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LETTER TO THE EDITOR

Lomustine use in combination with etoposide, cytarabine and melphalan in a brief conditioning regimen for auto-HSCT in patients with lymphoma: the optimal dose

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Autologous hematopoietic SCT (auto-HSCT) is widely employed as consolidation therapy in aggressive Non-Hodgkin lymphoma (NHL) and relapsed or refractory classic Hodgkin's lymphoma. However, there is no evidence regarding the best conditioning regimen to be used. New schemes have therefore been proposed to reduce the toxicity, costs related to the procedure and hospitalization time, without compromising the quality of life and survival of patients.[1] The maximum recommended dose of lomustine (CCNU) associated with etoposide and cyclophosphamide has been 600 mg/m^2.[2,3] However, when it is associated with a combination of etoposide, ara-C and cyclophosphamide, or etoposide, ara-C and melphalan, a dose of 200 mg/m^2 has been used.[4–6]

Although the success of auto-HSCT depends on several variables, the lower the toxicity and the duration of neutropenia the smaller the treatment-related mortality.

Given that lomustine has low pulmonary toxicity, is easy to administer, and does not yet have a defined maximum tolerated dose (MTD) when used in combination with melphalan, ara-C and etoposide for conditioning regimens in auto-HSCT in patients with lymphoma, we proposed to carry out a phase 1 study with dose escalation of lomustine.[2] The study was approved by the local ethics committee under the number 139-420-2011, CAAE 0102.0.420.000-11.

To determine the MTD of lomustine we realized a prospective study with a traditional 3:3 dose scaling, with three cohorts involving three patients. If a patient presented dose-limiting toxicity (DLT), three more patients were included in the same cohort. If two patients exhibited DLT, then the dosage used by that cohort of patients was considered as exceeding MTD and another intermediate dose to the one previously used was tested. The absence of medullary grafting or platelets after 30 days of infusion of HSC, or the presence of grade 4 non-hematologic toxicity, or grade 3 non-hematologic toxicity, such as a fever, infection, skin rash, fatigue, mucositis, electrolyte imbalance, dehydration, pain, glucose intolerance, pulmonary toxicity, acute toxicity related to treatment or death by any cause, was defined as DLT.

The initial cohort received lomustine (Citostal) at a dose of 200 mg/m^2 (L200), and the subsequent cohort at a dose of 400 mg/m^2 (L400). Because L400 exceeded the MTD, a third cohort with lomustine at a dose of 300 mg/m^2 (L300) was analyzed. The lomustine was administered on day 4 of conditioning, the other drugs were administered in the following days and doses: etoposide 1000 mg/m^2 (day 3), cytarabine 4000 mg/m^2 (day 2) and melphalan 140 mg/m^2 (day 1). The infusion of HSC was administered on day 0 (zero) 24 h after the end of melphalan.

We evaluated 14 patients with a mean age of 36 years (16–58). Six patients had PR and eight were in CR at the time of auto-HSCT. The characteristics of the patients are described in Table 1.

Six patients participated in the cohort L200, and since one out of six (16.5%) presented DLT (death by sepsis), three more patients had to be included in this cohort. In the cohort L400, two out of the two (100%) patients presented DLT (grade 4 gastrointestinal toxicity and sinusoidal obstruction syndrome). Given that 400 mg/m^2 of lomustine proved to exceed the MTD, another cohort with lomustine at a dose of 300 mg/m^2 (L300) was evaluated. From the three patients initially analyzed, one out of three (33.3%) presented reversible grade 4 neurological toxicity, which meant that three more patients had to be included in this cohort. In the end, the dose of 300 mg/m^2 was determined to be the the MTD of lomustine. The main toxicities observed in patients according to the WHO (World Health Organization) criteria are described in Table 2.

The patients received an average of 6.91×10^6 (1.37 to 18.8×10^6) CD34+ cells per kg. The average length of hospitalization was 22 days (15–70) and the mean duration of neutropenia (neutrophil count $< 500/mm^3$) was 7.8 days (6–18), which was below our historical control of 13 days observed with the CBV protocol (cyclophosphamide, 1.2 g/m^2/day on day -6, -5, -4 and -3; Carmustine, 300 mg/m^2 on day -6; Etoposide, 200 mg/m^2/day, 12/12 h on day -6, -5 and -4).[7]

The grafting of neutrophils and platelets occurred on day +10 and day +12 after auto-HSCT, respectively. Interestingly, we observed a significant reduction in the need for hemocomponents compared with our historical series. Only 6/14 (42.8%) patients needed RBC transfusion and 4/14 (28.5%) patients did not require any transfusion support.

Table 1. Characterization of patients

Characteristics	N	%
Gender		
Male	8	57.1
Female	6	42.9
Hodgkin lymphoma		
Nodular sclerosis	7	50
Mixed cellularity	1	7.1
Non-Hodgkin Lymphoma		
Diffuse large B-cell lymphoma	3	21.4
Follicular lymphoma	1	7.1
Mantle cell lymphoma	1	7.1
T-cell lymphoma, NOS	1	7.1
Bulky		
Yes	8	57.1
No	6	42.9
Status		
Partial remission	6	42.9
Complete remission	8	57.1

Abbreviation: NOS = not otherwise specified.

Table 2. Toxicities of the analyzed patients

Toxicity	N	%
Temporary alopecia		
Grade I	0	0
Grade II	2	14.3
Grade III	12	85.7
Grade IV	0	
Mucositis		
Grade I	2	14.2
Grade II	1	7.1
Grade III	1	7.1
Grade IV	0	0
Gastro-intestinal toxicity		
Grade I	4	28.5
Grade II	2	14.2
Grade III	3	21.4
Grade IV	0	
Cutaneous toxicity		
Grade I	1	7.1
Grade II	0	0
Grade III	0	0
Grade IV	0	0
Renal toxicity		
Grade I	1	7.1
Grade II	0	0
Grade III	0	0
Grade IV	0	0
Neurological toxicity		
Grade I	1	7.1
Grade II	0	0
Grade III	0	0
Grade IV	0	0
Sinusoidal obstruction syndrome	2	14.2
Infection	7	50

Our results confirm recent study data, which found low toxicity and a medullary grafting time similar to ours using lomustine at a dose of 200 mg/m^2, also associated with ara-c, etoposide and melphalan.[5] In the same way, higher doses of lomustine have been used in other chemotherapy schemes because of its lower pulmonary toxicity when compared with carmustine. Pulmonary toxicity usually occurs with lomustine when doses higher than 1000 mg/m^2 are used.[2,3]

In our study we were therefore able to develop a new protocol using conventional doses of lomustine, which allowed us to reduce the hospitalization time and the days of conditioning, but without reducing the number of drugs recommended or the planned total dose. In addition, we reduced the period of neutropenia and the hospitalization time compared with the conditioning protocol previously used in our institution.

At the same time, we evaluated the MTD of lomustine in association with ara-c, etoposide and melphalan. We observed 1/14 (7.2%) deaths from pneumonia during the hospitalization and 3/14 (21.4%) patients presented grade 4 toxicity, one with a dose of 300 mg/m^2 and two with 400 mg/m^2. We therefore established the MTD to be 300 mg/m^2 for lomustine combined with high doses of etoposide, Ara-C and melphalan in conditioning of auto-HSCT in patients with lymphoma.

In conclusion, the LEAM protocol (lomustine, 300 mg/m^2 on day 4; etoposide, 1000 mg/m^2 on day 3; cytarabine, 4000 mg/m^2 on day 2 and melphalan, 140 mg/m^2 on day 1), proved to be a feasible conditioning regimen that could be administered rapidly, associated with a short period of neutropenia and acceptable toxicity. We are currently conducting a phase 2 study with a dose of 300 mg/m^2 of lomustine.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KB dos Santos[1], LJ Costa[2], A Atalla[3], J Pereira[4] and AE Hallack-Neto[3]
[1]*Universidade Federal de Juiz de Fora, Division of Hematology and Bone Marrow Transplantation, Minas Gerais, Brazil;*
[2]*Medical University of South Carolina, Division of Hematology/Oncology, Charleston, SC, USA;*
[3]*Universidade Federal de Juiz de Fora, Division of Clinical Medical, Minas Gerais, Brazil and*
[4]*Universidade Federal de São Paulo, Division of Hematology, São Paulo, Brazil*
E-mail: abrahallack@uol.com.br

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