Erythropoietin-dependent transformation of myelodysplastic syndrome to acute monoblastic leukemia


Acute monoblastic leukemia (acute myeloid leukemia [AML], French-American-British type M5a) with leukemia cutis developed in a patient 6 weeks after the initiation of erythropoietin (EPO) therapy for refractory anemia with ringed sideroblasts. AML disappeared from both marrow and skin after the discontinuation of EPO. Multiparameter flow cytometric analysis of bone marrow cells demonstrated coexpression of the EPO receptor with CD45 and CD13 on the surface of blasts. The incubation of marrow cells with EPO, compared to without, resulted in 1.3- and 1.6-fold increases, respectively, in tritiated thymidine incorporation and bromodeoxyuridine incorporation into CD13+ cells. Clinical and laboratory findings were consistent with the EPO-dependent transformation of myelodysplastic syndrome (MDS) to AML. It is concluded that leukemic transformation in patients with MDS treated with EPO may be EPO-dependent and that management should consist of the discontinuation of EPO followed by observation, if clinically feasible. (Blood. 2001;98:3492-3494)

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EPO-dependent transformation of MDS to AML

Discontinuation of EPO showed reversion to MDS, without increased blasts (Figure 1C) and without abnormal myeloid cells by MFC; the B-cell clone persisted. Anemia worsened again, necessitating transfusions. The patient had a fatal myocardial infarction 4 months later; leukemia had not recurred.

Laboratory studies

Samples. BM mononuclear cells obtained by Ficoll-Hypaque density centrifugation at presentation of AML, 3 months earlier, and 6 weeks later were cryopreserved before the initiation of EPO therapy and regressed after its discontinuation. Transformation to acute leukemia was unexpected, given the RARS subtype of MDS, the normal karyotype, and the presence of anemia as the sole cytopenia. Adriamycin administered to treat Hodgkin disease could have been leukemogenic, but MLL gene rearrangement, characteristic of topoisomerase II inhibitor-induced AML,17 was not found. The development of AML during EPO therapy and the disappearance of leukemia from BM and skin after the discontinuation of EPO were consistent with EPO-dependent transformation of MDS to AML. In vitro results also support this hypothesis; myeloid blasts expressed the EPO receptor and proliferated in response to EPO. Relatively modest EPO-induced proliferation in vitro is explained by the absence of leukocyte-conditioned medium or costimulatory cytokines in the cultures.18,19 Of note, the B-cell clone detected by MFC might possibly have produced costimulatory factors in vivo.

EPO has been reported to stimulate clonogenic leukemic erythroid progenitors in erythroleukemia20 and leukemic blast colony growth in the presence of phytohemagglutinin-stimulated, leukocyte-conditioned medium in other AML subtypes.18,19 EPO receptor expression was found on leukemia cells in 81 of 136 patients, all with expression of the receptor.21 Moreover, compared with those without EPO receptor expression, remission duration was shorter in patients whose cells expressed the EPO receptor and proliferated in response to EPO.21

To our knowledge, this is the first demonstration of EPO-dependent leukemic transformation of MDS. EPO is used increasingly in patients with MDS, and close observation for leukemic transformation is warranted. EPO therapy should be discontinued in patients with MDS that progresses to AML, and, if clinically feasible, those patients should be observed for the regression of AML.

Results and discussion

AML developed in our patient during EPO therapy and regressed after its discontinuation. Transformation to acute leukemia was unexpected, given the RARS subtype of MDS, the normal karyotype, and the presence of anemia as the sole cytopenia. Adriamycin administered to treat Hodgkin disease could have been leukemogenic, but MLL gene rearrangement, characteristic of topoisomerase II inhibitor-induced AML,17 was not found. The development of AML during EPO therapy and the disappearance of leukemia from BM and skin after the discontinuation of EPO were consistent with EPO-dependent transformation of MDS to AML. In vitro results also support this hypothesis; myeloid blasts expressed the EPO receptor and proliferated in response to EPO. Relatively modest EPO-induced proliferation in vitro is explained by the absence of leukocyte-conditioned medium or costimulatory cytokines in the cultures.18,19 Of note, the B-cell clone detected by MFC might possibly have produced costimulatory factors in vivo.

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References

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