LONG-TERM OUTCOME OF CHILDREN WITH B-NON-HODGKIN'S LYMPHOMA: RESULTS FROM BRAZILIAN NATIONAL CANCER INSTITUTE

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BACKGROUND

Brazil is a very large country with a remarkable social-economic heterogeneity. There is a compelling requirement for finding treatment strategies applicable to centers or regions with different health care resources. In this scenario, the challenge in Brazil is to plan treatment intensity so that morbidity is manageable while increasing the survival rate.

OBJECTIVES

To evaluate the efficacy and toxicity of the modified B-NHL Berlin-Frankfurt-Münster (BFM) protocol in Brazilian children with B-NHL.

METHODS

Eligibility, staging and diagnosis

From September 1997 to December 2007, 85 untreated patients (age less than 16 yr) were enrolled and treated at the National Cancer Institute, Rio de Janeiro, Brazil. The diagnosis were confirmed according to the morphologic criteria defined by WHO classification. Clinical stage was based on the St. Jude staging system.

Treatment

The patients were stratified by risk factors (Stage and LDH level) and treated with BFM 86/90 (Berlin-Frankfurt-Münster) based protocol. All patients received a cytoreductive phase with prednisone and cyclophophamide. Patients with stage I and II completely resected disease were stratified for group 1. This group received four courses A, B, A, and B. Group 2 included stage II not resected and stage III with LDH level below 2-fold normal value (Figure 1). Therapy in this group consisted of 6 courses A, B, A, B, A, and B. Stage IV patients (BM and CNS involvement) and stage III with LDH level close (6 patients) to or higher than 2-fold the normal value were stratified for the most intensive arm of therapy (group 3). Treatment plan in group 3 consisted of 6 courses AA, BB, CC, AA, BB, and CC. The dose of metotrexate was 2g/m^2 in this group (Table 1).

Statistical analysis

We evaluated event-free survival (EFS) as the time from diagnosis to relapse, progression, death due to any cause and second malignancy. Survival curves were calculated by the Kaplan-Meier method, and comparison was made using the Log-Rank test. The statistical analysis was carried out using the Statistica 8.0 (StatSoft.Inc, USA) program.

RESULTS

The median age of the patients was 6 years (range 1-16 yr); 61 patients were male and 24 patients were female. Of these patients, 69 (81%) had Burkitt's lymphoma, 9 (11%) had diffuse large B-cell lymphoma (DLBL), 3 (3%) Burkitt-like lymphoma, and 4 (5%) were not further classified. According to the St Jude staging system, 18% of patients had stage I/II, and 82% stage III/IV disease (Table 2). At a median follow-up of 43 months, the event free survival (pEFS) for all patients was 80% +/- 4%, with 93% for stages I/II, and most notably, 78% +/- 5% for stage III/IV (Figure 2 A and B). There was statistically significant difference (p = 0.009) in pEFS between the two groups of patients: LDH level lower (69% +/- 7%), and higher than 1000 U/L (94%+/- 3%), respectively (Figure 2 C). The major toxicity complications were myelosuppression and mucositis. Events were as follows: progression during therapy, n = 8; relapse after therapy, n = 4; second malignancy, n = 1. There was only one death from sepsis related to treatment (Table 3).

TABLE 1. Treatment courses of modified BFM 86/90 protocol

Drug	Dose	Day
Prephase		
Cyclophosphamide (IV 1h)	200 mg/m^2	1-5
Prednisone (orally)	30mg/m^2	1-5
Course A		
Ifosfamide (IV 1 h)	800 mg/m^2	1-5
Mesna	800 mg/m^2	1-5
Cytarabine (IV)	150 mg/m^2	4-5 (12-12h)
Vindesine (IV)	100 mg/m^2	4-5
Dexametasone (IV)	10 mg/m^2	1-5
Methotrexate (24 h) *	**500 mg/m^2**	1
IT chemotherapy **		1
Course B		
Cyclophosphamide (IV 1h)	200 mg/m^2	1-5
Doxorubicin (IV 1h)	25 mg/m^2	4-5
Dexametasone (IV)	10 mg/m^2	1-5
Methotrexate (24 h) *	**500 mg/m^2**	1
IT chemotherapy **		1
Course AA		
Ifosfamide (IV 1 h)	800 mg/m^2	1-5
Mesna	800 mg/m^2	1-5
Cytarabine (IV)	150 mg/m^2	4-5 (12-12h)
Vindesine (IV)	100 mg/m^2	4-5
Dexametasone (IV)	10 mg/m^2	1-5
Vincristine (IV)	1.5mg/m^2	1
Methotrexate (24 h) *	**2 g/m^2**	1
IT chemotherapy **		1
Course BB		
Cyclophosphamide (IV 1h)	200 mg/m^2	1-5
Doxorubicin (IV 1h)	25 mg/m^2	4-5
Dexametasone (IV)	10 mg/m^2	1-5
Vincristine (IV)	1.5mg/m^2	1
Methotrexate (24 h) *	**2 g/m^2**	1
IT chemotherapy **		1
Course CC		
Cytarabine (IV 3h)	**2g/m^2**	1-2 (12-12h)
Vincristine (IV)	1.5mg/m^2	1
Etoposide (IV 1h)	150 mg/m^2	3-5
Dexametasone (IV)	10 mg/m^2	1-5
IT chemotherapy **		1

* 1/10 of dose within 0.5 hours, and 9/10 of dose IV over 23.5 hours, leucovorin rescue 15 mg/m^2 at 48, 54, 60, and 66 hours.
** Intratecal chemotherapy with metotrexate, cytarabine, and prednisolone. Doses were adjusted according to age.

Risk Group	Stage	Treatment Plan						
G 1	I , II R	Prephase	A	B	A	B		
G 2	II NR, III LDH < 2X normal value	Prephase	A	B	A	B	A	B
G 3	IV, LLA B, III LDH > 2X normal value	Prephase	AA	BB	CC	AA	BB	CC

LDH, Lactate dehydrogenase; R, complete resection; NR, not resected.

Figure 1. Plan of treatment according to the different risk groups.

TABLE 2. Demographic and clinicopathological features of 85 children with B non-Hodgkin's lymphoma

	Histologic subtype			
	Burkitt's lymphoma	Diffuse Large cell Lymphoma	Burkitt-like Lymphoma	Not classified
N° of patients (%)	69 (81)	9 (11)	3 (3)	4 (5)
Age				
1-4	26	0	2	0
5-9	28	0	0	1
10-16	15	9	1	3
Sex				
Male	48	7	2	4
Female	21	2	1	0
Site*				
Abdomen	48	7	3	4
Bone marrow	16	1	0	0
CNS	5	0	0	0
Head and neck **	23	1	1	0
Other sites ***	19	3	3	1
Clinical stage				
I-II	14	1	0	0
III-IV	35	8	3	4
LDH level				
1000 U/L	27	6	1	3
1000 U/L	41	3	1	1

Classification was based on the morphologic criteria of WHO.
Abbreviations: CNS, Central nervous system involvement; LDH, Lactate dehydrogenase. * Some patients had more than 1 site of involvement. ** Three patients had jaw involvement.*** Other sites included: orbita; testis; liver; kidney.

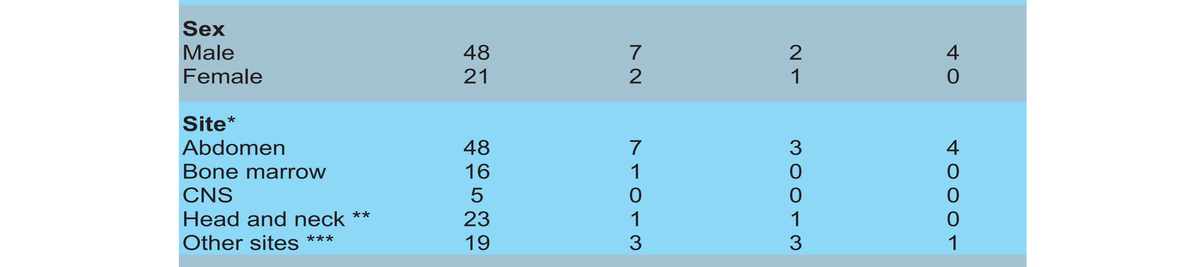

Figure 2. Kaplan-Meier estimate of EFS for all patients (A) , according to the stages of disease (B), and LDH levels.

TABLE 3. Events according to the stage

Description of event	Stage I/II	Stage III	Stage IV
Patients			
Death in induction *	-	1	-
Progressive disease	1	5	2
Relapse	-	1	3
Second malignancy * *	-	-	1
Total = 14	1	7	6

* Early death associated to sepsis
* * Second Burkitt lymphoma of different clonality 4.8 years after the first disease.

CONCLUSIONS

In this study we have shown that the application of treatment tailored by risk is effective in developing countries even in patients with advanced disease. Our strategy was feasible in children with infectious and other clinical complications at diagnosis and the results were comparable to the other contemporary groups, and represented an increase in cure rates in our country.

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