Early-onset Therapy-related Myelodysplastic Syndrome Originating from Prolonged Myelosuppression after Fludarabine-based Therapy

Sho Yamazaki¹, Fumihiko Nakamura¹, Yasuhiro Nannya¹, Masahiro Nakagawa¹, Motoshi Ichikawa¹ and Mineo Kurokawa¹,²

Abstract

Fludarabine-based therapy is widely approved as a first-line treatment for chronic lymphocytic leukemia (CLL). This treatment is occasionally associated with prolonged myelosuppression. We herein describe the cases of CLL who underwent fludarabine, cyclophosphamide and rituximab (FCR) therapy. Bone marrow examinations performed during periods of prolonged myelosuppression revealed definite myelodysplastic changes in the myeloid and erythroid lineages. G-banded karyotyping analyses revealed cytogenetic abnormalities. The patients were diagnosed with therapy-related myelodysplastic syndrome (t-MDS). Further administration of cytotoxic therapy was aborted, and no progression of t-MDS was recorded throughout the follow-up period in either case. In these cases, the t-MDS was characterized by a short latency interval and a benign clinical course. Because typical t-MDS with aggressive outcomes also occurs during prolonged myelosuppression, the transition of the clinical course in this setting should therefore be carefully watched.

Key words: chronic lymphocytic leukemia, fludarabine-based therapy, prolonged myelosuppression, therapy-related myelodysplastic syndrome


Introduction

Chronic lymphocytic leukemia (CLL) is a type of lymphoproliferative neoplasm characterized by monoclonal expansion of mature B lymphocytes that coexpress CD5 and CD23 with minimal surface immunoglobulins (1). The disease is incurable with currently available treatment, with the possible exception of allogeneic hematopoietic stem cell transplantation. Moreover, patients with CLL usually exhibit a benign clinical course. Hence, they are monitored under a wait-and-see strategy until they show some evidence of either progressive or symptomatic disease. For patients with clear treatment indications, fludarabine-based therapy is now widely approved as a first-line therapy. Among a variety of regimens, the combination of fludarabine, cyclophosphamide and rituximab (FCR) seems to be the most promising option. The administration of FCR chemoimmunotherapy in patients with previously untreated CLL resulted in an overall response rate of 95%, a complete remission rate of 72% and a 6-year overall survival rate of 77% (2). A regimen of fludarabine with cyclophosphamide (FC) or fludarabine with rituximab (FR) may otherwise be selected, although these combinations are less effective than FCR.

The adverse events of fludarabine-based therapy are mostly associated with myelotoxicity and infection (3). Cytopenias caused by myelotoxicity occasionally last for more than three months and are referred to as prolonged myelosuppression. The incidence of prolonged myelosuppression has been identified to be 19-43% depending on the use of previous cytotoxic therapy and the cut-off for cytopenia (2, 3). The median time to resolution of anemia, neutropenia and thrombocytopenia was 7, 8, and 10 months, respectively.

¹Department of Hematology and Oncology, Graduate School of Medicine, The University of Tokyo, Japan and ²Department of Cell Therapy and Transplantation Medicine, The University of Tokyo Hospital, Japan

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Correspondence to Dr. Mineo Kurokawa, kurokawa-tky@umin.ac.jp
We reviewed 28 Japanese cases that had been diagnosed with CLL at our institution between January 2000 and December 2011. The collection of medical records was approved by the ethics committee of our institution. A total of 8 patients were treated with FCR regimen. Remarkably, 4 patients (50%) showed complication of prolonged myelosuppression and 2 patients (25%) developed early-onset therapy-related myelodysplastic syndrome (t-MDS) during periods of prolonged myelosuppression. We would therefore like to introduce the clinical features and outcomes of early-onset t-MDS developing after the administration of FCR therapy by presenting these cases.

Case Reports

Case 1

A 69-year-old woman was referred to our institution after having been found to have leukocytosis at another hospital. On presentation, her hemoglobin level was 112 g/L, white blood cell (WBC) count was 27.8×10^9/L with 83% lymphoid cells and platelet count was 177×10^9/L. The lymphoid cells exhibited a mature and small morphology. The immunophenotypes of the lymphocytes were CD5+, CD11c dim, CD19+, CD20+, CD22-, CD23+, CD38- and FMC7 dim. These findings were consistent with the diagnosis of CLL. The patient was monitored under a wait-and-see strategy for the following 15 months. Finally, the disease showed apparent progression with a hemoglobin level of 89 g/L and a WBC count of 622×10^9/L. The bone marrow aspirate disclosed a normocellular marrow with a CLL infiltrate of approximately 90%. A cytogenetic study showed a normal karyotype in all metaphases analyzed. A planned total of 6 cycles of FCR regimen (fludarabine: 25 mg/m^2 on days 2-4, cyclophosphamide: 250 mg/m^2 on days 2-4 and rituximab: 375 mg/m^2 on day 1) were commenced. However, prolonged myelosuppression became evident after 4 cycles of treatment (Fig. 1). The patient required frequent transfusions of red cells and platelets. The bone marrow was slightly hypocellular with nuclear hypolobation in neutrophils and multinuclearity in erythroblasts. Myeloblasts accounted for 1% of all nucleated cells (ANCs). A flow cytometric analysis showed a complete disappearance of CD5/CD23-coexpressing CLL cells. A G-banded karyotype analysis was notable for trisomy 8 as the sole abnormality in 2 of the 8 metaphases examined. These results together, the patient was diagnosed with t-MDS according to the World Health Organization (WHO) classification. Further courses of FCR therapy were aborted. The pancytopenia began to gradually ameliorate after 6 months when blood transfusions were no longer required. Laboratory data obtained 2 years after the discontinuation of FCR therapy showed a hemoglobin level of 95 g/L, a WBC count of 5.2×10^9/L with a normal differential and a platelet count of 11.5×10^9/L. A fluorescence in situ hybridization (FISH) analysis of the peripheral blood continued to show 4% (eight of 200 cells) mosaicism for trisomy 8. There was no evidence of recurrent CLL.

Case 2

A 47-year-old woman presented with general malaise and dyspnea. Her hemoglobin level was 71 g/L, WBC count was 4.3×10^9/L with 36% lymphoid cells and platelet count was 112×10^9/L. The bone marrow was normocellular with dominant proliferation of small to medium-sized mature lymphoid cells. Immunostaining revealed that the cells were CD5+, CD11c+, CD20 weak, CD23+, CD38+ and FMC7-. A cytogenetic examination showed a normal karyotype in all metaphases analyzed. A computed tomography scan detected moderate splenomegaly. Since the level of monoclonal B lymphocytes in the peripheral blood did not exceed 5×10^9/L, the present case did not meet the WHO criteria for the diagnosis of CLL. However, the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria allows for monoclonal B lymphocytosis less than 5×10^9/L if accompanied by lymphadenopathy, organomegaly, cytopenia or disease-related symptoms (4). Therefore, the diagnosis of CLL with bicytopenia and splenomegaly was made according to the IWCLL criteria. Initial chemotherapy was administered with 6 cycles of FC regimen, which resulted in complete remission and complete hematological improvement. There were no episodes of prolonged myelosuppression during this treatment. Two years later, bicytopenia reappeared with a hemoglobin level of 104 g/L, a WBC count of 4.6×10^9/L with 21% lymphoid cells and a platelet count of 87×10^9/L. A bone marrow examination confirmed recurrent CLL. At that time, treatment with FCR regimen was commenced. Hematological toxicity began to worsen after 4 cycles of treatment. Prolonged myelosuppression with transfusion dependency became evident after 6 cycles of treatment, which lasted for as long as 6 months and gradually recovered thereafter. The bone marrow aspirate revealed normocellular marrow with myeloblasts accounting for 0.6% of ANCs. Mature neutrophils were small and possessed hypolobated nuclei (Fig. 2A). Erythroblasts showed multinuclearity and megaloblastic changes (Fig. 2B). Flow cytometry confirmed the disappearance of CD5/CD23-coexpressing CLL cells. A G-banding analysis disclosed add(7)(q11.2) as

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**Figure 1.** The clinical course of Case 1. The arrows and closed boxes indicate FCR therapy and transfusion dependency, respectively.
the sole chromosomal abnormality in 2 of the 20 metaphases examined. Therefore, we made the diagnosis of t-MDS. The pancytopenia continued to ameliorate, and laboratory data obtained 2.5 years after diagnosis showed almost normal peripheral blood counts except for mild thrombocytopenia. The bone marrow then was normocellular without myeloblasts. Our patients did not show circulating myeloblasts during their clinical courses. However, bone marrow specimens revealed definite dysplastic changes in the myeloid and erythroid lineages (Fig. 2A, 2B), and cytogenetic studies demonstrated clonal chromosome abnormalities. These findings collectively fulfilled the WHO criteria for the diagnosis of t-MDS.

Discussion

Therapy-related MDS/acute myeloid leukemia (t-MDS/AML) has been recognized to be a devastating late complication of fludarabine-based therapy. Its crude incidence in previously untreated CLL patients undergoing FCR chemotherapy was found to be 4.5% over a follow-up period of 44 months (5). The median latency period from the first cycle of FCR therapy to the diagnosis of t-MDS/AML was found to be 35 months. Previous exposure to cytotoxic agents (6) and an age over 60 years (5, 7) both increase the risk for developing this complication. The morphological findings of t-MDS/AML vary from slight to definite dysplastic changes. In contrast, cytogenic abnormalities are almost inevitably recorded and frequently involve aberrations of chromosomes 5 and 7. In most cases, the disease is rapidly progressive and associated with a poor overall prognosis. The median survival time after diagnosis ranges from 7 to 11 months.

In this report, we documented 2 cases of MDS that occurred following FCR therapy for CLL. One may ask whether these cases really represented t-MDS because dysplastic changes in hematopoietic cells are frequently observed after cytotoxic therapy. Indeed, making a correct diagnosis of t-MDS is very difficult in patients with myelosuppression, especially when there are no increases in the numbers of myeloblasts. Our patients did not show circulating myeloblasts during their clinical courses. However, bone marrow specimens revealed definite dysplastic changes in the myeloid and erythroid lineages (Fig. 2A, 2B), and cytogenetic studies demonstrated clonal chromosome abnormalities. These findings collectively fulfilled the WHO criteria for the diagnosis of t-MDS. Although we were fortunately able to detect clonal cytogenetic abnormalities, G-banded karyotyping frequently results in a lack of mitoses under myelosuppression. In order to avoid underestimating the presence of chromosomal abnormalities, we recommend adding FISH analyses to more easily confirm the diagnosis of t-MDS.

The present t-MDS cases exhibited several distinct features. First, in both cases, the diseases became evident under prolonged myelosuppression occurring after FCR therapy. The latency period from the initiation of FCR therapy to the diagnosis of t-MDS was as short as 6 to 10 months. It is unlikely that the MDS was coexistent with CLL prior to FCR therapy because the cytogenetic abnormalities manifested only after treatment. Second, our patients showed benign clinical courses. Progression of t-MDS was not recorded throughout the follow-up period of approximately 2 years in either case. We ceased administering further cytotoxic therapy after the diagnoses of t-MDS were made, which might have favorably influenced the outcomes. Of note, the cytogenetics of the bone marrow metaphases spontaneously normalized in Case 2. The neoplastic clones might have survived only under the transient immunosuppressive conditions that occurred following FCR therapy.

In conclusion, we reported 2 cases of atypical early-onset t-MDS that originated from prolonged myelosuppression after FCR therapy. These myeloid neoplasms were characterized by short latency periods and benign clinical outcomes. Because typical t-MDS/AML with aggressive clinical courses also manifests during periods of prolonged myelosuppression (5), the transition of the clinical courses should be watched carefully in this setting.

The authors state that they have no Conflict of Interest (COI).

References