# Positron emission tomography-computed tomography before autologous stem cell transplant in follicular lymphoma: coming too late?

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The report from Eyre *et al*. in the current issue of *Haematologica* describes the value of positron emission tomography (PET) and computed tomography (CT) performed before autologous stem cell transplant (ASCT) to predict the outcome of patients with follicular lymphoma receiving this therapy.[1] This lymphoma is characterized by an extremely variable clinical course driven by significant biological heterogeneity. The current standard of care for first-line treatment produces a remarkable overall survival rate of 80% at 10 years although relapses continue to occur. Early reports from single centers and one abbreviated randomized study in the late 1990s established that ASCT is a valuable option for patients with relapsed chemosensitive disease. Studies showed that the median progression-free survival and overall survival were around 5 and 8 years, respectively, which compared favorably with survival rates of historical controls.[2] Even in the rituximab era and building on the concept of "*in vivo* purging", ASCT represented an option for patients at the time of disease recurrence. However, ASCT is not a risk-free procedure, since it is associated with a non-relapse mortality of around 3% at 3 years, and a significantly increased risk of secondary malignancies. Together with the absence of solid randomized data, the lack of a demonstrative plateau in progression-free survival curves indicative of the curative potential of this approach, and new agents progressively available for patients with relapsed or refractory follicular lymphoma, significant disparities regarding the use of ASCT were observed in recent years. For instance, according to data from the Center for International Blood and Marrow Transplant Research (CIBMTR), only 137 patients with follicular lymphoma underwent ASCT in 2020,[3] while many active European centers have recently restricted its use (LYSA, *unpublished data*).

A better characterization of patients with relapsed or refractory follicular lymphoma who might benefit from ASCT has also emerged. One study examined the outcome of patients enrolled in the PRIMA trial (immunochemotherapy followed or not by rituximab maintenance in first line) in whom first-line therapy had failed. It was observed that ASCT appeared to improve the overall survival of patients presenting at progression with histological transformation, but not that of patients with documented indolent histology.[4] Another retrospective study indicated that an apparent benefit of ASCT was observed primarily in patients having progressive disease within 24 months of therapy initiation (POD24), with a 5-year progression-free survival of 51% *versus* 19% for ASCT *versus* standard therapy, respectively, and an overall survival of 77% *versus* 59%, respectively. Of note, when analyzing these data in all patients intended to receive ASCT, only the difference in progression-free survival, but not overall survival, was found to be statistically significant.[5] Comparing two registries, Casulo *et al*. also reported that ASCT was associated with a favorable outcome among POD24 patients only when a transplant was planned early after relapse, i.e. within the first year.[6] Shedding light on these different findings, recent data indicated that a significant proportion of patients with early progression present with histological transformation. Indeed from 19% up to 76% of patients with POD24 were documented to have transformed lymphoma,[4,7,8] with this wide range likely reflecting variability in systematic biopsy at the time of progression, expert pathology review of the specimen as well as previous exposure to an anthracycline.

In this issue of *Haematologica*, Eyre *et al*. report for the first time the predictive value of PET-CT response (defined as complete metabolic response) in 172 patients with follicular lymphoma undergoing ASCT, assembled across 30 centers. The median time from the diagnosis of follicular lymphoma to ASCT was 4.2 years, the median number of prior lines of treatment was three (range, 1-6) and prior histological transformation was documented in 22 (13%) patients (but patients with transformed disease at the time of relapse preceding ASCT were excluded). POD24 data were available for 73 patients, of whom 45% were considered as POD24 after first line, without significant association with PET status before ASCT. At the time of transplant, 57 patients (33%) did not have a complete metabolic response, whereas 115 (67%) did.

Of the patients who did not have a complete metabolic response and had a post-ASCT PET, 64% obtained a complete metabolic response after the transplant. At a post-ASCT median follow-up of 27 months, median post-transplant progression-free survival was 28 months and overall survival was 57 months, with a 1-year non-relapse mortality of 6%. Eyre *et al*. found that PET status at the time of transplant was highly predictive of outcome: in patients with complete metabolic response, the median progression-free survival was 36 months and the 3-year progression-free survival rate was 50%; the corresponding figures for patients without a complete metabolic response were 22 months and 22% (hazard ratio = 1.8, *P*=0.01). Patients not achieving a complete metabolic response prior to ASCT also tended to have a non-significantly reduced overall survival as well as an increased risk of relapse. In multivariate analysis, age and PET status remained significant for progression-free survival whereas prior lines of therapy, lower performance status, PET-CT status and age were associated with overall survival. Of note, POD24 status was not associated with outcome. Overall, this is the first study reporting the predictive value of PET-CT prior to ASCT in patients with relapsed or refractory follicular lymphoma. These data indicate that ASCT is unlikely to provide a benefit for patients not in complete metabolic response although it is not known whether another strategy would improve their outcome. The main pitfall of the study is the heterogeneity of patients and prior therapies, inherent to its retrospective design. Nevertheless, these results add further to others supporting the use of PET-CT as a valuable predictive tool in patients with follicular lymphoma.

However, while this study shows that achieving a complete metabolic response prior to ASCT predicts a prolonged PFS, it does not establish whether ASCT constitutes the optimal therapeutic strategy for patients with chemosensitive relapsed follicular lymphoma, including those with early disease progression. Lenalidomide with anti-CD20 antibody combinations are already widely used alternatives to cytotoxic regimens. With respective overall and complete response rates of 96-86% and 77-69% recently reported for axicabtagene ciloleucel[9] and tisagenlecleucel,[10] chimeric antigen receptor T cells also emerge as very effective tools even for patients with refractory disease. Chimeric antigen receptor T-cell therapies are accompanied with specific and significant toxicities and while the follow-ups of these studies remain short, with 12- to 18-month progression-free survival rates of around 65%, this treatment modality will challenge the remaining indications for ASCT in patients with relapsed or refractory follicular lymphoma. Other forms of efficient immunotherapies, such as bispecific antibodies, will likely be available soon. As always with follicular lymphoma, tradeoff between toxicity and efficacy, as well as costs and patients' preference, will play a role regarding the optimal sequencing of therapies. Thus, given the uncertainty regarding current and future management, the findings reported by Eyre *et al*. need to be interpreted cautiously.

**Disclosures**

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**Contributions**

*CS and GS co-wrote this editorial.*

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