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Therapeutic effectiveness of the ALL-XH-99 protocol for childhood acute lymphoblastic leukemia

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Abstract: **Objective** The ALL-XH-99 protocol for the treatment of childhood acute lymphoblastic leukemia (ALL) has been performed in the Union Hospital for 10 years. This study aimed to evaluate the therapeutic effectiveness of the protocol for childhood ALL and to investigate the prognostic factors for childhood ALL. **Methods** This is a retrospective study. The eligible patients were treated with the ALL-XH-99 protocol. However a minor modification based on the ALL-XH-99 protocol was performed in this study, i. e., the high-risk patients as the low- and moderate-risk patients were not administered with cranial irradiation. Event-free survival (EFS) was evaluated using the Kaplan-Meier method and the differences of the EFS among groups were compared with the log-rank test. Prognostic factors for childhood ALL were investigated by the stepwise Cox proportional hazard model. **Results** One hundred fifteen patients were eligible for the ALL-XH-99 protocol clinical study. The 115 patients consisted of 62 low-risk, 12 moderate-risk and 41 high-risk patients. The overall EFS at 5 years in the 115 patients was 69.0 ± 5.0%. The 5-year-EFS in the low-risk, moderate-risk and high-risk patients was 82.0 ± 6.0%, 77.0 ± 15.0% and 43.0 ± 11.0%, respectively ($P < 0.01$). Relapse occurred in 16 patients (13.9%) in a median time of 17 months. Without administering cranial irradiation to all of the patients, the incidence of CNS leukemia relapse (2/115, 1.7%) was not higher than that previously reported. Multivariate analysis showed that the risk degree of leukemia, the presence of *t* (9; 22)/bcr/abl fusion gene and leukocyte count were independent adverse prognostic factors for ALL and their hazard ratio was 1.867, 3.397 and 2.236 respectively. **Conclusions** The therapeutic effectiveness of the ALL-XH-99 protocol for childhood ALL is satisfactory, with an EFS rate comparable to that of the developed countries. *t* (9; 22)/bcr/abl is the most important adverse independent prognostic factor for childhood ALL. Cranial irradiation may be eliminated to reduce late adverse effects in all of ALL patients.

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Key words: Acute lymphoblastic leukemia; Prognostic factor; Event-free survival; Child

ALL-XH-99 方案治疗儿童急性淋巴细胞性白血病疗效分析

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[**摘　要**] **目的** 由上海新华医院/上海儿童医学中心制定的治疗儿童急性淋巴细胞性白血病(ALL)的ALL-XH-99 方案已在该院实施 10 年了。该文旨在评估应用此方案治疗儿童急性淋巴细胞性白血病(ALL)的疗效,并探讨儿童 ALL 的预后因素。**方法** 回顾分析 1998 年 1 月 ~2007 年 4 月在该院采用 ALL-XH-99 方案治疗的儿童 ALL 的临床资料。该研究在 ALL-XH-99 方案的基础上作了一些小的修订,即对高危患儿也未给予颅脑放射治疗。采用 Kaplan-Meier 方法评估患儿的无事生存率(EFS),组间患儿 EFS 差异用 log-rank 检验。采用逐步 Cox 比例风险模型分析 ALL 的预后因素。**结果** 115 例患儿得到了全程的 ALL-XH-99 方案治疗,其中低、中、高危患儿分别为 62、12、41 人。这 115 例患儿总的 5 年 EFS 率为(69.0 ± 5.0)%,其中低危、中危、高危组 5 年的 EFS 率分别为(82.0 ± 6.0)%、(77.0 ± 15.0)% 和 (43.0 ± 11.0)% ($P < 0.01$)。16 例(13.9%)复发,复发的中位时间为 17 个月。所有病例均未采取颅脑放疗,中枢神经系统白血病复发率(2/115,1.7%)并未高于既往报道。多因素分析显示白血病危险分度、*t*(9;22)/bcr/abl 融合基因和白细胞计数是儿童 ALL 独立的不利预后因素,其风险比例分别为 1.867、3.397和2.236。**结论** 采用 ALL-XH-99 方案治疗儿童 ALL 疗效满意,取得了与发达国家类似的 EFS 率。

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t(9;22)/bcr/abl 融合基因为儿童 ALL 最重要的不利预后因素。在强有力的系统化疗和鞘内注射条件下,对所有患儿可取消颅脑放疗以减少副作用。

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The prognosis for childhood acute lymphoblastic leukemia (ALL) has greatly improved over the last 40 years, reaching a long-term event-free survival (EFS) of approximately 75%[1-2] and an overall survival of approximately 80%[3] in the developed countries. A similar therapeutic effect for childhood ALL has been achieved in China in recent years[4]. Age, sex, leukocyte count, response to prednisone, and immunophenotype are considered as important prognostic factors for childhood ALL. Making an appropriate therapeutic regimen for patients is very important based on the prognostic factors[5]. The ALL-XH-99 protocol for the treatment of childhood ALL provided by Shanghai Xinhua Hospital/Shanghai Children's Medical Center has been performed for 10 years in the Union Hospital of Tongji Medical College of Huazhong University of Science and Technology. This paper aimed to evaluate its therapeutic effect and to investigate prognostic factors for childhood ALL by a retrospective study.

Methods

Patients

ALL was confirmed based on morphological and cytochemical evaluation of bone marrow smears as well as immunophenotypical and cytogenetical criteria and classified into T-cell and B-cell leukemia. The patients who met the following criteria were eligible for this study: 1) being newly diagnosed with ALL at the Union Hospital of Tongji Medical College of Huazhong University of Science and Technology from January 1998 to April 2007; 2) no history of tumors; 3) no chemotherapy before admission; 4) age < 14 years at diagnosis; 5) receiving treatment with ALL-XH-99 protocol after admission, with written informed consent for the protocol use from the patient's parents or guardians.

Treatment

All eligible patients were treated according to the ALL-XH-99 protocol[6]. However a minor modification based on the ALL-XH-99 protocol was performed in this study, i.e., the high-risk patients as the low- and moderate-risk patients were not administered with cranial irradiation. During the remission induction, patients received triple intrathecal chemotherapy (MTX + Ara-C + DXM) once a week. High-dose MTX + CF + triple intrathecal injection were administered to the patients for the prevention of extramedullary leukemia. Supportive treatment included transfusion of platelets and erythrocytes and injection of granulocyte colony-stimulating factors and antibiotics.

Evaluation of therapeutic effects

Complete remission (CR) was defined as the presence of all of the following: less than 5% of blasts in bone marrow; no leukemic blasts in peripheral blood (PB); recovery of PB values to a neutrophil count of at least 1.5×10^9/L; hemoglobin of at least 90 g/L

Table 1 Clinical and biological data and treatment outcome

Features	Number of patients (%)	Number of CR patients (%)	5-year EFS (%)	*P* value
Risk				
Low	62 (53.9)	61 (98.4)	82.0±6.0	0.000
Moderate	12 (10.4)	11 (91.7)	77.0±15.0	
High	41 (35.7)	32 (78.0)	43.0±11.0	
Age				
< 1 y	2 (1.7)	2 (100)	0	0.002
1-10 y	93 (80.9)	86 (92.5)	69.0±6.0	
>10 y	20 (17.4)	16 (80.0)	41.0±16.0	
Sex				
Male	73 (63.5)	67 (91.8)	62.0±7.0	0.464
Female	42 (36.5)	37 (88.1)	74.0±8.0	
Leukocyte count				
$<10 \times 10^9$/L	73 (63.5)	73 (100)	77.0±6.0	0.000
$(10\text{-}49) \times 10^9$/L	21 (18.3)	18 (85.7)	64.0±12.0	
$(50\text{-}99) \times 10^9$/L	12 (10.4)	8 (66.7)	34.0±16.0	
$\geq 100 \times 10^9$/L	9 (7.8)	5 (55.6)	36.0±18.0	
Immunophenotype				
T-cell	9 (7.8)	4 (44.4)	44.0±22.0	0.487
B-cell	106 (92.2)	100 (94.3)	68.0±5.0	
t(9;22)/bcr/abl				
Positive	3 (2.7)	1 (33.3)	0	0.004
Negative	112 (97.3)	103 (92.0)	68.0±5.0	
Marrow examination on day 19				
Blasts < 5%	82 (71.3)	79 (96.3)	76.0±6.0	0.008
Blasts >5%	33 (28.7)	25 (75.8)	48.0±9.0	
Serum LDH				
<450 U/L	44 (38.3)	43 (97.7)	85.0±5.0	0.000
≥450 U/L	71 (61.7)	61 (85.9)	44.0±8.0	
Induction therapy				
Prednisone	38 (33.0)	35 (92.1)	72.0±9.0	0.291
Dexamethasone	77 (67.0)	69 (89.6)	62.0±6.0	
Prednisone test				
Sensitive	102 (88.7)	96 (94.1)	71.0±6.0	0.000
insensitive	13 (11.3)	8 (61.5)	32.0±14.0	

and a platelet count of at least 100×10^9/L; and no evidence of extramedullary leukemia. Those who failed to attain CR after two courses of induction therapy were regarded as failure cases. Relapse was defined as the presence of at least one of the following: recurrence of more than 10% leukemic cells in bone marrow or of any leukemic cells in PB or extramedullary sites.

The treatment outcome was evaluated in terms of EFS. The duration of EFS was calculated from the day of diagnosis to the date of first treatment failure (induction failure, relapse, death or the occurrence of second malignancy) or the date of final follow-up visit.

Statistical analysis

EFS rate was evaluated using the Kaplan-Meier method. The differences in the EFS rate between the groups were compared with the log-rank test. Relationships between variables (patients' clinical characteristics and treatment approaches) were evaluated using the stepwise Cox proportional hazard model. Statistical analyses were done using SPSS 13.0 software.

Results

Remission induction

From January 1998 to April 2007, 323 children (201 males and 122 females) were confirmed with newly-diagnosed ALL. From this group, 150 patients received induction chemotherapy. After treatment, 139 cases (92.7%) achived CR. According to the ALL-XH-99 protocol 115 patients (73 males and 42 females) were eligible for this study. Patients' clinical and biological features are shown in Table 1. Patients' median age at diagnosis was 6 years (9 months-14 years). Median leukocyte count was 11.6×10^9/L (2.4×10^9/L - 229.7×10^9/L). Median time of CR was 34 days (28- 45 days). A total of 115 patients were classified into high ($n = 41$), moderate ($n = 12$) and low risk ($n = 62$) groups based on initial white blood cell count, age, immunology, cytogenetics and response to treatment. Of the 115 patients, 104 (90.4%) achived CR, including 61 cases in the low-risk group, 11 cases in the moderate-risk group and 32 cases in the high-risk group.

Treatment outcome

Follow-up visits were suspended on April 30, 2007, with a median observation duration of 21 months (1-84 months). The overall EFS rate at 5 years in the 115 patients was 69.0 ± 5.0%. The EFS rate in the low-risk, the moderate-risk and the high-risk groups was 82.0 ± 6.0%, 77.0 ± 15.0% and 43.0 ± 11.0%, respectively ($P < 0.01$). Cytogenetic results were available in 50 patients. Of which 21 showed abnormal chromosome and 3 showed bcr/abl fusion gene.

Four patients (including 2 T-ALL) received allogeneic transplantation. One survived with mental retardation, 1 (T-ALL) had secondary lymphoma and 2 event-free survived. Induction failure was found in 11 cases, isolated bone marrow relapse in 11 cases, isolated CNS relapse in 1 case, bone marrow along with CNS relapse in 1 case, secondary malignancy in 2 cases, testicular leukemia complicated by second malignancy (acute myeloid leukemia, AML) in 1 case, and 5 died from fungal sepsis or disseminated intravascular coagulation secondary to bacterial sepsis. Relapse occurred in a median time of 17 months. Table 2 shows the adverse events after treatment.

Prognostic factors for ALL

By analyzing clinical and biological features, risk degree of leukemia, age, lactate dehydrogenase (LDH) concentration, response to remission induction, t (9;22)/bcr/abl fusion gene and leukocyte count were all prognostic factors for ALL. Multivariate analysis to the entire cohort showed that risk degree of leukemia [hazard ratio: 1.867; 95% confidence interval (*CI*): 1.209-2.883; $P = 0.005$), the presence of t (9;22)/bcr-abl fusion gene (hazard ratio: 3.397; 95% *CI*: 1.409-8.194; $P = 0.006$) and leukocyte count (hazard ratio: 2.236; 95% *CI*: 0.982-5.093; $P = 0.045$) were independent poor prognostic factors for ALL. The presence of t (9;22)/bcr-abl fusion gene showed a highest risk for poor prognosis.

Discussion

Early continuous and intensive chemotherapy can result in a reduction in minimal residual disease and drug resistance and increase the rate of long-term EFS in ALL patients. However, continuous and intensive chemotherapy leads to an increase in toxicity and other side effects. In order to reduce adverse effects, the

Table 2 Adverse events after treatment

Group	Induction failure	bone marrow relapse	CNS relapse	bone marrow + CNS relapse	Second malignancy	testicular leukemia + second malignancy	Death after induction remission	Other effects
Low-risk	1	6	0	0	0	0	1	2
Moderate-risk	0	1	0	0	0	1	0	0
High-risk	10	4	1	1	2	0	4	1

ALL-XH-88 protocol was modified and the ALL-XH-99 protocol was produced. According to the ALL-XH-99 protocol, ALL patients with different clinical features were classified into low-, moderate- and high-risk groups and treated with stratified therapy. The protocol increases the chemotherapy intension for high-risk patients but decreases the chemotherapy intension for low-risk patients. The patients' 5-year-EFS rate in this study was comparable to that in the developed countries. However, the patients' induction remission rate was lower than previously described [7]. This may be attributed to the increased number of patients receiving induction therapy (14.4% before 1997 vs 35.6% after 1997), especially the increased number of high-risk patients who received more intensive chemotherapy.

Since the 1980's, the early treatment response of ALL has been regarded as an independent prognostic factor and an important criterion for risk grading [7]. The ALL-XH-99 protocol adjusts patients' risk grading according to the results of prednisone test of cure or bone marrow examination on day 19 and then individual chemotherapy is performed in order to reduce side effects. In this study, only 3 (2.6%) out of the 115 patients underwent acute renal failure, pancreatitis or myocarditis. The incidence of side effects was obviously reduced compared with that previously reported [8].

Now that cranial irradiation can cause many major late complications such as second cancers, neuro-cognitive deficits and endocrinopathy, some cancer research institutes have reduced the dosage of cranial irradiation or even eliminated it [9]. The therapy of high-dose MTX plus CF is effective for the prevention for extramedullary leukemia. Hence, the ALL-XH-99 protocol has eliminated cranial irradiation in the low- and moderate-risk patients. In this study the high-risk patients were not administered with cranial irradiation and the CNS leukemia relapse rate (2/115, 1.7%) was not higher than that previously reported. The rate of therapy-related malignancies was not associated with etoposide-containing continuation treatment [10]. The patients in this study received etoposide-containing treatment and the incidence of secondary malignancies (2.6%) was lower than that previously reported [11].

This study showed that the risk degree of leukemia, the presence of t (9; 22)/bcr-abl fusion gene and leukocyte count were independent poor prognostic factors for childhood ALL and that the presence of t (9; 22)/bcr/abl was the most important one. However it should be realized that only one-third patients received standard treatment and two-thirds had to decline or discontinue therapy on account of various causes. So it is quite honest to say that selecting treatment for children with ALL is the only prognostic factor [12].

In summary, this study shows that the ALL-XH-99 protocol is effective for the treatment of childhood ALL. The treatment outcome of children with ALL improved significantly over 10 years in the Union Hospital. This study also suggests that cranial irradiation may be eliminated in children with newly-diagnosed ALL in the context of systemic and intrathecal chemotherapy to reduce late adverse effects.

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