Etoposide e dexametasona como primeira linha em idosos com comorbidades portadores de Linfoma Difuso de Grandes Células B

Etoposide-dexamethasone-based first-line therapy in aged DLBCL patients with severe comorbidities

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Mr. Editor

A third of non-Hodgkin lymphoma (NHL) patients are diagnosed at over 75 years of age and the predominance of the Diffuse Large B-cell Lymphoma (DLBCL) sub-type is found in 40% of the cases.[1] In spite of this, the number of aged patients in clinical trials is rather small with the median age being about 50 years old. Three DLBCL patients, including one suffering from a severe heart comorbidity, who were treated with an alternative oral chemotherapeutic regimen at the Hematology Service of HC-FMUSP are described.

Case 1

An 86-year-old woman with dilated myocardiopathy taking digitals, with 40% ejection fraction measured by echocardiography, history of several hospitalizations due to heart complications was referred to the Hematology Service of the HC-FMSP and diagnosed as DLBCL, ECIIB with low intermediate IPI. Therapy used etoposide (50 mg/day) for 5 days plus dexamethasone (20 mg/day) for 5 days during 6 cycles. After the 2nd cycle the patient presented with complete remission but did not suffer from clinical toxicity during the treatment. Complete remission was maintained to the last evaluation with overall survival and disease-free survival rates of 35.1 and 31.9 months, respectively. The patient died of heart failure.

Case 2

A 90-year-old female Jehovah's Witness, with no pathological records, was referred to the Hematology Service of the HC-FMSP and diagnosed as DLBCL, Ki 67 ranging from 80 to 90%, ECIIx A, (bulky cervical tumor of 15 cm) with low intermediate IPI. Prescribed treatment involved etoposide (100 mg/day) for 21 days and dexamethasone (20 mg/day) for 7 days, although 250 mg/day for 8 days was incorrectly used. The patient evolved to Grade 3 non-febrile neutropenia with no clinical evidence of infection, which was reverted by using GCSF, obtaining a 60% mass tumor reduction soon after the 1st cycle. After the 2nd cycle the patient achieved complete remission and was submitted to 3 cycles in total when, in a joint decision, consolidation with radiotherapy was chosen. Complete remission was kept up to the last evaluation, with overall survival and disease-free survival rates of 39.4 and 38.2 months, respectively.

Case 3

A 94-year-old woman was referred the Hematology Service of the HC-FMUSP and diagnosed as DLBCL, EC IIIsxA (x = bulky cervical tumor of 13 cm) with high risk IPI. Treatment was started using etoposide (50 mg/day) and dexamethasone (12 mg/day) in both alternate and continuous schemes. She achieved complete remission after the 4th cycle, with a total of 8 cycles being performed. She kept complete remission up to the last evaluation with overall survival and disease-free survival rates of 20.3 and 17.1, respectively.

In Brazil 49.9% of deaths among over 65-year-old patients are with malignant tumors proving to be the third most common cause of death in this group. Data from IBGE (Brazilian Institute of Geography and Statistics) show an increase in the aged population from the current 7.8% to 13% by 2020. An increased life expectancy will thus require clinical trials directed at the elderly.

As for aged DLBCL patients, when no comorbidity is found, anthracycline regimens (CHOP, CTVP) are preferred to mitoxanthrone or non-anthracycline regimens. The former have been tested in an attempt to reduce cardiotoxicity, though with anti-neoplastic effects similar to anthracyclic drugs.[2,3] Despite the fact that the CHOP protocol has been considered the standard treatment for DLBCL, with better results compared to third-generation protocols, the remission rate for these patients is 40%. Adding rituximab to the regimen has resulted in better complete remission, disease-free survival and overall survival rates for Bcl2+ patients, although this is far from becoming an everyday practice in developing countries and cannot be considered a non-toxic regimen.[3]

Older age has had a negative impact on the survival of patients who develop aggressive lymphomas. According to the IPI analysis, age over 60 years old is considered an adverse prognostic factor for relapse. Old age is also related to comorbidities.[4] Recent studies on aged NHL patients showed that 60% of them had associated diseases at the

time of diagnosis. The risk of death in this group was twice as high as the group with no comorbidities, regardless of IPI.5 As this group of patients is often excluded from clinical trials, the results found in most studies may not apply.

VP-16 is an effective topoisomerase II inhibitor in refractory and relapsed NHL patients. Since this enzyme is inhibited at specific stages of the cell cycle, long-term etoposide treatment increases its efficacy, with a larger number of tumor cells being exposed to the drug.[6]

In our study all the three patients treated with etoposide and dexamethasone achieved complete remission with low toxicity levels. Both disease-free survival and overall survival were significantly long despite the patients' ages and severe comorbidities. Although only a small number of patients were tested, VP-16 and dexamethasone have proved to be an alternative treatment for those patients who do not fit into the standard treatment. It has a low-cost, low-toxicity and is an easy-to-use, effective regimen even for aggressive and bulky mass cases.

Resumo

Pacientes idosos com linfoma difuso de grandes células B (LDGCB) são frequentemente excluídos de estudos clínicos. A utilização de terapias curativas muitas vezes é impossibilitada em virtude das comorbidades apresentadas por esta população ao diagnóstico. Nós adotamos um protocolo alternativo de quimioterapia oral combinando um inibidor da topoisomerase II e dexametasona. Apresentamos os resultados parciais com este protocolo em três pacientes portadores de LDGCB com idade superior a 80 anos e comorbidades severas. Todos alcançaram remissão completa com baixa toxicidade. Esses resultados demonstram que protocolos curativos alternativos devem ser testados em pacientes idosos portadores LDGCB a despeito da presença de comorbidades severas. Rev. Bras. Hematol. Hemoter. 2009;31(1):49-50.

***Palavras-chave**: Linfoma de grandes células; idosos; quimioterapia.*

References

1. Hallack Neto AE, Pereira J, Sabóya R, Beitler B, Pracchia LF, Dulley FL, *et al.* Risk stratification of large B-cell lymphomas. Rev Bras Hematol Hemoter. 2006;28(4):296-300.
2. Bastion Y, Blay JY, Divine M, Brice P, Borderssoule D, Sebban C, *et al*. Elderly patients with aggressive non-Hodgkin's Lymphoma: disease presentation, response to treatment, and survival - a Groupe d'Etude des Lymphomes de l'Adulte study on 453 patients older than 69 years. J Clin Oncol. 1997;15(8):2945-53.
3. Mounier N, Briere J, Gisselbrecht C, *et al*. Rituximab plus CHOP (R-CHOP) overcomes bcl-2-associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL). Blood. 2003;101(11):4279-84.
4. Yancik R, Havlik RJ, Wesley MN, *et al.* Cancer and comorbidity in older patients: a descriptive profile. Ann Epidemiol. 1996;6(5): 399-412.
5. Janssen-Heijnen ML, van Spronsen DJ, Lemmens VE, Houterman S, *et al.* A population-based study of severity of comorbidity among patients with non-Hodgkin's lymphoma: prognostic impact independent of International Prognostic Index. Br J Haematol. 2005;129(5):597-606.
6. Hande KR. The importance of drug scheduling in cancer chemotherapy: Etoposide as an example. Oncologist. 1996;1 (4):234-9.

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