doi: 10.13241/j.cnki.pmb.2014.13.032

Clinical Analysis of 23 children with Hodgkin Lymphoma*

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ABSTRACT Objective: To investigate the pathological characteristic, clinical features and prognosis in children and adolescent with Hodgkin's lymphoma. **Methods:** 23 patients of childhood and adolescent with Hodgkin's lymphoma were treated in department of pediatric Hematology of the affiliated Hospital of Qingdao university from 2001 to 2013. The clinicopathological and follow-up data of the patients were retrospectively reviewed. The clinical rate in the difference of groups was analyzed by x^2 test and fisher exact test. **Results:** 23 cases were diagnosed in the study. The mean age was 7.5 years. The sex-ratio was 6.7:1. Stage I, II, III and IV were accounted for 13.0%, 26.2%, 30.4%, 30.4% respectively. There was 1 patient of NLPHL (4.3%), 10 patients of MC (43.5%), 11 patients of LP (47.9%) and 1 patient of NS (4.3%). The involved parts were mostly the cervical lymph node, followed by mediastinum, enterocoelia, retroperitoneal, spleen, skeleton and lung tissue, of which there were 2 patients with huge mediastinum mass. 8 patients had B symptoms (34.7%) at diagnosis. After 2 cycles of initial chemotherapy, the overall response rate (ORR) reached 100%. And complete response (CR) rate was 69.6% while partial response (PR) rate was 30.4%. The CR rate of patients at stage I and II (100%) was significantly higher than that at stage III and IV (50%), $P<0.05$. 7 of 23 patients were relapsed. The recurrence rate of stage III and IV was higher than that at stage I and II (46.2% verse 11.1%, $P=0.0098$). For the recurrence rate of patients, there was significantly statistical difference between patients with B symptoms and those without B symptoms ($P=0.019$). 2 patients with mediastinal neoplasm were relapsed. There was no statistical difference between the relapse of disease and each histological subtype ($x^2=2.695$, $P>0.05$). **Conclusions:** The prognosis of children and adolescent with Hodgkin's lymphoma is better, but the patients of stage III and IV or ones with B symptom and huge mediastinal lump have higher recurrence rate. The hierarchical therapy is adopted for children with HL in order to reach the long-term survival.

Key words: Hodgkin lymphoma; Children; Clinical feature; Prognosis; Relapse

Chinese Library Classification (CLC): R725.5 Document code: A

Article ID: 1673-6273(2014)13-2517-05

Introduction

Hodgkin lymphoma (HL), indicating the curable tumor of lymph gland and lymphoid tissue with relatively low grade malignancy, is the common malignant tumor in children and adolescent. Along with the upgrading of diagnosis and treatment measures, the 5-year overall survival (OS) and 5-year disease-free survival (DFS) could reach 95% and 90% separately [1]. Compared with the Europe, American and other countries, the morbidity of HL in chinese children is very low, accounting for 6% of children and adolescent with malignant tumor. It is difficult to accumulate the cases and there are few reports at home. In this study, 23 children and adolescent with HL treated in the department of pediatrics of our hospital from May 2001 and August 2013 will be analyzed.

1 Patients and methods

1.1 Clinical data

Children who were diagnosed and treated between May 2001 and August 2013 of our hospital were enrolled into the study. All the patients had a full clinical, laboratory and imaging examination, and the final diagnosis according to the pathological morphology and immunohistochemical results of the biopsy specimen. Pathological samples were reviewed centrally and classified based on the WHO guidelines[2]: Nodular lymphocyte predominant HL (NLPHL), classical HL included lymphocyte predominant (LP), Nodular sclerosis (NS), Mixed cellularity (MC) and lymphocyte deplete(LD). Disease was staged base on the Ann Arbor system[3].

1.2 Treatment strategy

The patients of May 2001 to August 2011 were treated with the hybrid COPP/MOPP (cyclophosphamide, vincristine, natulane, prednisone/chlormethine, vincristine, natulane, prednisone), ABVD(pirarubicin, bleomycin A5, vincristine, dacarbazine), IE(ifosfamide, etoposide) and CHOP (cyclophosphamide, pirarubicin, vincristine/eldisine, prednisone). The process lasts 10-20 months (the median, 13.6 months). The patients of September 2011 to August 2013 were treated with the hybrid A (cyclophosphamide, vincristine, amethopterin, prednisone/pirarubicin, bleomycin A5, eldisine) and B(ifosfamide, etoposide, amethopterin, vincristine, pred-

*Foundation item: The Natural Science Foundation of China (31100824)

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(Received: 2013-12-24 Accepted: 2014-01-21)

nisone, mesna), which continued 6-8 cycles (The total of process lasts 8-14 months with a median for 9 months). Patients of recurrence and refractory were given salvage chemotherapy: DHAP (cisplatin, high dose of cytarabbine, dexamethasone) +G-CSF (granulocytecolony-stimulating factor), ICE (ifosfamide, carboplatin, etoposide). The part of the patients with residual tumors after chemotherapy received involved field radiotherapy (IFRT), the average radiation dose was 24Gy.

1.3 Response assessment

According to clinical symptoms, physical examination and manifests of iconography, patients were grouped into four categories[4,5]: complete response(CR), partial response(PR), progress free(PF), disease progress(DP).

1.4 Statistical analysis

The x^2 test and fisher exact test were used to compare the data by SPSS17.0, and $P<0.05$ was considered significantly different.

2 Results

2.1 Clinical characteristics and Characteristics of Laboratory

Table 1 Shows the clinical and laboratory features of 23 patients at the time of original diagnosis.

2.1.1 Date A total of 23 patients were enrolled in this study. The age at diagnosis ranged from 1 to 12 years (median, 7.5 years). The sex ratio was 20 in favor of boys: 87% against 13%. The mean time from the development of symptoms to diagnosis was 5.4 months, ranging from 0.5 to 19 months.

2.1.2 Stage and Histological Subtype Stage was as follows: stage I 3 (13.0%), stage II 6 (26.2%), stage III 7 (30.4%) and stage IV 7 (30.4%). Classical HL was the predominant subtype (22 of 23, 95.7%), including 10 MC (43.5%), 11 LP (47.9%) and 1 NS (4.3%).

2.1.3 Involved positions and symptoms Most of the correlated parts were the cervical lymph node (91.3%), followed by mediastinum, enterocoelia, retroperitoneal, spleen, skeleton lung tissue and pericardium. There were 2 patients (8.7%) with huge mediastinum mass. And 8 patients (34.7%) had B symptoms at diagnosis.

2.1.4 Erythrocyte sedimentation rate (ESR) and hemoglobinconcentration (HGB) ESR got a higher level (>25mm at first hour) in 7 of 23 cases (30.4%), including 5 cases with B symptoms. 5 patients (21.7%) had a hemoglobin level below 12 g/dl.

2.1.5 EBV virus detection result There were 4 positive cases of 14 cases in children who were used In Situ Hybridization (ISH) to detect EBER. The positive rate was 28.6%, 1 MC and 3 LP.

2.2 Therapeutic Effect

After 2 cycles of initial chemotherapy, the overall response rate (ORR) was 100%. 16 patients (69.6%) achieved a complete response, while 7 (30.4%) achieve a partial response. CR rate of patients at stage I and II reached 100% while that at stage III and IV only reached 50% (100% verse 50%, $P<0.05$). 7 patients were relapsed in 2-26 months (medium, 16.1months) after drug withdrawal during the follow-up visit. 1 patient went worse after getting chemotherapy for 3 months, but he was at the PR status after given the DHAP salvage chemotherapy.

Table 1 Characteristics of patients

Characteristics	Number	Percentage
Age		
<5 year	4	17.4%
5-12 year	19	82.6%
Sex		
Male	20	87.0%
Female	3	13.0%
Histological Subtype		
NLPHL	1	4.3%
MC	10	43.5%
LP	11	47.9%
NS	1	4.3%
Stage		
Stage Ⅰ	3	13%
Stage Ⅱ	6	26.2%
Stage Ⅲ	7	30.4%
Stage Ⅳ	7	30.4%
B symptom		
yes	8	34.7%
no	15	65.3%
ESR		
high	7	30.4%
normal	16	69.6%
Involved positions		
cervical lymph node	21	91.3%
mediastinal lymph node	10	43.5%
mediastinal mass	2	8.7%
enterocoelia and retroperitoneal lymph node	6	26.2%
spleen	3	13.0%
skeleton	2	8.7%
lung	2	8.7%
pericardial	1	4.3%

The analysis of relapse-related factors (Table 2): (1) The recurrence rate of patients at stage III and IV was significantly higher that at stage I and II, $P=0.0098$. (2) For the recurrence rate of patients with B symptom, it was higher than that of those without B symptom, $P=0.019$. (3) There was no statistical difference between the relapse of disease and each histological subtypes, $P>0.05$ ($x^2=2.695$).

2.3 Acute and Long-Term Toxicity

According to the adverse drug reaction evaluation system of international tumor chemotherapy—CTCAE_V4.0: there were 7

Table 2 The analysis of therapeutic effect and relapse-related factors

relapse-related factors	patients	CR+PR△ n(%)	RE△ n(%)	P value
total	23	16(69.6%)	7(30.4%)	
Stage				0.0098
Stage I and II	9	8(88.9%)	1(11.1%)	
Stase III and IV	14	8(53.8%)	6(46.2%)	
B symptom				0.019
yes	8	3(37.5%)	5 (62.5%)	
no	15	13(86.7%)	2(13.3%)	
Histological Subtype				＞0.05
NLPHL	1	0(0%)	1(100%)	
MC	10	6(60%)	4(40%),	
LP	11	8(72.7%)	3(27.3%)	
NS	1	1(100%)	0(0%)	

△: patient's status during follow-up

patients (30.4%) got treatment-related adverse events of hematology toxicity of grade 2 and 3. Neutropenia concurrent severe infection included 5 patients (21.7%), respectively merging bacterial pneumonia, fungal pneumonia (candida albicans was cultured from sputum), fungemia (smooth candida mycoderma bacteria was cultured with blood), periapical abscess and tuberculosis, all cured. There were 12 patients (52.2%) with adverse reaction (nausea and stomachache, etc.) of 1-level gastrointestinal tract. The occurrence rate of drug-induced hepatic lesions were 17.4% (4/23). No patient developed second malignancies in this study.

3 Discussion

HL is a common malignant tumor in children and adolescents, seldom coming down with the disease before the age of 5, but the morbidity was gradually rising after the age of 5. The morbidity proportion of males and females at the age of 5-11 was 3:1 and 1.5:1 at the age of 11-19. In this study, there were 23 patients whose average age was 7.5 year old. The male to female ratio was 6.7:1, higher than that reported in documents at home and abroad. However, the histological subtype and characteristic was basically the same with that in documents [6]. There were 21 patients of LP and MC, accounting for 91.4%.

The prognosis of children and adolescent with Hodgkin's lymphoma is better, 90% of the patients get long-term survival. Factors associated with a poor outcome and termed unfavorable include : stage IIIb and IV, bulky mediastinal or peripheral lymphadenopathy, extranodal extension of disease, male sex and B symptoms [7, 8]. According to the recent reports of Ananth Shankar, we learned that mediastinal tumor remnant and poor staging of patients after chemotherapy was the independent prognosis factor of DFS as shown by the result of pure chemotherapy for the patients after the clinical analysis of 381 children patients. Nevertheless, B symptoms was not taken as an important factor to evaluate prognosis [9]. In our study, 5 of 8 patients with B symptoms were relapsed (62.5%), higher than those without B symptoms(13.3%). It suggested that the relapse of disease and B symptom features certain correlation. The recurrence rate of patients at stage III and IV stood at 46.2%, which was apparently higher than that at stage I and II 11.1%. 2 patients with mediastinal neoplasm were relapsed, which illustrated that the patients with poor staging and huge mediastinal lump have high recurrence rate and poor prognosis. ESR was expedited (＞50mm/h) before relapse for 5 relapsed patients. It hinted that ESR had important role of hinting the relapse of HL. The foregoing results are approximate to that in document reports at home and abroad [8,10]. The current research presents that EBV is closely associated with HL [11-13]. Diepstra and his team found that the positive rate of EBER of HL patients was relevant to the tissue typing while MC was higher than other types. However, the domestic reports showed that there was no difference in positive rate of EBER with different histologic subtypes [12,13]. In this study, the positive rate of EBER of 14 patients reached 28.6% (4/14), lower than that in the reports (72.2%) of Zheng-De Xie, et al [13]. The 4 patients were stage IV, and 1 patient was relapsed and 1 went worse. The statistical analysis was not carried out due to the few patients. Nowadays, the relationship between EBV infection and palindromia was equivocal, and further research is needed.

Considering good prognosis of HL and serious adverse effect of chemoradiotherapy on the survival quality, the hierarchical therapy is adopted for HL patients. The intensity of treatment of patients at stage I and IIA is reduced to avoid the secondary adverse reactions[14]. The treatment of patients with stage IIB , III and IV is intensified (the chemotherapy was united with the low-dose involved field radiotherapy) to strengthen the control of tumor [15, 17].

In consequence, both of the possibility of complication and relapse is reduced[16]. The GPOH-HD95 study group of Germany have only used different chemotherapeutic regimens for patients with HL at stage I and IIA and have OS and EFS of 97% and 88%, respectively, at 5 years. Therefore, the intensity of treatment of HL children with good prognosis and sensitive to chemotherapy can be reduced and the radiotherapy can not be adopted for them [17, 18]. The studies of Ananth Shankar, et al, showed that the 5-year DFS of patients with bad stage in chemoradiation group was higher than those in the pure chemotherapy group, featuring less relapse[9]. The radiotherapy is additionally adopted for most children with HL at stage IIB , III and IV to prevent from local recurrence[16, 17, 19]. In the study of Beijing Children's Hospital, 34 patients were treated with the modified CCG5942 protocal by referring to the overseas experience. The chemotherapy drugs were the same with or similar to those in this study. And the 5-year DFS of reached 94.1%, both of the effective rate of initial cycle and mid-stage of therapy was 100%. At the mid-stage of therapy, CR rate was 64.7% and PR rate was 35.3% [20]. In this study, the assessment of 23 patients was made after 2 cycles of hierarchical chemotherapy. The ORR was 100%, CR rate 69.6% and PR rate 30.4%, approximate to that in the reports of Yan-Long Duan and Pu-Yuan Xing, et al [8, 20]. However, the recurrence rate still reached 31.8%, higher than that in the documents at home and abroad [8, 16, 17, 20]. For 3 among 7 relapsed patients adopted IFRT based on chemotherapy. Thus, the clinical symptom and imaging examination was evidently improved and all survive with tumor. Regarding to many factors, such as growing development and involved field, IFRT adopted for the patients with tumor remnant and poor staging after the chemotherapy is more widom to prevent from the local recurrence. However, the reduction in radiotherapy dose is still the main tendency in the future.

To sum up, the prognosis of children with HL is better, featuring long survival time. However, there are still several factors contributed to the high relapse rate and poor prognosis, including be at stage III and IV, B symptoms and huge mediastinal lump. Chemotherapy and radiotherapy remains the mainstay of therapies for children and adolescent with HL. Considering the long term side effects of children and adolescent with HL by radiotherapy, the reduction in radiotherapy dose has become common knowledge of medical community. And it's still necessary to explore more rational treatment modes for patients of recurrence and refractory.

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23 例儿童霍奇金淋巴瘤临床分析 *

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摘要 目的:分析儿童青少年霍奇金淋巴瘤(HL)患者的病理特征、临床表现及其预后影响因素。**方法:**收集青岛大学医学院附属医院血液儿科 2001 年 5 年至 2013 年 8 月收治的 23 例经病理确诊的儿童青少年 HL 患者的临床资料,采用 Fisher 确切概率法等进行各组间差异检验。**结果:** 确诊病例共 23 例,中位年龄 7.5 岁,男:女发病比例 =6.7:1,Ⅰ期、Ⅱ期、Ⅲ期、Ⅳ期分别占 13.0%、26.2%、30.4%、30.4%;结节性淋巴细胞为主型(NLPHL)1 例(4.3%),经典型 HL22 例(95.7%):混合细胞型(MC)10 例(43.5%),淋巴细胞为主型(LP)11 例(47.9%),结节硬化型(NS)1 例(4.3%);受累部位以颈部淋巴结最多见,其次依次为纵隔、腹腔及腹膜后、脾、骨骼、肺组织等,其中巨大纵隔肿块者 2 例;具有 B 症状者 8 例(34.7%)。化疗 2 个疗程评估总有效率为 100%,完全缓解(CR)率 69.6%,部分缓解(PR)率 30.4%。Ⅰ期和Ⅱ期患者 CR 率 100%,明显高于Ⅲ期和Ⅳ期患者(50%),P<0.05;23 例患者 7 例复发,复发率Ⅲ期和Ⅳ期患者为 46.2%,Ⅰ期和Ⅱ期患者为 11.1%,前者高于后者(P=0.0098);有 B 症状与无 B 症状患者之间复发率有显著统计学差异(P=0.019);2 例有巨大包块患者皆复发;各病理分型与疾病的复发间差异无统计学意义(x^2=2.695,P>0.05)。**结论:** 儿童霍奇金淋巴瘤预后相对较好,但Ⅲ期和Ⅳ期、合并 B 症状及大肿块或大纵隔肿瘤的患者复发率高,应依据疾病危险度分层治疗,以期更好的预后。

关键词:霍奇金淋巴瘤;儿童;临床特征;预后;复发

中图分类号:R725.5 **文献标识码:**A **文章编号:**1673-6273(2014)13-2517-05

* 基金项目:国家自然科学基金项目(31100824)

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(收稿日期:2013-12-24 接受日期:2014-01-21)