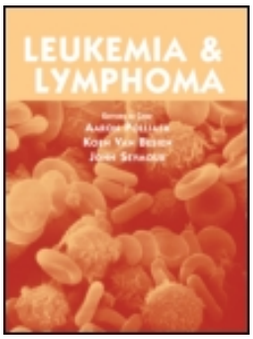

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

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To cite this article: Michael Dickinson (2012) Is autologous stem cell transplantation for transformed follicular lymphoma still justifiable?, Leukemia & Lymphoma, 53:5, 754-755, DOI: 10.3109/10428194.2012.656637

To link to this article: https://doi.org/10.3109/10428194.2012.656637

Leukemia & Lymphoma, May 2012; 53(5): 754–755

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2012.656637

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COMMENTARY

Is autologous stem cell transplantation for transformed follicular lymphoma still justifiable?

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Histologic transformation of follicular lymphoma into an aggressive lymphoma, typically diffuse large B-cell lymphoma (DLBCL), heralds a marked worsening of prognosis for the patient and a particular challenge for the managing hemato-oncologist, for standard intensity treatments lead to unsatisfactory results [1–3]. With the exception of a recently published phase II study [4], all data are retrospective. Further, almost all of the published data precede the inclusion of rituximab as a standard component of induction or maintenance therapy for follicular lymphoma, which may prolong the time to transformation and, as discussed below, may affect subsequent responsiveness to treatment.

From the three largest published case series (all pre-rituximab), we have learned that approximately 3% of patients with follicular lymphoma develop transformation annually, which, while definitively diagnosed histologically, may be clinically identified by an abrupt change in the tempo of lymph node growth, a rapid rise in lactate dehydrogenase (LDH), involvement of unusual extranodal sites or the new development of B symptoms [1–3]. Positron emission tomography (PET) can be especially useful to differentiate sites of transformation from sites of low-grade disease, to direct optimal biopsy or radiotherapy [5].

Clinical risk factors for transformation include the presence of advanced disease (stage III, IV, or stage I/II with B symptoms or bulky disease ≥ 10 cm) [1], a high International Prognostic Index (IPI) or Follicular Lymphoma International Prognostic Index (FLIPI) score, reduced albumin or elevated β_2-microglobulin [1–3]. Disease that ultimately requires multiple lines of chemotherapy appears to have a higher risk for transformation [1]. Historically, over half of patients die within a year of transformation [1–3].

The approach to treatment depends on therapies previously delivered, patient age, comorbidities and performance status. Some have treated transformed disease as they would *de novo* diffuse large B-cell lymphoma, with anthracycline-containing CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone), at times abbreviated to three cycles for those where radiotherapy to the involved field is feasible. Outcomes for patients treated in this manner were, with the exception of selected cases of early-stage transformation, poor [1]. The addition of rituximab to the regimen appears to improve outcome for those who are rituximab-naive [6]. However, for those previously treated with CHOP, doxorubicin retreatment is rarely an option. This consideration will apply increasingly if rituximab-CHOP induction followed by maintenance rituximab is adopted widely as a standard of care for follicular lymphoma, as supported by the PRIMA study [7,8].

In this edition of ***Leukemia and Lymphoma***, Ban-Hoefen and colleagues present outcomes of autologous stem cell transplant (ASCT) for transformed follicular lymphoma [9]. ASCT can be justified as an approach to transformed disease on the basis of the historically poor outcomes of conventional doses of chemotherapy [1–3], its standard role in relapsed DLBCL and its ability to prolong time to progression in follicular lymphoma [10]. In their discussion, Ban-Hoefen *et al*. summarize the data from six small retrospective studies (each 23–50 patients), reporting a 5-year overall survival (OS) following ASCT of between 37 and 70% with progression- or disease-free survival ranging from 25 to 47%. The recent prospective study reported a 5-year progression-free survival (PFS) following ASCT of 30% and OS of 43% [4]. These results compare favorably with conventionally dosed chemotherapeutic treatments from that era. Data from Ghesquières and colleagues further support the role of ASCT for transformed disease [11]. Although the numbers are small and include patients with transformed marginal zone lymphoma, it suggests that for patients whose initial presentation is with transformed disease, consolidation ASCT in first remission improves survival outcomes when compared to chemotherapy alone [11].

It is reasonable to doubt that ASCT now offers the same utility in patients previously treated with rituximab, given recent data from the prospective CORAL study of

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This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

rituximab-containing salvage chemotherapy followed by autologous transplant for relapsed DLBCL, where those previously exposed to rituximab had substantially poorer survival outcomes compared to their rituximab-naive counterparts (however, this analysis was confounded by the correlation between prior rituximab use and a shorter time from initial treatment due to the time period of recruitment to that study) [12]. Rituximab-containing salvage treatment appears to offer a greater PFS benefit than ASCT for relapsed rituximab-naive follicular lymphoma [13]. It may be inferred that patients with lymphoma that progresses after rituximab-containing combination therapy may harbor more biologically refractory disease and are less likely to benefit from ASCT.

Ban-Hoefen *et al*. present the outcome of 18 patients treated with ASCT for transformed disease, of whom 12 had previously been exposed to rituximab [9]. This study provides ASCT outcomes relevant to today's treatment paradigm. The 2-year PFS for the rituximab-exposed group was 36.4% versus no events at the same time point in the six rituximab-naive patients. Clearly the numbers are small, confidence intervals are wide and meaningful comparisons may be affected by patient characteristics; however, the difference in outcome is consistent with the observations of CORAL with respect to the impact of prior rituximab exposure on disease biology at relapse. Nonetheless, for a heavily treated group of patients, that five of 12 remain free of relapse at 2 years is worthy of note. The authors rightly conclude that autologous transplant cannot yet be discarded as an effective treatment for patients with transformed disease.

Of course we await larger studies to validate these claims. Allogeneic transplant, previously discussed in this journal by Dr. Ritchie, represents a reasonable and potentially curative alternative for a smaller subset of eligible patients; however, recently presented data suggest that overall outcomes may be comparable to ASCT [14,15]. Otherwise, there are no good alternative systemic treatment options, and unfortunately very few options for patients who are ineligible for high-dose procedures. Local radiotherapy in conjunction with chemotherapy for patients with PET-proven localized transformation, especially peri-ASCT, should not be forgotten. I do not share Ban-Hoefen and colleagues' optimism regarding radioimmunotherapy, with the only likely role being for those patients who have achieved the deepest of responses, where a rationale is eradication of the chemorefractory cancer stem cell population with a predisposition for transformation. Until novel treatments for aggressive lymphoma demonstrate their effectiveness, it is reasonable to continue to utilize ASCT for patients with transformed disease.

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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