Original article

Risk-adapted chemotherapy without procarbazine in treatment of children with Hodgkin lymphoma

Yi-Jin Gao, Jing-Yan Tang, Ci Pan, Feng-Juan Lu, Hui-Liang Xue, Jing Chen
Shanghai, China

Background: **Because procarbazine is not available in the mainland of China, a risk-adapted chemotherapy without the drug was adopted for children with Hodgkin lymphoma (HL) in two tertiary referral centers for childhood cancer in Shanghai. The objective of the present study was to obtain the results comparable with those of previous studies.**

Methods: **From January 1998 to December 2009, patients below 18 years with newly diagnosed, untreated HL were enrolled in the study. The patients were stratified into risk groups R1 (early stage), R2 (intermediate stage) and R3 (advanced stage). All the patients who had attained a complete remission were not given involved field radiotherapy.**

Results: **Fifty-six patients were eligible for the study. The 4-year event-free survival (EFS) rate was 100%, 80.3%±7.2%, and 62.5%±12.1% for the risk groups R1, R2, and R3, respectively. There was statistically significant difference in EFS between patients with and those without B symptoms (P<0.001). In group R2, the EFS rate was higher for patients treated with chemotherapy combined with radiation (100% *vs.* 75%±8.8%). But no statistical difference was observed (P=0.177). At the time of evaluation (December 31, 2010), secondary malignancy was not observed.**

Conclusions: **A significant fraction of children with early stage or intermediate stage HL can be cured with a chemotherapy regimen without procarbazine. Complete response to chemotherapy seems not to be a determinant to omit radiotherapy.**

World J Pediatr 2013;9(1):32-35

Key words: **chemotherapy; children; Hodgkin lymphoma; outcome**

Author Affiliations: Children's Hospital, Shanghai Medical College, Fudan University, Shanghai, China (Gao YJ, Lu FJ); Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai, China (Tang JY, Pan C, Xue HL, Chen J)

Corresponding Author: Jing-Yan Tang, MD, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China (Tel: 86-21-38626161-5471; Fax: 86-21-58756539; Email: yantfk@gmail.com)

doi: 10.1007/s12519-012-0390-0

Introduction

Hodgkin lymphoma (HL) is rare in Asians.[1] The annual incidence of HL for children under the age of 15 years in Shanghai is 0.6 per million,[2] which is considerably lower than that reported in Western countries. The cure rates for HL in children are very high with use of modern effective chemotherapy in combination with involved field radiotherapy (IFRT). Most current standard chemotherapy for children with HL consists of cyclophosphamide, vincristine, procarbazine, and prednisone (COPP); doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD); or variants of these regimens.[3] Because procarbazine, vinblastine and dacarbazine are not available in the mainland of China, we adopted a chemotherapy regimen without these drugs. The objective of the present study was to obtain the results comparable with those of previous studies. Two tertiary referral centers for childhood cancer in Shanghai participated in the study.

Methods

Patients

From January 1998 to December 2009, 56 patients younger than 18 years with newly diagnosed, untreated HL were enrolled into this retrospective study. The study was approved by the ethical committees of the two participating hospitals.

Diagnostic work-up

The diagnosis was established by histological examination of biopsy specimens from lymph nodes. The patients were classified according to the Lukes-Butler pathologic classification.[4] Staging was dependent on thorough examination, chest radiography, ultrasonography of the neck, axillae, abdomen, and pelvis in addition to computed tomography (CT) of the chest, abdomen, and pelvis. Surgical staging was

not routinely performed. Bone marrow biopsy was mandatory. Clinical staging criteria were defined by the Ann Arbor staging system.[5] "B" symptoms were defined by one or more of the following findings: unexplained weight loss >10%, unexplained recurrent fever >39ºC, or drenching night sweats.

Restaging to determine the response was performed after 2, 4, 6 and 9 cycles of chemotherapy. Complete response was defined as tumors not visible on CT, chest X-ray, or ultrasound. Patients with residual diseases in the mediastinum or abdomen could be considered as showing complete response if there is a 70% reduction of tumor volume or each mass is less than 2 cm.[3] A partial response was defined as a <70% but ≥50% reduction in the tumor volume on physical examination, ultrasound or CT scan. Follow-up examinations were performed quarterly during the first year, semiannually during the second to fifth year, and annually thereafter. Biopsy confirmation of suspected recurrence was mandatory before salvage therapy was initiated.

Treatment strategy

The patients were stratified into 3 risk groups according to the CCG5942 classification.[3] Group R1 comprised stage I and stage IIA patients (no bulk disease, no hilar adenopathy, <4 nodal regions involved). Group R2 consisted of other stage I-III patients. Group R3 comprised stage IV patients. All patients who had attained a complete response were not subjected to IFRT. Patients showing partial response were given IFRT. The treatment regimens are shown in Table 1 and Fig. 1. Salvage therapy after disease progression during therapy or the first recurrence was at the discretion of physicians.

Statistical analysis

Life-table calculations were performed according to the Kaplan-Meier method. Event-free survival (EFS) was calculated from the day of diagnosis to an event (disease progression, death of any reason or second malignancy). For overall survival, death of any cause was considered as an event. The cutoff date for analysis was December 31, 2010.

Results

Patient characteristics

In the 56 patients, 48 were boys and 8 were girls. Their median age was 7.7 years (range, 2.6 to 16.1 years). Patient characteristics are listed in Table 2. In this series, 4 patients were at stage I, 10 stage II, 26 stage III, and 16 stage IV. Fourteen patients had B symptoms at presentation. Histologically, mixed cellularity was observed in 36 patients (64.3%), nodular sclerosis in 7 (12.5%), and lymphocyte predominant in 12 (21.4%).

After chemotherapy, 14 patients received radiation treatment at sites with residual lymphoma. The cumulative local doses were 20 to 25 Gy in 9 patients, 35 Gy in 1, and uncertain in 4.

Table 1. Therapy courses

	Drug	Dose	Day
Course A (COMP/ABV)	Cyclophosphamide IV	600 mg/m^2	D1
	Vincristine IV	1.4 mg/m^2 (max <2 mg)	D1
	Methotrexate IV	30 mg/m^2	D1
	Prednisone orally	45 mg/m^2 per day	D1-14
	Doxorubicin IV	35 mg/m^2	D8
	Bleomycin IV	8 mg/m^2	D8
	Vindesine IV	3 mg/m^2 (max <4 mg)	D8
Course B (EA)	Cytarabine IV	2000 mg/m^2 q12h	D1, 2
	Etoposide IV	150 mg/m^2 q12h	D1, 2
Course C (CHOP)	Cyclophosphamide IV	1200 mg/m^2	D1
	Doxorubicin IV	25 mg/m^2	D1, 2
	Vincristine IV	1.4 mg/m^2 (max <2 mg)	D1
	Prednisone orally	100 mg/m^2	D1-5

IV: intravenously.

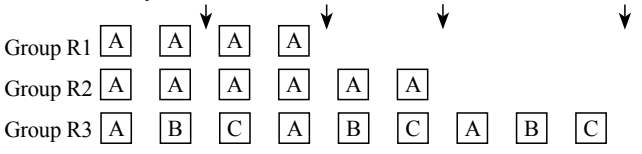

Fig. 1. Therapy scheme of protocol HL-98. The composition of therapy course is given in Table 1. Restaging to determine the response was performed after 2, 4, 6 and 9 cycles of chemotherapy. Patients in complete remission received no involved field radiotherapy.

Table 2. Patient characteristics

	No. of patients (*N*=56)	%
Boys:girls	48:8	
Ratio	6:1	
Age, y		
Median	7.7	
Range	2.6-16.1	
Age distribution		
≤5 y	17	30.3
5 to ≤10 y	23	41.1
10 to ≤15 y	15	26.8
15 to ≤18 y	1	1.8
Histologic subtypes		
Lymphocyte rich	12	21.4
Nodular sclerosis	7	12.5
Mixed cellularity	36	64.3
Lymphocyte depletion	0	0.0
Unclear	1	1.8
Stage		
I	4	7.1
II	10	17.9
III	26	46.4
IV	16	28.6
Treatment groups		
R1	8	14.3
R2	32	57.1
R3	16	28.6

Table 3. Treatment outcome according to risk groups and B symptoms

	All	Risk group, *n*			B symptoms	
		R1	R2	R3	Positive	Negative
No. of patients	56	8	32	16	14	42
Progression during therapy	4	0	0	4	4	0
Relapse	8	0	6	2	3	5
Radiotherapy	14	1	7	6	2	12
Alive without disease	47	8	28	11	7	40
In first remission	42	8	24	10	6	36
In second remission	5	0	4	1	1	4
Death	5	0	0	5	5	0
Related to HL	5	0	0	5	5	0
Unrelated to HL	0	0	0	0	0	0
Second malignancy	0	0	0	0	0	0
Lost to follow-up	4	0	4	0	2	2
In first remission	2	0	2	0	1	1
On relapse	2	0	2	0	1	1

Treatment results

Treatment outcomes during and after treatment are shown in Table 3. Four patients experienced disease progression and died while on treatment. Two patients with complete remission were lost to follow-up 2 and 10 months after diagnosis. Eight patients (6 boys and 2 girls) had relapse of the disease 7 to 18 months (median, 10 months) after diagnosis; none of them received radiation therapy. One of the 8 patients died of refractory disease, 2 were lost to follow-up after the recurrence, and 5 showed second complete remission after salvage therapy (chemotherapy with or without autologous stem-cell transplantation) 6, 8, 9, 9, and 12 months after the relapse of the disease respectively. At the time of evaluation (December 31, 2010), secondary malignancy was not observed. Overall, 5 of the 56 patients died from disease progression or recurrence. Therapeutic course A or C was delivered at an outpatient setting. Course B was given on an inpatient basis. There were no treatment-related toxic deaths. The 4-year overall survival rate was 88.9±4.3% in all patients, 100% in the R1 group, 96.8±3.2% in the R2 group, and 68.8±11.6% in the R3 group. Multivariate analysis revealed that B symptoms remained as an independent significant risk factor.

Event-free survival

At a median follow-up of 4 years (range: 0.2-12.4 years), the 4-year EFS rate and overall survival rate were 78%±5.6% (standard error) and 88.9%±4.3% for all of the patients, respectively. The 4-year EFS rates were 100%, 80.3%±7.2%, and 62.5%±12.1% in the R1, R2, and R3 groups, respectively (Fig. 2). There was a statistically significant difference in EFS rate between patients with and those without B symptoms (46.2%±13.8% *vs.* 88.0%±5.0%, $P<0.001$, Fig. 3). In the group R2, the 4-year EFS rates were 100% for patients who received radiotherapy and 75%±8.8% for those who received no further treatment ($P=0.177$).

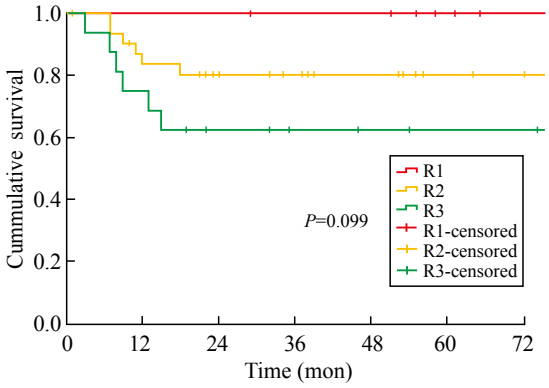

Fig. 2. Kaplan-Meier probabilities of event-free survival at 4 years according to risk groups R1, R2, and R3.

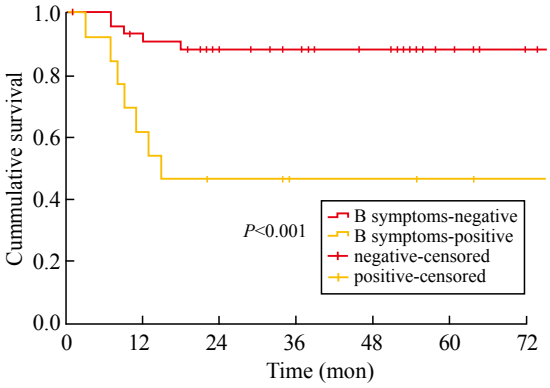

Fig. 3. Kaplan-Meier probabilities of event-free survival at 4 years according to B symptoms.

Discussion

In children with HL, the 5-year survival rate was reported to be 90%.[6,7] Recent research on pediatric HL focused on minimizing toxicity while preserving efficacy. In our patients in groups R1 and R2, the 4-year EFS rates were 100% and 80.3%±7.2% respectively, which are comparable with the reported rates.[3,8-11] Thus, risk-adapted chemotherapy without procarbazine, vinblastine and dacarbazine seems efficacious comparable to a classic regimen for localized HL. In the German/Austrian DAL-HD 85 study, treatment efficacy was compromised when procarbazine was completely eliminated from the chemotherapy.[12] For patients in the group R3 (stage IV) in our study, the EFS rate and overall survival rate at 4 years were 62.5%±12.1% and 68.8±11.6% respectively. The results showed the inferiority of this regimen for patients with advanced stage disease compared to previous studies.[3,9,13,14] More intensive (likely increasing dose of cytarabine and etoposide in course B) or diverse systemic chemotherapy regimen was indicated.

In our study, patients in any group who achieved

a complete remission to chemotherapy were not subjected to further radiotherapy. In the R2 group, the EFS rate was higher than that of patients treated with combined chemotherapy and radiation (100% *vs.* 75%±8.8%). But statistically, no significant difference was observed between the two groups (P=0.177). Considering the small sample size of our study and the data of CCG5942 and German HD-95,[3,9,15] we assume that some patients treated with radiotherapy had improved EFS compared with those who received no radiotherapy. Thus, complete response to chemotherapy is not taken as a determinant for omitting radiotherapy.

There was no patient with secondary malignancy in our study. However, short follow-up must be considered when interpreting these results. As there are reduced cumulative dose of etoposide and omission of procarbazine, the rate of secondary hematologic malignancies remains low.

Overall, there is a significant fraction of children with early stage or intermediate stage HL who can be cured with a chemotherapy regimen without procarbazine, but for patients in advanced stage (likely stage IV), its omission will compromise the treatment outcome. The strategy to identify those who can be cured with chemotherapy alone is still unclear. Besides response to chemotherapy, some adverse effects seem to be included. Given the results in our study and the situation in China (procarbazine unavailable), further studies should focus on intensive chemotherapy regimens for patients in group R3 (stage IV) and additional predictors for defining patients who will not receive radiotherapy.

Funding: None.

Ethical approval: This retrospective study was approved by the ethical committees of the two participating hospitals. Informed consent from study participants were waived because the data analyses were from spread sheets.

Competing interest: None declared.

Contributors: Gao YJ wrote the main body of the article. Tang JY contributed to the project conception, data collection, data interpretation and manuscript revision. Pan C, Lu FJ, Xue HL, and Chen J contributed to data collection and interpretation.

References

1 Liang RHS, Yau CC, Muckaden MA, Dinshaw KA, Todd D. Hodgkin's disease in Asia. In: Mauch PM, Armitage JO, Diehl V, Hoppe RT, Weiss LM, eds. Hodgkin's Disease. Philadelphia: Lippincott Williams & Williams, 1999: 771-780.
2 Bao PP, Zheng Y, Wang CF, Gu K, Jin F, Lu W. Time trends and characteristics of childhood cancer among children age 0-14 in Shanghai. Pediatr Blood Cancer 2009;53:13-16.
3 Nachman JB, Sposto R, Herzog P, Gilchrist GS, Wolden SL, Thomson J, et al. Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. J Clin Oncol 2002;20:3765-3771.
4 Lukes R, Butler J. The pathology and nomenclature of Hodgkin's disease. Cancer Res 1966;26:1063-1083.
5 Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswald meeting. J Clin Oncol 1989;7:1630-1636.
6 Schwartz CL. The management of Hodgkin disease in the young child. Curr Opin Pediar 2003;15:10-16.
7 Hochberg J, Waxman IM, Kelly KM, Morris E, Cairo MS. Adolescent non-Hodgkin lymphoma and Hodgkin lymphoma state of the science. Br J Haematol 2009;144:24-40.
8 Landman-Parker J, Pacquement H, Leblanc T, Habrand JL, Terrier-Lacombe MJ, Bertrand Y, et al. Localized childhood Hodgkin's disease: response-adapted chemotherapy with etoposide, bleomycin, vinblastine, and prednisone before low-dose radiation therapy—results of the French Society of Pediatric Oncology Study MDH90. J Clin Oncol 2000;18:1500-1507.
9 Dorffel W, Luders H, Ruhl U, Albrecht M, Marciniak H, Parwaresch R, et al. Preliminary results of the multicenter trial GPOH-HD 95 for the treatment of Hodgkin's disease in children and adolescents: analysis and outlook. Klin Padiatr 2003;215: 139-145.
10 Kung FH, Schwartz CL, Ferree CR, London WB, Ternberg JL, Behm FG, et al. POG8625: a randomized trial comparing chemotherapy with chemoradiotherapy for children and adolescents with stages I, IIA, IIIA1 Hodgkin disease: a report from the Children's Oncology Group. J Pediatr Hematol Oncol 2006;28:362-368.
11 Donaldson SS, Link MP, Weinstein HJ, Rai SN, Brain S, Billett AL, et al. Final results of a prospective clinical trial with VAMP and low-dose involved field radiation for children with low-risk Hodgkin's disease. J Clin Oncol 2007;25:332-337.
12 Schellong G, Brämswig JH, Hörnig-Franz I, Schwarze EW, Pötter R, Wannenmacher M. Hodgkin's disease in children: combined modality treatment for stages IA, IIB, and IIA. Results in 356 patients of German/Austrian Pediatric Study Group. Ann Oncol 1994;5(Suppl 2):113-115.
13 Weiner MA, Leventhal B, Brecher ML, Marcus RB, Cantor A, Gieser PW, et al. Randomized study of intensive MOPP-ABVD with or without low-dose total-nodal radiation therapy in the treatment of stages IIB, IIIA2, IIIB, and IV Hodgkin's disease in pediatric patients: a Pediatric Oncology Group study. J Clin Oncol 1997;15:2769-2779.
14 Hudson MM, Krasin M, Link MP, Donaldson SS, Billups C, Merchant TE, et al. Risk-adapted, combined-modality therapy with VAMP/COP and response-based, involved-field radiation for unfavorable pediatric Hodgkin's disease. J Clin Oncol 2004;22:4541-4550.
15 Rühl U, Albrecht M, Dieckmann K, Lüders H, Marciniak H, Schellenberg D, et al. Response-adapted radiotherapy in the treatment of pediatric Hodgkin's disease: an interim report at 5 years of the German GPOH-HD95 trial. Int J Radiat Oncol Biol Phys 2001;51:1209-1218.

Received October 17, 2011
Accepted after revision February 8, 2012