haematologica
Journal of The Ferrata Storti Foundation

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by Clémentine Sarkozy and Gilles Salles

Received: May 10, 2022.
Accepted: May 10, 2022.

Citation: Clémentine Sarkozy and Gilles Salles. PET-CT before autologous stem cell transplant in follicular lymphoma: coming too late?
Haematologica. 2022 May 19. doi: 10.3324/haematol.2022.281255. [Epub ahead of print]

PET-CT before autologous stem cell transplant in follicular lymphoma: coming too late?

Clémentine Sarkozy[1], Gilles Salles[2],
[1]DITEP, Gustave Roussy, Villejuif, France.
[2]MSKCC, New York, United States.

Corresponding author: Gilles Salles – e-mail: sallesg@mskcc.org

The report from Eyre T et al. in the current issue of Haematologica reports the value of PET-CT performed before autologous stem cell transplant (ASCT) to predict the outcome of patients with follicular lymphoma (FL) receiving this therapy[1]. This lymphoma is characterized by an extremely heterogeneous clinical course driven by significant biological heterogeneity. Current standard of care in first line allows a remarkable overall survival (OS) rate of 80% at 10 years, however so far, a continuous pattern of relapse persists. Early single center reports and one abbreviated randomized study in the late 90's established ASCT has a valuable option for patients with relapsed chemosensitive disease. Studies showed median progression free survival (PFS) and OS respectively around 5 and 8 years, comparing favorably to historical controls[2]. Even in the rituximab era and building on the concept of "in vivo purging", ASCT represented an option for patients at time of disease recurrence. However, ASCT is not a risk-free procedure with a non-relapse mortality (NRM) around 3% at 3 years, and a significant increased risk for secondary malignancies. Together with the absence of solid randomized data, the lack of demonstrative plateau in PFS curves indicative of the curative potential of this approach, and new agents progressively available for patients with relapse or refractory (R/R) FL, significant disparities regarding the use of ASCT were observed in recent years. For instance, the CIBMTR data reported only 137 patients with FL receiving ASCT in 2020[3], while many active European centers have recently restricted its use (LYSA unpublished data).

A better characterization of patients with R/R FL who might benefit from ASCT has also emerged. One of this study examined the outcome of patients enrolled in the PRIMA trial (immunochemotherapy followed or not by rituximab maintenance in first line) who have failed first line therapy. We observed that ASCT appeared to improve OS for patients presenting at progression with histological transformation, but not for patients with documented indolent histology[4]. Another retrospective study indicated that ASCT apparent benefit was primarily observed in patients presenting a progressive disease within 24 months from therapy initiation (POD24), with a 5-year PFS of 51% vs 19% and OS 77% versus 59% for ASCT versus standard therapy, respectively. Of note, when analyzing these data in all patients intended to receive ASCT, only PFS, but not OS, was found significant[5]. Comparing two registries, Casulo et al. also reported that ASCT was associated with a favorable outcome within 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 having transformed lymphoma[4,7,8] this wide range likely reflecting

variability in systematic biopsy at time of progression, expert pathology review of the specimen as well as previous exposure to anthracycline.

Eyre et al. report for the first time the predictive value of PET-CT response assessment (defined as complete metabolic response, CMR) in patients with 172 patients with FL assembled across 30 centers and receiving ASCT. Median time from FL diagnosis to ASCT was 4,2 years, number of prior lines of treatment was 3 (range 1-6) and prior histological transformation was documented in 22 (13%) patients (but patients with transformed disease at time of relapse preceding ASCT were excluded). POD24 data was available for 73 patients, of whom 45% were considered as POD24 after first line, without significant association with PET status pre-ASCT. At time of transplant, 57 patients (33%) had a non-CMR and 67% a CMR. Of the non-CMR patients who had a post ASCT PET, 64% obtained a CMR post ASCT. At a post-ASCT median follow-up of 27 months, median PFS post-ASCT was 28 months and OS 57 months, with 1-year NRM of 6%. Eyre et al. found that PET status at time of transplant was highly predictive of outcome: in patients with CMR, median PFS was 36 months and 3-year PFS 50% versus 22 months and 22% for those with non-CMR (HR 1.8, p=0.01). Patients not achieving CMR prior ASCT also tended to have a reduced non-significant overall as well as an increased risk of relapse. In multivariate analysis, age and PET status remained significant for PFS whereas prior lines of therapy, lower performance status, PET-CT status and age were associated with OS. 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 R/R FL. These data indicate that ASCT is unlikely to provide a benefit for non-CMR patients although it is unknown if 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. But these results further add to others supporting the use of PET-CT as a valuable predictive tool in patients with FL.

However, if this study shows that achieving a CMR pre-ASCT predicts a prolonged PFS, it does not establish if ASCT constitutes an optimal therapeutic strategy for patients with chemosensitive relapsed FL, including those with an early disease progression. Lenalidomide with anti-CD20 antibody combinations provide already a widely used alternative 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], CAR T-cells also emerge as very effective tools even for those with refractory disease. CAR T therapies are accompanied with specific and significant toxicities and while the follow-up of these studies remain short, with 12-18-month PFS around 65%, this modality will challenge the remaining indications of ASCT in patients with R/R FL. And 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 these therapies. Thus, given the uncertainty for current and future management, the reported findings by Eyre et al. need to be cautiously interpreted.

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