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Transplantation in follicular lymphoma: not "yes or no" but "whom and when"

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After years of debate, the question as to what is the optimal use of transplantation strategies in indolent lymphoma remains controversial. In the July issue of Haematologica, a study was published by the EBMT Lymphoma Working Party that aims to define indications for hematopoietic stem cell transplantation in follicular lymphoma in Europe.[1]

While autologous stem cell transplantation (ASCT) still offers the possibility of turning follicular lymphoma (FL) into a chronic rather than a life-threatening disease, with a modest impact on Quality of Life, allogeneic hematopoietic stem cell transplantation (allo-HSCT) as a treatment option has curative potential. However, its use has been limited to a selected patient population in which the disease risk outweighs the procedure-related morbidity and mortality. It, therefore, has been applied mainly after failure of autologous SCT. Now the introduction of dose-reduced intensity conditioning (RIC) with or without T-cell depletion has lowered the treatment-related mortality of allo-HSCT. In a recently published retrospective analysis of EBMT Registry data on patients in 2nd or higher treatment line, the survival curves for progression free (PFS) and overall (OS) survival appear to cross in favor of allogeneic SCT beyond the 2nd or the 8th year, respectively, despite an adverse risk profile of the allo-transplanted cohorts.[2] So, in the light of these improvements, could allogeneic SCT become the standard treatment for all eligible patients in relapse?

To answer this, it is important to understand how alternative treatment options have been developed. Prior to the introduction of new agents in the treatment of lymphoma (namely rituximab), life expectancy was dramatically decreased by the diagnosis of FL, and responses to first-line treatment, and especially to later treatment lines, were frequently moderate and/or short lived. However, the introduction of the first anti-CD20 antibody has turned FL into a chronic disease for many patients. In addition, new treatment options, e.g. inhibitors of the B-cell receptor pathway, have appeared on the horizon and these promise new and potentially better treatment options. As the non-relapse mortality (NRM) of allo-HSCT still remains within the range of 15-25%, these developments make it hard to decide in favor of this type of treatment. So, should we forget about allogeneic transplantation?

Not yet! Although the last 15 years have seen improvements in allogeneic HSCT and in conventional therapy that, ironically, seem to favor opposing trends with a tendency to low-intensity treatments, we must bear in mind that patients continue to die of this disease. The younger the patients are, the higher the likelihood is they will lose many years of life. Consequently, the question has to be not "if", but "whom, how and when" to apply transplantation strategies in FL.

But how can we identify the right patient? There is an unfortunate lack of prospective randomized trials and comprehensive retrospective studies. Furthermore, primary treatment of FL is more diversified than in other

lymphoma entities, and algorithms for 1st and subsequent treatment lines vary substantially in between different centers. Considering all these aspects, discussion about the role of autologous and allogeneic transplantation sometimes resembles a question of faith rather than a scientific debate.

Given the lack of evidence, there is a strong urge for expert guidance in this field. In this issue of Haematologica, Montoto and colleagues report on the consensus project of the EBMT Lymphoma Working Party that aimed to develop recommendations for the use of transplantation in FL.[1] They have chosen a so-called RAND-modified Delphi procedure. This approach collects scores given anonymously to pre-defined statements and reports the range of answers rather than a consensus on each separate statement; this is useful if there is disagreement about specific points. While this is an advantage, choosing the members of the expert group from among the EBMT working party, as well as formulating predefined statements, opens up the possibility of study bias. The Authors agreed on 3 issues: 1) clinical course is important rather than biological factors; 2) high-risk disease defined by IPI and relapse after HDT are indications for allo-SCT; and 3) RIC-regiments are preferable over myeloablative conditioning. These findings are in line with other recommendation, e.g. as suggested by evidence-based reviews.[3] However, for a variety of other important issues, no consensus was established and these questions remain unanswered. Is there a need for an autologous SCT in patients not in CR after first-line treatment? What is the role of allo-HSCT for low-risk FL, e.g. in patients with long-term remission following ASCT? Is allo-HSCT appropriate as second-line therapy for young patients with high-risk disease? What is the role of allo-HSCT in comparison to maintenance treatment, new antibodies, radioimmunotherapy, etc.?

Controversy about allo-HSCT can to some degree be expected. But the complexity of the topic is underlined by the fact that it was not possible to identify a consensus even for issues concerning autologous SCT. Most of the evidence for the use of this procedure is based on studies performed prior to the introduction of rituximab. Two major schools of thought with regard to autologous SCT have their origin in that era: 1) ASCT as consolidation therapy in first-line treatment increases the PFS but fails to lead to an improved OS[4,5]; and 2) ASCT is the treatment of choice for patients in second-line treatment.[6] Whereas the first statement has been reproduced also in patients receiving rituximab,[7] the role of ASCT in the era of lymphocytotoxic antibodies still remains to be formally demonstrated. ASCT has been associated with secondary malignancies, mainly myelodysplasia and secondary AML, and have a negative impact on the benefit of these procedures. But again, this may be avoided by elimination of total-body irradiation in the current conditioning regimen.

Defining a standard of care that implies high-dose therapy followed by autologous or allogeneic stem cell transplantation remains a goal. In the absence of better evidence, standard of care today needs to be defined by a consensus of experts in the field combining a clear knowledge of the literature with an understanding of current developments and future potential, plus clinical practice with either therapy. Nevertheless, in the end, it still leaves us with an individual patient-based decision. As the natural history of FL and current available options offer multiple treatment options for our patients, it will not suffice to focus on single modalities. What is more, the sequence of their use is of major interest, especially in younger patients. As lymphoma-treating physicians, we should stress the point that future randomized trials applying new agents in FL should also address the aspect of sequence in that we ask for overall rather than event-free survival. The study groups and working parties should stimulate experimental treatment arms that are randomized against either autologous or allogeneic stem cell transplantation following the current standard of care as defined by the best available evidence, even if this is "only" a consensus of experts. Otherwise, the possible economic impact of new and potentially effective pharmacological agents will direct the attention away from defining a more definite role for ASCT and allo-HSCT in the therapeutic sequence for patients with follicular lymphoma.

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