Indications for hematopoietic stem cell transplantation in patients with follicular lymphoma: a consensus project of the EBMT-Lymphoma Working Party

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ABSTRACT

The aim of this project was to define indications for hematopoietic stem cell transplantation in follicular lymphoma in Europe. In the absence of evidence-based data, a RAND-modified Delphi procedure was used by an expert panel. After pre-defining statements, these were individually/anonymously scored by each participant using a 9-point scale. Consensus was reached that: 1) high-dose therapy with autologous stem cell rescue is not an appropriate option to consolidate first remission in patients responding to immuno-chemotherapy outside clinical trials; 2) in patients with first chemo-sensitive relapse, high-dose therapy with autologous stem cell rescue is an appropriate option to consolidate remission, especially in patients with a short response after immuno-chemotherapy or with high-risk FLIPI; 3) high-dose therapy with autologous stem cell rescue is also appropriate in second/subsequent chemo-sensitive relapses; 4) allotransplant (preferably a reduced intensity conditioning-allotransplant) should be considered at relapse after high-dose therapy with autologous stem cell rescue. No consensus was reached on the role of high-dose therapy with autologous stem cell rescue in low-risk first relapse, or on when an allotransplant should be preferred over high-dose therapy with autologous stem cell rescue. In the absence of evidence-based data, the consensus method used was a valuable tool to define indications for hematopoietic stem cell transplant in follicular lymphoma.

Introduction

In recent years, the significant advances in the management of patients with follicular lymphoma (FL) have resulted in a substantial improvement in their outcome.[1-3] However, in spite of this, FL remains an incurable disease using standard therapies. Although allogeneic transplantation and high-dose therapy with autologous stem cell rescue (HDT-ASCR) are effective treatment options, the considerable morbidity and mortality associated with these therapeutic options has to be taken into account. Thus, defining the role of hematopoietic stem cell transplant (HSCT) in the therapeutic algorithm of patients with FL is one of the major challenges in the management of this disease. This task has become even more difficult in recent years, thanks to the significant improvement in the outcome of patients with FL. The demonstration that maintenance rituximab at relapse prolongs progression-free survival (PFS) (and, in some studies, overall survival, OS)[4-7] has been used as an argument against consolidation of second remission with HDT-ASCR. Moreover, the advent of reduced intensity conditioning regimens (RIC) has considerably reduced the mortality associated with allogeneic transplantation, broadening the population of patients who are potentially candidates for such a procedure and raising the question as to whether its benefits can outweigh those of HDT-ASCR.[8-16]

In the absence of randomized controlled trials (RCT) addressing these questions, systematic reviews inevitably fail to provide conclusions helpful for clinical decision making,[17] whereas traditional narrative reviews are prone to be biased by the individual view and expertise of the authors. Therefore, the European Group for Blood and Marrow Transplantation (EBMT) launched a project to define indications for HDT-ASCR and for allogeneic transplantation in patients with FL in the rituximab era in Europe following a RAND-modified Delphi consensus method.

Consensus methods are well-defined processes used in the health field to obtain expert opinion when no evidence-based data are available by providing a systematic, transparent and explicit method to reach consensus.[18] The Delphi consensus method is characterized by the fact that participants rate the statements individually and anonymously in at least two rounds of evaluation. In the modified version of the method, a face-to-face meeting with presentation of the results precedes the second round of rating.[19]

Design and Methods

Selection of the panel

Panel members were selected on the basis of their expertise in the field, as demonstrated by their record of peer-reviewed publications

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and leadership of clinical trials on the subject, and by their involvement in national and international lymphoma or transplant organizations. The aim was to put together a team with a balanced distribution of 'lymphoma' and 'transplant' experts. A panel made up of 12 members was considered appropriate in order to cover a representative spectrum of different fields of expertise, views, and European nationalities, whilst keeping administrative efforts manageable, as recommended by Murphy *et al.*[19]

Overview of the process

Following a RAND-modified Delphi process, the participants were invited to submit their suggestions for the issues that they considered should be discussed during the consensus procedure. An up-to-date summary of the published literature on the field was prepared by the project co-ordinator (SM). The suggestions were subsequently discussed by teleconference and 16 statements were produced. The decision on the definition and on the threshold to declare consensus was also made during the teleconference. Subsequently, the participants rated each statement individually and sent the ratings to the project co-ordinator who analyzed and summarized the results while keeping the individual ratings anonymous. This was followed by a face-to-face meeting of the panel at which the project co-ordinator presented the results of the first round of rating to the members. The discussion of the results led to the re-formulation of some statements and the addition of 3 further statements. Hence, 19 statements were finally agreed for the second and final round of rating. Again, this was completed individually and semi-anonymously (that is, only known by the co-ordinator) by each member of the panel (Table 1).

Definition of consensus

The participants rated every statement using a 9-point scale from 1-3 ('*disagree*': 1, strongly; 2, disagree; 3, moderately) to 7-9 ('*agree*': 7, moderately; 8, agree; 9, strongly); scores of 4-6 corresponded to '*neither agree nor disagree*'. For each statement, the highest and lowest scores were discarded and consensus was reached if all the other scores fell in the same group. No consensus was reached if there was at least one score in the '*disagree*' group and one or more scores in the '*agree*' group. Partial consensus was reached if the rates were split between the 'neither agree nor disagree' and either the 'disagree' or the '*agree*' group. A less stringent criteria (consensus >75% agreement) was considered and rejected in favor of a more strict definition of consensus.

Results

Participation

All members of the panel participated in at least the two crucial steps of the process, i.e. the rating rounds. A minimum participation of 55% of the members was achieved for each step of the process, with a total rate of participation of 79% and two-thirds of the members participating in at least 5 of the 6 steps (Figure 1).

Initial statements and results of the first round of rating

The members of the panel suggested nine issues for discussion that were formulated into 16 statements after the first teleconference (Table 2). After the first round of rating, consensus on 5 statements was reached; in addition, there was partial consensus in favor of 2 further statements.

Re-formulation of statements and final consensus

Following the presentation of the summary of the first round of rating at the face-to-face meeting, the discussion of the results led to the re-formulation of some of the statements to improve clarity and the addition of 3 further statements.

After the second round of rating, agreement in favor of 8 statements (statement ns. 1, 5, 9, 10, 12, 13, 18 and 19) was reached; there was also consensus against statement ns. 2 and 3. In addition, there was partial consensus in favor of statement n. 11, and partial consensus against statement n. 4. Summaries of the 12 statements on which consensus was reached are given in Tables 3 and 4 (grouped according to topic). No consensus was reached on the remaining 7 statements (statement ns. 6-8 and 14-17) (Table 5). The median, range and distribution of scores for all statements are shown in Tables 6-9.

Discussion

In the absence of evidence-based data, formal consensus

Table 1. Description of the steps involved in the RAND-modified method.

Who	What	How
All panel members	Send suggestions of issues for discussion to SM/PD	E-mail
Project co-ordinator	Send summary of published data List questions/statements	–
All panel members	Define threshold required for consensus Formulate statements	Teleconference
All panel members	Rate statements (1st round)	Individually
Project co-ordinator	Rank statements Send interim results to all members	–
All panel members	Presentation of results by the project co-ordinator Group discussion on the ranking of the statements Group discussion on the formulation of the statements	Face-to-face meeting
All panel members	Re-formulation of statements	Teleconference
All panel members	Rate statements (2nd round)	Individually
Project co-ordinator	Rank statements Send final results to all members	–
All panel members	Agree on final consensus report	–

Table 2. The 16 statements formuled after the first teleconference.

Statement n.	Agreed statement
1	Autologous transplant is not indicated in first-line therapy in patients responding to immuno-chemotherapy, outside the setting of clinical trials
2	Autologous transplant is indicated in first-line therapy in patients with poor risk features such as high-risk FLIPI at diagnosis
3	Autologous transplant is indicated in first-line therapy in patients with poor risk features such as grade 3a FL
4	Autologous transplant is indicated in first-line therapy in patients with poor risk features such as PR after immuno-chemotherapy
5	Autologous transplant is indicated in patients in 1st relapse with chemosensitive disease
6	Autologous transplant is not indicated in 1st relapse in patients with good risk features such as a long response duration (3-5 years) after immuno-chemotherapy
7	Autologous transplant is not indicated in 1st relapse in patients with good risk features such as low-risk FLIPI at relapse
8	Autologous transplant is not indicated in 1st relapse in patients with good risk features such as rituximab-naïve patients
9	Autologous transplant is indicated in patients in second or subsequent relapses with chemo-sensitive disease
10	Allogeneic transplant should be considered in patients with relapse after autologous transplant
11	In very young patients (<40 years) with poor risk features such as a short response duration (<2 years), allogeneic transplant should be considered before an autologous transplant
12	In very young patients (<40 years) with poor risk features such as high-risk FLIPI at relapse, allogeneic transplant should be considered before an autologous transplant
13	In very young patients (<40 years) with poor risk features such as PR after salvage treatment, allogeneic transplant should be considered before an autologous transplant
14	Total-body irradiation (TBI) is generally not recommended in the transplant conditioning regimen
15	Myeloablative conditioning regimens are generally not recommended in patients receiving an allogeneic transplant
16	In FL, the available biological, genetic and clinical risk factors are not sufficient to guide treatment decisions. Treatment decisions including the indication for autologous and allogeneic transplantation are exclusively guided by the clinical course

Table 3. Final consensus in favor.

Consensus n.	Statement n.	Agreed statement
1	1	**HDT-ASCR is *not* an appropriate treatment option to consolidate first remission in patients with FL responding to immuno-chemotherapy, outside the setting of clinical trials.**
2	5	**In patients in first relapse with chemo-sensitive disease HDT-ASCR is an appropriate treatment option to consolidate remission.**
	9	Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients with a short response duration (<3 years) after immuno-chemotherapy.
	10	Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients with high-risk FLIPI at relapse.
	11*	Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients previously treated with rituximab.*
3	12	**Remission consolidation with HDT-ASCR is an appropriate treatment option in patients in second or subsequent relapses with chemo-sensitive disease.**
4	13	**Allogeneic transplantation should be considered in patients with relapse after HDT-ASCR.**
	18	*Reduced-intensity*/ non-myeloablative conditioning regimens are generally more appropriate in patients receiving an allogeneic transplant.
5	19	**In FL, the available biological and genetic risk factors are not sufficient to guide treatment decisions. Treatment decisions including the indication for HDT-ASCR and allogeneic transplantation are mainly guided by the clinical course.**

**Partial consensus only*

Table 4. Final consensus against.

Consensus n.	Statement n.	Rejected statement
1	2	HDT-ASCR is an appropriate treatment option to consolidate first remission in patients with high-risk FLIPI at diagnosis.
	3	HDT-ASCR is an appropriate treatment option to consolidate first remission in patients with grade 3a FL.
	4*	HDT-ASCR is an appropriate treatment option to consolidate first remission in patients with **partial remission** after immuno-chemotherapy.*

**Partial consensus against only.*

development methods such as the one used in this project, are valuable tools to define indications for HSCT in patients with FL. Consensus methods were initially developed for forecasting in the setting of the emergence of new technologies and were first used in the health field in the 1950s.[19] Several papers have recently been published reporting 'consensus' indications or guidelines on different hemato-oncology topics.[20-25] Many of them, however, do not follow formal consensus methods but they are a summary of experts' recommendations, with no details on how the experts have been selected or, more importantly, how the decision to recommend a specific approach has been made.

In contrast, formal consensus methodology, such as the RAND-modified Delphi procedure followed here,[19] provides a reproducible, systematic, transparent and explicit process to reach consensus. When this project was initially launched, there were neither recommendations on which consensus development method was preferable nor any formal guidelines on the process itself. More recently, the American Society of Clinical Oncology (ASCO) proposed a modified Delphi approach and established the steps involved in detail, recognizing the importance of such methods for the development of guidelines when evidence-based data is scarce.[18] What differentiates this manuscript from the many other excellent reviews on the role of HSCT in patients with FL[17, 26, 27] is the fact that, in the current paper, the recommendations following the exhaustive review of the literature result from a systematic and objective procedure, rather than summarizing the pre-established views of a limited number of authors. Consensus methods increase the objectivity of experts' recommendations by guaranteeing that all participants involved in the process will be able to express their opinions and that all views will be equally valued. In a disease such as FL, with a highly heterogeneous management and multiple treatment options, this is crucial to ensure the objectivity of the process and to strongly increase the value of the resulting recommendations. Whereas the recommendations included in this manuscript are, obviously, based on 'expert opinion', the strength of this project is that such recommendations are made following a strict, well-defined and objective process based on consensus methodology.

The main conclusion of this European consensus project is that HDT-ASCR plays a significant role in the management of patients with relapsed FL even in the rituximab era. The advent of rituximab might have jeopardized the position of HDT-ASCR in the therapeutic algorithm of FL, as the improved PFS associated with maintenance rituximab could render HDT-ASCR unnecessary to prolong remission in relapsed FL. The data from the Lympho-care study at relapse[28] and those of the updated EORTC 20981 trial,[7] amongst others, seems to suggest that the enthusiasm for HDT-ASCR to consolidate remission in patients with relapsed FL has decreased in the rituximab era, with only a small proportion of patients (<2-7%) reported as receiving such treatment in those studies.

In the current project there was consensus to support HDT-ASCR in patients with relapsed FL. In particular, there was agreement in considering HDT-ASCR an appropriate option in first relapse, in general, and, more specifically, in patients with allegedly poor-risk features such as a short response duration or a high-risk FLIPI at first relapse, two recognized poor risk factors at recurrence in the pre-rituximab era.[29,30] There was only partial consensus to recommend HDT-ASCR in first relapse in patients previously treated with rituximab, as some participants argued that patients might have received single agent rituximab and/or no maintenance, and they could not be considered as 'high-risk' patients not having received previous combination of chemotherapy and rituximab, the 'optimum' treatment. Moreover, it remains to be shown in FL if relapse after rituximab-containing first-line treatment is associated with a poorer prognosis than relapse after rituximab-free treatment[31] as seems to be the case with aggressive B-cell lymphoma.[32] The role of HDT-ASCR in patients with relapsed FL in the rituximab era is supported by the studies published by Sebban *et al.*[33] and Le Gouill *et al.*[34] Moreover, a recent EBMT study has demonstrated that rituximab does

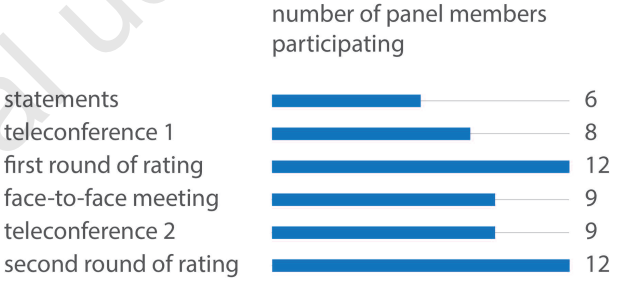

Figure 1. Participation of panel members (PM). Number of PM participating at each step. S: statements (suggestion of issues to discuss); TC1: teleconference 1 (formulation of statements and definition of threshold for consensus); R1: first round of rating; M: face-to-face meeting (discussion of ratings and statements); TC2: teleconference 2 (re-formulation of statements); R2: second round of rating.

Table 5. Statements for which no consensus was achieved.

Statement n.	
6	Remission consolidation with HDT-ASCR is *not* an appropriate treatment option in 1st relapse in patients with long response duration (longer than 3-5 years) after immuno-chemotherapy.
7	Remission consolidation with HDT-ASCR is *not* an appropriate treatment option in 1st relapse in patients with low-risk FLIPI at relapse.
8	Remission consolidation with HDT-ASCR is *not* an appropriate treatment option in 1st relapse in rituximab-naïve patients.
14	In young patients (<40 years) with a very short response duration (<2 years) and requiring transplant, allogeneic transplant should be considered instead of HDT-ASCR.
15	In young patients (<40 years) with high-risk FLIPI at relapse and requiring transplant, allogeneic transplant should be considered instead of HDT-ASCR.
16	In young patients (<40 years) with PR after salvage treatment and requiring transplant, allogeneic transplant should be considered instead of HDT-ASCR.
17	TBI is generally not recommended in the transplant conditioning regimen of HDT-ASCR.

not impair the effectiveness of HDT-ASCR but, in fact, the outcome after HDT-ASCR is significantly better in patients who received monoclonal antibodies (MoAb) prior to HDT-ASCR.[35] Finally, the Lym01 study, although performed in patients who relapsed after rituximab-free first-line therapy, suggests that HDT-ASCR and rituximab maintenance could synergize in improving disease control in patients with recurrent FL.[36]

Contrasting with the consensus on HDT-ASCR in high-risk first relapse, there was no agreement on the possibility of obviating HDT-ASCR to consolidate second remission in patients with low-risk characteristics at first relapse (i.e. low-risk FLIPI, long first remission, or rituximab-naïve), with around one-third of the panel members considering that HDT-ASCR was indicated at first relapse even in patients with 'good-risk' features.

There was also agreement in rejecting HDT-ASCR to consolidate first remission outside the setting of clinical trials, even in allegedly high-risk patients such as those with high-risk FLIPI. This is in line with experience from the pre-rituximab era confirmed in a recent meta-analysis showing an advantage of HDT-ASCT over conventional chemotherapy in terms of EFS with no significant differences in OS.[37] In the current project, HDT-ASCR was not recommended as part of first-line therapy even in patients with high-risk disease. There was, however, an element of discrepancy, as there was only partial agreement against recommending HDT-ASCR to consolidate first remission in patients in partial response (PR) after immuno-chemotherapy. This disagreement was driven by the different meanings of 'PR',

Table 6. Median, range and distribution of scores for statements for which the final consensus was in favor.

	Disagree			Neither agree nor disagree				Agree (range)		Median
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	
1. HDT-ASCR is **NOT** an appropriate treatment option to consolidate 1st remission in patients responding to immuno-chemotherapy, outside the setting of clinical trials	0	0	0	0	0	0	1 (8%)	3 (25%)	8 (67%)	9 (7-9)
5. In patients in 1st relapse with chemo-sensitive disease, HDT-ASCR is an appropriate treatment option to consolidate remission	0	0	0	0	1 (8%)	0	2 (17%)	6 (50%)	3 (25%)	8 (5-9)
9. Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients with a short response duration (<3 years) after immuno-chemotherapy	0	0	0	0	0	0	1 (81%)	8 (67%)	3 (25%)	8 (7-9)
10. Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients with high-risk FLIPI at relapse	0	0	0	0	0	0	3 (25%)	6 (50%)	3 (25%)	8 (7-9)
12. Remission consolidation with HDT-ASCR is an appropriate treatment option in patients in second or subsequent relapses with chemo-sensitive disease	0	0	0	1 (8%)	0	0	3 (25%)	6 (50%)	2 (17%)	8 (4-9)
13. Allogeneic transplant **SHOULD** be considered in patients with relapse after HDT-ASCR	0	0	0	0	0	0	2 (17%)	6 (50%)	4 (33%)	8 (7-9)
18. Reduced-intensity/non-myeloablative conditioning regimens are generally more appropriate in patients receiving an allogeneic transplant	0	0	0	0	1 (81%)	0	1 (8%)	7 (58%)	3 (25%)	8 (5-9)
19. In FL, the available biological and genetic risk factors are not sufficient to guide treatment decisions. Treatment decisions including the indication for HDT-ASCR and allogeneic transplantation are mainly guided by the clinical course	0	0	0	0	0	0	2 (17%)	5 (42%)	5 (42%)	8 (7-9)

Table 7. Median, range and distribution of scores for statements for which the final consensus was against.

	Disagree			Neither agree nor disagree			Agree		Median (range)
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	
2. HDT-ASCR is an appropriate treatment option to consolidate 1st remission in patients with high-risk FLIPI at diagnosis (1-3)	6 (50%)	5 (42%)	1 (8%)	0	0	0	0	0	0	1.5
3. HDT-ASCR is an appropriate treatment option to consolidate 1st remission in patients with grade 3a FL	8 (67%)	3 (25%)	1 (8%)	0	0	0	0	0	0	1 (1-3)

according to, for example, how response is assessed. In this sense, the results of the PRIMA study showing a very poor outcome for patients achieving a PR as assessed by PET,[38] would support the use of HDT-ASCR in these circumstances for some of the participants. It was argued, however, that there is no evidence that HDT-ASCR improves the outcome of this high-risk population.

Regarding allotransplant, there was consensus in recommending this procedure (using an RIC regimen) in patients relapsing after HDT-ASCR. None of these decisions is surprising. There is ample evidence that graft-*versus*-lymphoma (GVL) activity is highly effective in FL, even in patients having failed HDT-ASCR, to support the use of RIC regimens.[8-15] Accordingly, several guidelines recommend allotransplant in patients relapsing after HDT-ASCR,[39,40] and RIC transplants have practically replaced myeloablative transplants in FL, accounting for 82% of all allogeneic HSCT procedures in FL registered with the EBMT in 2011 (*EBMT, data on file*). The median age of patients with FL also support this strategy. However, some panel members argued that there might be exceptions, such as very young patients in whom a myeloablative regimen should be preferred.

With regard to the lack of consensus on further potential indications for allogeneic transplantation, it has to be noted that the conclusion of the present study is not that there is consensus against allotransplant prior to HDT-ASCR, but that there is no agreement about this indication. This polarization of views underlines the need of an RCT comparing HDT-ASCR with allogeneic transplantation. However the difficulties in setting up transplantation trials in FL are highlighted by a Blood and Marrow Transplant Clinical trials

Table 8. Median, range and distribution of scores for statements for which partial consensus was reached.

	Disagree			Neither agree nor disagree			Agree			Median (range)
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	
11. Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients previously treated with rituximab	0	0	0	0	2 (17%)	0	2 (17%)	8 (67)	0	8 (5-8)
4. HDT-ASCR is an appropriate treatment option to consolidate 1st remission in patients with PR after immuno-chemotherapy	2 (17%)	3 (25%)	3 (25%)	1 (8%)	1 (8%)	1 (8%)	1 (8%)	0	0	3 (1-7)

Table 9. Median, range and distribution of scores for statements for which no consensus was achieved.

	Disagree			Neither agree nor disagree			Agree			Median (range)
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	
6. Remission consolidation with HDT-ASCR is not an appropriate treatment option in 1st relapse in patients with a long response duration (longer than 3-5 years) after immuno-chemotherapy	0	2 (17%)	2 (17%)	0	0	0	4 (33%)	2 (17%)	2 (17%)	7 (2-9)
7. Remission consolidation with HDT-ASCR is not an appropriate treatment option in 1st relapse in patients with low-risk FLIPI at relapse	0	3 (25%)	1 (8%)	2 (17%)	2 (17%)	0	3 (25%)	0	1 (8%)	4.5 (2-9)
8. Remission consolidation with HDT-ASCR is not an appropriate treatment option in 1st relapse in rituximab-naïve patients	0	3 (25%)	1 (8%)	0	2 (17%)	0	2 (17%)	2 (17%)	2 (17%)	6 (2-9)
14. In young patients (<40 years) with a very short response duration (<2 years) and requiring transplant, allogeneic transplant should be considered instead of HDT-ASCR	1 (8%)	0	3 (25%)	2 (17%)	1 (8%)	0	2 (17%)	2 (17%)	1 (8%)	4.5 (1-9)
15. In young patients (<40 years) with high-risk FLIPI at relapse and requiring transplant, allogeneic transplant should be considered instead of HDT-ASCR	1 (8%)	2 (17%)	5 (42%)	1 (8%)	0	1 (8%)	0	2 (17%)	0	3 (1-8)
16. In young patients (<40 years) with PR after salvage treatment and requiring transplant, allogeneic transplant should be considered instead of HDT-ASCR	1 (8%)	1 (8%)	4 (33%)	1 (8%)	0	0	2 (17%)	3 (25%)	0	3.5 (1-8)
17. TBI is generally not recommended in the transplant conditioning regimen of HDT-ASCR	1 (8%)	0	1 (8%)	0	1 (8%)	0	1 (8%)	4 (33%)	4 (33%)	8 (1-9)

Network (BMT CTN) prospective study comparing RIC-allotransplant with HDT-ASCR (with a 'biological' randomization) which was prematurely closed due to slow recruitment, partly due to physician's preferences.[41]

No consensus was reached either on the role of TBI in the conditioning regimen of HDT-ASCR. Several studies, largely from the pre-PBSC era[42-44] (including an EBMT analysis with a very long follow-up)[45] have shown an association between the risk of secondary myelodysplastic syndromes/acute myelogenous leukemia (sMDS/AML) and the use of TBI, resulting in a higher non-relapse mortality (NRM) and a lower OS for patients receiving TBI. However, a recent EBMT study – albeit with a shorter follow up - did not detect any significant differences in NRM, with a trend towards a better OS for patients who received TBI compared with those who received the chemotherapy-only conditioning regimen BEAM.[35] This data and the fact that TBI reduces the risk of relapse in some reports,[45,46] were argued in favor of the use of TBI.

Finally, there was consensus that, unlike other hemato-oncological diseases such as AML and chronic lymphocytic leukemia,[24,47] the available biological and genetic risk factors are not yet sufficient to guide treatment decisions including the indication for HDT-ASCR and allogeneic transplantation in FL. Instead, these should be guided by the clinical course. Though systematic, the consensus process used here has some obvious limitations: the results are influenced by the selection of the panel (thus we cannot exclude that a different panel would have resulted in different conclusions), the formulation of the statements, and the threshold chosen to define consensus. The fact that only half of the members participated in the first step (submission of initial statements for discussion) might have influenced the results; however, additional opportunities were taken by the participants to add/discuss the wording of the statements in the two teleconferences and in the face-to-face meeting, where up to three-quarters of the members participated. In this regard, the authors are not oblivious to the fact that many other relevant questions in the field (such as the role of HSCT in transformed lymphoma or the place of maintenance with rituximab) were not considered for discussion for practical reasons and remain unanswered. As in any expert-opinion based recommendations, there is an element of subjectivity. Nevertheless, the structured methodology used adds an additional level of objectivity and reduces inter-expert bias, thereby supporting the use of consensus development methods to draw recommendations or guidelines when evidence-based data are scarce. Ideally, the crucial questions in the context of HSCT in FL (i.e. HDT-ASCR *versus* rituximab maintenance, HDT-ASCR *versus* RIC-allogeneic transplant) should be answered by RCT, but examples of the difficulties involved in setting up these studies have been discussed previously.

It is obvious that consensus development methods cannot replace RCT, but they provide valuable tools to identify areas for future research and to help design the studies that will advance knowledge in the field. In this sense, it is crucial to take into account the moving landscape in which this project was developed: the management of patients with FL is rapidly evolving with the emergence of new drugs which will obviously have an impact on the role of HSCT in FL. Going forward, this project has identified a clear area in which consensus was not reached that would benefit significantly from prospective studies including RCTs, i.e. the role of allogeneic transplant prior to HDT-ASCR.

However, the extreme views of the participants against or in favor of an allogeneic transplant, might partially explain the failure of prior attempts to run a RCT on this question. Maybe the answer lies in exploring alternative procedures, such as prospective audits, that can provide better evidence-based data than those currently available before investigators can decide whether such a trial is not only feasible but also still necessary.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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