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Autologous hematopoietic stem-cell transplant in small-sized and peripheral centers: a 10-year experiment

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Abstract

Background: Along with continuing changes in therapeutic modalities, indications of autologous hematopoietic stem-cell transplantation (ASCT) have been emerging and changing considerably, especially in the era of targeted therapy and small molecule inhibitors. Patients treated with novel agents tend to have a longer survival period, thus eventually reaching higher ages at ASCT. Herein, and to address the question of ASCT outcomes in small, community-based, peripheral French centers, we report the 10-year follow-up results of 136 patients who received ASCT in our eight-bed ASCT unit, situated in an urban area.

Methods: We retrospectively analyzed a cohort of 136 patients treated between 2008 and 2017 at the Duchenne Hospital Center. Of these 136 patients, 75 underwent ASCT for myeloma, while 61 underwent ASCT for lymphoma, amongst which 57 patients were treated for B-cell lymphoma. The median age was 65 years (range, 27–72) for myeloma patients, and 62 years (range, 27–71) for patients with lymphoma.

Results: The cohort median follow up was estimated at 33 months; 10-year overall survival (OS) and progression-free survival (PFS) were 71% and 64% for B-cell non-Hodgkin lymphoma, and 75% and 45% for myeloma, respectively. No statistically significant differences were found for OS or 1-year PFS between patients who received ASCT from 2008 to 2012, and those who received it from 2013 to 2017.

Conclusions: In the absence of randomized trials studying the role of center size, experience, and standardization procedure for ASCT outcome, these results may suggest that ASCT in peripheral accredited small-sized centers could be a viable option to facilitate follow up and enable access to this treatment, especially for elderly patients, in comparison with referring the patient to central large hospitals to undergo ASCT.

Keywords: Autologous, transplantation, center, size

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Introduction

The use of high-dose chemotherapy (HDT) followed by reinfusion of autologous hematopoietic cells [autologous hematopoietic stem-cell transplantation (ASCT)] was first reported as treatment for myeloma patients in 1983.[1] Along with continuing changes in therapeutic modalities, ASCT indications have been emerging and changing considerably, especially in the era of targeted therapy and small molecule inhibitors.[2] Novel treatments were thought by some to have replaced ASCT once and for all. However, new studies suggest that the combined novel treatments–ASCT were at least not inferior, and probably even superior to novel treatments alone for the majority of patients, thereby leading to the rediscovery of ASCT as part of a potentially curative treatment for some pathologies such as multiple myeloma.[3,4] This point had many major effects on ASCT modalities, as patients treated

with novel agents tend to have longer survival, hence eventually reaching higher ages at ASCT,[5] with potential supplementary consolidation and maintenance therapy.[6] As a result, delegating the care of these older patients undergoing long-term treatment to local peripheral community-based hospitals may be a more adapted option in order to facilitate implementing their families in their care and support, along with easier reintegration of these patients into their local communities.[7]

HDT followed by reinfusion of hematopoietic cells is usually offered to patients less than 60 years of age. However, studies and research on the complications associated with this treatment option have extended the age limit to individual over 70 years. An increasing trend has been observed, with the percentage of patients aged 70 years and above undergoing ASCT rising from 6% in 1994–1995 to 25% in 2004–2005.[8] This trend was encouraged by the, at least, comparable results obtained with elderly patients.[9]

The conditioning regimens most often used for lymphoma are BCNU-based regimens, such as CBV (cyclophosphamide, BCNU, etoposide) and BEAM (bendamustine or carmustine, etoposide, cytarabine, and melphalan), with or without rituximab.[10] High-dose melphalan is the most common conditioning regimen for myeloma.[11] The response rate for lymphoma depends on several factors: histological type, prognostic factors [e.g. IPI for diffuse large B-cell lymphoma (DLBCL), FLIPI for follicular type, and MIPI for mantle cell lymphoma], early or late relapse, and pretransplant status, along with patient's comorbidities.[12–14] In the literature, the center's type (size of ASCT unit: e.g. small $<$10 transplant beds), experience, and capacity have been controversial points for assessing survival, ASCT-related mortality, lymphoma morbidity, and myeloma morbidity. In a study published in 2017, Schetelig and colleagues highlighted the importance of center-related characteristics in HSCT outcome[15]; the central concept was that the standardization of procedure, along with center's experience, have a beneficial effect. This latter article, among other similar publications, discussed the effect of center size on results. They found that differences between small and large centers were not statistically important. More interestingly, it was found that growth trends, in terms of total numbers of patients treated and the number of centers by size category, were at least comparable between small centers and other center sizes in many countries.[15–17]

Delegating the application of health care procedures to community-based and local peripheral providers has been elaborated more and more in recent years in the USA as well as in Europe, both as a response to the need to modernize health care systems and guided by data supporting the benefits of such delegation. These benefits include easier accessibility, lower costs, and, in certain cases, better efficacy.[7,18]

Beyond feasibility, and in order to address the question of precise procedures outcomes in small community-based peripheral French centers, more specifically in the context of ASCT, we compiled and studied 10 years of follow-up data, including progression-free survival (PFS) and overall survival (OS), from 136 patients who received ASCT for lymphoma and myeloma in the Duchenne hospital center's eight-bed ASCT unit, situated in an urban area.

Patients and methods

A total of 138 patients received ASCT between 2008 and 2017 at the Duchenne hospital center. Of these, 75 patients were autografted for myeloma, while 61 underwent ASCT for lymphoma and 2 for acute myeloblastic leukemia. The median age for myeloma patients was 65 years (range 27–72) and 62 years (range 27–71) for patients with a lymphoma diagnosis.

The majority of myeloma patients underwent ASCT as a part of their first-line treatment, while a few underwent ASCT after their first relapse. Patients with myeloma were intensified by melphalan-based regimen. All patients with a lymphoma diagnosis underwent ASCT in chemosensitive relapse status, after rituximab-based chemotherapy regimen for B-cell lymphomas, followed by conditioning by a melphalan-based regimen (BEAM: bendamustine, etoposide, Ara-C, and melphalan).

This work was conducted in accordance with the Helsinki declaration. No special funding was obtained for this work. Informed consent for the data collection linked to this work was obtained from all patients.

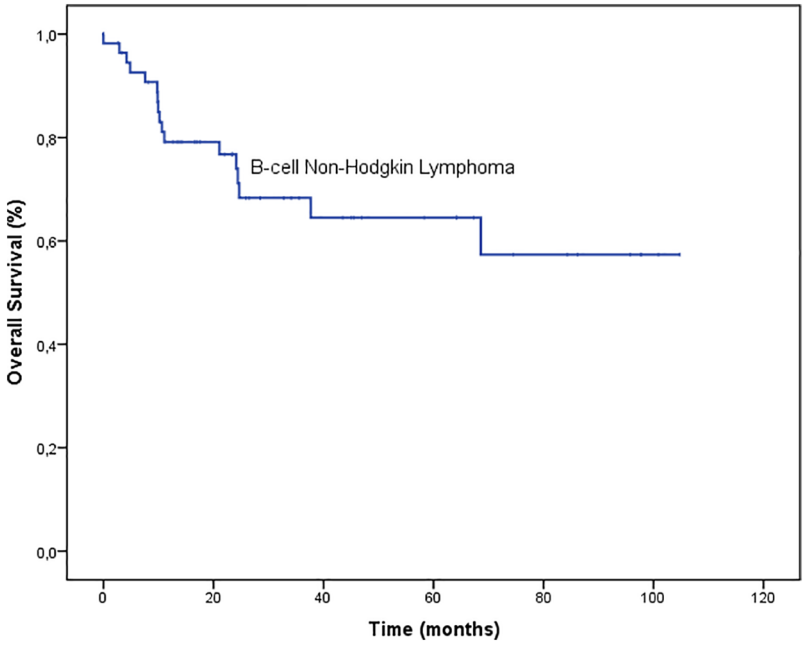

Figure 1. Overall survival (in months) for patients with B-cell lymphoma.

All data from the two patients treated with ASCT for acute myeloblastic leukemia were excluded from statistical analysis.

Statistical analysis

SPSS v.20 was used in the statistical analysis. Estimations of survival were established and generated using the Kaplan–Meier/log rank method. Both OS and PFS were calculated starting from the day of stem-cell infusion.

Results

The myeloma type was free light chain in 41 patients, IgG or IgA for 38, IgD in one case, IgM for one patient, plasma cell leukemia in five patients. Concerning pretransplant status, 15 were in complete remission (CR), 34 in very good partial response (VGPR), 16 in partial response (PR), 7 had stable disease, and 3 had refractory disease, according to international myeloma working group (IMWG) criteria.[8] All patients were considered eligible for high-dose chemotherapy treatment. However, we reduced the melphalan dose to 140 mg/m^2 for patients over 68 years old, or with a creatinine clearance of less than 45 ml/min.

For lymphoma, tumor samples were classified as B high grade or diffuse large B-cell lymphoma in 25 patients, 2 patients had primitive central nervous system (CNS) lymphoma, 10 follicular lymphoma, 8 mantle cell lymphoma, 4 T cell lymphoma, 2 Burkitt or Burkitt-like lymphoma, and 10 patients were classified otherwise. Pretransplant status was CR in 24 patients, PR in 29, and 8 had refractory disease. The cohort median follow up was estimated at 33 months.

Five patients died before the 100th day of ASCT: three patients, one with lymphoma and two patients with myeloma died due to their pathology early progression after ASCT; these three patients were not in CR before ASCT.

One myeloma patient died before day 100 post-ASCT due to severe digestive system infection, while one lymphoma patient died early after undergoing an Allo-HSCT directly after the ASCT (Tandem Auto-Allo). A total of 27 patients were marked as dead at the date of data analysis. Ten-year overall survival (OS) and progression-free survival (PFS) were 71% and 64%, respectively, for B-cell non-Hodgkin lymphoma as shown in figure 1, and 75% and 45%, respectively, for myeloma, as shown in figure 2.

When comparing results of patients who underwent ASCT before 2013 and those who received ASCT from 2013 to 2017, we observed a mortality

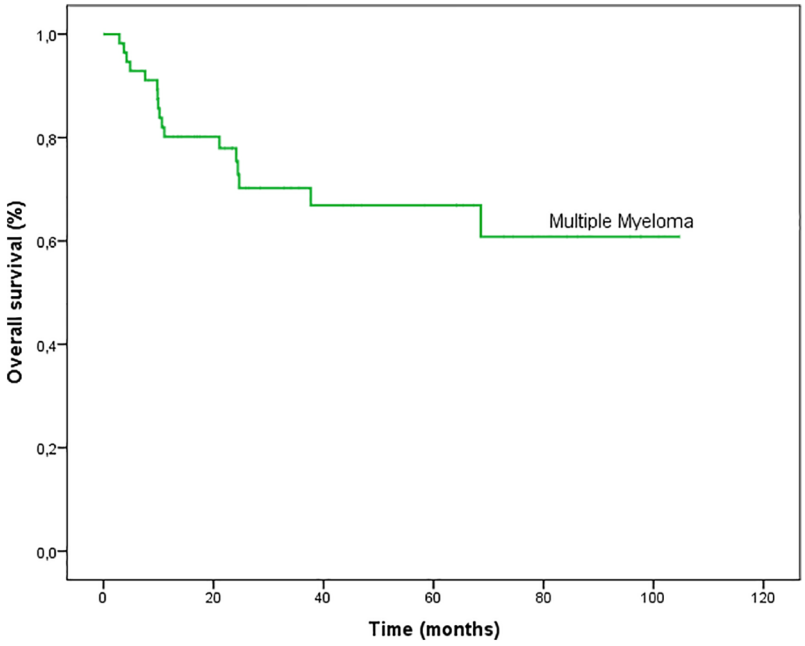

Figure 2. Overall survival (in months) for patients with multiple myeloma.

rate of 12% of the more recent cohort in comparison with 40% for the period of 2008–2012.

We found no statistically significant difference in terms of 3-year overall survival (87% for 2013–2017 subgroup *versus* 76% for 2008–2012 subgroup, $p = 0.195$), as shown in Figure 3.

The 1-year PFS was 84.2% for the patients who received ASCT between 2013 and 2017 *versus* 89.5% for the patients who received treatment between 2008 and 2012, with no statistically significant difference, $p = 0.554$.

It is noteworthy that 11 patients were excluded from survival rates calculations because of inability to complete follow up. The two AML patients were excluded because of data insufficiency to generate log-rank estimation for this subgroup (no relapse-related mortality after 3 and 8 years of follow up for these two patients).

Discussion

The median age at diagnosis with multiple myeloma (MM) is 65 years.[19] The most commonly used therapeutic agents include corticosteroids, immune-modulatory drugs (IMiDs; thalidomide, lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib), compounds targeting specific molecules, monoclonal antibodies, and chimeric antigen receptor T cells (CAR-T).[20] In addition, ASCT in combination with high-dose chemotherapy could be considered as a frontline strategy for younger MM patients.[21] Although these novel therapies (e.g. proteasome inhibitors, IMiDs, and monoclonal antibodies) dramatically increased patient's response rate and survival rate, conditioning is still based on conventional chemotherapy regime. Superiority of melphalan, 200 mg/m^2, in comparison with the older regimen of melphalan 140 mg/m^2 and 8 Gy total body irradiation (TBI), is widely demonstrated.[19,20] In our group of patients, patients under 68 years, of fit status, received a high dose of melphalan 200 mg/m^2, while melphalan 140 mg/m^2 was used for the others, especially in case of renal function impairment, with comparable outcome with European and international studies.[15,22–25]

It is well established that lymphoma has diverse biological, histological, and clinical features and thus various prognoses. Despite the remarkable advances in treatment, including the addition of novel monoclonal antibodies, targeted therapies, immune activators, and CAR-T cells, ASCT remains not only a standard-of-care curative option for aggressive NHL, but also an important therapeutic option for indolent NHL.[26]

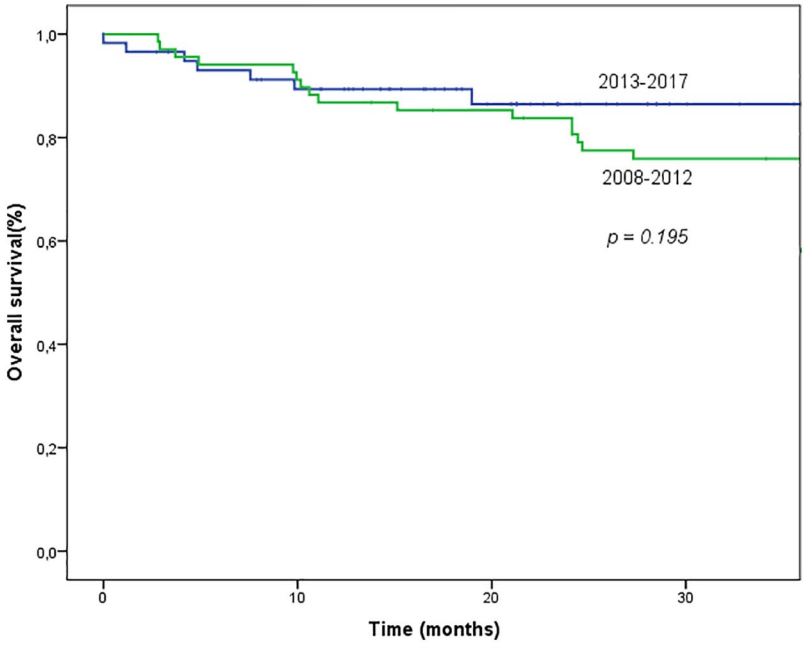

Figure 3. Three-year overall survival (in months) for patients according to ASCT date, 2008–2012 in green, 2013–2017 in blue.

In our cohort for relapsed/chemo-sensitive lymphoma, including high and advanced-stage indolent type, 10-year PFS and OS were compatible with other European cohorts.[25,27–29]

We consider that the main advantage for procedure delegation to our peripheral, small, ASCT center is the continuity of health care services as well as homogeneity between the first line of treatment and ASCT along with its related long-term follow up.[24,25,30–33]

We believe that this aspect, along with better accessibility for the patient's family in order to participate in patient support, has a positive effect on patient physical and mental well-being, especially in the case of the elderly patient population.

We believe, through analysis of these results and their comparison with results from larger centers throughout Europe, that the effect of center size, if any, may be overcome by the proper procedure standardization following international accreditation guidelines, for example, JACIE (Joint accreditation committee ISCT-Europe), good practice training, and monitoring, along with team experience.

The difference observed between the 40% total mortality rate for the less recent group of patients (2008–2012) and 12% for the more recent one (2013–2017) can be explained by the longer period of follow up for the less recent group, including, as expected, more late mortality in the less recent group amplifying the total death rate for this group.

No significant differences in term of OS and PFS were obtained when comparing patients treated before 2013 with those treated between 2013 and 2017. This may be explained by extension of indications of ASCT to more complicated situations and older patients in recent years, and our center's procedural standardization stability during this period may have contributed to this aspect also.

Conclusion

Beyond feasibility, and in the absence of randomized trials studying the role of center size, experience, and procedural standardization on ASCT outcome, these results may suggest that ASCT in peripheral accredited small-sized centers instead of referring patients to distant large central hospitals could be a viable option to facilitate both follow up and access to this treatment, especially for elderly patients.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics statement

The data used in this manuscript is the result of a cross-matching process between documented papered data, electronic data, and clinicians' observations and analysis.

This data processing was done with respect to the Helsinki declaration and applied laws in addition to patients' privacy, after delivering an informed consent. This is considered to be a retrospective data analysis of patients' series, thus, no prior ethical board approval was needed.

Only data that respect the aforementioned aspects could be communicated, thus, it was summarized in the text and preserved by the corresponding author.

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