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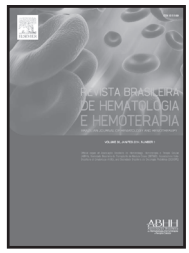

Original article

Outcomes of autologous transplantation for multiple myeloma according to different induction regimens

Edvan de Queiroz Crusoe[a,], Fabiana Higashi[a], Maria Paula Nalesso Camargo Padilha[a], Eliana Cristina Martins Miranda[b], Adriana Alvares Quero[a], Manuella de Souza Sampaio Almeida[a], Ana Lucia M. Peres[a], Priscilla Cury[a], Carlos Chiattone[a], Jose Carlos Barros[a], Vania Tietsche de Moraes Hungria[a]*

[a] *Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo, SP, Brazil*
[b] *Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil*

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ABSTRACT

Background: Induction therapy followed by high-dose chemotherapy and autologous transplantation is the standard treatment for suitable patients with multiple myeloma.
Objective: The aim of this study was to assess whether induction therapy with thalidomide-containing regimens was associated with improved results compared to vincristine, doxorubicin, and dexamethasone, and whether cyclophosphamide, thalidomide, and dexamethasone were associated with better results than thalidomide and dexamethasone.
Methods: The records of 152 patients who underwent autologous transplantation at this institution from August of 2004 to January of 2012 were reviewed, selecting those with at least partial response to a maximum of eight cycles of induction therapy and sufficient follow-up information for analysis.
Results: This study included 89 patients; 44 were female, with a mean age of 55 years (there was a significant trend for increasing age over the years of the study). The median number of induction therapy cycles was four, again with a trend of increase over the years. At least a very good partial response to induction therapy was achieved more often in the cyclophosphamide, thalidomide, and dexamethasone group (61.1%) and in the thalidomide and dexamethasone group (59.2%) than in the vincristine, doxorubicin, and dexamethasone group (16.2%). The overall median progression-free survival was 34 months, with no statistically significant difference between the three groups. The overall median survival was not reached, and there was no significant difference between the three groups; the estimated five-year overall survival was 55%.
Conclusion: Although the quality of responses appeared to be better with thalidomide-containing regimens, these improvements did not translate into improved long-term outcomes. Given its track record, cyclophosphamide, thalidomide, and dexamethasone is currently considered the preferred regimen for first-line induction therapy in the Brazilian public health system.

*Corresponding author at: Faculdade de Ciências Médicas da Santa Casa de São Paulo, Rua Marquês de Itu, 579 - 3º andar, 01223-001, São Paulo, SP, Brazil.
E-mail address: edvancrusoe@gmail.com (E.Q. Crusoe).
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Introduction

The use of induction chemotherapy followed by high-dose chemotherapy and autologous transplantation has become the standard treatment for suitable patients with multiple myeloma, in view of increased response rates and improved overall survival (OS) when compared with conventional chemotherapy.[1-4] In parallel, the use of thalidomide has emerged as an interesting option for the treatment of relapsed or newly diagnosed multiple myeloma.[5-7] Given its typically lower hematologic toxicity than with conventional chemotherapy regimens and its lack of interference with stem-cell mobilization,[8] thalidomide was rapidly incorporated into induction regimens.[9] One of the new combinations that has demonstrated superiority to the classic vincristine, doxorubicin, and dexamethasone (VAD) regimen is thalidomide and dexamethasone (TD).[10] Moreover, randomized trials that assessed triple thalidomide combinations, such as thalidomide, doxorubicin, and dexamethasone (TAD), cyclophosphamide, thalidomide, and dexamethasone (CTD), and bortezomib, thalidomide, and dexamethasone (VTD), have shown significantly improved responses with the triple combinations containing thalidomide, in comparison with corresponding control groups.[11-13]

Patient access to novel agents is limited in the Brazilian public health system, despite the attempt of this system to provide full and comprehensive care to the citizens.[14] However, thalidomide has been available for patients with multiple myeloma through the Brazilian public health system for several years, thus becoming a good option for induction therapy prior to autologous transplantation in the Santa Casa de São Paulo Medical School. The present study aimed to describe results with different induction treatments used in patients with multiple myeloma undergoing autologous transplantation.

Methods

Patient selection for analysis

For inclusion in this study, 152 patients with multiple myeloma who underwent autologous transplantation at this institution from August of 2004 to January of 2012 were retrospectively selected based on eligibility criteria for the current analysis. The key inclusion criterion was indication for autologous transplantation according to institutional guidelines (based chiefly on patient performance status and the presence of comorbidities). At least a partial response (PR) – according to the International Myeloma Working Group (IMWG) criteria – to induction regimens was present in all but two patients, who were referred for transplantation as this was deemed the best therapy for them at the time. The number of treatment cycles during the induction phase was three or four, based on the contemporary institutional protocol, which changed from VAD to TD to CTD over the years. Additional selection criteria were the receipt of a maximum of eight cycles of induction regimens (VAD, TD, or CTD) before transplantation, and enough follow-up information to allow for post-transplantation response assessment, as some patients had returned to their original institution for post-transplantation care. The protocol for the current study was approved by the institutional review board, which waived an informed consent from patients given the retrospective nature of the analysis.

Induction treatment regimens

Patients were treated with one of three induction regimens administered on an outpatient basis: (1) VAD; vincristine, 0.4 mg/day for four days intravenously (IV), doxorubicin, 9 mg/m^2/day for four days IV, and dexamethasone, 40 mg/day on days 1 to 4, 9 to 12, and 17-20 orally; (2) TD; thalidomide, 100 to 200 mg/day according to tolerance, and dexamethasone 40 mg/week orally every 28 days continuously; or (3) CTD; cyclophosphamide, 50 mg/day orally, thalidomide, 100 to 200 mg/day according to tolerance, and dexamethasone, 40 mg/week orally every 28 days continuously. The cyclophosphamide schedule was based on the GBRAM 0002 CTD protocol (NCT01532856),[15] comparing three different combinations with thalidomide for patients not eligible for autologous transplantation. Patients treated with VAD underwent transplantation from August of 2004 to September of 2009; those treated with TD, from May of 2007 to June of 2011; and those treated with CTD, from February of 2009 to January of 2012. Mobilization was performed with granulocyte colony-stimulating factor (G-CSF) alone (15 to 20 µg/kg/day for five days) for all patients in the TD and CTD groups, and in ten patients in the VAD group. Twenty-nine patients in the VAD group were mobilized with cyclophosphamide (4 g/m^2) + G-CSF (10-15 µg/kg/day); of note, 28 patients in this group came from the randomized GBRAM 0001 trial (NCT01296503),[16] designed to assess the role of thalidomide with or without dexamethasone as a maintenance therapy for patients after a single autologous transplantation. All patients had infection prophylaxis with trimethoprim-sulfamethoxazole (800/160 mg four times a week) during induction and after transplantation. Patients who received thalidomide during the induction treatment were given aspirin (100 mg/day) for prophylaxis of deep vein thrombosis, unless contraindicated.

Response assessment

During induction treatment, patients were examined monthly for response using the IMWG criteria, without evaluation of the free light chains.[17] A further category [minimum response (MR)], defined by the European Bone Marrow Transplantation (EBMT) criteria, was added in the evaluation of response, which is defined as a reduction in the monoclonal component by more than 25%, but less than 50%.[18] An overall response to induction treatment was considered when the response was at least a PR by the IMWG criteria or MR by the EBMT criteria. Patients were reassessed for response at approximately 100 days after transplantation. Response improvement was considered when the response changed between the end of the induction phase and after transplantation from PR to at least a very good PR (VGPR), or if VGPR was maintained between the two phases. None of the patients analyzed in the current study had a failed induction treatment, since all underwent transplantation.