LETTER TO THE EDITOR

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Mixed-phenotype acute leukemia treated with decitabine

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To the Editor,

Mixed-phenotype acute leukemia (MPAL) is a type of acute leukemia in which antigens of more than one lineage are co-expressed by the same blast cells or by two different populations of blast cells. It is a rare disease, accounting for less than 3% of all acute leukemias. It is known by a variety of terms, including biphenotypic leukemia, bilineage leukemia, and mixed lineage leukemia. In 2008, the World Health Organization (WHO) classification grouped all acute leukemias of ambiguous lineage, including biphenotypic and bilineage leukemias, together as "mixed phenotypic acute leukemias" [1].

Unfortunately, the optimal therapy for MPAL has not been established and the prognosis is unfavorable. Matutes et al. [2] analyzed the clinical features and outcomes of 100 patients with MPAL. Response to therapy was seen in 67 patients. Of these, 27 had been treated with protocols for acute lymphoblastic leukemia (ALL), 34 with protocols for acute myeloid leukemia (AML), five with a combination of therapies for ALL + AML, and one with imatinib alone. Complete response (CR) was seen in 85% of patients receiving ALL-directed therapy and in 41% of those receiving AML-directed therapy. The overall median survival was 18 months and the 5-year survival rate was 37% [2].

In routine practice, clinicians must decide between therapies for AML, ALL, or combination therapy based on immunophenotypic, cytogenetic, and molecular data. Herein, we present a case of MPAL treated with decitabine, which targets both myeloid and lymphoid lineages.

An 81-year-old woman was referred to our hospital for incidentally detected pancytopenia in July 2013. At that time, her complete blood count results were as follows: white blood cells, 5.4×10^9/L; hemoglobin, 7.7 g/dL; and platelets, 51×10^9/L. Neither splenomegaly nor lymphadenopathy was present. A bone marrow biopsy was performed, and bone marrow aspirate analysis revealed 60.8% of blast cells (Fig. 1). Immunophenotyping by flow cytometry revealed co-expression of myeloid-associated antigens (e.g., myeloperoxidase) and T-cell antigens (i.e., CD2, CD3, CD5, and CD7) on blast cells, along with the expression of CD34 and human leukocyte antigen (HLA)-DR. Chromosomal karyotyping revealed a 46, XX karyotype without abnormalities. Molecular analyses for *MLL*, *BCR/ABL*, *AML1-ETO*, and *PML-RARA* were all negative. On the basis of the immunophenotyping results, the patient was considered to have MPAL, T/myeloid, not otherwise specified, according to the WHO 2008 classification.

We decided to treat our patient with decitabine rather than cytotoxic chemotherapy because of her poor per-

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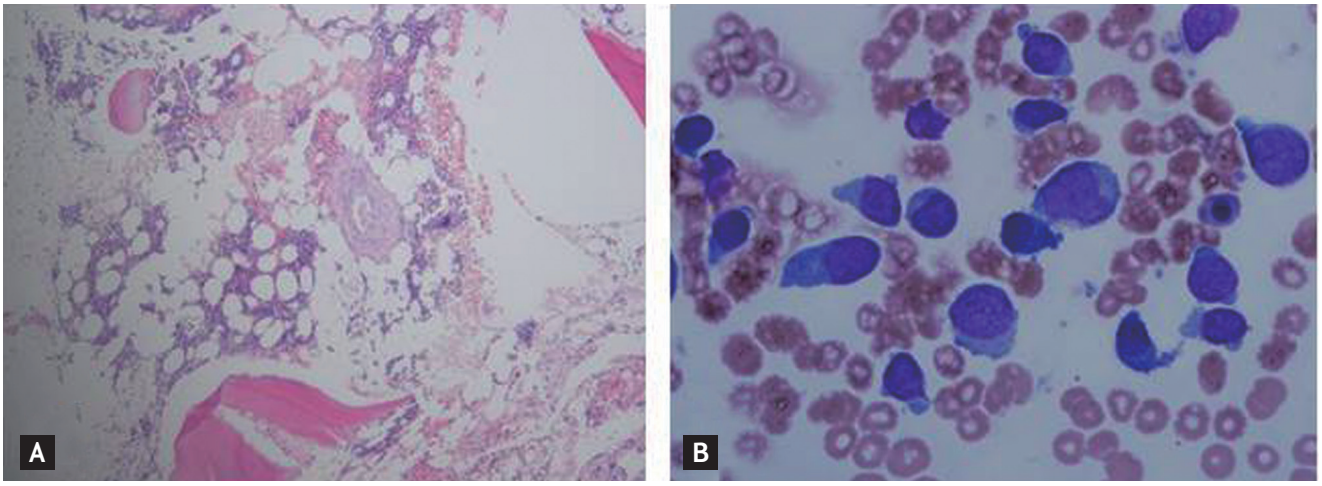

Figure 1. Bone marrow biopsy and aspiration at diagnosis. The majority (60.8%) of scattered cells were immature blast cells. The blasts were small to medium in size with fine nuclear chromatin, distinct nucleoli, and scanty basophilic cytoplasm. Some also had cytoplasmic protrusions. Auer rods were not found, while the proportions of other hematopoietic cells were decreased. (A) Bone marrow biopsy (H&E, ×100). (B) Bone marrow aspiration (Wright-Giemsa stain, ×1,000).

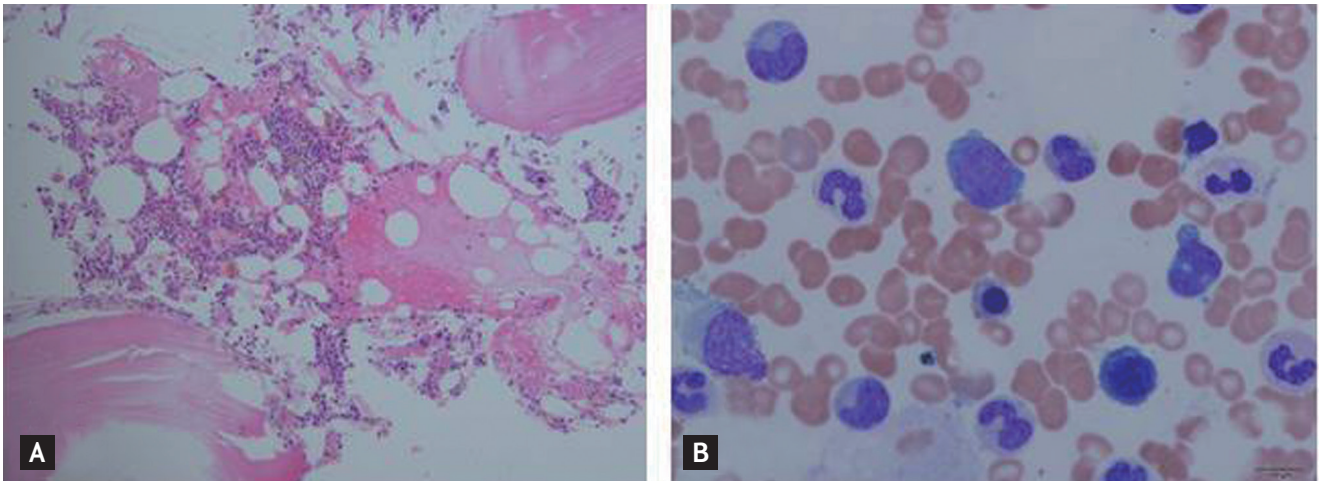

Figure 2. Bone marrow biopsy and aspiration after four cycles of decitabine. No conspicuous immature lymphoid and myeloid cell clusters can be noted. (A) Bone marrow biopsy (H&E, ×100). (B) Bone marrow aspiration (Wright-Giemsa stain, ×1,000).

formance status, which was characterized by general overall weakness. The dose regimen administered was similar to that used for myelodysplasia and AML (20 mg/m^2, 1-hour continuous intravenous infusion for 5 days, every 4 weeks). After four cycles of chemotherapy, in December 2013, she achieved complete remission by bone marrow analysis (Fig. 2). Complete blood count results at the time of complete remission were as follows: white blood cells, 5.3 × 10^9/L; hemoglobin, 8.3 g/dL; and platelets, 247 × 10^9/L. Mild oral mucositis was observed during decitabine treatment, while there were no other notable side effects. The patient underwent another three cycles of chemotherapy. She subsequently requested discontinuation of chemotherapy for financial reasons. At the time of writing, the patient was remission for 5 months.

Decitabine is a hypomethylating agent that inhibits the activity of DNA-methyltransferase and leads to reactivation of the expression of tumor suppressor genes. It also has direct and indirect cytotoxic effects that lead to apoptosis of tumor cells.

Decitabine has shown clinical activity in myeloid malignancies and is approved for the treatment of myelo-

dysplastic syndrome and AML in older patients. In addition, *in vitro* studies have demonstrated that decitabine has a cytotoxic effect on ALL cells. In this regard, two clinical trials investigating decitabine in patients with ALL have been carried out. Garcia-Manero et al. [3] conducted a phase I trial of decitabine with or without hyper-CVAD (cyclophosphamide, vincristine, adriamycin, anddexamethasone) in adult patients with relapsed/refractory ALL. CR was achieved in seven of 30 patients (23%) receiving decitabine alone and in 13 of 25 patients (52%) receiving a combination of decitabine and hyper-CVAD. More recently, a phase II study investigated the efficacy of decitabine and vorinostat plus chemotherapy in patients with relapsed/refractory ALL [4]. Decitabine (15 mg/m^2 intravenous infusion over 1 hour, for 4 days) and vorinostat (230 mg/m^2 divided twice daily orally, for 4 days) were administered followed by vincristine, prednisone, pegylated-asparaginase, and doxorubicin. Four of the 13 patients (30.8%) achieved complete remission. The overall response rate (CR + partial response) was 46.2%.

Elderly patients with leukemia have limited treatment options owing to the toxicity associated with standard therapies. However, decitabine is well tolerated with a manageable toxicity profile in elderly AML patients. A randomized phase III trial in elderly patients with AML reported that the incidence of adverse events (AEs) was similar for decitabine and low-dose cytarabine, even if exposure to study medication was longer with decitabine than with low-dose cytarabine. Grade 3 or 4 drug-related AEs occurred in 141 patients (59%) treated with decitabine and in 144 patients (55%) treated with low-dose cytarabine. The most common drug-related AEs with decitabine were thrombocytopenia (27%), anemia (21%), neutropenia (24%), and febrile neutropenia (21%) [5].

Since there are no established treatments for MPAL, we chose to use decitabine since it shows benefit for both lymphoid and myeloid blast cells. Safety and tolerability were also important in our patient since she was elderly with a poor performance status. In fact, decitabine is effective in both lymphoid leukemia and myeloid leukemia, and it is associated with a favorable safety profile and good tolerability in elderly patients. In our patient, decitabine was both effective and well tolerated, and the patient has remained in remission for at least 5 months.

Thus, we present a case of MPAL that was treated successfully with decitabine. Moreover, if administered for longer periods of time, it can be expected that decitabine treatment would further improve survival, although four cycles were also found useful. We suggest therefore that decitabine can be considered a valid treatment option in MPAL.

Keywords: Mixed-phenotype acute leukemia; Decitabine

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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