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Clinical Characteristics of Acute Myeloid Leukemia with t(8;21) in Japan and Western Countries

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1. Introduction

Acute myeloid leukemia (AML) with t(8;21) (q22;q22)translocation (t(8;21)AML) is one of the major disease group of AML, accounting for 7 to 8% of adult AML, with most classified as M2 by FAB classification (Ferrara & Del Vecchio, 2002). In the reports from Western countries to date, it has been reported that the survival rate of patients with t8;21-associated AML can be improved by employing consolidation therapy with high-dose cytarabine, which has a good remission and survival rate compared to other AML (Byrd *et al*, 1999) (Grimwade *et al*, 1998).

According to recent research by the Group B Study of Cancer and Leukemia, it has been suggested that the treatment outcome of t(8;21)AML may differ depending on race (Marcucci *et al*, 2005). This indicates that the knowledge from past research in Western countries cannot necessarily be directly transferred to Japanese patients, but the reality is that research related to the clinical features of Japanese t(8;21)AML is very limited. Of these publications, the best summarized report is the analysis of patients participating in a clinical study of Japan adult leukemia study group (JALSG) by Nishii et al. in 2003 (Nishii *et al*, 2003). This report reveals that the overall 5-year survival rate was 52%. However, this report mainly focuses on the additional chromosome abnormality of t(8;21)AML. Many clinicians felt the need for new research in order to clarify the clinical features of t(8;21)AML in Japanese patients, such as prognosis and treatment outcomes.

The research group of the authors appealed to clinicians and researchers aware of such issues, arranged participation of institutes for which approval was obtained, and conducted a retrospective study with the purpose of clarifying clinical features in Japanese patients. (Narimatsu *et al*, 2008b) This article will compare reports from Western countries to date focused on the outcome, and explain the clinical characteristics of t(8;21)AML in Japanese patients.

2. Japanese t(8;21)AML patients have a favorable survival rate

The authors retrospectively investigated clinical features of 46 adult t(8;21)AML patients newly diagnosed at facilities participating in the research from 2000 to 2005 as the subjects (Narimatsu et al, 2008b). The comparison of its outcome with prior researches (Appelbaum *et al*, 2006; Marcucci *et al*, 2005; Nguyen *et al*, 2002; Schlenk *et al*, 2004) is shown in Table 1. First off, the 3-year overall survival rate of Japanese t(8;21)AML patients reported by the authors was 70%. A definite conclusion cannot be drawn due to the short follow-up period, but close to 70% were estimated to have a 5-year survival rate. This is a good number compared to past reports from Western countries, in which 5-year survival rate ranged from 45% to 59% (Appelbaum *et al*, 2006; Marcucci *et al*, 2005; Nguyen *et al*, 2002). On the other hand, age, which is the greatest risk factor for the survival of leukemia patients, was older in reports from Japan compared to reports from Western countries. Moreover, white blood cell counts and blood platelet counts at the initial visit, which are also believed to be risk factors, were the same in reports from Japan and reports from Western countries. From these comparisons, it was suggested that the prognosis of Japanese t(8;21)AML patients was better than the prognosis of Westerners, and a possibility that racial differences may be involved as its cause, rather than the inclusion of background factors such as age and white blood cell count at initial visit, was suggested.

The authors also compared the survival rate of t(8;21)AML patients and leukemia patients that were diagnosed in each institute at the same time as AML(M2) having no t(8;21) abnormality(Narimatsu *et al*, 2008b). As a result, the overall survival rate of t(8;21)AML patients was significantly better than AML(M2) patients without t(8;21) (70% vs. 43% for 3-year overall survival rate). However, the age of AML(M2) patients without t(8;21) was significantly higher compared to t(8;21)AML, so the overall survival rate was compared by limiting patients to those 60-years old or younger. As a result, the 3-year survival rate was 71%(n=35, patients with t(8;21)) and 58% (n=49, patients without t(8;21)), respectively, narrowing the difference, with no significant difference observed between the two groups. Furthermore, when prognosis factor analysis was conducted with all these patients as subjects, the presence of t(8;21) was not a significant prognosis factor(Narimatsu *et al*, 2008b). These results suggest that young age is the main reason for good prognosis in t(8;21)AML patients, which is very interesting.

3. Prognosis factor

It was revealed from the investigation of Japanese t(8;21)AML patients by the authors that the older the age, the higher the white blood cell count at the initial visit, and the worse the survival rate. This, as shown in Table 1, can be said to be almost the same as the outcome of the research in Western countries. However, chromosome abnormalities additionally occurring in t(8;21), such as the deficiency of a sex chromosome and/or chromosome-9-abnormality that have been pointed out in much prior research, was not an apparent prognosis factor. This is the same finding as the research by Nishii et al. from JALSG, and there is a possibility that this may be the difference with Western patients (Nishii *et al*, 2003).

Moreover, although not included in the research by the authors, the report by Nishi et al. showed that the prognosis of patients with an addition of trisomy 4 is extremely poor, and

	Narimatsu et al	Nguyen et al	Schlenk et al	Marcucci et al	Appelbaum et al
Number of patients	46	161	191	144	174
Age (median (range))	49.5 (18-86)	28 (3-63)	43 (16-60)	37 (17-75)	36 (16-77)
White blood cell count at the initial visit (median (range))	9.3 (0.9-54.9)	12.0 (1.4-68.0)	10.8 (1.2-152)	10.5 (0.9-252)	10.6 (0.3-107)
White blood cell count at the initial visit (median (range))	34 (6-99)	-	30 (3-470)	40 (6-311)	37 (3-658)
Extramedullary infiltration	0.18	0.08	0.09	0.22	-
Remission rate	0.91	0.96	0.87	0.89	0.89
Overall survival rate	70%（3 years）	59%（5 years）	65%（3 years）	46%（5 years）	45%（5 years）
Prognosticator	Age White blood cell count	White blood cell count index	White blood cell count Blood platelet count Sex chromosome abnormality	Age Blood platelet count	Age† Percentage of peripheral blood blasts† Complex karyotypic abnormality†

† Analysis result combining t (8;21) and inv (16) AML

Table 1. Research on the recent clinical characteristics of t(8;l21)AML within Japan and other overseas countries

clinicians should make note of this fact. In one of those patients, Nishii et al showed c-kit mutation of the leukemia cells (Langabeer *et al*, 2003). KIT mutation may related to this unfavorable outcome, which needs to be clarified in further large study.

4. Is high dose cytarabine therapy effective?

It has been reported by prior research in Western countries that high dose cytarabine therapy can improve the treatment outcome of t(8;21)AML patients(Byrd *et al*, 1999; Ferrara & Del Vecchio, 2002). The authors also investigated whether or not the same can be said of Japanese patients. As a result, the survival rate of 14 patients who underwent consolidation therapy with a standard dose of cytarabine and that of 19 patients who underwent consolidation therapy with a high-dose cytarabine was approximately the same. However, numbers of those patients are small and the consolidation regimen of these patients covered various grounds, and it is difficult to discuss the efficacy of high dose cytarabine therapy from this result. Increased fatal side effects such as infectious diseases are a concern with high dose cytarabine therapy, but from this result, it is suggested that high-dose cytarabine can also be conducted in Japanese patients.

Recently, the outcome of a randomized controlled trial of consolidation therapy with high dose cytarabine therapy and multi-drug therapy was reported by a JALSG group. According to their report, although high dose cytarabine therapy shows a better outcome for disease free survival and overall survival compared to multi-drug therapy at a standard dosage, the results did not have any apparent significant differences (Miyawaki *et al*, 2011). This differs from the research report accounting for the usefulness of high-dose cytarabine in Western countries represented by the research by Bloomfield et al (Bloomfield *et al*, 1998). On the other hand, documented severe infections are common in high-dose cytarabine groups. This difference is presumed to be related to the difference in the incidence of tyrosine kinase such as KIT, etc., which is believed to affect the prognosis, and there is a need to clarify this in future research.

Taking the above outcomes into account, at this point, the decision regarding whether or not to apply high-dose cytarabine to Japanese t(8;21)AML patients must be determined by the on-site clinician.

5. The significance of measuring minimal residual disease

RUNX1 (AML1)/MTG8 (ETO) transcript occurs as a result of t(8;21)(q22;q22) translocation. The minimal residual disease can be evaluated by qualitatively and quantitatively measuring this transcript by the PCR method. In some small scale research from Western countries, it has been reported that patients with a high risk for relapse can be determined by evaluating minimal residual disease. (Krauter *et al*, 2003; Leroy *et al*, 2005; Perea *et al*, 2006; Tobal *et al*, 2000) (Weisser *et al*, 2007) Therefore, in the same way, the authors also investigated the clinical significance of minimal residual disease in Japanese t(8;21)AML patients by collecting the outcome of RUNX1/MTG8 quantitative tests from the clinical records of 26 t(8;21)AML patients that reached complete remission (Narimatsu *et al*, 2008a). As a result, between the group that reached less than 1,000 copies of RUNX1/MTG8 transcript when remission was reached (n=13) and the group that did

not (n=7), the relapse-free survival rate was better in the latter group. This shows that in contrast to reports from Western countries, in Japanese patients, the number of copies of RUNX1/MTG8 transcript when remission is reached does not necessarily reflect prognosis; however, number of study patients are small and it is difficult to make a definite conclusion. On the other hand, relapse is expected in patients in whom RUNX1/MTG8 transcript increased during the remission period, and monitoring RUNX1/MTG8 transcript during the remission period was suggested to have significance in terms of early prediction of relapse.

6. Conclusion - Issues to be solved in the future

The motivation for the group of the authors to initiate research was the hypothesis of the authors, "Reports on t(8;21)AML from Western countries do not match the feeling of actual clinical practice." Outcomes actually investigated also suggested a possibility of clinical features differing between Western t(8;21)AML patients and Japanese t(8;21)AML patients. It will be necessary to conduct large-scale research and/or a prospective study on Japanese patients as well in the future, in order to create evidence for Japanese t(8;21)AML patients. The following are listed in concrete terms.

1. It is necessary to conduct a large-scale retrospective study to compare the survival rate of t(8;21)AML to that of AML with other chromosome abnormalities or AML without any. Furthermore, it is necessary to clarify if t(8;21) translocation is a significant prognosis factor of AML (as in the research by the authors, if the young age of t(8;21)AML patients is responsible for good prognosis).

2. It is necessary to clarify the molecular biological characteristics of t(8;21)AML in Japanese patients. Particularly, investigation into whether or not the frequency of tyrosine kinase mutation, N-Ras mutation,,which are believed to have an effect on prognosis, is different between t(8;21)AML in Japan and Western countries, should be useful.

3. It is also necessary to reinvestigate the clinical significance of minimal residual disease by research designed so as to unify when specimens were retrieved and the method of examination with patients treated, using the same regimen as the subject.

The clarification of clinical features of t(8;21)AML in Japanese and Western patients and the establishment of optimum therapy customized for every ethnicity is hoped for in the near future.

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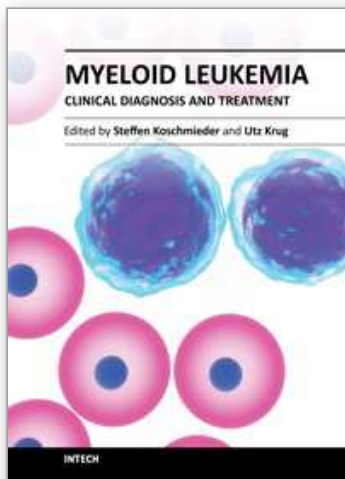
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