CASE REPORT

Chronic Myeloid Leukemia Developing After Successful Treatment of Acute Promyelocytic Leukemia

Fang Huang¹ · Jun Chang¹ · Chao Du¹ · Rong Tao¹

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Abstract Acute promyelocytic leukemia (APL) has been regarded as a highly curable disease. Therapy-related leukemia is one of the important late complications that affect long-term survival rates in APL patients. Therapy-related acute myeloid leukemia and myelodysplastic syndrome are the major forms of therapy-related leukemias. We report a rare event of chronic myeloid leukemia (CML) that developed after successful treatment of APL with all-trans-retinoic acid in combination with chemotherapy. Rather unexpectedly, CML developed 7 years after APL. Cytogenetic and molecular studies proved the independence of these two entities. It was found that CML progressed rapidly after a short-term response to a combination therapy with hydroxyurea, interferon- α and arsenic trioxide. We propose that optimization of chemotherapy regimen and treatment intensity may reduce the risk of developing a secondary leukemia, while long-term monitoring cytogenetics of APL patients after treatment may help determine the development of a secondary leukemia at early stage.

Keywords Acute promyelocytic leukemia · Chronic myeloid leukemia · Therapy-related leukemia

Introduction

Acute promyelocytic leukemia (APL) has been regarded as a curable disease since the innovation of molecular-targeted therapy based on all-trans-retinoic acid (ATRA) and

arsenic trioxide (ATO) in combination with chemotherapy. With the improvement of cure rates and long-term survival for many APL patients, therapy-related malignancies come into prominence as an important late complication after chemotherapy and stem cell transplantation. Therapy-related acute myeloid leukemia (t-AML) and myelodysplastic syndrome (t-MDS) are the major forms of therapy-related malignancies. The t-MDS and t-AML patients usually had a poor response to conventional chemotherapy and were reported with an overall median survival of 10 months (range 7–22 months) [1]. We would like to report a rare case of chronic myeloid leukemia (CML) that developed after successful treatment of APL.

Case Report

A 43-year old man presented in 2001 with fever and sternal pain. Peripheral blood cell counts showed pancytopenia as follows: hemoglobin 92 g/L, white blood cells $3.2 \times 10^9/L$ and platelet $56 \times 10^9/L$. Bone marrow aspiration revealed 86 % hypergranular promyelocytes. Flow cytometry analysis on bone marrow sample showed that leukemic cells were positive for CD13 and CD33, and negative for CD34, CD14, CD3, CD7, CD41 and CD61. Cytogenetic study found chromosomal translocation of t(15;17)(q22;q21) and RT-PCR confirmed PML/RARA fusion gene expression (Fig. 1). This patient was diagnosed as APL and received induction therapy with daunorubicin (60 mg, day 1–3) and cytarabine (200 mg, day 1–7) plus ATRA (45 mg, daily). Hematologic complete remission (CR) was achieved after 4 weeks. He was then treated with consolidation regimens consisting of three courses daunorubicin (60 mg, day 1–3) plus cytarabine (6.0 g, day 1–3) alternating with two courses of mitoxantrone (10 mg, day 1–3) plus cytarabine

✉ Rong Tao
hikutao@hotmail.com

¹ Department of Hematology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, 1665 Kongjiang Rd., Shanghai 200092, People's Republic of China

Fig. 1 RT-PCR detection of PML/RARA fusion gene expression at diagnosis of APL. PCR primers were designed according to the report of BIOMED-1 program. Total RNA was extracted from bone marrow mononuclear cells. 1 GAPDH amplified from the patient's sample as a positive control, 2 short form of PML/RARA transcript (214 bp) amplified from the patient's sample, 3 RNA sample from healthy person, 4 patient genomic DNA, 5 H₂O, 6 and 7 short form control for PML/RARA transcript (214 bp), 8 and 9 long form control for PML/RARA transcript (289 bp), M DNA marker

(200 mg, day 1–7). ATRA was given as a combination with these regimens for 15 days at the beginning of each consolidation. CR was retained at the end of consolidations. Then he was advised to take maintenance regimen consisting of methotrexate (15 mg, weekly) plus 6-mercaptopurine (50 mg, daily) alternating with courses of ATRA (45 mg daily for 15 days, every 3 months). The patient retained complete remission at the end of 2 years' maintenance therapy, and thereafter he was advised to stop therapy. Monitoring of PML/RARA transcripts by RT-PCR was continued for additional 3 years, and no evidence of disease relapse at molecular level was noticed during the whole course.

In August 2008, the patient complained fatigue and sternal pain. Peripheral blood cell counts presented leukocytosis as follows: hemoglobin 114 g/L, white blood cells $53.8 \times 10^9/L$ and platelet $547 \times 10^9/L$. A routine peripheral blood smear showed 0.4 % myeloblasts, 1.2 % promyelocytes, 12.4 % myelocytes, 17.2 % metamyelocytes, 22.4 % band granulocytes, 35.2 % segmented granulocytes, 4.0 % basophils, 3.2 % eosinophils, 0.8 % monocytes and 3.2 % lymphocytes. His spleen was not palpable because he underwent splenectomy after a traffic accident when he was 10 years old. Bone marrow smear showed markedly hypercellular. Granulopoiesis was dominant with 2 % myeloblasts, 4 % promyelocytes, 20 % myelocytes, 10 % metamyelocytes, 18 % band granulocytes, 33.2 % segmented granulocytes, 3.6 % basophils, 2.8 % eosinophils, 1.2 % polychromatic normoblast, 2.8 % orthochromatic normoblast and 2.4 % lymphocytes, which suggested chronic myeloid leukemia at chronic phase. Cytogenetic study showed the presence of chromosomal translocation of t(9;22)(q34;q11). Molecular analysis by RT-PCR confirmed the expression of b3a2 form of BCR/

Fig. 2 RT-PCR detection of BCR/ABL fusion gene expression at diagnosis of CML. PCR primers were designed according to the report of BIOMED-1 program. Total RNA was extracted from bone marrow mononuclear cells. 1 positive control for e1a2 form of BCR/ABL transcript (521 bp), 2 positive control for b2a2 form of BCR/ABL transcript (342 bp), 3 positive control for b3a2 form of BCR/ABL transcript (417 bp), 4 RNA prepared from K562 cells (417 bp), 5 RNA sample from healthy person, 6 patient genomic DNA, 7 H₂O, 8 patient's sample (417 bp), M DNA marker

ABL fusion gene (Fig. 2). The chromosomal translocation of t(15;17) was not found and expression of PML/RARA was not significant (data not shown). Therefore, a diagnosis of CML was made as a second leukemia in this patient since the cytogenetic study didn't support the CML transformed from the APL cells. The patient refused to take imatinib mesylate for reasons of medical expenses. He was then introduced a medication with a combination of hydroxyurea (2.0–3.0 g, daily), interferon- α (3.0 million IU/m², three times weekly) and ATO (10 mg, daily for 4 weeks). Short-term hematologic response was observed and peripheral blood cell counts returned to normal ranges after 1 month. However, 2 months later, the patient presented rapid disease progression to accelerating phase with leukocytosis and thrombocytosis as well as progressive anemia. He stopped to take further treatment and discontinued follow-ups. Only 2 months later, he died of sudden digestive hemorrhage.

Discussion

In APL patients, t-MDS and t-AML are sporadically reported [1, 2], which were observed in about 6.5 % patients [3]. Patients usually developed t-MDS or t-AML with a latency ranging from 22 to 46 months after receiving chemotherapy [3]. Cytogenetic abnormalities such as losses or deletions of chromosome 7 and/or 5 and recurrent balanced translocations involving 11q23 and 21q22 are frequently observed in t-AML and t-MDS, and are regarded as important hallmarks for the diagnosis of these two entities [4]. Our patient demonstrated unusual clinical features. The information provided by cytogenetic studies at the onset of APL and diagnosis of CML showed that the

two malignant entities originated from two genetically unrelated clones. This means that the patient developed CML as a second leukemia 7 years after the eradication of APL. Although typical alterations on chromosomes as are usually observed in therapy-related leukemias were not found in the patient, this doesn't rule out the possibility that CML is a therapy-related malignancy, at least from a clinical viewpoint. Firstly, there was no cytogenetic evidence that supports the coexistence of CML clone with APL at the diagnosis of APL. Secondly, previous treatment with topoisomerase II inhibitors (i.e. daunorubicin and mitoxantrone) predisposed this patient to develop a second leukemia. This patient was diagnosed CML with a latency of 7 years after receiving chemotherapy, which is consistent with the median time (60 months) to develop a clinical identifiable CML after the diagnosis of primary tumors [5]. In addition to the well-known t-AML and t-MDS, an increasing number of cases of therapy-related CML (t-CML) have been reported after primary hematological malignancies such as Hodgkin lymphoma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia and acute myeloid leukemia, as well as solid tumors including ovarian cancer, breast cancer, uterine cervical cancers, etc. [6, 7]. t-CML was reported to account for about 13.3 % cases in secondary leukemias [5]. Preceding radiotherapy, chemotherapy and immunosuppressive therapy are recognized as major risk factors for the development of t-CML. The time to develop a clinical identifiable t-CML varies greatly, and is supposed to be dependent on preceding malignancies and prior treatment options [7]. Clinical outcome of t-CML patients may be favorable if imatinib-based targeted therapy is applied [8]. Our patient presented short-term response to a combinational therapy of hydroxyurea, interferon and ATO and progressed rapidly. We suppose if imatinib or allogeneic hematopoietic stem cell transplantation is applicable to this patient, his outcome may be significantly improved.

Although therapy-related myeloid neoplasms are commonly reported on patients after chemotherapy for APL, CML is a rare form developing after treated APL. There was only one documented case in literature, in which CML developed 5 years after remission in APL [9]. As APL is a highly curable disease, therapy-related leukemia has become one of the major concerns since it limits long-term survival in APL patients. Based on Japanese study, patients with APL who received VP-16 for consolidation therapy had a high incidence (10.2 %) of therapy-related myeloid neoplasms (t-MN) [10]. Furthermore, the accumulation of chemotherapeutic agents in maintenance phase may also increase the risk of t-MN [11]. Data from Programa Español para el Tratamiento de Enfermedades Hematológicas study showed that t-MN developed in 1.8 % APL patients who received ATRA and anthracycline-based chemotherapy

[12]. Elimination of VP-16 may explain partially the lower incidence of t-MN as compared with the Japanese study. Therefore, we propose that optimization of chemotherapy regimen and chemotherapy intensity, including avoiding the use of drugs with high risk of inducing secondary malignancies or reducing their accumulative dosage, may decrease the incidence of t-MN in APL patients. As ATO is used increasingly in APL patients and is a well known carcinogen, special attention should be paid to APL patients who received therapy with ATO. Hu et al. recently reported that no secondary carcinoma was observed in 89 APL patients received ATRA and ATO combinational therapy with a median follow-up of 70 months [13]. However, there was initially observed an increased risk of second solid tumors subsequent to ATO treatment for APL [14], and there was a reported case that t-AML developed after APL receiving chemotherapy and arsenic agent as maintenance treatment [15]. Whether ATO is potentially leukemogenic requires long-term follow-up of a large number of patients to warrant its safety. As 79 % patients with therapy-related myeloid neoplasms developed after APL were documented cytogenetic abnormalities, and 38 % patients developed therapy-related myeloid neoplasms 5 years after treatment with APL [10], we suggest the necessity of long-term cytogenetic monitoring to early detect the potential development of a secondary leukemia in APL patient post ATO therapy.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement Informed consent for the collection of medical information for research and publication was obtained from the patient.

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