The Role of Allogeneic Bone Marrow Transplantation in Children with Acute Myeloid Leukemia Carrying t(8; 21) (q22; q22): a Survey of 51 Cases from the Tokyo Children's Cancer Study Group.

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Abstract

Currently, many co-operative groups exclude patients with childhood acute myeloid leukemia (AML) carrying t(8; 21) (q22; q22) from eligibility for allogeneic bone marrow transplantation (BMT) in first remission. However, since data supporting this strategy are insufficient, we thus examined the survival benefit of allogeneic BMT for patients in first remission. Fifty-one children with AML carrying t(8; 21) (q22; q22) were enrolled in two consecutive AML trials conducted by the Tokyo Children's Cancer Study Group (TCCSG) between 1991 and 1998. (TCCSG M91–13 and M96–14). In the M91–13 trial, patients received induction therapy consisting of cytarabine, mitoxantrone, and etoposide, and four courses of consolidation chemotherapy including two high-dose cytarabine (HD-Ara-C) containing courses. Subsequently, patients with HLA matched related donors (MRD) underwent allogeneic BMT, whereas the remaining patients were assigned to receive another four courses of chemotherapy including four HD-Ara-C courses, or to autologous stem cell transplantation, at the institution's discretion. In the M96–14 trial, the last two HD-Ara-C courses were omitted from the chemotherapy arm. The median follow-up of the surviving patients was 112 months (range: 68 to 149 months). Fifty patients (98%) achieved a complete remission. Of the 10 patients who had MRD, 8 received allogeneic BMT. Of the remaining patients, 8 received autologous BMT, one patient received HLA mismatched related BMT, one patient received unrelated BMT, and the others were treated with chemotherapy alone. The 5-year overall survival (OS) and event-free survival (EFS) were 60.8% (95% confidence interval: 48.8%–77.8%) and 72.4% (61.1%–85.8%), respectively. There were no significant differences in EFS or OS between the two arms (p=0.83 and p=0.70, respectively). Treatment-related mortality in first remission was observed only in one patient who received HLA mismatched related BMT. In an intent-to-treat analysis, the 5-year EFS and OS in patients with MRD were 50.0% (26.9%–92.9%) and 60.0% (36.2%–99.5%), respectively, whereas the results in patients without MRD were 61.9% (48.8%–78.5%) and 73.8% (61.6%–88.4%), respectively. We found no significant differences in EFS or OS between the patients who had MRD and those who did not (p=0.56 and p=0.34, respectively). These results suggest that the repetitive use of HD-Ara-C lessened the benefit of allogeneic BMT in first remission in children with AML carrying t(8; 21) (q22; q22).

Key words

Childhood acute myeloid leukemia, t(8; 21) translocation, allogeneic bone marrow transplantation, high-dose cytarabine
Introduction

One of the most frequent chromosomal abnormalities recognized in leukemic cells of acute myeloid leukemia (AML) involves t(8; 21) (q22; q22). In children, 5–22% of AMLs are in this subgroup. The prognosis in patients with t(8; 21) (q22; q22) has improved by intensive chemotherapy, including high-dose cytarabine (HD-Ara-C). Many clinical co-operative study groups defined this type of AML to be favorable or low-risk. However, some groups have reported that long-term disease-free survival among patients with t(8; 21) AML did not appear to be as excellent as assumed, with probabilities of 5-year EFS below 50%. The need for allogeneic BMT has been debated in childhood AML. Currently, most, if not all, pediatric groups exclude patients with t(8; 21) AML from eligibility for allogeneic BMT in first remission, because of their favorable outcome with chemotherapy alone and the potential risk of late toxicity and mortality related to allogeneic BMT. However, data supporting this strategy is insufficient in children with AML carrying t(8; 21) (q22; q22). Thus, we examined the survival benefit of allogeneic BMT for patients in first remission by an intent-to-treat analysis.

Patients and Methods

Consecutive patients under the age of 15 years, with a primary diagnosis of AML, as defined by the French-American-British classification, were enrolled in the TCCSG M91–13 trial between May 1991 and April 1994, and in the TCCSG M96–14 trial between May 1994 and December 1997. Among the 191 patients without Down syndrome or acute promyelocytic leukemia who were enrolled in these trials, cytogenetics was available for 171 patients. Of them, 51 patients had been diagnosed through standard cytogenetics as having t(8; 21) (q22; q22). Molecular criteria, such as fluorescent in situ hybridization and reverse transcriptase-polymerase chain reaction, were not considered when typing these patients.

Treatment

The therapies administered to the patients are listed in Table 1. In the M91–13 trial, patients received induction therapy consisting of cytarabine, mitoxantrone, and etoposide, and four courses of consolidation chemotherapy including two HD-Ara-C-containing courses. Triple intrathecal therapy was given as a part of each course. Subsequently, patients with HLA matched related donors (MRD) underwent allogeneic BMT, whereas the remaining patients were assigned to receive another four courses of chemotherapy including four HD-Ara-C courses, or autologous stem cell transplantation, at the institution’s discretion. In the M96–14 trial, the last two HD-Ara-C courses were omitted from the chemotherapy arm. Written informed consent was obtained from the parents or guardians of the patients prior to the therapy.

Statistical methods

The duration of follow-up was as the time until the last assessment for survivors. Event-free survival (EFS) was calculated from the day of study entry to relapse, or death from any cause. Overall survival (OS) was calculated from the day of study entry to death from any cause. EFS was evaluated in patients who achieved complete remission. OS was evaluated in all patients with t(8; 21) (q22; q22). The probabilities of EFS and OS were estimated using the Kaplan-Meier method. Confidence intervals were calculated using Greenwood’s formula.
The log-rank test was used for univariate comparisons. The significance of observed differences was tested using $X^2$ test for catorgic data and the Wilcoxon rank sum for continuous variables. Reported comparisons were based on regimens to which patients were allocated at the end of induction ("intent-to-treat"). All P values are two-sided, with a type I error rate fixed at 0.05.

## Results

### Patients

Table 2 shows the characteristics of the 51 patients (23 female and 28 male) with AML carrying t(8;21) (q22; q22). The median age was 8 years. Eight patients had extramedullary disease, which was diagnosed as granulocytic sarcoma in all of them. The most frequent additional chromosomal abnormality was loss of a sex chromosome, which was observed in 8 patients. Additional 9q deletion was observed in 2 patients. The median WBC count was $10.2 \times 10^9$/L (range: 0.2–132 $\times 10^9$/L), with only 2 patients having a WBC count of 50.0 $\times 10^9$/L or more. The clinical variables did not differ between the patients who had MRD and those who did not. Thirty-nine patients were treated in the M91–13 trial and 12 in the M96–14 trial.

### Overall Outcome

Fifty patients (98%) achieved a complete remission. The median follow up of the surviving patients was 112 months (range 68 to 149 months). The 5-year EFS and OS were 60.8% (95% confidence interval: 48.8%–75.8%) and 72.4% (61.1%–85.8%), respectively. There were no significant differences in EFS or OS between the two arms ($p=0.83$ and $p=0.70$, respectively).

### Comparison of outcome; Patients with MRD versus those without MRD

Of the 50 patients achieving a complete remission, 10 patients had MRD. Of the 10 patients who had MRD, 8 received allogeneic BMT and 2 received chemotherapy alone. Of the patients without MRD, 8 received autologous BMT, one patient received HLA mismatched related BMT, one patient received unrelated BMT, and the others were treated with chemotherapy alone.

The preparative regimen for allogeneic BMT from MRD included busulfan 16 mg/kg, cyclophosphamide 120 mg/kg and melphalan 140 mg/kg in 5 patients, and total-body irradiation 12 GY, cyclophosphamide 120 mg/kg and cytarabine 1000 mg/kg in 3 patients. Graft-versus-host disease (GVHD) prophylaxis for allogeneic BMT from MRD included cyclosporine alone in 4 patients, and cyclosporine and short-term methotrexate in 4. The preparative regimen for allogeneic BMT from an unrelated donor included busulfan 16 mg/kg, cyclophosphamide 200 mg/kg and etoposide 60 mg/kg. GVHD prophylaxis for allogeneic BMT from an unrelated donor included tacrolimus and short-term methotrexate. The preparative regimen for allogeneic BMT from a mismatched related donor included cyclosporine and short-term methotrexate.

The preparative regimen for autologous BMT included total-body irradiation 12 GY and cyclophosphamide 120 mg/kg in 3 patients, busulfan 16 mg/kg and cyclophosphamid 200 mg/kg in 3, and busulfan 16 mg/kg and melphalan 180 mg/kg in 2. It was recommended that patients receive at least $3 \times 10^9$ nucleated donor marrow cells in allogeneic bone marrow transplantation.

The preparative regimen for autologous BMT included total-body irradiation 12 GY and cyclophosphamide 120 mg/kg in 3 patients, busulfan 16 mg/kg and cyclophosphamid 200 mg/kg in 3, and busulfan 16 mg/kg and melphalan 180 mg/kg in 2. It was recommended that patients receive at least $2 \times 10^9$ CD34 positive cells in autologous

### Table 2. Characteristics of Patients with AML

| Carrying t(8; 21) (q22; q22) Treated in the TCCSG M91–13 and M96–14 Studies: Comparison between the patients who had MRD vs. those who did not. |
|---|---|---|---|---|
| Overall | MRD | No MRD | P value* |
| Age, y | | | | |
| Median | 8.0 | 10 | 7 | 0.329 |
| Range | 2.15–15.4 | 4–15 | 2–19 | |
| Gender | | | | |
| Male | 28 | 7 | 21 | 0.284 |
| Female | 23 | 3 | 20 | |
| WBC count, $10^9$/L | | | | |
| Median | 10.2 | 11.0 | 10.6 | 0.636 |
| Range | 0.2–132 | 0.24–25.7 | 0.2–132 | |
| Extramedullary disease | | | | |
| Yes | 8 | 2 | 6 | 0.777 |
| No | 43 | 8 | 35 | 0.882 |
| FAB classification | | | | |
| M1 | 4 | 1 | 3 | |
| M2 | 47 | 9 | 38 | |
| Karyotype | | | | |
| t(8;21) alone | 25 | 5 | 20 | |
| Jc(17) | 8 | 1 | 7 | |
| d(a)(16) | 2 | 1 | 1 | |
| Other additional abnormalities | 15 | 4 | 11 | |

Abbreviations: AML, acute myeloid leukemia; TCCSG, Tokyo Children’s Cancer Study Group; MRD, matched sibling donor; WBC, white blood cell; FAB, French-American-British.

*Comparison between patients who had MRD (MRD) and those who did not (No MRD).

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Allogeneic BMT in Childhood AML with t(8; 21) (q22; q22)
bone marrow transplantation.

Treatment-related mortality in first remission was observed only in one patient who received HLA mismatched related BMT. Of the 10 patients with MRD, 5 patients relapsed, 4 of whom subsequently died. Of the 40 patients without MRD, 11 had relapsed, 3 of whom had received autologous BMT in first remission, 5 of whom remain disease-free after receiving allogeneic BMT from unrelated donors in second remission.

The 5-year EFS and OS in patients with MRD were 50.0% vs 26.9% and 60.0% vs 92.9%, respectively, whereas the results in patients without MRD were 61.9% (48.8–78.5) and 73.8% (61.6–88.4), respectively (Figure 1 and Figure 2). We have not observed any significant difference in EFS or OS between the patients who had MRD and those who did not (p=0.34 and p=0.56, respectively).

Discussion

The results of the TCCSG M91–13 and M96–14 trials have been already reported. Of the 171 patients in whom cytogenetics was available, 51 (30%) had t(8; 21) (q22; q22) translocation. The high frequency of t(8; 21) (q22; q22) in these trials encouraged us to examine the survival benefit of allogeneic BMT in childhood AML with t(8; 21) (q22; q22).

The role of allogeneic BMT in children with AML has been controversial. The Medical Research Council (MRC) Group has reported no survival benefit for AML children receiving allogeneic BMT, comparing 86 patients who had MRD, of whom 61 were transplanted, with 229 who did not. The Children’s Cancer Group (CCG) has reported a significant survival benefit for patients with MRD (60% vs 53%) in a larger trial. Neither groups has shown the value of allogeneic BMT among patients with the t(8; 21) subtype because of the small number of patients. Patients who actually received allogeneic BMT may already be a selected group based on the fact that patients who relapsed while waiting for a transplant are excluded. In order to avoid this time censoring effect, both groups adopted an intent-to-treat analysis. We also chose to compare the patients who had MRD and those who did not in an intent-to-treat analysis. In the present study, the M91–13 and M96–14 were analyzed as the same group, because the strategy was almost the same and the outcome was similar. Since the aim of this study was to examine the benefit of allogeneic BMT, the patients receiving autologous BMT were included in the chemotherapy group. Although concerns have been raised that many patients scheduled to receive the transplant do not receive it for various reasons, making it difficult to compare transplanted patients with a control group, such cases were relatively few in our present study.

We did not observe the survival advantage of allogeneic BMT either in EFS or in OS. The MRC 10 trial has shown the advantage in EFS, but not in OS, because patients receiving chemotherapy alone...
could be salvaged even after relapse\(^1\). We also observed that more patients who relapsed after chemotherapy alone have been salvaged. CCG has shown that allogeneic BMT had more antileukemic effect than chemotherapy alone, but that the toxicity and mortality related to it counterbalanced this favorable effect\(^2\). However, transplant-related mortality was tolerable in our patients receiving allogeneic BMT from MRD in first remission, and no patients died from transplant-related causes in the trials.

Our results were in part attributable to the intensity of chemotherapy, because the EFS of the patients without MRD in our study were almost equivalent to the EFS with transplants in the CCG report. The Berlin-Frankfort-Munster group has reported that the 5-year overall survival in patients receiving at least 3 courses of HD-Ara-C was 76% compared to 44% in those only receiving one course \(^3\). Our regimen included at least 4 courses of HD-Ara-C for the patients receiving chemotherapy alone. These intensive post-remission therapies in chemotherapy regimen probably produced a better overall outcome in our trials.

The superior outcome for the patients without MRD may be attributable to the effect of autologous BMT, since 8 patients received autologous BMT in first remission. However, it is not likely because the estimated EFS or OS was similar between the patients who received chemotherapy alone and those who received autologous BMT on as-treated analysis (data not shown).

In conclusion, although the number of patients was small, our results have justified the recent strategy excluding patients with childhood AML carrying t(8; 21) (q22; q22) from eligibility for allogeneic BMT in first remission. Chemotherapy in children with AML continues to achieve improving results. Thus, allogeneic BMT in children with AML carrying t(8; 21) (q22; q22) in first remission does not appear to be beneficial.

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Appendix

The following members of the TCCSG participated in this study:

K Koike, M Tsuchida (Ibaraki Children’s Hospital, Mito); K Tabuchi, H Kigasawa (Kanagawa Children’s Medical Center, Yokohama); R Hanada, A Kikuchi (Department of Hematology-oncology, Saitama Children’s Medical Center, Iwatsuki); K Sugita, S Nakazawa (Yamanashi University, School of Medicine, Yamanashi); A Manabe, R Hosoya (St. Luke’s International Hospital, Tokyo); A Ohara, I Tsukimoto (Toho University, School of Medicine, Tokyo); M Kumagai, Y Tsunematsu (National Center for Child Health and Development, Tokyo); D Tomizawa, M Kajiwara (Tokyo Medical and Dental University, Tokyo); M Maeda (Nippon Medical School, Tokyo); Y Okimoto (Chiba Children’s Hospital, Chiba); T Kaneko, H Yoneyama (Tokyo Metropolitan Kyose Children’s Hospital); A Makimoto (National Cancer Center, Tokyo); T Kamijo (University of Shinsyu, School of Medicine, Nagano); Y Hirota, K Isoyama (Showa University, School of Medicine, Fujigaoka Hospital, Yokohama); H Takahashi (Yokohama City University, School of Medicine, Yokohama); H Kurukawa, K Sugita (Dokkyo Medical College, Tochigi Yamanashi University); M Akiyama (Jikei University, School of Medicine, Tokyo); M Saito (Juntendo University School of Medicine, Tokyo); H Yabe (Tokai University, School of Medicine, Isehara); K Ida (The University of Tokyo, Faculty of Medicine, Tokyo); H Shimada, T Mori (Keio university, School of Medicine, Tokyo)

References


t(8; 21) 転座を伴う小児急性骨髄性白血病における
同種骨髄移植の有用性の検討

抄録

t(8; 21) 転座を伴う急性骨髄性白血病（AML）の予後は比較的良好とされ、第一観察期には同種骨髄移植を行なわないことが一般的になりつつある。われわれは、この治療戦略の妥当性を検証するため、東京小児がん治療研究グループ M91-13 および M96-14 研究に登録された t(8; 21) 転座を伴う AML 患者 51 例における同種骨髄移植の有用性について検討を行なった。エトボンド、シタラビン、ミトキサントロンによる覚解導入療法後、M91-13 研究では計 6 コースの大量シタラビン療法を含む計 8 コースの強化療法が行なわれ、M96-14 研究では最終 2 コースが削除された。HLA 適合同胞ドナーがいる場合は強化 4 コース終了後に同種骨髄移植の適応となり、いない場合は施設判断により化学療法ないしは自家造血幹細胞移植が選択された。51 例中 50 例が覚解し、10 例で同種骨髄（血緣者間移植 9 例、非血縁者間移植 1 例）、8 例で自家造血幹細胞移植、32 例で化学療法が行われた。全体の 5 年無病生存率は 60.8% (95% confidence interval: 48.8%–75.8%)、年無病生存率は 74.2% (61.1%–85.8%) であった。ドナーの有無で intent-to-treat 分析を行なったところ、ドナーのいる患者（n=10）の 5 年無病生存率は 50% (26.9%–92.9%)、5 年無病生存率は 60% (36.2%–99.5%)、ドナーのいない患者（n=41）での 5 年無病生存率は 61.9% (48.8%–78.5%)、5 年無病生存率は 73.8% (61.6%–88.4%) で、ともに有意差を認めなかった（p=0.56、p=0.34）。この結果は t(8; 21) 転座を伴う AML に対して第一観察期の同種骨髄移植を行なわないとする治療戦略の妥当性を支持すると考えられる。