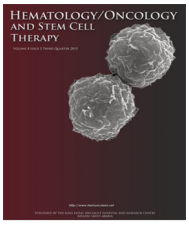
Hematol Oncol Stem Cell Ther (2017) xxx, xxx–xxx

Available at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/hemonc



Comparison of cyclophosphamide–thalidomide–dexamethasone to bortezomib–cyclophosphamide–dexamethasone as induction therapy for multiple myeloma patients in Brazil

Suelen Vigolo [a], Joice Zuckermann [b], Rosane Isabel Bittencourt [c], Lúcia Silla [c], Diogo André Pilger [a,*]

[a] *Departamento de Análises, Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul — UFRGS, Porto Alegre, RS, Brazil*
[b] *Serviço de Farmácia, Hospital de Clínicas de Porto Alegre — HCPA, Porto Alegre, RS, Brazil*
[c] *Serviço de Hematologia e Transplante de Medula Óssea, Hospital de Clínicas de Porto Alegre — HCPA, Porto Alegre, RS, Brazil*

Received 31 October 2016; accepted 8 May 2017

KEYWORDS
Multiple myeloma;
CTD;
VCD

Abstract
Objective/background: Chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) remains the standard treatment for multiple myeloma (MM). Thalidomide or bortezomib may be combined with cyclophosphamide and dexamethasone, in what are known as the CTD and VCD protocols, respectively. The objective of this study was to evaluate the clinical characteristics and response rates obtained with CTD and VCD, observing whether the inclusion of bortezomib to treat MM patients in Brazil increases therapeutic efficiency.
Methods: Forty-three MM patients treated with induction protocols CTD and VCD between January 2010 and March 2015 were included. The parameters analyzed were staging, frequency of comorbidities prior to treatment, response rates obtained at each induction cycle, progression-free survival, and overall survival of patients.
Results: Very good partial response and complete response obtained with the VCD protocol were superior, compared with the CTD treatment. The presence of comorbidities was similar

* Corresponding author at: Laboratório de Análises Bioquímicas e Citológicas, Departamento de Análises, Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, Av. Ipiranga 2752, Bairro Santana, CEP 90610-000 Porto Alegre, RS, Brazil.
E-mail address: diogo.pilger@ufrgs.br (D.A. Pilger).

http://dx.doi.org/10.1016/j.hemonc.2017.05.027

Please cite this article in press as: Vigolo S et al., Comparison of cyclophosphamide–thalidomide–dexamethasone to bortezomib–cyclophosphamide–dexamethasone as induction therapy ..., *Hematol Oncol Stem Cell Ther* (2017), http://dx.doi.org/10.1016/j.hemonc.2017.05.027

in the two groups, except kidney failure, which prevailed in the VCD group. Also, 78.3% and 48.3% of patients treated with the VCD and CTD protocols underwent autologous HSCT, respectively. In patients given the VCD protocol, 45.5% had complete response before autologous HSCT. Among those given CTD, this number was only 7.1% ($p = 0.023$). Disease progression after autologous HSCT did not differ between the two groups.

Conclusion: VCD afforded better responses than the CTD protocol, and improved patient condition before autologous HSCT. However, more studies are necessary including more patients and addressing various clinical conditions, besides the analysis of cost-effectiveness of these treatments.

Introduction

Multiple myeloma (MM) is a malignant neoplasm of B cells characterized by the uncontrolled proliferation of plasma cell in the bone marrow and by the presence of monoclonal protein (M-protein) in serum and urine. The condition represents 1% of all neoplasms and 13% of hematologic neoplasms [1]. The main clinical manifestations of MM are bone disease, kidney failure, hypercalcemia, and high risk of developing infection [1,3].

Currently, several therapeutic protocols are used to treat MM [4]. Induction chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) continues to be the standard treatment to patients that are eligible for transplantation [5,6]. Phase II studies have suggested the use of protocols based on three drugs during the induction stage, although four classes of drugs are commonly used, such as corticosteroids, alkylating agents, immunomodulators, and proteasome inhibitors [7,8]. In recent years, proteasome inhibitors such as bortezomib and immunomodulators such as thalidomide have promoted considerable clinical progress in the treatment of MM [9,11].

Thalidomide acts against MM cells, and may be prescribed both at remission and in a recently diagnosed disease, mainly when combined with other agents, such as dexamethasone. The reason for including thalidomide in induction therapy strategies to treat patients eligible for transplant is due to the better response rates and progression-free survival, when compared with strategies that do not include the drug. Thalidomide does not cause myelosuppression, and the good overall tolerance as well as the acceptable incidence of side effects is further advantages in using the drug in induction strategies [12]. Currently, the Brazilian health service includes thalidomide as one of the drugs used in induction therapy before autologous HSCT [5,13]. The cyclophosphamide, thalidomide, and dexamethasone (CTD) drug protocol are the most efficacious, with good response rates and less adverse effects, compared with more traditional strategies [1,13]. Although some studies have discussed the good results of thalidomide in induction therapy such as prolonged progression-free survival and good overall survival, the drug has also been shown to induce no improvement in overall survival [13]. The main adverse effects of thalidomide are peripheral neuropathy, constipation, and somnolence, though deep vein thrombosis, pulmonary embolism, and fatigue are also observed in some cases [14,16]. In Brazil, thalidomide is used because its analog lenalidomide is not approved by the country's drug control authority.

Bortezomib (Velcade) was the first proteasome inhibitor approved by the USA Food and Drug Administration for the treatment of MM and mantle cell lymphoma [17,18]. The drug acts in the ubiquitin–proteasome pathway, inhibiting proteasome 26S, an enzyme that degrades abnormal proteins, mainly those with a role in the cell cycle [17,18]. Importantly, the prescription of bortezomib is indicated by the Diagnostic and Therapeutic Guidelines Multiple Myeloma, and the clinical results have been promising both in the treatment of relapsing and refractory MM [14], and of newly diagnosed cases of the condition [21,22]. However, the treatment with bortezomib is rather costly, and Brazil's national health service does not reimburse therapy costs privately paid by patients [20]. Besides being the treatment of choice for patients who may or may not be eligible for autologous HSCT [19], prescription of bortezomib is indicated in maintenance therapeutic protocols due to increased survival, compared with conventional treatments [18,22]. The bortezomib–cyclophosphamide–dexametha sone (VCD) protocol affords good results and fast response. Although peripheral neuropathy may be one of the adverse effects of VCD, toxicity of the protocol is manageable and may be reverted [21,23]. Protocols based on bortezomib are prescribed to patients who are eligible or not for transplantation. When followed by HSCT and maintenance therapy, bortezomib protocols are prescribed to high or intermediate risk patients or even to those that present the t(4;14) translocation. The reasons are the good complete response (CR) rates afforded by bortezomib and the power to maintain them. Bortezomib protocols are also the main choice in the early treatment of acute kidney failure caused by light-chain nephropathy, since the pharmacokinetics and the primary metabolic pathway of the compound are not affected by kidney failure [18,22,24]. Although peripheral neuropathy and thrombocytopenia are the main adverse effects of bortezomib, and the compound has only a weak relationship with increased risk of thromboembolism [11,25].

An indirect systematic review comparing melphalan, prednisone, and bortezomib with melphalan, prednisone, and thalidomide did not observe any difference in progression-free survival or in overall survival, although the melphalan, prednisone, and bortezomib scheme were shown to induce better CR and less adverse effects [27].

Please cite this article in press as: Vigolo S et al., Comparison of cyclophosphamide–thalidomide–dexamethasone to bortezomib–cyclophosphamide–dexamethasone as induction therapy ..., *Hematol Oncol Stem Cell Ther* (2017), http://dx.doi.org/10.1016/j.hemonc.2017.05.027