Leukemia Research 78 (2019) 34–35

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Commentary

Should patient age be an obstacle for high-dose therapy and stem cell rescue?

Diffuse large B-cell lymphoma (DLBCL) is reported to comprise over 30% of all cases of lymphoma in the USA. Using the SEER data, Griffiths et al [1] looked at differences in the treatment and survival in DLBCL patients aged 65 years and older, with a median age at diagnosis of 77 years. Notably, 14% of these patients were 66–69 years old and 22.4% were 70–74 years old, indicating that one third of older DLBCL patients could tolerate presently used standard immuno-chemotherapy.

In the current issue of Leukemia Research, Lemieux et al report a retrospective study focusing on the role of autologous stem cell transplantation (Auto-SCT) in older patients with B-cell lymphoma who were fit and chemo-sensitive [2]. This study assessed a small cohort (n = 90) of consecutive patients (median age 63 years; range 61–69) with non-Hodgkin lymphoma (NHL), including 38% of DLBCL, 36% of follicular B cell lymphoma and 20% of mantle cell lymphoma (MCL), that were treated in a single center between 2008 and 2014. This study is an addition to several other cohort studies demonstrating the benefit of high-dose chemotherapy with stem cell rescue in patients aged 60 years and above.

Nowadays, nobody would think of obstructing the access to therapeutic procedures based on gender or ethnicity. In the analysis by Griffiths et al, a significantly improved overall survival (OS) in the population of DLBCL patients aged ≥65 years, was found between the years 2001 and 2005. However, age older than 70 years was associated with a significantly higher hazard ratio for death both from NHL and other causes, demonstrating an unmet need for an optimal treatment modality in this continuously growing population [1].

I have recently visited my uncle, a 90-year old civil engineer who takes no medications and still practices his morning exercises, including 20 pushups, that he had learned to do as a draftee in the Korean war. I luckily arrived after he completed the morning training as thus I was saved from the necessity to explain why I could not do 20 pushups without having back pain. Such examples emphasize the fact that decision-making regarding patient eligibility for a specific medical procedure should be based on the parameters weighing the patient individual risk related to the procedure against its putative benefit. This is particularly relevant to the places where the national healthcare system is primarily guided by age-related criteria in providing medical services and patients have no other alternatives. To my mind, it is unethical to consider a 65-year old patient with chemo-sensitive disease who has no limiting organ failures as unfit for Auto-SCT, given the currently available supportive care and the amounting literature reporting both good outcomes and low treatment-related mortality among sexagenarians. The EBMT registry analysis of using Auto-SCT in DLBCL patients between years 2000–2005 demonstrates results of 463 patients (18% of the total patients) who were 60–69 years old at transplantation, with 100-day and 1-year non-relapse mortality (NRM) rates of 4.4% and 8.7%, respectively. The relapse rate at 3 years was 38%, while PFS and OS were 51% and 60%, respectively [3].

The study by Lemieux C et al also supports the performance of Auto-SCT in patients up to 69 years old with no limiting comorbidities. The data demonstrate low NRM of 1% at 1 and 5 years post-transplantation, which is in line with other studies reporting transplant-related mortality (TRM) of 2.5–8.7 [3–7]. Similarly, the 5-year PFS and OS of 47% and 60%, respectively, observed in the present study, are comparable to previously reported data [3,5,4–7]. These PFS and OS values are not inferior to those initially reported two decades ago by Philip et al. in young patients [8].

The hematopoietic cell transplantation-specific comorbidity index (HCT-CI) (Sorror score) assessing patient risk during transplantation, wisely, does not include age as an evaluating parameter. Indeed, in the current cohort, the high score ≥3 at time of transplant was associated with more days of intravenous antibiotic therapy, and not with an inferior outcome. These results support the findings by Hosing et al who report a higher toxicity rate with a CI above 2, but no effect on OS [6].

In the seminal article by Philip et al [8], the 5-year EFS in patients undergoing transplantation (median age 43 years; range 18–60) was 46%, while it was 12% only in those receiving conventional salvage chemotherapy and radiation therapy. This 4-fold difference makes any randomized controlled study in older patients unethical and leaves us to evaluate the results of retrospective patient cohorts. Dahi et al reported the outcomes of 202 NHL patients (including, among others, 74 cases of DLBCL and 69 – of MCL) aged 60–74 years (median 65 years) [9]. The majority of DLBCL patients were transplanted in second complete remission (CR) and the majority of MCL patients were transplanted in first CR. The 3-year PFS in these groups were 54% and 67%, respectively with OS of 65% and 89%, respectively. Of interest, the TRM in this cohort was 4% with no difference between low, intermediate or high HCT-CI.

Chihara et al reported the results of the Japanese registry analysis of 484 DLBCL patients aged ≥60, who underwent Auto-SCT between the years 1993 and 2010 [7]. In that cohort of patients with a median age of 64 years (range 60–78), including 39 individuals aged 70 years or above, the NRM on day 100 post-transplantation was 4.1%, with no significant difference between the age groups (60–64, 65–69 and ≥70) even at 3 years post-transplantation. The 3-year relapse rate was 47.7% for the whole group and the multivariate analysis revealed a significant hazard ratio for relapse for age ≥70 years, performance status 2–4, and failure to achieve CR or partial response (PR) prior to Auto-SCT. Remarkably, patients with a chemo-sensitive disease prior to Auto-SCT had a superimposed OS curves in all the three age groups.

In conclusion, the present study strongly supports the available evidence that Auto-SCT should be considered as standard of care in patients aged 60–70 years with a chemo-sensitive disease who are fit for this procedure. The NRM rate in this group is low (about 1–4.4%)

https://doi.org/10.1016/j.leukres.2019.01.010
Received 9 January 2019
Available online 25 January 2019

during the acute 100-day period and the 3-year PFS varies between 48% and 69%. Less solid data are available regarding the outcome of patients older than 70 years. While higher NRM is expected in older patients at a longer follow-up, their current acute TRM is low. This group of patients is also at a higher risk for lymphoma-related mortality, myelodysplastic syndromes and secondary leukemia. The available data suggest that age alone should not be considered a barrier to conducting Auto-SCT in fit NHL patients with a chemo-sensitive disease.

Declarations of interest

None.

Author contribution

Eldad J. Dann: wrote the manuscript, approved the final version of the manuscript

References

[1] R. Griffiths, M. Gleeson, K. Knopf, M. Danese, Racial differences in treatment and survival in older patients with diffuse large B-cell lymphoma (DLBCL), BMC Cancer 10 (2010) 625.
[2] C. Lemieux, I. Ahmad, N. Bambace, L. Bernard, S. Cohen, J.-S. Delisle, et al., Outcome of autologous hematopoietic stem cell transplant in older patients with B cell lymphoma when selected for fitness and chemosensitive disease, Leuk. Res. (2019).
[3] E. Jantunen, C. Canals, A. Rambaldi, G. Ossenkoppele, B. Allione, D. Blaise, et al., Autologous stem cell transplantation in elderly patients (& or =60 years) with diffuse large B-cell lymphoma: an analysis based on data in the European Blood and Marrow Transplantation registry, Haematologica 93 (2008) 1837–1842.
[4] S.H. Gohil, K.M. Ardeshna, J.M. Lambert, M.A. Pule, S. Mohamedbhai, A. Virchis, et al., Autologous stem cell transplantation outcomes in elderly patients with B cell Non-Hodgkin Lymphoma, Br. J. Haematol. 171 (2015) 197–204.
[5] E. Jantunen, C. Canals, M. Attal, K. Thomson, N. Milpied, A. Buzyn, et al., Autologous stem-cell transplantation in patients with mantle cell lymphoma beyond 65 years of age: a study from the European Group for Blood and Marrow Transplantation (EBMT), Ann. Oncol. 23 (2012) 166–171.
[6] C. Hosing, R.M. Saliba, G.J. Okoroji, U. Popat, D. Couriel, T. Ali, et al., High-dose chemotherapy and autologous hematopoietic progenitor cell transplantation for non-Hodgkin's lymphoma in patients &65 years of age, Ann. Oncol. 19 (2008) 1166–1171.
[7] D. Chihara, K. Izutsu, E. Kondo, R. Sakai, S. Mizuta, K. Yokoyama, et al., High-dose chemotherapy with autologous stem cell transplantation for elderly patients with relapsed/refractory diffuse large B cell lymphoma: a nationwide retrospective study, Biol. Blood Marrow Transplant. 20 (2014) 684–689.
[8] T. Philip, C. Guglielmi, A. Hagenbeek, R. Somers, H. Van der Lelie, D. Bron, et al., Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma, N. Engl. J. Med. 333 (1995) 1540–1545.
[9] P.B. Dahi, R. Tamari, S.M. Devlin, M. Maloy, V. Bhatt, M. Scordo, et al., Favorable outcomes in elderly patients undergoing high-dose therapy and autologous stem cell transplantation for non-Hodgkin lymphoma, Biol. Blood Marrow Transplant. 20 (2014) 2004–2009.

Eldad J. Dann[a,b,*]
[a] *Rambam Health Care Campus, Haifa, Israel*
[b] *Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel*
E-mail address: e_dann@rambam.health.gov.il.

[*] Correspondence to: Blood Bank and Apheresis Unit, Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, 8, Ha'Aliya Street, Haifa, 3109601, Israel.