To the Editor:

Erythropoietin (EPO) has proved useful for the recovery of anemia under the condition of renal insufficiency or myeloma. In vitro colony assay has shown that EPO stimulates the growth and differentiation of burst-forming unit-erythroid and colony-forming unit-erythroid colonies of bone marrow progenitor cells. It has been noted that marrow erythroblasts in erythroleukemia were decreased after transfusion, suggesting that a humoral factor such as EPO in serum may contribute to the regulation of erythroleukemia cells. However, clinicians have withheld application of EPO in erythroleukemia because this agent may stimulate the proliferation of leukemia cells; on the other hand, it has not yet been shown that EPO is capable in vitro to force differentiation of erythroleukemia cells, as all-trans retinoic acid has been observed to do for promyelocytic leukemia cells. We present here a case of erythroleukemia who
achieved complete remission after it was confirmed in vitro that EPO had brought about differentiation of leukemia cells.

A 17-year-old male was admitted to our hospital for anemia. His red blood cell (RBC) count was $266 \times 10^6/\mu L$; hemoglobin (Hb) 9.5 g/dL; reticulocyte count 2.7%; white blood cell (WBC) count 1,700/\mu L with 42% neutrophils, 54% lymphocytes, and 4% monocytes; and platelet count 7.5 $\times 10^4/\mu L$. Nuclear RBCs were found in 36 of 100 RBCs. The bone marrow aspirate disclosed an erythroid dominant marrow with a nuclear cell count of 206,000/\mu L, with 68% erythroid cells. The percentage of blasts among nonerythroid mononuclear cells was 37.8%. The erythroblasts showed a high nuclear/cytoplasmic ratio and were positive for Periodic acid Schiff stain. A diagnosis of erythroleukemia (M6 in the French-American-British classification) was made and he was subsequently treated with several chemotherapies, including daunomycin, 6-mercaptopurine, prednisolone, and behenoyl cytosine arabinoside, etc; however, these were not effective.

We then investigated the potential of differentiation therapy. The patient’s bone marrow aspirates were subjected to Ficoll-Hypaque discontinuous centrifugation and mononuclear cells were obtained. The cells were incubated in 10% fetal calf serum supplemented with Iscove’s modified Dulbecco’s Medium for 7 days and cultured for another 7 days in the presence of EPO. After EPO addition, the total cell number ($0.5 \times 10^5/mL$) started to increase, reached a plateau ($3.5 \times 10^5/mL$) at day 5, and thereafter rapidly decreased. It was noteworthy that the leukemic blasts in culture had almost disappeared and that the erythroblasts and mature RBCs increased by day 7, as shown in the photomicrograph (Fig 1). These in vitro studies showed that differentiation can be stimulated in erythroleukemia cells by EPO.

As the patient was refractory to conventional chemotherapies, we explained his situation and the results of the in vitro study to his family and obtained informed consent to use EPO. EPO was administered subcutaneously at a dose of 12,000 U/day. The patient’s clinical course is shown in Fig 2. After 6 days of EPO administration, the Hb value started to increase and the nuclear RBCs had disappeared in the peripheral blood at day 14. Bone marrow aspirate showed a remarkable decrease in megaloblasts and an increase in polychromatic and orthochromatic erythroblasts. By 2 weeks of administration of EPO, the leukemia had gone into remission without any other cytotoxic drugs. We decided to continue daily administration of EPO because it appeared to be the decisive factor in the patient’s general improvement as well as his increase in the Hb, WBC, and platelet count. No donor for a bone marrow transplant could be found with matching HLA. However, 3 months after his first treatment with EPO, the patient developed pancytopenia and showed an increase of unclassified blasts both in peripheral blood and bone marrow. Conventional chemotherapies including cytosine arabinoside and other drugs were ineffective. These blasts were also refractory to EPO addition in vitro. The patient died from cerebral hemorrhage.

Erythroleukemia is still one of the leukemias with a poor prognosis, because it has a high tendency to deteriorate into acute nonlymphocytic leukemia. Our patient’s clinical course strongly suggests that EPO has potential for differentiation therapy of erythroleukemia. As far as we known, this is the first reported case in which EPO
has stimulated differentiation of erythroleukemia cells in vitro as well as substantively improving a patient's condition. Further clinical studies of this agent seem to be warranted; however, users must take the potential for tumor growth stimulation into account and interrupt the treatment promptly if rapid progression occurs.

ACKNOWLEDGMENT

We thank Kirin Brewery Co (Tokyo, Japan) for providing recombinant EPO for the management of this case.

REFERENCES


Remission after erythropoietin administration for erythroleukemia--a case study [letter]

E Miyazaki, Y Kohgo, M Hirayama, J Kawanishi, J Kato, S Sakamaki and Y Niitsu