HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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Scientific Comment

Induction therapy and stem-cell mobilization in myeloma, look at the past to plan the future

Rony Schaffel *

Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article history:
Received 17 September 2019
Accepted 17 September 2019
Available online 8 October 2019

High-dose chemotherapy and autologous stem-cell transplant (ASCT) remains the standard of care for first-line therapy in eligible patients with symptomatic multyple myeloma. This is quite remarkable given the number of new drugs incorporated in myeloma therapy after the classical Attal et al. manuscript published 25 years ago showing the superiority of ASCT (using melphalan and TBI and bone marrow as stem-cell source) over an outdated chemotherapy regimen (VMCP-VBAP).[1] This superiority still stands out as shown by the 2019 ASCO report of the FORTE trial when ASCT reduced the risk of early relapse in high-risk patients treated with the triplet carfilzomib, lenalidomide, dexamethasone.[2] Currently, multiple myeloma is the leading indication of ASCT with more than 9000 patients reported to the CIBMTR in 2017.[3]

Complete remission after ASCT has been shown to be predictive of better progression-free survival and overall survival.[4] The disease status after induction therapy and before ASCT is very important as well and more potent combinations are favored.[5,6] Moreover, there is a growing tendency to analyse the impact of clinical trials results in relation of real world data because of the tendency to include younger and fitter patients in clinical trials.[7]

This is the landscape where the article from Figueiredo et al. fits in.[8] The analysis of 472 patients with myeloma included in an ASCT program for more then two decades enable them to show the difference in stem-cell collection efficiency comparing older induction treatments such as VAD (most popular before 2005) and botezomib-based combinations still being used today. Their main finding was that therapy with bortezomib-dexamethasone (BD) was associated with the collection of a higher median number of CD34+ cells/Kg, less failures, less number of apheresis and a better safety-profile than VAD or bortezomib-cyclophosphamide-dexamethasone (CyBorD) therapies. This is in line with other studies such as Musto et al. that evaluated 1348 patients with myeloma and showed that hematological toxicity of the induction therapy, which is higher for CyBorD, was the most importante adverse prognostic factor for stem-cell collection.[9]

Those findings should be viewed with great caution as triplets, such as CyBorD or VTD, are the standard of care for

☆ Please cite this article as: Schaffel R. Induction therapy and stem-cell mobilization in myeloma, look at the past to plan the future. Hematol Transfus Cell Ther. https://doi.org/10.1016/j.htct.2019.09.001

* *Corresponding author at*: Universidade Federal do Rio de Janeiro, Hospital Universitário Clementino Fraga Filho. Rua Rodolpho Paulo Rocco, 255 - Ilha do Fundão, sala 4A12 Serviço de Hematologia Ilha do Fundão, CEP: 21941590, Rio de Janeiro, RJ, Brazil.
E-mail address: rony@hucff.ufrj.br

https://doi.org/10.1016/j.htct.2019.09.001

induction therapy in myeloma patients eligilble for ASCT.[6] As a real-world study, the induction therapy was part of the center's policy and both BD and CyBorD were used during the same period (between 2010 and 2015). Although they showed that the groups were similar in terms of general baseline conditions, the only way to avoid a selection bias would have been the randomization of the patients. Moreover, poor mobilization prognostic factors such as prior radiotherapy, baseline cytopenias and disease response after induction were not compared. Other important features such as baseline cytogenetic risk were not informed.

Almost all the patients were mobilized with variable-dose cyclophosphamide and filgrastim and this had no impact in disease response before high-dose chemotherapy. Given this finding, filgastrim-only mobilization may be a better strategy because it is more predictable and less toxic specially with a preemptive plerixafor strategy.

Given the large time-span of the study it would have been interesting to know if different practices before and after the transplant in the real-world setting would translate into the same outcomes as those reported in the clinical trials. Unfortunately, no survival curve was generated probably because most patients go back to the referral centers and the contact is lost. This information woud add a lot to the study specially considering the comparison between BD (good mobilization but less effective) and CyBorD patients which seem to have comparable follow up.

We are constantly being exposed to clinical trials designed with the aim to test new drugs specially in the myeloma field. In general, follow up is relatively short and outcomes such as response or progression-free survival are being favored over overall survival. Those trials are very importante because myeloma is still a very difficult disease in 2019. However, studies such as the one presented by Figueiredo et al. are of comparable importance because they can provide the information regarding external validity of the different therapies over a longer period of time. Look at the past is the way to reassure our present and make changes for the future.

Conflicts of interest

The authors declare no conflicts of interest.

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