A Complete Remission Can be Achieved Despite Persistence of Abnormal Bone Marrow Promyelocytes in Acute Promyelocytic Leukemia — Experience in 2 patients —

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Acute promyelocytic leukemia (APL) is a distinct subset of acute myeloid leukemia (AML) and is distinguished from other subsets of AML by its distinctive morphology, specific chromosomal abnormality, associated consumptive coagulopathy, and response to treatment. Interestingly, patients with APL frequently enter complete remission without undergoing a characteristic period of bone marrow hypoplasia. In two cases in this report, complete remission was achieved without bone marrow hypoplasia without further additional course of chemotherapy despite the appearance of persistent malignant cells in the bone marrow after first induction chemotherapy.

During the period of treatment, severe coagulopathy occurred in both cases but resolved as the patients entered into remission. Remission in patients with APL may occur even when induction therapy fails to cause marrow hypoplasia or to eradicate replicative cells. To avoid unnecessary exposure to toxic therapy, caution should be exercised in assessing the adequacy of remission induction treatment.

Key Words: *Acute promyelocytic leukemia, Bone marrow hypoplasia, Differentiation of leukemic cells*

INTRODUCTION

Acute promyelocytic leukemia (APL) is a distinct subset of acute myeloid leukemia (AML) associated with unique features such as a distinctive morphology, specific chromosomal abnormality, and consumptive coagulopathy (Stone RM 1990, Tallman MS 1992). Patients with APL appear to have a higher complete remission rate than individuals with other subtypes of AML. Remission may be achieved with administration of conventional anthracycline-cytarabine combination or all-trans retinoic acid (Kantarjian HM 1985, Huang ME 1988, Castaigne 1990, Warell RP 1991). Whereas a phase of complete marrow hypoplasia with an absence of myeloblast was thought to be essential in

achieving complete remission in patients with other subtypes of AML, bone marrow examinations following initial chemotherapy in patients with APL frequently continue to demonstrate an excess of dysmorphic promyelocytes. Nonetheless the patients enter into complete remission without further chemotherapy (Kantarjian HM 1986, Stone RM 1988).

We experienced 2 patients with APL in whom dysplastic appearing promyelocytes remained in the bone marrow and marrow hypoplasia was difficult to achieve throughout the period of induction therapy; however the patients subsequently achieved complete remission. The cases were presented to emphasize the fact that the absence of therapy-induced bone marrow hypoplasia in APL is not necessarily an induction failure or a poor ultimate outcome.

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CASE REPORT

Case 1

In October, 1990, a 19-year old man presented with a week history of easy fatigability and hemorrhagic rash in the oral cavity. Two days prior to admission, he was given an intramuscular injection of antipyretics and a large hematoma was formed on the buttock at the site of the injection. Physical examination on admission revealed multiple skin ecchymoses, gum bleeding and retinal hemorrhage. Neither palpable hepatosplenomegaly nor lymphadenopathy were noted. The workup on admission showed the following; hemoglobin 12.8 g/dl, leukocyte count $6.3 \times 10^3/\mu\text{l}$ with 10% blasts and 37% promyelocytes, and platelet count $27 \times 10^3/\mu\text{l}$. The coagulation profile showed a prothrombin time of 16.6 second (normal control 12.9 second), activated partial thromboplastin time of 35.9 second with normal control 29.0 second, fibrinogen level 188 mg/dl, and fibrin degradation products (FDP) $80 \mu\text{g/ml}$. The bone marrow was 95% cellularity with 6.6% myeloblasts and 83.6% promyelocytes (Fig 1A).

Auer rods were present in myeloblasts and promyelocytes. Marrow morphology was M3 by the French-American-British (FAB) classification.

A remission induction chemotherapy was begun with cytosine arabinoside 200 mg/m^2 intravenously over 24 hours daily for 7 days and daunorubicin 40 mg/m^2 intravenously over 24 hours daily for 3 days. He received fresh frozen plasma for coagulopathy. Platelets were transfused to keep the platelet count over $20 \times 10^3/\mu\text{l}$.

On the 4th day of chemotherapy, the coagulation profile showed a feature of disseminated intravascular coagulation with a prolonged prothrombin time of 22.8 second (normal control 13.1 second), fibrinogen level 175 mg/dl and FDP $320 \mu\text{g/ml}$. The gum bleeding and ecchymoses worsened. Fresh frozen plasmas were transfused daily.

On the 14th day of chemotherapy a bone marrow examination showed 100% cellularity with 0.4% myeloblasts and 75.4% promyelocytes having Auer rods

Fig. 1. The changes in bone marrow and peripheral blood findings according to the days of chemotherapy (A: Case 1, B: Case 2).

(Fig. 1A). Serum FDP level was $40\mu\text{g/ml}$ and his bleeding tendency improved clinically. Repeated chemotherapy using identical doses of the first course of chemotherapy was given due to the failure to achieve of bone marrow hypoplasia and the persistence of malignant-appearing cells. Subsequent bone marrow examinations were performed on the 26th and the 33rd days of the first course of induction chemotherapy. Each marrow showed a persistence of malignant appearing dysplastic promyelocytes, 32.8% and 33.8%, respectively, and cellularity of 70% in both marrows (Fig. 1A). No additional chemotherapy was given to the patient.

On the 40th day, a marrow aspiration and biopsy showed 15% cellularity with 2.8% myeloblasts, 1.8% promyelocytes and confirmed achievement of complete remission. Granulocytic series in this marrow showed normal maturation sequences and peripheral blood leukocyte count was $2.2 \times 10^3/\mu\text{l}$ with 24% segmented neutrophils having numerous coarse granules (Fig. 1A).

Subsequently, the patient received 3 courses of consolidation chemotherapy consisting of cytosine arabinoside and daunorubicin and one course of intensification therapy with high dose cytosine arabinoside (1g/m^2 intravenously every 12 hours for 5 days). He has maintained a status of complete remission for over 26 months at the time of this writing.

Case 2

In July, 1991, a 29-year old man presented with a two weeks' history of easy fatigability, gum bleeding, and petechiae on the trunk. Physical examination on admission revealed multiple petechiae on the upper body. The initial laboratory findings were as follows: hemoglobin 13.9g/dl , leukocyte count $1.1 \times 10^3/\mu\text{l}$ with 16% blast and 17% promyelocytes, and platelet count $65 \times 10^3/\mu\text{l}$. A bone marrow aspiration and biopsy showed 100% cellularity with 20% myeloblasts and 36.2% promyelocytes (Fig. 1B). Bundles of Auer rods were seen in the myeloblasts and promyelocytes, and the leukemic cells appeared to possess fine cytoplasmic granules. Specific esterase staining was strongly positive. A diagnosis of APL, FAB M3 variant, microgranular type was made (Fig. 2A) (Davey FR 1989). The coagulation profile was normal with a serum fibrinogen level of 151mg/dl and FDP of less than $40\mu\text{g/ml}$.

An induction chemotherapy was given with cytosine arabinoside 200mg/m^2 intravenously over 24 hours daily for 7 days and mitoxantrone 12mg/m^2 intravenously daily for 3 days.

On the 3rd day of the chemotherapy, gum bleed-

A. marrow aspiration at diagnosis; AML M3 microgranular type (Wright, $\times 1000$).

B. on the 19th day of chemotherapy, dysmorphic promyelocytes remain in the marrow. (Wright, $\times 1000$).

C. by the 31st day, neoplastic promyelocytes in the marrow have disappeared without any additional course of chemotherapy (Wright, $\times 400$).

Fig. 2. The photographs of bone marrow findings of Case 2.

ing developed with a drop in fibrinogen level to less than 90mg/dl and an increment of FDP to $160\mu\text{g/ml}$.

Heparin of 500 unit/hour and fresh frozen plasmas were given daily with resolution of further bleeding. A bone marrow examination on the 12th day showed the presence of malignant appearing cells with 30% cellularity, 10.6% promyelocytes and 0.8% myeloblasts (Fig. 1B). At that time, peripheral blood film showed severe leukopenia with only mature lymphocytes without any malignant appearing cells. The coagulation profile was normal without any evidence of clinical bleeding. Subsequent bone marrow examination on the 19th day (Fig. 1B, Fig. 2B) also showed the persistence of the leukemic cells with 70% cellularity. A marrow aspiration and biopsy on the 31st day of induction chemotherapy finally showed the findings of complete remission with 60% cellularity, 3.0% myeloblasts and 1.0% promyelocytes (Fig. 2C). There were no malignant appearing cells in the peripheral blood smears. White blood cell count was $4,500/\mu\text{l}$ with 67% neutrophils, 16% lymphocytes and 17% monocytes and platelet count was $345 \times 10^3/\mu\text{l}$ (Fig. 1B).

He received three courses of consolidation chemotherapy and one course of intensification chemotherapy (cytosine arabinoside $1\text{g}/\text{m}^2$ intravenously every 12 hours for 5 days). He remains free of disease at the 16th month.

DISCUSSION

Acute promyelocytic leukemia (APL) accounts for approximately 10 to 15% of cases of acute myeloid leukemia. The disease is associated with a specific cytogenetic abnormality, translocation of a portion of the long arm of chromosome 17 on to the long arm of chromosome 15; $t(15;17)$ ($q22;q12-21$) (Stone RM 1990). Disseminated intravascular coagulation during induction chemotherapy is a life-threatening complication. (Tallman MS 1992, Mark AG 1985). Patients with APL generally have a 70% to 80% likelihood of entering remission, and are thought to have a more favorable prognosis than individuals with other types of AML (Cordonnier C 1985, Cunningham I 1989).

One of the unique features of this leukemia is the achievement of remission despite the persistence of malignant-appearing promyelocytes, as presented in this report. The unusual persistence of an excess number of dysplastic promyelocytes in the bone marrow and the absence of marrow hypoplasia 2 to 6 weeks after the initiation of therapy are commonly observed (Wallace PJ 1989). Kantarjian et al. (1986) reported "a pattern of differentiation" in 20 of 43 patients with APL, eight of whom having complete remission without further therapy and 12 of whom showing improvement

at the time of initiation of the second course. Stone et al. (1988) also reported the leukemic cell differentiation in 25 of 34 patients and proposed that neither the persistence of bone marrow hypercellularity nor the persistence of dysplastic promyelocytes during induction exerted any influence on the probability for survival. They suggested that complete remission in APL is due to leukemic cell differentiation or selective cytotoxicity, which was further supported by the observation of in vitro maturation of HL-60 cells to granulocytes, defined by morphologic, immunophenotypic and genetic methods after exposure to chemotherapeutic agents such as cytarabine (Oliveria NI 1991, Castaigne S 1983) or a differentiating agent, all-trans retinoic acid (Chen ZX 1991).

In both of our cases, chemotherapy induced a progressive decrement of malignant cells in the bone marrow, which is documented by serial bone marrow examination. Clinically evident coagulopathy in our patients improved gradually as the malignant cells decreased in the bone marrow and it further supports the view that the malignant cells differentiated into mature cells.

Unfortunately, we did not perform the cytogenetic study in the above two cases. It was found that essentially all patients with APL have been reported to have a $t(15;17)$ (Larsen RA 1984). The $t(15;17)$ observed in APL is presumed to hold pathogenetic significance, however whether these translocations play a primary causative role in the development of the disease is unclear.

As presented in the latter cases, approximately 25% of patients with APL display features consistent with a "microgranular" variant of APL (FAB M3V), wherein promyelocytes have abundant numbers of less prominent, fine granules demonstrable by ultrastructural analysis (Golomb HM 1980). No differences in the duration of complete remission or survival time have been observed between the two subgroups. However, Davey FR et al. (1989) reported that patients with M3V tended to have a initial higher leukocytes count and platelet count than those with M3 morphology and not to enter complete remission at the same rate as those with typical M3 morphology. Clinical comparisons between the two subgroups show an increased proportions of females, nonwhites, and higher likelihood for infection at the time of diagnosis among patients with microgranular variants but two subtypes tended to have similar degrees of bleeding (Davey FR et al, 1989).

In conclusion, remission in patients with APL may occur even when induction therapy fails to cause marrow hypoplasia or to eradicate replicative cells. To avoid

unwarranted exposure to toxic therapy, caution should be exercised in utilizing immediate postinduction marrow morphologic studies in assessing the adequacy of treatment. About the determining factors of adequacy of treatment, Kantarjian et al. (1985) suggested that the patients could be observed without second induction therapy as long as the clinical and hematologic picture is stable or improving without evidence of recurrence of DIC. New strategies may be necessary to identify early in the treatment, which patients with APL would require only one course of induction chemotherapy to enter into successful remission.

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