Clinical Courses of Two Pediatric Patients with Acute Megakaryoblastic Leukemia Harboring the CBFA2T3-GLIS2 Fusion Gene

CBFA2T3-GLIS2 Füzyon Geni Taşıyan İki Pediatrik Akut Megakaryoblastik lösemi Hastasının Klinik Seyri

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Abstract

Acute megakaryoblastic leukemia (AMKL) in children without Down syndrome (DS) has an extremely poor outcome with a 3-year survival of less than 40%, whereas AMKL in children with DS has an excellent survival rate. Recently, a novel recurrent translocation involving CBFA2T3 and GLIS2 was identified in about 30% of children with non-DS AMKL, and the fusion gene was reported as a strong poor prognostic factor in pediatric AMKL. We report the difficult clinical courses of pediatric patients with AMKL harboring the CBFA2T3-GLIS2 fusion gene.

Keywords: Acute megakaryoblastic leukemia without Down syndrome, CBFA2T3-GLIS2 fusion gene

Introduction

Acute megakaryoblastic leukemia (AMKL) is classified as M7 in the FAB (French-American-British) classification. AMKL accounts for approximately 10% of pediatric acute myeloid leukemia (AML) cases and 1% of adult AML cases [1,2,3]. Pediatric AMKL is divided into two subgroups: AMKL arising in patients with Down syndrome (DS-AMKL), and AMKL arising in patients without DS (non-DS-AMKL). Although patients with DS-AMKL have an excellent survival rate, patients with non-DS-AMKL have an extremely poor outcome with a 3-year survival of less than 40% [1,2,4]. Recently, two studies identified a novel recurrent translocation involving CBFA2T3 and GLIS2 in about 30% of children with non-DS-AMKL. The CBFA2T3-GLIS2 fusion gene was reported as a strong poor prognostic factor in pediatric AMKL [5,6]. We report the difficult clinical courses of two pediatric patients with AMKL harboring the CBFA2T3-GLIS2 fusion gene.

Case Presentation

Between 2003 and 2012, six patients were diagnosed with AMKL at the Department of Pediatrics of Yokohama City University Hospital. We analyzed the fusion gene, CBFA2T3-GLIS2, in the six leukemic samples at the time of diagnosis by reverse transcription polymerase chain reaction (PCR) and direct sequencing, according to a previous report [5]. We compared characteristics between the patients who were diagnosed with AMKL with or without the CBFA2T3-GLIS2 fusion gene.

Two patients had DS-AMKL harboring a GATA1 mutation and four had non-DS-AMKL. None of them had inv(16)/t(16;16)
chromosomal abnormalities upon G-band karyotyping. Two patients with non-DS-AMKL (Patient 1 and Patient 3) had the CBFA2T3-GLIS2 fusion gene (Table 1). Reverse transcription PCR and direct sequencing revealed that exon 11 of CBFA2T3 was fused to exon 3 of GLIS2 in both cases (Figures 1A and 1B). Neither of them achieved complete remission (CR) after induction therapies. They died from the primary disease after stem cell transplantation (SCT). The other 4 patients remain alive in CR (Table 1).

Patient 1 with the CBFA2T3-GLIS2 fusion gene was treated under the AML05 protocol of the Japanese Pediatric Leukemia/Lymphoma Study Group [7] and could not achieve CR after induction 1 therapy (Figure 1C). After induction 2 therapy, Patient 1 under non-CR conditions was treated with unrelated cord blood SCT (CBSCT) after a myeloablative conditioning regimen. Three months after CBSCT, her AMKL relapsed. She underwent two courses of chemotherapy. She received a haploidentical SCT

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**Table 1. Patient details.**

| Patient No. | Sex | Age at Onset (Months) | Non-DS | DS | Clinical Course | Karyotype | Outcome |
|-------------|-----|-----------------------|--------|----|----------------|----------|---------|
| 1           | F   | 11                    | Non-DS |    | BM             | 73XX,–X,–8,–12,–14,–15,–19,–20, +21 | Dead (30 months) |
| 2           | F   | 20                    | Non-DS |    | PBMC           | 46XX,–7,add(11)(p12), +mar4 | Alive (4 years) |
| 3           | F   | 13                    | Non-DS |    | PBMC           | 46XX,add(3)(p21),add(4)(q11.1),add(17)(q21),add(20)(q13),–17,–19, +mar1, +mar2, +mar3, +mar4 | Alive (7 years) |
| 4           | F   | 20                    | Non-DS |    | BM             | 46XX,add(11)(p12),add(17)(q21),add(20)(q13),–17,–19, +mar1, +mar2, +mar3, +mar4 | Alive (6 years) |
| 5           | M   | 20                    | DS     |    | BM             | 47XY,+21 | Alive (5 years) |
| 6           | M   | 21                    | DS     |    | BM             | 47XY,+21 | Alive (5 years) |

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**Figure 1.** Clinical courses of two Acute megakaryoblastic leukemia patients with the CBFA2T3-GLIS2 fusion gene. A) Reverse transcription polymerase chain reaction for the CBFA2T3-GLIS2 fusion gene in our patients. Two patients with non-Down syndrome-acute megakaryoblastic leukemia (patients 1 and 3) had the CBFA2T3-GLIS2 fusion gene. NC: Negative control. B) Direct sequencing for the polymerase chain reaction product of the CBFA2T3-GLIS2 fusion gene in patient 1 revealed that exon 11 of CBFA2T3 was fused to exon 3 of GLIS2. C) Clinical course of patient 1. FLAG: Fludarabine, cytarabine, G-CSF; FK506: tacrolimus. D) Magnetic resonance imaging of patient 1 revealed an extramedullary lesion at the thoracic spinal cord (Th9). E) Clinical course of patient 3. CAG: Cytarabine, aclacinomicin, G-CSF; GO: gemtuzumab ozogamicin; IDA: idarubicin; VPL: vincristine, prednisolone, L-asparaginase.
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In Patient 3 with CBFA2T3-GLIS2-positive AMKL, chemotherapy regimens used to treat AML were not effective, but chemotherapy with VPL, commonly used to treat ALL, seemed to be more effective. When some of the treatment strategies commonly used to treat AML are not effective, the type of chemotherapy used to treat ALL might be effective in a subpopulation of patients with AMKL. There is a possibility that the conventional treatment commonly used to treat ALL may be effective for AMKL with this fusion gene. Eventually, the AMKL in both of the CBFA2T3-GLIS2-positive patients in our cohort became intractable to treatment, including SCT. Despite some chemotherapy regimens and SCT, the two patients with the CBFA2T3-GLIS2 fusion gene had poor prognosis. As previously reported, CBFA2T3-GLIS2 expression enhances BMP2/BMP4 signaling [5]. The development of treatments including novel targeted therapy drugs is desired.

Conclusion

Clinical courses of pediatric patients with AMKL harboring the CBFA2T3-GLIS2 fusion gene are poor due to resistance to chemotherapies and SCT. New treatment strategies are necessary.

Ethics

Ethics Committee Approval: The protocol of this survey and research plan has been approved by the Clinical Ethics Committee of Yokohama City University (A130725002), Informed Consent: It was taken from patients and/or their parents.

Authorship Contributions

Concept: Masakatsu D.Yanagimachi; Design: Masakatsu D. Yanagimachi, Hiroaki Goto, Shumpei Yokota; Data Collection or Processing: Mayu Ishibashi, Tomoko Yokosuka, Masakatsu D. Yanagimachi, Fuminori Iwasaki, Shin-ichi Tsujimoto, Koji Sasaki, Masanobu Takeuchi, Reo Tanoshima, Hiromi Kato, Ryosuke Kajiwara, Fumiko Tanaka, Hiroaki Goto, Shumpei Yokota; Analysis or Interpretation: Mayu Ishibashi, Tomoko Yokosuka, Masakatsu D. Yanagimachi; Literature Search: Mayu Ishibashi, Tomoko Yokosuka, Masakatsu D. Yanagimachi, Fuminori Iwasaki, Shin-ichi Tsujimoto, Koji Sasaki, Masanobu Takeuchi, Reo Tanoshima, Hiromi Kato, Ryosuke Kajiwara, Fumiko Tanaka, Hiroaki Goto, Shumpei Yokota; Writing: Mayu Ishibashi, Tomoko Yokosuka, Masakatsu D. Yanagimachi, Fuminori Iwasaki, Shin-ichi Tsujimoto, Koji Sasaki, Masanobu Takeuchi, Reo Tanoshima, Hiromi Kato, Ryosuke Kajiwara, Fumiko Tanaka, Hiroaki Goto, Shumpei Yokota.

Conflict of Interest: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.
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