Characteristics of hematologic malignancies with coexisting t(9;22) and inv(16) chromosomal abnormalities

Eunhee Han¹, Hyeyoung Lee¹, Myungshin Kim¹, Yonggoo Kim¹, Kyungja Han¹, Sung-Eun Lee², Hee-Je Kim², Dong-Wook Kim²

¹Department of Laboratory Medicine, ²Department of Hematology, Department of Internal Medicine, Catholic Blood and Marrow Transplantation Center, The Catholic University of Korea, Seoul, Korea

Background
The coexistence of t(9;22)(q34;q11.2) and inv(16)(p13q22) chromosomal abnormalities is extremely uncommon, and only a small number of such cases have been reported. Here, we characterized 7 cases of hematologic malignancy exhibiting t(9;22) and inv(16) coexistence.

Methods
We reviewed the cytogenetic data for hematologic malignancies treated at the Catholic Blood and Marrow Transplantation Center between January 2004 and June 2013. We identified 7 cases exhibiting t(9;22) and inv(16) coexistence. In addition, we analyzed mutations in the IKZF1, NPM1, FLT3, N-RAS, K-RAS, c-KIT, and TP53 genes.

Results
Four cases of chronic myelogenous leukemia (CML; 1 chronic phase, 2 accelerated phase, and 1 blast phase) and 3 cases of acute myeloid leukemia (AML; 1 de novo and 2 therapy-related) were identified. The percentages of circulating blasts and bone marrow eosinophils were higher in AML cases than in CML cases (53% vs. 5% and 30% vs. 5.5%, respectively). The proportions of each chromosomal abnormality were used along with follow-up karyotyping results to identify secondary changes. In BCR/ABL, a p210 fusion transcript was associated with CML, whereas a p190 fusion transcript was associated with AML. One patient with AML harbored 2 mutations: c-KIT D816V and TP53 E11Q. All patients except 1 with CML blast phase sustained clinical remission after treatment, which included an imatinib mesylate regimen.

Conclusion
This study shows that observations of bone marrow morphology, initial and follow-up cytogenetic studies, and karyotyping of BCR/ABL and CBFB/MYH11 provide valuable information for characterizing hematologic malignancies exhibiting t(9;22) and inv(16) coexistence.

Key Words Chronic myelogenous leukemia; Acute myeloid leukemia; t(9;22); BCR/ABL1; inv(16); CBFB/MYH11
of the t(9;22) and inv(16) chromosomal aberrations is a rare occurrence that has been described in CML (mainly the myeloid blast phase [CML-BP]), de novo AML, and a few cases of therapy-related AML (t-AML) [2-6]. Most of the de novo forms of AML with the t(9;22) and inv(16) chromosomal abnormalities have a favorable prognosis comparable to that of AML with inv(16) alone [6]. However, the majority of cases, in which these abnormalities coexist are CML-BP, which is typically characterized by an aggressive clinical course with rapid disease progression and resistance to chemotherapy [4]. Therefore, discriminating between these disease types is important in the formulation of appropriate treatment plans. However, few cases have been analyzed. Herein, we describe 7 cases of hematologic malignancy accompanied by the coexistence of t(9;22) and inv(16). In addition, we analyze the presence of mutations in several other genes associated with the hematologic malignancies in these cases.

MATERIALS AND METHODS

Patients

We reviewed all cytogenetic data for patients with hematologic malignancies who received treatment at the Catholic Blood and Marrow Transplantation Center between January 2004 and June 2013. We observed 716 cases of t(9;22), including 705 with CML, 151 cases of acute lymphoblastic leukemia/acute biphenotypic leukemia, and 56 cases of AML. AML with inv(16) occurred in 104 cases. Among these cases, we identified 7 patients exhibiting both t(9;22) and inv(16). This study was performed according to the Declaration of Helsinki guidelines, and full approval was obtained from the institutional review board of St. Mary’s Hospital, which is affiliated with The Catholic University of Korea (IRB No: KC13ZISE0779).

Bone marrow examination and flow cytometry

We reviewed all available data, including peripheral blood (PB) smears, bone marrow (BM) aspirates, cytochemical staining, and core biopsy specimens. Clinical information was also reviewed when available; however, not all cases included the same types of data. Immunophenotyping of cells was performed with flow cytometry against CD3, CD41a, CD14, CD34, CD33, CD20, CD5, CD10, CD19, CD64, CD11c, CD13, CD117, CD56, CD2, CD27, HLA-DR, cytoplasmic CD22, cytoplasmic myeloperoxidase, cytoplasmic CD3, and cytoplasmic CD79a (BD Biosciences, San Jose, CA, USA). Leukemic blasts were analyzed with the FACSDiva program (BD Biosciences).

Conventional cytogenetics

Chromosomal analyses were performed by examining short-term cultures of BM specimens according to standard conventional cytogenetic protocols. At least 20 cells in metaphase were analyzed in each case. Clonal abnormalities were classified according to the 2009 International System for Human Cytogenetic Nomenclature guidelines [7].

Fluorescence in situ hybridization

In 6 of 7 cases, fluorescence in situ hybridization (FISH) analyses were performed to confirm Ph translocation and the presence of inv(16). These FISH analyses used pellets of cells remaining after conventional cytogenetic studies. Slides for FISH were prepared by using cells harvested for conventional cytogenetics and processing them for FISH according to the manufacturer’s guidelines (Abbott Vysis, Des Plaines, IL, USA). Analyses were performed on cells in either interphase or metaphase. An LSI BCR/ABL1 dual-color, dual-fusion probe (Abbott Vysis) was used to identify t(9;22) and its variants. A LSI CBFB dual-color break-apart rearrangement probe (Abbott Vysis) was used to identify rearrangements involving CBFB.

Reverse transcriptase-polymerase chain reaction (RT-PCR)

RNA from 6 patients was extracted from BM cells, reverse transcribed into complementary DNA using a QiaAmp RNA Blood Mini Kit (Qiagen, Chatsworth, CA, USA) according to the manufacturer’s instructions, and analyzed using RT-PCR designed to detect the BCR/ABL fusion transcript of t(9;22) or the CBFB/MYH11 fusion transcript of inv(16). Multiplex RT-PCR was performed to detect the presence of BCR/ABL1 (N=6) and CBFB/MYH11 (N=3) fusion products using a HemaVision kit (Bio-Rad Laboratories, Hercules, CA, USA).

Mutation analysis

Genomic DNA was extracted from BM specimens using a QiaAmp DNA Blood Mini Kit (Qiagen, Hilden, Germany). We analyzed an internal tandem duplication in FLT3, a mutation in the tyrosine kinase domain of FLT3 (Seegene, Seoul, Korea), mutations in c-KIT (BioSewoom Inc., Seoul, Korea), and mutations A and B in NPM1 (Ipsogen Inc., Stamford, CT, USA) following the manufacturers’ instructions for the appropriate kits. Mutations in N-RAS, K-RAS, and TP53 were evaluated via direct sequencing using primers designed using primer sequences. Amplicons were bidirectionally sequenced with a BigDye Terminator v3.1 cycle sequence kit (Applied Biosystems, Foster City, CA, USA) by using an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems). The targeted copy number of IKZF1 was analyzed using a SALSA MLPA probemix P202-B1 IKZF1 kit (IKAROS, MRC-Holland, Amsterdam, The Netherlands) according to the manufacturer’s instructions.

RESULTS

Clinical features

The clinical and laboratory characteristics of the patients analyzed in this study are summarized in Table 1. In total, 5 men and 2 women with a median age of 27 years (range, 10-61 years) were included. Four cases of CML and 3 cases of AML were identified. The incidence of inv(16) in the
patients with CML was 0.6% (4/705), and the incidence of t(9;22) in patients with AML with inv(16) was 2.9% (3/104). Among the 4 CML patients, 1 patient (case 2) presented with CML-chronic phase (CML-CP). Two patients were previously diagnosed with and treated for CML-CP and later progressed to CML-BP (cases 1 and 4). One patient initially presented with CML-BP. Among the 3 patients diagnosed with AML, 1 had de novo AML M4Eo and the other 2 were diagnosed with t-AML. One t-AML patient presented with Hodgkin’s lymphoma and was treated with doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy (case 6), and the other presented with follicular lymphoma and was treated with fludarabine, mitoxantrone, and dex-amethasone chemotherapy (case 7). Splenomegaly was documented in all cases except case 3. All patients received chemotherapy containing imatinib mesylate (Table 2). Two patients with CML and 3 patients with AML underwent either BM or PB stem cell transplantation. One patient died of sepsis 5 months after developing CML-BP (case 3). The other 6 patients were alive at the most recent follow-up examination.

Peripheral blood and BM findings

In the CML cases, clinical studies of PB revealed anemia (median Hb, 9.1 g/dL) and mild to severe leukocytosis (median WBC, 134.1×10^9/L). Thrombocytosis was observed in 2 patients with CML (cases 2 and 3). The other 2 patients with CML exhibited thrombocytopenia. In the AML cases, clinical studies of the PB revealed anemia (median Hb, 8.3 g/dL) and mild leukocytosis (median WBC, 91.3×10^9/L). All AML patients also exhibited thrombocytopenia (median platelet count, 29×10^9/L). The percentage of circulating blasts was variable and higher in AML patients than in CML patients (median, 53% vs. 5%, P=0.4). BM cellularity was nearly 100% and exhibited an increased number of blasts (median, 65% in CML; 60% in AML). The percentage of eosinophils in the BM of AML patients was higher than that in CML patients (median, 30% vs. 5.5%, P=0.057); furthermore, most of the eosinophils were abnormal with coarse basophilic granules. Flow cytometric analysis showed a large population of myeloid blasts with the following immunophenotype: CD13, CD33, CD34, CD11c, and myeloperoxidase.

Table 1. Patient characteristics.

| Case No./ Gender/Age (y) | Diagnosis | Peripheral blood | Bone marrow |
|--------------------------|-----------|-----------------|-------------|
|                          |           | WBC 10^9/L | Nø % | Eø % | Bø % | Blasts % | Hb g/dL | Plt 10^9/L | Blast % | Eø % |
| 1/M/18 CML-CP → BP^a    |           | 10        | 41   | 0    | 0    | 44       | 7.4     | 14      | 70       | 7     |
| 2/M/61 CML-CP^b          |           | 195.1     | 67   | 3    | 7    | 1        | 9       | 811     | 1       | 11    |
| 3/M/27 CML-BP^c          |           | 285.8     | 9     | 22   | 2    | 6        | 9.2     | 663     | 60       | 4     |
| 4/M/10 CML-CP-→ BP^d      |           | 73        | 6     | 0    | 0    | 90       | 9.9     | 56      | 80       | 4     |
| 5/M/30 AML, M4Eo          |           | 194.5     | 13    | 5    | 5    | 39       | 12.8    | 35      | 37       | 30    |
| 6/F/27 Hodgkin’s lymphoma→ t-AML |   | 91.3      | 6     | 5    | 2    | 53       | 8.3     | 29      | 65       | 30    |
| 7/F/57 Follicular lymphoma→ Eosinophilia→ t-AML | 10 | 10   | 0    | 0    | 80   | 8.2     | 24      | 60       | 30    |

^aPhase in which cytogenetic studies were performed.

Abbreviations: AML, acute myeloid leukemia; AP, accelerated phase; Bø, basophil; BP, blast phase; CML, chronic myelogenous leukemia; CP, chronic phase; Eø, eosinophil; Hb, hemoglobin; M4Eo, French-American-British Cooperative Group classification M4 with eosinophils; Nø, neutrophil; Plt, platelet; t-AML, therapy-related AML.

Cytogenetic and molecular findings

The cytogenetic and molecular findings of this study are summarized in Table 2. All patients exhibited t(9;22) and inv(16) at some point during the course of their disease. Five patients showed complex karyotypes with additional numerical chromosomal aberrations, structural chromosomal aberrations, or both. Of the 4 patients with CML, 1 patient had both abnormalities detected in the CML-CP sample, whereas the other 3 had both abnormalities detected in CML-BP samples. Of the 3 CML-BP cases, 2 cases included karyotype results for the time at which the patients exhibited CML-CP, and both showed t(9;22) without inv(16). Of the 3 patients with AML, 1 of the patients with t-AML (case 7) had the karyotype result from the previous illness, which showed inv(16) without t(9;22). Follow-up karyotype results were available for all patients. Cells in metaphase were documented for all CML-BP cases, with the occurrence of t(9;22) observed only after treatment. One CML-CP and 3 AML cases showed normal karyotype results after treatment.

The BCR/ABL1 fusion transcript resulting from the translocation of t(9;22) was analyzed with RT-PCR in 6 cases. A p210 fusion product was detected in all patients with CML and 1 patient with AML (case 5); moreover, a p190 fusion product was detected in the 2 patients with t-AML. The BCR/ABL1 fusion transcript was also confirmed with FISH in 6 patients. The CBFB/MYH11 fusion transcript was confirmed with RT-PCR or FISH. Interestingly, FISH analysis of 1 of the patients with CML (case 3) showed that the percentage of cells with CBFB/MYH11 rearrangement was lower than that with BCR/ABL1 rearrangement. On the contrary, the percentages of cells with both types of rearrangement were similar in patients with AML. In addition, each of the 3 cases in which CBFB/MYH11 RT-PCR was performed displayed a different transcript type. The patient with CML (case 3) exhibited type B, a patient with de novo AML (case 5) exhibited type E, and the patient with t-AML
Table 2. Molecular and cytogenetic findings and clinical outcomes.

| No. | Initial BM | Cytogenetic findings | Follow up BM (months) | Molecular findings | Treatment | Clinical outcome |
|-----|------------|----------------------|-----------------------|-------------------|-----------|-----------------|
|     |            | Presence of t(9;22) and inv(16) (months) |          | BCR/ABL1/RT-PCR | BCR/ABL1/ MYH11 RT-PCR | BCR/ABL1/ MYH11 FISH (%) |    |
| 1   | 46, XY, t(9;22) (q34;q11.2) [20] | 46, XY, t(9;22) (q34;q11.2), inv(16) (p13.1q22)[5]/46, idem, +8, +19[15] (2 mon) | 46, XY, (t(9;22) (q34;q11.2)[17]/46, XY[3]) | b2a2 | ND | 95% | 80% | Imatinib, dasatinib, idarubicine, cytarabine, uBMT | Alive at 48 mon |
| 2   | 46, XY, t(3;11) (p23;p15), t(6;16) (q15;p13.3), t(9;22) (q34;q11.2), inv(16) (p13.1q11.2)[20] | 46, XY[20] (5 mon) | b2a2 | ND | ND | ND | Hydroxyurea, imatinib | Alive at 41 mon |
| 3   | 46, XY, t(9;22) (q34;q11.2), inv(16) (p13.1q22)[20] | 46, XY, t(9;22) (q34;q11.2)[15]/46, XY[5] (2 mon) | b3a2 | CBFB/ MYH11(B) | 95% | 50% | Imatinib, dasatinib, uPBSCT | Alive at 6 mon |
| 4   | 46, XY, t(9;22) (q34;q11.2) [25] | 46, X, der(Y)(t;1) (q12;q21), der(4)(t;1;4) (q25;q31.3), t(9;22) (q34;q11.2), inv(16) (p13.1q22)[17]/47, ide, +der(22) y(9;22)[1]/46, XY, der(5)t(5;1q22)[12], der(9;9)[22] (q21;q11.2)[2] (67 mon) | ND | ND | 93.50% | 70.50% | Imatinib, hydroxyurea, cytarabine, etoposide | Died by sepsis |
| 5   | 46, XY, t(9;22) (q34;q11.2), inv(16) (p13.1q22)[13]/47, ide, +17[5]/48, ide, +8, +17[2] | 46, XY[20] (2 mon) | b3a2 | CBFB/ MYH11(E) | 98.80% | 98.50% | Idarubicine, cytosine arabinoside, imatinib, alloPBSCT | Alive at 15 mon |
| 6   | 46, XX, inv(16) (p13.1q22)[20] | 46, XX[20] (2 mon) | e1a2 | CBFB/ MYH11(A) | 98.80% | 98.50% | Idarubicine, cytosine arabinoside, imatinib, alloPBSCT | Alive at 5 mon |
| 7   | 46, XX, inv(16) (p13.1q22) [20] | 46, XX[20] (5 mon) | e1a2 | 67.50% | 91% | Idarubicine, cytosine arabinoside, imatinib, alloPBSCT | Alive at 99 mon |

a) Months from previous diagnosis. b) Months from presence of inv(16) and t(9;22).

Abbreviations: alloPBSCT, allogeneic peripheral blood stem cell transplant; BM, bone marrow; FISH, fluorescence in situ hybridization; ND, not done; RT-PCR, reverse transcriptase-polymerase chain reaction; uBMT, unrelated BM transplantation; uPBSCT, unrelated peripheral blood stem cell transplant.

(case 6) exhibited type A. Mutations in IKZF1, NPM1, FLT3, N-RAS, and K-RAS were not detected in any patient. The c-KIT D816V and TP53 E11Q mutations were identified in case 6.

DISCUSSION

Coexistence of t(9;22) and inv(16) is rare in hematologic malignancies. The few cases in which both of these aberrations have been reported have had either an AML or a CML...
Table 3. Previously reported cases of t(9;22) and inv(16) coexistence.

| Authors       | Gender/ age | Diagnosis | Molecular analysis | Cytogenetic study | Outcome from diagnosis at t(9;22) and inv(16) |
|---------------|-------------|-----------|--------------------|-------------------|---------------------------------------------|
| Wu et al. [5] | M/33        | CML-BP    | M-bcr              | 46, XY, t(9;22)(q34.1;q11.2)[18]/46, XY, idem, inv(16)/p13.1q22[2] | Died two failed allo-BMT                      |
| Wu et al. [5] | M/41        | CML-BP    | M-bcr              | 46, XY, t(9;22)(q34.1;q11.2), inv(16)/p13.1q22[20] | Alive 4 years after allo-BMT                  |
| Wu et al. [5] | F/62        | CML-BP    | M-bcr              | 46, XX, t(9;22)(q34.1;q11.2), inv(16)/p13.1q22[20] | Died 24 months                              |
| Ninomiya et al. [8] | F/63 | CML-BP | m-bcr              | 46, XY, t(9;22)(q34;q11.2), inv(16)/p13q22 | Died 7 months                                |
| Merzianu et al. [9] | F/43 | CML-BP | ND                 | 46, XX, t(9;22)(q34;q11.2), inv(16)/p13q22[20] | Died 3 months                                |
| Merzianu et al. [9] | F/61 | CML-BP | ND                 | 46, XX, t(9;22)(q34;q11.2), inv(16)/p13q22[20] | Died 3 months                                |
| Merzianu et al. [9] | M/47 | CML-BP | ND                 | 46, XY, t(9;22)(q34;q11.2), inv(16)/p13q22[20] | Died 1 month                                 |
| Merzianu et al. [9] | F/36 | CML-BP | ND                 | 46, XX, t(9;22)(q34;q11.2), inv(16)/p13q22[20] | Died 1 month                                 |
| Asou et al. [10] | M/51 | CML-BP | ND                 | 46, XX, t(9;22)(q34;q11.2), inv(16)/p13q22[20] | Died 3 months                                |
| Heim et al. [11] | M/21 | CML-BP | M-bcr              | 45, X, -Y, t(9;22)(q34;q11), inv(16)/p13q22 | Alive 48 months                              |
| Myint et al. [12] | M/29 | CML-BP | ND                 | 46, XY, t(9;22)(q34;q11.2), inv(16)/p13q22 | Died 0 month                                 |
| Tirado et al. [3] | M/13 | AML     | ND                 | 46, XY, inv(16)/p13.1q22[2]/46, idem, del(7)(q22q32)[1]/46, idem, t(9;22)/q34q11.2/p13.1[2] | Died 10 months                              |
| Secker-Walker et al. [13] | F/9 | AML M4Eo | m-bcr              | 46, XX, inv(16)/p13q22[21]/46, XX, t(9;22)(q34;q11.2), inv(16)/p13q22  | Died 7 months                                |
| Secker-Walker et al. [13] | M/25 | AML M4Eo | ND                 | 46, XY, t(9;22)(q34;q11.2), inv(16)/p13q22[16] | Died 15 months                              |
| Preudhomme et al. [14] | M/64 | AML M4Eo | m-bcr              | 46, XY, inv(16)/p13q22, t(9;22)(q34;q11.2)[30] | Died 13 months                              |
| Miura et al. [15] | M/40 | AML M4Eo | m-bcr              | 46, XY, inv(16)/p13q22[17]/46, idem, t(9;22)(q34;q11.2)[3] | Alive 27 months                              |
| Svaldi et al. [16] | F/40 | AML M1   | m-bcr              | inv(16)/Ph, inv(16)[18] | Unknown                                     |
| Siddiqui et al. [17] | M/23 | AML M4Eo | ND                 | 46, XY, t(9;22)(q34;q11.2), inv(16)/p13q22 | Died 36 months                               |
| Cividin et al. [18] | F/38 | AML M4Eo | m-bcr              | 46, XX[22]q71[46, XX, inv(16)/p13q22] t[21]/71]/46, idem, t(9;22)(q34;q11.2)[25]/71]/46, XX, t(9;22)(q34;q11.2)[21]/71]/46, XX, | Alive 12 months                              |

Abbreviations: AML, acute myeloid leukemia; AML M1, acute myeloblastic leukemia; allo-BMT, allogeneic bone marrow transplant; BP, blast phase; F, female; M, male; m-bcr, minor breakpoint region; M-bcr, major breakpoint region; M4Eo, French-American-British Cooperative Group classification M4 with eosinophils; ND, not done.

phenotype (Table 3). In this study, we identified 4 cases of CML and 3 cases of AML, in which both of these chromosomal abnormalities occurred. Although the prevalence of t(9;22) and inv(16) coexistence has not yet been fully evaluated, a previous study showed that the incidence of t(9;22) in AML with inv(16) is less than 1% (approximately 0.5%) [19]. Our data showed that the coexistence of these abnormalities was detected in 0.6% of CML cases and 2.9% of AML cases with inv(16).

The majority of documented AML patients with t(9;22) and inv(16) coexistence have exhibited M4Eo BM morphology, including an increased number of myelomonocytic cells and abnormal eosinophils with coarse basophilic granules [8]. The AML cases we studied had similar AML-M4Eo BM morphologies. However, because the CML-BP cases in this study also exhibited an increased number of myelomonocytic cells and abnormal eosinophils, we had difficulty in discriminating CML-BP from AML on a morphological basis alone. Patients with a history of CML-CP before the development of a "double positive" can be easily diagnosed with CML-BP. However, we found that patients with AML exhibited a higher number of circulating blasts and more severe BM...
Coexistence of t(9;22) and inv(16)

Eosinophilia than did patients with CML-BP.

Cytogenetically, the proportion of each chromosomal abnormality was informative for identifying secondary changes [3]. This study documented a CML patient with secondary inv(16) who also exhibited a minor proportion of a CBFB/MYH11 rearranged clone compared with that of a BCR/ABL1 rearrangement. AML patients in this study also harbored minor proportions of the BCR/ABL1 rearranged clone compared with that of the secondary CBFB/MYH11 rearranged clone. Follow-up karyotyping results showed that only the t(9;22) aberration remained after CML treatment. However, this observation may not always apply in the era of tyrosine kinase inhibitors, because a complete cytogenetic response is achieved even in the early stages of CML-BP treatment [20].

In most double-positive cases, the major p210 chimeric BCR-ABL1 protein is observed in CML, whereas the minor p190 form correlates with AML presentation. However, some exceptions to this tendency have also been reported [9, 21, 22]. In the present study, a p210 fusion was detected in all patients with CML and 1 patient with de novo AML; moreover, a p190 fusion was detected in the 2 patients with t-AML. These findings suggest that the presence of a p190 BCR-ABL1 fusion protein is associated with AML. In addition, rare CBFB/MYH11 fusion transcripts in AML with inv(16) have been shown to be associated with t-AML M4Eo [23]. However, 1 patient with t-AML (case 6) in the present study exhibited an A-type CBFB/MYH11 fusion transcript. We detected variant E-type CBFB/MYH11 fusion transcripts in the patient with de novo AML (case 5) and a variant B-type CBFB/MYH11 fusion transcript in the patient with CML-BP (case 3).

We also analyzed the presence of commonly observed mutations associated with inv(16) and t(9;22). Nacheva et al. [24] have shown that AML with t(9;22) is accompanied by the loss of IKZF1, CDKN2A, or both, a hallmark of ALL by Bacher et al. [19], cases of AML with t(9;22) carried mutations in NPM1 at a frequency similar to that in cases of AML without the abnormality. In the present study, mutations in IKZF1, NPM1, FLT3, N-RAS, and K-RAS were not detected in any of the studied cases. Alterations in TP53 are the most common molecular lesions in AML cases with complex karyotypes and have also been shown to be predictive for resistance to conventional chemotherapy and poor outcome [26]. In the present study, 1 patient with t-AML (case 6) exhibited c-KIT D816V and TP53 E11Q mutations. However, the significance of this result was difficult to investigate owing to the limited number of cases in the study.

De novo AML with coexisting t(9;22) and inv(16) chromosomal abnormalities appears to have a prognosis as favorable as that in AML with inv(16) alone, whereas CML with both t(9;22) and inv(16) seems to have an unfavorable or uncertain prognosis [4, 5]. However, our data show that only 1 patient with CML-BP died of sepsis, and the other patients sustained clinical remission. Imatinib mesylate has been used effectively and safely to treat CML-BP [27]. With the benefits of better tolerance and fewer side effects, it has also been useful as a first-line interim therapy or maintenance strategy to bridge hematopoietic stem cell transplantation in patients with AML [28].

An interesting finding in the present study is that the 2 patients with t-AML exhibited t(9;22) and inv(16) coexistence. Patients with t(9;22) represent 2% of all therapy-related cases of myelodysplastic syndromes and t-AML. Moreover, t(9;22) is significantly associated with previous therapy with topoisomerase II inhibitors [5]. Although inv(16) is a well-known recurrent abnormality in t-AML, it is most frequently observed in patients with breast cancer or lymphoma who have been treated with alkylating agents, topoisomerase II inhibitors, radiation therapy, or a combination thereof. The response rates to intensive antileukemic chemotherapy in patients with t-AML with inv(16) are comparable to those of patients with de novo AML. Overall, 85% of all patients obtain complete remission after intensive chemotherapy [29]. In the present study, 1 patient had follicular lymphoma treated with an alkylating agent, and t-AML occurred 14 months after finishing lymphoma treatment. The other t-AML patient had received chemotherapy including topoisomerase II inhibitors for follicular lymphoma and developed t-AML 10 months after completing treatment. Complex karyotype, reportedly the strongest prognostic indicator, predicts a poor prognosis for t-AML patients. One study has reported that the t-AML M3 phenotype has a good prognosis, but overall survival is significantly shorter in t-AML with a complex karyotype [30].

The present study shows that evaluations of the percentage of circulating blasts and BM eosinophils, careful comparison of initial and follow-up cytogenetics studies including FISH results, and karyotyping of BCR/ABL1 yield valuable information for characterizing hematologic malignancies with t(9;22) and inv(16) coexistence. The results also show that patients with CML-BP classified as double positive as well as patients with AML have favorable clinical courses in this era of targeted therapy. Future studies with larger numbers of patients, longer follow-up periods, and additional genetic evaluations are warranted to confirm and extend the results presented herein.

Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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