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Artigo / Article

Advanced Hodgkin's lymphoma: Results in 216 patients treated with ABVD in Brazil

Linfoma de Hodgkin em estádio avançado: Resultados do tratamento em 216 pacientes tratados com ABVD no Brasil

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*The outcome of Hodgkin's lymphoma (HL) has markedly improved over the last few decades, placing HL among the human cancers with highest cure rates. However, data about treatment outcomes in developing countries are scarce. From 1996 to 2005, 370 consecutive patients with HL treated in three public institutions in Rio de Janeiro were identified. A total of 216 patients who presented with advanced stage (IIB-IV) HL were selected for the present analysis. Patients with advanced disease were treated with ABVD, complemented or not by radiation therapy. The median follow-up time of survivors was 6.3 years (1-11.8). Fifteen patients died during first-line treatment. The complete remission rate was 80%. The 5-year progression-free survival (PFS) and the 5-year overall survival (OS) probabilities were 69% and 83%, respectively. The 5-year PFS in low-risk and high-risk patients were 81% and 62% (p=0.003), respectively. The 5-year OS in low-risk and high-risk International Prognostic Score patients were 89% and 78% (p=0.02), respectively. The present study provides a representative estimate of current treatment results for advanced HL in public institutions in an urban area in Brazil. It is clear that full treatment can be given to most patients, although those with very low socio-economic status might require special attention and support. Since Brazil is a large country, with substantial inter-regional heterogeneity, a nationwide registry of HL patients is currently being implemented. Rev. Bras. Hematol. Hemoter. 2010;**32**(4):303-307.*

Key words: *Hodgkin disease; chemotherapy; lymphoma.*

Introduction

The outcome of Hodgkin's lymphoma (HL) has markedly improved over the last few decades. Randomized clinical trials conducted by cooperative groups in North America and Europe have identified treatment schedules that provide higher efficacy and lower toxicity, placing HL among the human cancers with highest cure rates.

However, data about treatment outcomes in developing countries are scarce. The aim of this study was to retrospectively analyze the treatment results of advanced stage HL patients treated 'off-protocol' in a community setting, at three public hospitals in Rio de Janeiro.

Patients and methods

Patients' characteristics

From 1996 to 2005, 370 consecutive patients with Hodgkin's Lymphoma (HL), treated on initial diagnosis in

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three public institutions in Rio de Janeiro, were identified and included in the database. A total of 216 patients who presented with advanced stage (IIB-IV) HL were selected for the present analysis. Diagnoses were confirmed on review by three authors using criteria defined in the WHO classification.[1] Expression of CD30 was required for inclusion. Patients with positive HIV serology were excluded. All patients were staged according to the Ann Arbor system. The following baseline clinical characteristics were recorded: gender, age, stage, presence of bulky disease or B symptoms, performance status (ECOG) and blood counts. The International Prognostic Score (IPS) was determined for all patients. Patients were categorized as low risk IPS if they presented with up to two risk factors and as high risk IPS if three or more risk factors were present.

Treatment and response evaluation

All patients were treated with curative intent. Patients with advanced disease were treated with 6-8 cycles of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), complemented or not by radiation therapy according to the attending physician's discretion. Patients who failed primary therapy received either salvage chemotherapy or high-dose chemotherapy with autologous stem cell transplantation.

Response was assessed one month after the end of treatment. Complete remission was defined as the disappearance of all clinical and radiologic evidence of disease.

Statistical analysis

Comparison of categorical variables was performed with the Fisher's exact test (two-sided), while the Mann-Whitney test was used for numeric data. Overall survival was defined as the time interval between the date of diagnosis and the date of death or last follow-up. Progression-free survival was defined as the time interval between the date of initial diagnosis and the date of disease progression or death from any cause, whichever came first. Survival curves were estimated using the product-limit method of Kaplan-Meier and were compared using the log-rank test. The SPSS version 15.0 software (Chicago, IL, USA) was used for data analysis.

Results

A total of 216 advanced stage patients were included in the study. Their median age was 30 years (range, 15-82 years), with 24 being over 60 years of age. The patients' clinical characteristics at diagnosis are shown in Table 1.

Table 1. Clinical characteristics of advanced stage patients at diagnosis

Clinical characteristics	N = 216 (%)
Sex	
Male	120 (56)
Female	96 (44)
Age	
< 45 years-old	159 (74)
≥ 45 years-old	57 (26)
Stage	
IIB	70 (32)
IIIA	24 (11)
IIIB	36 (17)
IVA	21 (10)
IVB	65 (30)
IPS	
0-2	93 (43)
≥3	88 (41)
missing	35 (16)
Performance status	
0-1	177 (82)
≥ 2	35 (16)
missing	4 (2)
Histology	
Nodular sclerosis	154 (71)
Mixed cellularity	42 (20)
Lymphocyte-rich	2 (1)
Lymphocyte depletion	5 (2)
Non-classified	13 (6)
Bulky disease	
No	115 (53)
Yes	101 (47)
B symptoms	
No	45 (21)
Yes	171 (79)
Bone marrow infiltration	
No	164 (76)
Yes	27 (12)
missing	25 (12)

Seventy-seven patients (36%) were treated with 6 to 8 chemotherapy cycles plus radiotherapy (CT+RT) and 113 patients (52%) just received 6 to 8 chemotherapy (CT) cycles. Most remaining patients had HL in stage IIB, and were treated with two to four cycles of chemotherapy followed by radiation therapy.

Outcomes

The median follow-up time of survivors was 6.3 years (rate: 1 - 11.8 years). Fifteen patients died during first-line treatment. The complete remission rate was 80%. Complete remission rates of the low-risk IPS patients and high-risk IPS patients were 88% and 72%, respectively (p= 0.008).

The 5-year progression-free survival and the 5-year overall survival probabilities were 69% and 83%, respectively (Figure 1A and Figure 1B). The 5-year progression-free

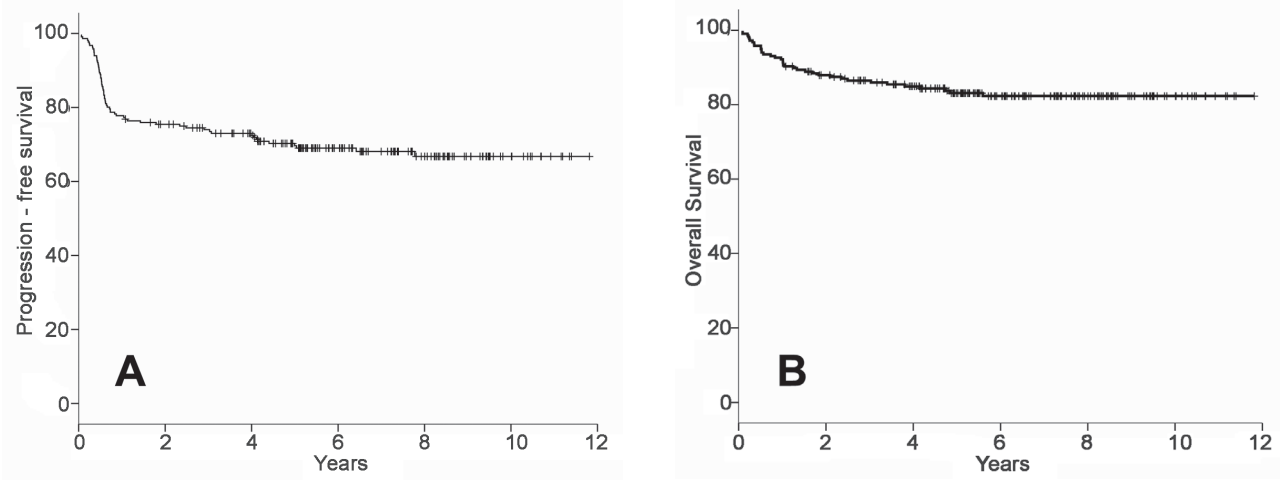

Figure 1. Progression free survival (A) and overall survival curves (B)

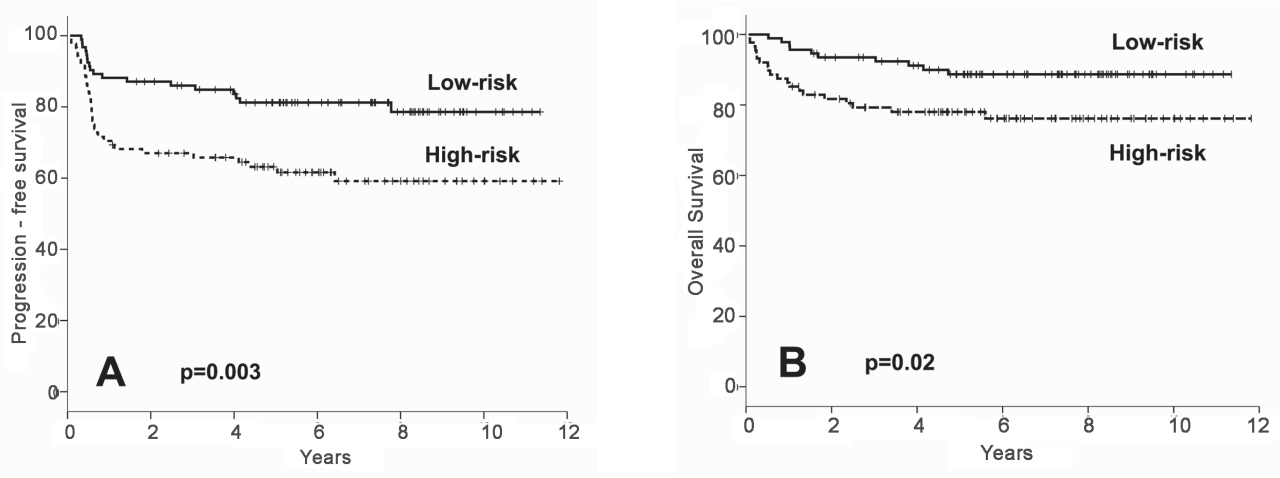

Figure 2. Progression free survival (A) an overall survival (B) curves stratified by the IPS

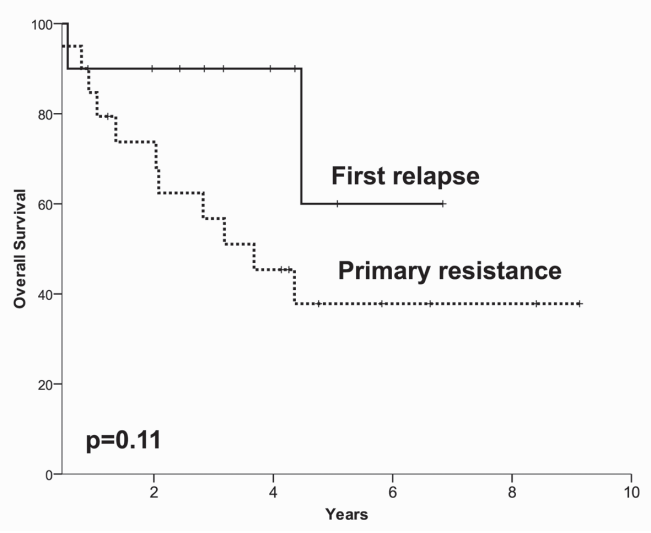

Figure 3. Overall survival curves after high-dose chemotherapy and autologous hematopoietic stem cell transplantation in patients who relapsed and in patients with primary resistance.

survival probability in low-risk and high-risk patients were 81% and 62% (p=0.003), respectively. The 5-year overall survival probability in low-risk and high-risk IPS patients were 89% and 78% (p=0.02), respectively (Figures 2A and 2B).

Second-line treatment

Sixteen patients relapsed after achieving complete remission. Among them, 62% (10/16) were treated with high-dose chemotherapy and autologous hematopoietic stem cell transplantation.

Twenty-nine patients did not achieve complete remission after first-line treatment. Among them, 69% (20/29) were treated with high-dose chemotherapy and autologous hematopoietic stem cell transplantation.

The 5-year OS after high-dose chemotherapy and autologous hematopoietic stem cell transplantation in patients who relapsed and in patients with primary resistance were 60% and 38%, respectively (p = 0.11) (Figure 3).

Discussion

In the current analysis, we sought to describe the outcomes of a long-term retrospective cohort of advanced HL patients treated with ABVD in three public hospitals in Rio de Janeiro, Brazil. The population treated for HL in these hospitals consists mostly of blue-collar workers and their families, as previously reported.[2] Their mean household income, estimated from questionnaires that evaluate the possession of goods and the degree of instruction, is as follows: only 6% have a mean household income of over US$ 3,000 per month; 40% have mean household incomes ranging from US$ 1,000 to 1,800; 31% have mean household incomes ranging from US$ 300-600, and 22% have mean household incomes below US$ 200 per month.

It is well established that patients in underprivileged societies present with malignancies in more advanced stages. There is good evidence of this phenomenon in breast cancer and in colorectal cancer.[3] In studies of HL patients treated in Brazil during the 1980s, most patients presented with advanced disease.[4,5] However, in the present cohort, among 370 patients diagnosed with HL, only 39% had stage III or IV disease, a distribution similar to that reported in developed countries.[6] Whether this represents a shift towards earlier diagnosis remains to be confirmed.

In 2003, the American Intergroup Trial reported the results of ABVD treatment in 443 patients with advanced HL.[7] The complete remission rate was 76%, failure-free at 5 years was 63% and overall survival at 5 years was 82%. Although these results are remarkably similar to the findings in the present study, only patients with stage $IIIA_2$ or higher were included in the Intergroup trial, and no radiotherapy was allowed.

In contrast, in the current study, almost 40% of the patients received radiotherapy after ABVD, and patients with stage IIB and $IIIA_1$ were included. Therefore, while the present results are certainly acceptable, with 83% of the patients with advanced HL alive at 5 years, there appears to be room for improvement, and for more judicious use of radiotherapy.

Fifteen (7%) of our patients died during initial treatment. We previously reported that those early deaths are more common in patients with a lower socio-economic status.[2] There are many potential reasons for this, including comorbidities, longer distance and transportation shortcomings between residences and treatment centers, a lower threshold in identifying symptoms related to life-threatening complications, and lack of social support.

The retrospective nature of this study imposed some limitations that could not be circumvented. Although all patients were treated with ABVD, decisions regarding the number of cycles and the use radiotherapy were often taken by the attending physicians during treatment, according to the interim clinical evaluation, without compulsory pre-allocation to a given treatment strategy. For instance, one patient with a good response after ABVD might have proceeded to radiotherapy, while another with evidence of disease might have been considered as treatment failure and sent for second-line treatment before attempting radiotherapy. Comparisons regarding these treatment variables were therefore avoided. Data regarding long-term follow-up were missing for many patients, and therefore it is not possible to assess whether the frequent use of associated radiotherapy had long-term consequences for these patients.

Conclusion

The present study provides a representative estimate of current treatment results for advanced HL in public institutions in an urban area in Brazil. It is clear that full treatment can be given to most patients, although those with very low socio-economic status might require special attention and support. Since Brazil is a large country, with substantial inter-regional heterogeneity, a nationwide registry of HL patients is currently being implemented.

Resumo

Os resultados do tratamento do linfoma de Hodgkin (LH) melhoraram substancialmente ao longo das últimas décadas e tornaram o LH uma das neoplasias humanas com maior chance de cura. Entretanto, os dados sobre tratamento em países em desenvolvimento são escassos. Entre 1996 e 2005, 370 pacientes consecutivos com LH tratados em três instituições públicas no Rio de Janeiro foram identificados. Destes, 216 em estádio avançado (IIB-IV) foram selecionados para esta análise. Os pacientes foram tratados com o protocolo ABVD (doxorrubicina, bleomicina, vinblastina e dacarbazina). A mediana do tempo de seguimento dos sobreviventes foi de 6,3 anos (1-11,8). Quinze pacientes morreram durante o tratamento de primeira linha. A probabilidade de sobrevida livre de progressão (SLP) em cinco anos e a probabilidade de sobrevida global (SG) em cinco anos foram de 69% e 83%, respectivamente. A SLP nos grupos de baixo risco e de alto risco, de acordo com o "International Prognostic Score", foi de 81% e 62% (p=0,003), respectivamente. A SG em cinco anos nos grupos de baixo risco e de alto risco foi de 89% e 78% (p=0,02), respectivamente. O presente estudo apresenta uma estimativa representativa dos resultados atuais do tratamento do LH avançado em instituições públicas no Brasil. Fica claro que o tratamento completo pode ser oferecido à grande maioria dos pacientes, embora aqueles com baixo status socioeconômico possam exigir atenção especial. Em vista das dimensões continentais do Brasil, com substancial heterogeneidade inter-regional, um registro nacional de pacientes com LH está sendo implementado. Rev. Bras. Hematol. Hemoter. 2010;32(4):303-307.

Palavras-chave: *Doença de Hodgkin; quimioterapia; linfoma.*

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