the consensus project, the steering committee conducted a systematic review of the literature to obtain and examine relevant evidence and thereby formulate preliminary consensus statements for the first round of voting (eAppendix; eTable 2; eFigure 1; and eFigure 2 in the Supplement).

The first voting survey included 22 consensus statements along with supporting evidence (if available). Panel members rated each statement electronically. The steering committee methodologist analyzed and summarized the results, while keeping the individual ratings anonymous. The results of first voting survey, along with the statements not reaching the threshold of consensus (defined in section below) were presented at the in-person meeting held in conjunction with the 2018 ASBMT and CIBMTR Tandem Meetings at Salt Lake City, Utah. 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 meeting and based on the discussions the statements were modified for revoting or dropped. The discussion also led to the addition of 1 new statement. The second voting survey was sent to all the panel members for rating of the reformulated or newly added statements.

All surveys were administered online using http://www.qualtrics.com (Qualtrics LLC, Provo) 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 (AHRQ) grading.[13]

Definitions

During the voting process, statements forwarded to the consensus panel were rated on a 5-point Likert scale (strongly agree = 1; somewhat agree = 2; neutral = 3; somewhat disagree = 4; and strongly disagree = 5).[9] A specific statement was defined as having achieved formal consensus, if at least 75% of the panel members voted to strongly agree or agree to the proposed statement.

Results

Member Participation

eTable 3 in the Supplement describes the baseline characteristics of consensus panel. Included were transplant physicians (>75% of practice time in HCT), nontransplant academic physicians, mixed clinicians, and a community-based clinician. A mixed practice was defined as clinicians devoting approximately 50% of clinical time to HCT and nontransplant-related lymphoma, each. In general, panelist participation and response rates were excellent (eFigure 3 in the Supplement). At the steering committee level complete participation was noted except for the teleconference where 5 of 6 members participated. During the voting process, 100% participation was noted for the baseline demographics and scope, first voting and second voting surveys. The in-person meeting was attended by 12 members including 1 member who called in. Two additional members unable to attend in person provided written feedback in advance.

First Voting Survey

The first voting survey consisted of 22 statements specific to the role of maintenance and/or consolidation therapies after auto-HCT in the following lymphoma histologies; cHL (6 statements), mantle cell lymphoma (MCL, 8 statements), diffuse large B-cell lymphoma (DLBCL, 3 statements), and follicular lymphoma (FL, 5 statements). All but 6 statements (cHL = 3, MCL = 2, and FL = 1) achieved consensus by predefined criteria (eTable 5 in the Supplement). In addition to electronically sharing with all panel members, the results of the first voting survey were also presented at the in-person meeting. The 16 statements meeting the preset definition of consensus were reviewed and approved unanimously. Next, the 6 statements not achieving consensus (<75% agreement) during the prior voting process were reviewed. The ensuing discussion resulted in 1 statement regarding cHL being abandoned and all other statements being revised. In total 6 statements were proposed (reformulated statements = 5, new statement = 1; cHL = 2, MCL = 3, FL = 1) for the second voting survey. eTable 6 in the Supplement shows outcomes of the in-person meeting.

Second Voting Survey

All statements included in the second voting survey (reformulated statements = 5, new statement = 1), met the predefined criteria for consensus (eTable 7 in the Supplement). The final consensus recommendations on maintenance and/or consolidation therapies after auto-HCT in patients with lymphoma consisting of 22 consensus statements are shown in **Table 1** (cHL = 5), **Table 2** (MCL = 9), and **Table 3** (DLBCL = 3, FL = 5).

Table 1. Final Clinical Practice Guidelines Consensus Statements on Maintenance Therapy After High Dose Therapy and Autologous Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Consensus Statements: Hodgkin Lymphoma	Grading of Recommendations[a]	Panelists in Agreement, % (n=26)
1. The panel recommends post-autologous HCT consolidation/maintenance with BV for 16 cycles in BV-naïve classic Hodgkin lymphoma (HL) with at least 1 or more high-risk features as defined by the AETHERA study[b]	A	92
2. The panel does not recommend postautologous HCT consolidation/maintenance with BV for HL with prior evidence of disease refractory to BV	C	96
3. The recommended duration of post-auto-HCT BV consolidation/maintenance therapy is for a maximum of 16 cycles every 3 weeks as described in AETHERA trial, or until unacceptable toxicity or disease relapse/progression (whichever occurs first)[b]	A	100
4. The panel recommends post-autologous HCT consolidation/maintenance with BV in HL with one or more high-risk features as defined by the AETHERA trial and limited prior exposure to BV (approximately 4-6 cycles) preceding the autologous HCT, but without any evidence of BV refractory disease	C	100
5. Sufficient data do not exist to use the preautologous-HCT PET (or PET/CT) scan status to guide the use of post-autologous HCT consolidation/maintenance therapy with BV for HL with one or more high-risk features as defined by AETHERA Trial	C	84

Abbreviations: BV, brentuximab vedontin; HCT, hematopoietic cell transplantation; HL, Hodgkin lymphoma; PET/CT, positron emission tomography/computed tomography.

[a] Agency of Healthcare Research and Quality (AHRQ) grading of recommendations based on level of evidence[13]: 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; and X, there is evidence of harm from this intervention.

[b] Consensus statement based on observed PFS benefit, but no OS benefit in randomized clinical trials.

Discussion

In clinical scenarios where 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. Expert opinions and recommendations in the form of review articles and treatment guidelines, although useful, lack methodological clarity and may be subject to bias. In contrast, formulation of expert recommendations using established approaches, such as the RAND-modified Dephi method, provides a formal, reproducible, and systematic process.[9,11] In this project a broadly representative panel

Table 2. Final Clinical Practice Guidelines Consensus Statements on Maintenance Therapy After High-Dose Therapy and Autologous Hematopoietic Cell Transplantation for Mantle Cell Lymphoma

Consensus Statements: Mantle Cell Lymphoma	Grading of Recommendations[a]	Panelists in Agreement, % (n=26)
1. Regarding upfront autologous HCT for chemosensitive MCL after 1 line of prior rituximab and cytarabine-containing therapy, the panel recommends maintenance therapy with rituximab every 2 months for 3 y[b]	A	96
2. Regarding upfront autologous HCT for chemosensitive MCL, the panel recommends maintenance therapy with rituximab (every 2 months for 3 y), regardless of the type of pretransplant induction treatment	B	92
3. Regarding upfront autologous HCT for MCL with a pretransplantation PET (or PET/CT) scan of Deauville score of 1-3, the panel recommends postautologous HCT rituximab maintenance therapy	C	96
4. Regarding upfront autologous HCT for chemosensitive MCL with no evidence of pretransplant minimal residual disease by PCR or next-generation sequencing, the panel recommends maintenance therapy with rituximab	C[b]	77
5. Recommended duration of postautologous-HCT rituximab maintenance therapy in MCL is every 2 mo for a maximum of 3 years as described in LYSA trial, or until unacceptable toxicity or disease relapse/progression (whichever occurs first)[b]	A	92
6. After autologous HCT for MCL, maintenance/consolidation therapy with agents other than rituximab (eg, bortezomib, lenalidomide, BTK inhibitors, BCL2 inhibitors, etc) should only be offered in a clinical trial	C	100
7. The panel does not recommend postautologous HCT rituximab maintenance/consolidation for rituximab-resistant MCL (ie, relapse or progression of MCL while on, or within 6 mo of receiving a rituximab-containing treatment regimen)	C	88
8. Regarding MCL patients undergoing a delayed autologous HCT who have not received rituximab maintenance previously and have demonstrated no evidence of rituximab resistance, the panel recommends postautologous HCT maintenance therapy with rituximab	C	100
9. Regarding patients with MCL undergoing a delayed autologous HCT who have previously received rituximab maintenance but have demonstrated no evidence of rituximab resistance, the panel recommends postautologous HCT maintenance therapy with rituximab	C	96

Abbreviations: HCT, hematopoietic cell transplantation; MCL, mantle cell lymphoma; PET/CT, positron emission tomography/computed tomography.

[a] Agency of Healthcare Research and Quality (AHRQ) grading of recommendations based on level of evidence[13]: 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; and X, there is evidence of harm from this intervention.

[b] Consensus statement based on overall survival benefit seen in randomized clinical trials.

Table 3. Final Clinical Practice Guidelines Consensus Statements on Maintenance Therapy After High-Dose Therapy and Autologous Hematopoietic Cell Transplantation for Diffuse Large B-cell and Follicular Lymphoma

Consensus Statements: Diffuse Large B-Cell Lymphoma and Follicular Lymphoma	Grading of Recommendations[a]	Panelists in Agreement, % (n=26)
Diffuse Large B-Cell Lymphoma		
1. The panel does not recommend postautologous HCT maintenance therapy with rituximab for relapsed or refractory DLBCL that is sensitive to rituximab-based salvage approaches	A	100
2. Regarding autologous HCT for high-risk DLBCL (high-risk IPI score, double or triple hit, double expressor, and/or those with failure of first-line therapy within 1 y of diagnosis), either in the upfront or relapsed or refractory setting, the panel does not recommend postautologous HCT maintenance/consolidation therapy with rituximab	C	100
3. Regarding autologous HCT for DLBCL, maintenance/consolidation therapy with novel agents (eg, monoclonal antibodies other than rituximab, bortezomib, lenalidomide, BTK inhibitors, BCL2 inhibitors, cellular therapies, etc) should only be offered in a clinical trial	C	100
Follicular Lymphoma		
1. The panel recommends postautologous HCT maintenance therapy with rituximab (375 mg/m^2 every 2 mo for 4 doses) for chemosensitive, relapsed, rituximab-naïve FL[b]	A	81
2. The panel recommends postautologous HCT maintenance therapy with rituximab in high-risk FL with early therapy failure (ie, relapse or progression of disease within 24 mo of diagnosis) and no evidence of rituximab resistance	C	77
3. The panel does not recommend postautologous HCT maintenance therapy with rituximab for rituximab-resistant FL (ie, relapse or progression of FL while on or within 6 mo of receiving a rituximab-based treatment regimen or single agent rituximab)	C	92
4. Regarding autologous HCT for FL, maintenance and/or consolidation therapy with novel agents (eg, monoclonal antibodies other than rituximab, bortezomib, lenalidomide, PI3K inhibitors, BCl2 inhibitors, etc) should only be offered in a clinical trial	C	100
5. Acknowledging the lack of prospective data, the panel recommends postautologous HCT maintenance therapy with rituximab in chemosensitive, relapsed, previously rituximab (or other CD20 antibody)-treated FL, without any prior evidence of rituximab resistance	B	84

Abbreviation: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCT, hematopoietic cell transplantation; IPI, International Prognostic Index; PET/CT, positron emission tomography/computed tomography.

[a] Agency of Healthcare Research and Quality (AHRQ) grading of recommendations based on level of evidence[13]: 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; and X, there is evidence of harm from this intervention.

[b] Consensus statement based on overall survival benefit seen in randomized clinical trials.

of lymphoma and transplant experts with diverse practice experience and geographical representation, endorsed by ASBMT, EBMT, and CIBMTR, was formed to provide consensus recommendations on the role of maintenance and/or consolidation therapies after auto-HCT in lymphomas. It should be noted that most panel members practiced in academic settings (96%) and were transplant physicians with or without non-HCT lymphoma practices, which could be a potential source of confirmation bias. Considering the limitations in existing data and the rapidly expanding repertoire of therapeutic options in lymphoma, such an undertaking was considered a priority and addresses a gap in existing literature. A systematic literature search and expert input identified the gaps in current knowledge and aided the formulation of statements aimed at addressing them. Reported here are 22 practice recommendations addressing the role of maintenance and/or consolidation therapies after auto-HCT in patients with lymphoma (cHL = 5, MCL = 9, DLBCL = 3, FL = 5) (Tables 1-3).

Five consensus statements were generated regarding postauto-HCT maintenance/consolidation therapy in cHL. Taking into account the results of the AETHERA trial,[6] the panel recommends BV maintenance/consolidation after auto-HCT in patients with cHL who have 1 or more trial-specified risk factors (ie, primary refractory cHL, relapsed cHL with an initial remission duration of <12 months, or extranodal involvement at the start of pretransplantation salvage chemotherapy) at 1.8 mg/kg intravenously every 3 weeks for 16 doses in BV-naïve patients with cHL. The consensus panel considered the fact that presence of more than 1 risk factor, per AETHERA trial criteria, may be associated with additive deleterious effects on patient outcomes. For example, a CIBMTR report showed that the prognosis of patients with cHL who had multiple (AETHERA-like) risk factors was poor.[14] Similarly, a post hoc analysis of the AETHERA study suggested that patients with cHL who had 2 or more risk factors derived greater progression-free survival (PFS) benefit from BV maintenance after auto-HCT.[6] The facts that routine use of BV maintenance and/or consolidation has not been shown to improve OS and that it may be associated with higher US health care costs compared with surveillance alone, were also considered.[15] However, the panel decided to drop the proposed statement limiting use of BV maintenance and/or consolidation to patients with more than 2 risk factors (eTable 6 in the Supplement), owing to the lack of high-quality evidence supporting this restriction. Of note, the AETHERA trial only enrolled BV-naïve patients with cHL. With the approval of BV in the frontline setting[16] and increasing use of this agent in pre–auto-HCT salvage regimens,[17-20] the number of patients with high-risk cHL who have prior BV exposure is likely going to increase. The panel discussed this important real-world clinical scenario, where high-quality prospective data are not available, underscoring the need for consensus recommendations. Accordingly, the panel recommended the use of BV maintenance and/or consolidation in patients with prior limited exposure to BV (defined as approximately ≤4-6 cycles), undergoing auto-HCT who otherwise meet the AETHERA risk criteria and did not demonstrate prior resistance or intolerance to BV. The panel acknowledge that "limited prior exposure" in our statement is empirical but agreed to include it as a consideration because no data are available to suggest a benefit associated with BV maintenance and/or consolidation in patients with prior prolonged exposure to this agent. Preautograft positron emission tomography (PET) scan status is an important determinant of patient prognosis.[21] The panel deliberated the possibility of a PET-based risk-adapted approach in recommending BV maintenance and/or consolidation therapy after auto-HCT (eTable 6 in the Supplement). Because no robust data are available to show lack of benefit with BV maintenance and/or consolidation in patients with PET-negative high-risk cHL, the panel concluded that sufficient data do not exist to use the pretransplant PET (or PET/CT) scan status to guide the use of BV maintenance and/or consolidation therapy after auto-HCT.

In patients with MCL undergoing upfront auto-HCT after rituximab and cytarabine-containing induction, a randomized trial[7] showed improved PFS and overall survival (OS) with rituximab maintenance compared with observation. This was in line with an earlier retrospective study.[22] Based on these results, the panel achieved consensus to recommend maintenance rituximab every 2 months for a maximum of 3-year (or until unacceptable toxic effects or disease relapse or progression [whichever occurs first]) in patients with MCL undergoing upfront auto-HCT consolidation following induction with rituximab and cytarabine-based therapy. The panel acknowledged that the efficacy of rituximab maintenance (at least in transplant noneligible patients), is dependent on the type of frontline therapy, where the benefit is more pronounced after R-CHOP induction, and may be lacking following fludarabine- or bendamustine-based approaches.[23,24] With this limitation in mind, the panel did reach consensus to recommend maintenance rituximab in patients with MCL undergoing upfront auto-HCT consolidation, regardless of the induction regimen received (grade, C; grading defined in footnote of Table 2), and in patients with MCL undergoing delayed auto-HCT (but without any prior evidence of rituximab resistance [grade, C]). We acknowledge that there are only limited retrospective data that support these statements,[25] and that these statements in large part reflect expert consensus (grade, C recommendation). No data exist to use pretransplant PET or minimal residual disease (MRD) status in determining the need for maintenance rituximab in patients with MCL undergoing auto-HCT. Considering the OS benefit associated with rituximab maintenance in the LYMA trial,[7] the panel reached a consensus to recommend maintenance even in PET or MRD-negative patients. We acknowledge that in MRD-negative patients, monitoring and preemptive rituximab therapy in those with molecular relapse has been shown to induce subsequent molecular responses[26]; however, no data exist to show if this preemptive approach is comparable (better, or inferior) to rituximab maintenance. Of note, the recently activated US Intergroup trial (NCT03267433) is randomizing MRD-negative patients with MCL to auto-HCT or no auto-HCT. In this study all MRD-negative patients irrespective to study arm, will receive rituximab maintenance for 3 years.

In DLBCL, consensus was achieved to not recommend rituximab maintenance after auto-HCT in relapsed or refractory DLBCL that was sensitive to rituximab-based salvage approaches. These recommendations are supported by the final analysis of the CORAL study,[8] which showed no event-free survival improvement associated with maintenance rituximab compared with observation. Similarly, the panel did not endorse maintenance and/or consolidation therapies in patients with high-risk DLBCL (based on either clinical, histologic, or genomic criteria). Although lenalidomide has been shown to improve PFS in elderly patients with DLBCL after frontline therapy,[27] no data are available to supports its use following auto-

HCT. An ongoing randomized, intergroup trial is comparing ibrutinib vs placebo after auto-HCT in activated B-cell subtype of DLBCL (NCT02443077) and may clarify the role of maintenance and/or consolidation therapy guided by cell-of-origin.

In FL, the panel endorsed rituximab maintenance after auto-HCT for chemosensitive, relapsed, rituximab-naïve patients, primarily based on the EBMT study findings (grade, A).[5] However, the panel acknowledges that rituximab-naïve status at the time of auto-HCT in patients with FL in the current era would be rare, thus limiting the clinical impact of this statement. Although patients with FL receiving other CD20 antibodies before auto-HCT (eg, obinutuzumab) but not rituximab are arguably rituximab-naïve, the panel cautions against extrapolating the above recommendation to this population, especially because the toxic effects profile of rituximab maintenance after prior obinutuzumab exposure is not well defined. This scenario is relevant given the survival benefit associated with obinutuzumab in the relapsed (PFS and OS) and frontline (PFS) settings.[28,29] For the clinically more relevant, rituximab-treated patients with FL, no prospective data for the use of maintenance rituximab after auto-HCT exist. Limited retrospective data in this setting suggest improved 3-year PFS (86% vs 46%, $P = .004$) and a trend toward improved OS (96% vs 78%, $P = .06$) with maintenance rituximab compared with observation.[30] In addition, a prospective trial as well as an individual patient data meta-analysis showed that rituximab maintenance improved PFS and OS, respectively, in rituximab-pretreated patients outside the transplant setting.[31,32] However, although the panel recommended rituximab maintenance in previously rituximab (or other CD20 antibody)-treated patients with FL (without any prior evidence of rituximab resistance), the lack of quality data supporting this consensus statement is also clearly acknowledged (Table 3). Early failure of chemoimmunotherapy (within 2 years) identifies patients with FL with a poor prognosis.[33] Recent retrospective data suggest improved outcomes in a subset of such patients with auto-HCT[34-36] but disease relapse remains common. In this challenging subset, rituximab maintenance was recommended with the caveat that patients should not be rituximab refractory.

The panel unanimously voted to discourage the off-label use of novel agents as maintenance and/or consolidation therapies after auto-HCT and recommend such use only in the context of a clinical trial. Throughout the consensus project we adopted a commonly used definition of rituximab resistance (ie, evidence of relapsed or resistant or progressive disease while taking or within 6 months of receiving a rituximab-based regimen). This definition, although routinely used, has the inherent limitation that it cannot distinguish whether the disease is truly resistant to rituximab or to the accompanying chemotherapy agents (in patients getting rituximab with chemotherapy). We also acknowledge that these consensus statements are not a substitute for prospective controlled data, but mainly aim to provide guidance where gaps in knowledge exist. The duration of maintenance after auto-HCT recommended in the consensus statements is based on available prospective data, however, early cessation of maintenance should be considered for intolerance and toxic effects. Disease relapse continues to remain the leading cause of postauto-HCT mortality. With changes in the therapeutic landscape of lymphoma treatment, incorporation of novel agents in the peri-HCT period to mitigate the risk of therapy failure remains an attractive but underinvestigated option.

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