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Modified Magrath IVAC regimen as second-line therapy for relapsed or refractory aggressive non-Hodgkin's lymphoma in developing countries: The experience of a single center in Brazil

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Abstract

Background: The purpose of this retrospective study was to investigate the efficacy, toxicity and mobilization rate after modified Magrath IVAC (mIVAC) chemotherapy regimen prescribed in relapsed disease (RD) or primary refractory disease (PRD) in aggressive non-Hodgkin lymphoma (NHL).
Patients and methods: Twenty-four patients (16 males, 8 females) aged 18–59 years (median age 37 year) were analyzed. The most frequent histopathological subgroup was diffuse large B-cell lymphoma (DLCL-B) ($n = 21/24$), 13 (54%) were considered RD and 11 (46%) PRD. The mIVAC consisted of ifosfamide (IFM), high dose cytarabine and etoposide repeated every 28 days.
Results: The overall response (OR) after three cycles of mIVAC was 66. 6%. Among the patients with PRD, OR was 45.5% (5 out of 11) and with RD was 86.4%, $p > 0.05$, however, it was observed in RD better complete response (CR) than PRD $53.8 \times 9.1\%$ ($p < 0.05$). Eighty-eight percent (14 out of 16) of patients with chemosensitive disease to mIVAC underwent autologous stem cell transplantation (ASCT). The median number of collected CD34+ cells was 2.86×10^6 (range 2.17×10^6 to 4.9×10^6). The median overall survival rate (OS) for chemosensitive to mIVAC was 16.3 months, with a median follow-up of 16 months. Grades III–IV neutropenia was observed in 85.6% per cycles and grades III–IV thrombocytopenia in 87.5%. Grades III–IV febrile neutropenia was the most common nonhematological toxicity, it occurred in 28% of the cycles and no deaths by toxicity were observed.
Discussion: Although a statistic comparative study was not carried out for these 24 patients, the rate of OR to mIVAC was alike the other second-line infusion regimens. The mobilization failure rate was 57.1% and it was similar to other regimens with high dose cytarabine, but it did not limit performed ASCT.

Keywords: Second-line therapy; Relapsed; Refractory; Aggressive non-Hodgkin's lymphoma

1. Introduction

Non-Hodgkin lymphoma is the fifth most common cancer in Brazil with incidence of 55,000 cases/year [1]. Approximately 45% of aggressive NHL patients that are treated with standard anthracycline regimens present relapsed disease (RD) or primary refractory disease (PRD) [2]. These patients should be submitted to salvage chemotherapy. The currently available salvage regimen combines platinum compound with dexamethasone and cytarabine (DHAP) [3], or ifosfamide (IFM) with methotrexate and etoposide (IMVP-16) [4], or a combination of IFM, carboplatin and etoposide (ICE) [5]. However, there are no comparative studies between these regimens and no uniformly effective second-line regimen has been demonstrated. Their overall response (OR) ranges from 45 to 60% and poor long-term survival is observed. The only therapy that has improved these results is the high-dose chemotherapy (HDCT) followed by autologous

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stem cell transplantation (ASCT), but it is only effective for chemosensitive patients in second-line regimen [6–9]. In developing countries, there is a reduced number of hospital beds. Thus, it was decided to prescribe the B regimen of CODOX-M/IVAC protocol [10], because it could be applied on an outpatient basis. This chemotherapy regimen consists of drugs that are not used in first-line treatment but are efficient to NHL with acceptable toxicity and could also be administered on an outpatient basis. The purpose of this retrospective study was to investigate the efficacy, toxicity and mobilization rate after ambulatory modified Magrath IVAC (mIVAC) regimen in RD or PRD aggressive NHL patients.

2. Patients and methods

2.1. Selective criteria

The salvage chemotherapy regimen included RD or PRD patients that were treated with at least one regimen at the Hematology Service of the Clinical Hospital of São Paulo University (São Paulo, Brazil) from January 2001 up to December 2003. The age range was 18–60 years and the performance status one or two. It was included patients with aggressive NHL (according to the World Health Organization Classification) [11] that received at least one chemotherapy regimen with anthracycline. Only patients with diffuse large B-cell lymphoma or unspecified peripheral T-cell lymphoma were included. RD or PRD were found through physical exams and computerized tomography (CT) scans of the neck, chest, abdomen and pelvis. This study was a retrospective analysis, thus data were only obtained by reviewing medical records. The status of the patients at registration into mIVAC regimen was classified by the international prognostic index (IPI) [12]. It was excluded patients with positive serology anti-HIV.

2.2. Chemotherapy regimen

The planned three cycles mIVAC salvage chemotherapy treatment administered on an outpatient basis consisted of the following: IFM (1500 mg/m^2) was administered in 1 h on an outpatient basis on 1 to 5 days of each cycle, mesna (300 mg/m^2) was administered in bolus infusion at 0, 4 and 8 h after IFM; cytarabine (2000 mg/m^2) was administered twice a day in 1 h at 8:00 a.m. and 4:00 p.m. on 1 to 2 days of each cycle; and etoposide (60 mg/m^2) was administered on 1 h infusion on 1 to 5 days. Beginning on Day 7, granulocyte colony stimulating factor (G-CSF) was administered subcutaneously at 300 μg/day until the absolute neutrophil count was more than 1.5×10^9 L^{-1} for two consecutive days. It was prescribed that the cycles would be administered at 4-weeks interval. Dose reductions were not allowed, but treatment was delayed until the absolute neutrophil count was more than 1.5×10^9 L^{-1} and the platelet count was more than 100×10^9 L^{-1}. All patients received prophylactic antibiotic for Pneumocystosis infection with trimethoprim-sulphamethoxazole three times/week. CT scans of the neck, chest, abdomen and pelvis were performed after three cycles. Chemosensitive patients in mIVAC, with OR, underwent ASCT according to the BEAM (BCNU, etoposide, cytarabine and melphalan) [13] or the CVB (cyclophosphamide, etoposide and carmustine) regimen [14]. Peripheral blood stem cells were mobilized after the third cycle of mIVAC chemotherapy using cyclophosphamide 120 mg/kg and G-CSF 10 mcg/kg/day SC. For the patients that it was not possible to mobilize stem cells, bone marrow was collected by aspiration. Refractory patients and patients with progressive disease were treated with alternative chemotherapy.

2.3. Assessment of response and toxicity

Response to mIVAC regimen was assessed after three cycles through physical exams and CT scans of neck, chest, abdomen and pelvis. A bone marrow biopsy was also obtained after three cycles in case it was positive before the treatment. Complete response was defined as complete disappearance of all detectable clinical examination and all disease-related symptoms with normal CT scans of neck, chest, abdomen and pelvis. Partial remission (PR) was defined as a decrease more than 50% in tumor size measured by it greatest transverse diameter (GTD) in CT scans, with no evidence of new sites of disease. Refractory and progressive response were defined as a decrease less than 50% in tumor size measured by it GTD in CT scans or increase of tumor size or new sites of disease in CT scans, respectively. Toxicity was graded to National Cancer Institute common toxicity criteria.

2.4. Statistical methods

Categorical variables in the analyses of OR were compared using the two-sided Fischer exact test to detect difference at the 0.05 level of significance. Overall survival (OS) was measured from the time of diagnosis of RD or PRD until death, or progression from NHL, or last day of clinic evaluation [15]. Survival curves were constructed using the method of Kaplan and Meier [16]. Differences in survival rates between individual patients' groups were analyzed using the log-rank test [17]. SPSS 10.0 software was used.

3. Results

3.1. Patients

Twenty-four RD or PRD aggressive NHL patients (16 males, 8 females) were treated with mIVAC regimen. The patients aged 18–59 years (median age 37). Twenty-one patients presented DLCL-B and three were classified as having unspecified peripheral T-cell lymphoma. Ten patients were at high or high-intermediate IPI score. RD group was formed by 13 patients and PRD by 11 (Table 1). Only 12.5%