·Original Article in English·

Relationship Between t(8;21) and Clinical Manifestation, Prognosis of the Children with Acute Myelocytic Leukemia M_2

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Abstract: Objective To study the influence of t(8;21) on the curative effect and prognosis of children with acute myelocytic leukemia M_2 (AML-M_2). **Methods** The clinical characteristics, curative effects, relapse rate, mortality and event-free survival (EFS) rate of 14 cases of M_2 children with t(8;21) and 21 cases of M_2 children without t(8;21) were analysed. **Results** There was no statistical difference in age, initial WBC count and clinical characteristics between the M_2 patients with t(8;21) and without t(8;21) ($P > 0.05$). The complete remission rate (92.9%) in M_2 patients with t(8;21) was significantly higher than that (57.1%) of children without t(8;21) ($P < 0.05$), while the relapse rate and mortality were of no marked difference between the two groups ($P > 0.05$). The overall EFS rate in M_2 children with t(8;21) was lower (69.2%) than that (77.8%) of children without t(8;21) ($P < 0.05$). **Conclusions** The prognosis of the M_2 children with t(8;21) was not better than that of the M_2 children without t(8;21). The infuence of t(8;21) on the prognosis of M_2 might be different from race and region.

[Chin J Contemp Pediatr, 2003, 5(3): 189 - 191]

Key words: t(8;21); Child; Acute myelocytic leukemia; Clinical characteristics; Prognosis

t(8;21)与儿童 AML - M_2 临床表现及预后的相关性探讨

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[**摘 要**] **目的** 探讨 t(8;21)对儿童 AML - M_2 的疗效和预后的影响。**方法** 对 14 例有 t(8;21)和 21 例无 t(8;21)的 M_2 患儿的临床特征、疗效、复发率、死亡率及无病生存率进行分析。**结果** 14 例 t(8;21)和 21 例无 t(8;21)的 M_2 患儿在年龄、白细胞数等临床特征上的差异无统计意义($P > 0.05$)。t(8;21)组的完全缓解(CR)率明显高于无 t(8;21)组(92.9% vs 57.1%)($P < 0.05$),而两组的复发率和死亡率差异无显著性($P > 0.05$)。总的无事生存率 t(8;21)组低于无 t(8;21)组(69.2% vs 77.8%)($P < 0.05$)。**结论** t(8;21)的儿童 M_2 并不一定具有良好的预后。t(8;21)对 M_2 预后的影响可能存在人种及地区的差异。

[**中国当代儿科杂志,2003, 5(3): 189 - 191**]

[**关 键 词**] t(8;21);儿童;急性髓性白血病;临床特征;预后

[**中图分类号**] R733.71 [**文献标识码**] A [**文章编号**] 1008 - 8830(2003)03 - 0189 - 03

With the improvement of the diagnostic ability for children leukemia, especially the progress of MICM (morphology, immunology, cytogenetics and molecular biology) technology, it can be discovered that more and more leukemia patients have their own different cytogenetical and molecular biological characteristics. t(8;21) (q22;q22) (AML1/ETO) is the most common kind of chromosome transposal of children with acute myelocytic leukemia. We studied the influence of t(8;21) on the curative effect and prog-

[Received] October 12, 2002; [Revised] February 14, 2003
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nosis of children with acute myelocytic leukemia M_2.

1 Subjects and mothods

Subjects

Between Janurary, 1996 and December, 2001, 35 patients who were diagnosed as M_2 by FAB and MIC in our hospital were enrolled. Among them, 14 cases of M_2 with t(8;21)(q22;q22) were classified as group A, AML1-ETO amalgamation gene were found in 10 of them. They aged from 28 months to 13 years old, the average middle age was 9.09. Twenty-one cases without t(8;21) were classified as group B. They aged from 32 months to 15 years old, and the average middle age was 9.44.

The therapy project

Induction project: DNR 40 mg/m^2 (day 1-3); Ara-C 200 mg/m^2 (day 1-7); Vp16 100 mg/m^2 (day 5-7).

Consolidation project was the same with the induction project.

Radical cure after revival: DNR 40 mg/m^2 (day 1-2)/Vp16 150 mg/m^2 (day 1-2). HDAra-C 2 g/m^2 q12 h ×6 times. The therapy was repeated 3 cycles with the interval of 4 - 6 weeks.

HA project: Homoharringtonie 3 - 4 mg/m^2 (day 1-9), Ara-c 200 mg/m^2 (day 1-7)

After 2 courses of HA, one course of radical cure was followed. After repeated for 3 cycles, the treatment finished. Intracranial treatment was administered two times after complete remission (CR), and then repeated every half of a year.

Clinical observation

Curative effect, relapse rate, event-free survival (EFS) time and EFS rate were observed. Curative effects were estimated according to the state standard[1]. All of them were followed-up until May, 2002. The longest time of follow-up was 75 months, the shortest was 6 months. Four cases were failed in visiting (1 case in group A, 3 cases in group B).

Statistics analysis

Wilcoxon signed rank test was used.

Results

Clinical data

There was no significant difference in age, WBC count and P170 between group A and B ($P > 0.05$). See Table 1.

Table 1 Comparisons in age, initial WBC count and P170 between two groups

Groups	n	Male/female	Average middle age (year)	Average middle WBC count ($\times 10^9$/L)	Average middle P170(%)
A	14	11/3	9.09	22.12	2.61
B	21	10/11	9.44	34.76	5.13
P		>0.05	>0.05	>0.05	>0.05

The estimation of curative effect

After 1 course of induction, the CR rate of group A was higher than that of group B (92.9% vs 57.1%). In group A, there was 1 case who got complete remission by two courses of induction, while in group B there were eight. There was one case in group B who had not completely revived all the time, and died.

Comparisons of relapse rate and mortality

The relapse rate and mortality of group A was 30.8%, 23.1%. Three of them did not attain the second complete remission (CR_2) and died. The relapse rate and mortality of group B was 17.7% (3/17), 16.7% (3/8). Two of them did not attain CR_2 and died, one case attained and remained C R_2 during the 18 months of follow-up. The relapse rate and mortality were of no marked difference between the two groups ($P > 0.05$). See Table 2.

Table 2 Comparisons of relapse rate and mortality between two groups [Number (%)]

Groups	n	Relapse rate	Mortality
A	14	1	3(23.1)
B	21	3	3(16.7)
P		>0.05	>0.05

The comparisons of the EFS rate

The EFS time of group A and B were 25.8, 22.8 months respectively. The EFS rate in group A was lower than that in group B (69.2% vs 77.8%) ($P < 0.05$).

Discussion

The change of chromosome karyotype is one of the clone symbols of acute leukemia. The rate of the chromosome karyotype abnormality in acute leukemia is about 50 % - 70 %. In 1973, Rowley firstly discovered t(8;21) (q22;q22) karyotype, and since then a series of investigations indicated that t(8; 21) had much to do with M_2. At the international conference of MIC typing of acute myelocytic leukemia in 1986, they were named as M_2/ t(8;21)[2]. In children with acute myelocytic leukemia, t(8;21) (q22;q22) accounts for about 10 % - 15 %. It accounts for about 55 % in M_2, and 90 % in M_2b[3,4]. So t(8;21) has much to do with M_2b. AML1-ETO amalgmation gene caused by t(8;21) may inhibit transcription of the genes related with the multiplication and differentiation of hematopoietic cells, which are regulated by AML1/ CBFβ; disturb the function of the other members of AML1 family; inhibit the function of other transcription factors except for AML1, such as C/ EBP-α, MRD1 and so on. Besides the gene also may disturb the function of ETO and other family members, and activate the target genes which were regulated by AML1 or AML1-ETO. Recent researches have discovered that AML1-ETO/ CBFβ may directly or indirectly restrain the transformation of leukemic cell induced by P53 tumour restrain gene. At the same time, some experiments found the obstacle of differentiation and maturity of hematopoietic precursor cell expressing AML1-ETO, which induced the occurrence of leukemia.

Our results revealed that the rate of t(8;21) accounted for 40 % in M_2, and it was similar to the related report that AML1-ETO accounted for 40 %[5] in M_2. There was no statistical difference in gender, age, initial WBC count between M_2 children with or without t(8;21), which indicated that t(8;21) had no relatonship with these characteristics. After a course of treatment, the rate of CR in group A was higher than that in group B, which was similar to that reported by foreigner[6]. It might be related with that AML1-ETO/ CBFβ restrained the transcription of MRD1 gene. The relapse rate and mortality of group A were not different from those of group B. And the overall EFS rate of group A was lower than that of group B. They were accordant with the data from Hong Kong that M_2 with t(8;21) had higher CR rate, but PEFS was not better than that of M_2 without t(8;21)[7]. However, M_2 patients with t(8;21) were found to have better prognosis in Chicago conference[8]. So whether the influence of t(8;21) on the prognosis of M_2 is different from region and race is worth further studying.

Trying to degrade AML1-ETO or disturbing the formation of AML1-ETO/ CBFβ or restraining the activity of HDAC may be helpful for reversing the obstacle of differentiation and maturation of leukemia cells. So investigating benzene butyric acid and other drugs which can induce the differentiation of leukemia cells of M_2 with t(8;21) may be a direction in treating M_2 with t(8;21).

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(Edited by Yan YU)