

Case Report

Are we underestimating the leukemogenic risk of hydroxyurea

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ABSTRACT

Hydroxyurea is an established drug that has been used for the treatment of myeloproliferative disorders and some solid tumors for some time. In recent years it has also been found to be effective in the treatment of sickle cell disease. Short term side effects are not serious, and are manageable. The major concern is the potential leukemogenesis with long term use. The risk of leukemogenesis is not defined with its use in benign hematological conditions. We report a case of acute myeloid leukemia with no preceding myelodysplastic syndrome, occurring after 2 years of hydroxyurea therapy in a patient with sickle cell disease.

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Hydroxyurea (HU) was shown in a prospective randomized study to be effective in ameliorating the manifestations of sickle cell disease (SCD).¹ It is generally well tolerated, but adverse reactions may affect many tissues and organs.² The most frequent side effect is reversible myelosuppression which improves with dose reduction or withholding the drug. The most serious side effect is the potential for teratogenesis, mutagenesis and carcinogenesis. Acute leukemias associated with the use of hydroxyurea have been reported in patients with myeloproliferative disorders which are known to be pre-leukemic.³⁻⁵ In SCD, cases of acute leukemia associated with the use of HU have been reported.^{6,7} We report here a case of acute myeloid leukemia (AML), which was diagnosed in a young woman with SCD, following 2-years of HU use. To our knowledge this is the first case report describing this condition occurring after such a relatively short period of HU use.

Case Report. The patient was a 25-year-old Saudi Arabian woman suffering from SCD with frequent vaso-occlusive crises. She had more than 6 episodes per year requiring hospital admissions. She also had hepatitis C. Examination was remarkable for splenomegaly extending 4 cm below the left costal margin. There were no other significant physical findings. She was enrolled in our hydroxyurea study after written informed consent was obtained in November 1998. She was started initially on a dose of 500 mg per day. The same dose was given for 15-months. The dose was reduced to 500 mg daily for 5-days per week because of thrombocytopenia. She responded very well to HU with a reduction in the number of crises. Only 3 mild painful crises developed during the first year of HU therapy, which did not require hospitalization. When the dose was reduced, mild to moderate painful crises recurred. The dose was increased to 1000 mg alternating with

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500 mg per day, 6-days per week for 6-months. During this period, she was completely asymptomatic. During the 2-year period of HU therapy, she had no significant side effects apart from transient episodes of headache, which disappeared after adjustment of the timing of dose intake. She had transient elevation of alanine aminotransferase (ALT) for 2-months, which resolved with temporary dose reduction. There was a rise in fetal hemoglobin from a baseline level of 19-29% of total hemoglobin (Hb) after 7-months of HU treatment. In February 2001 cytopenia was noted. Neutrophils were $0.75 \times 10^9/L$ and reticulocytes were $30 \times 10^9/L$. Hydroxyurea was withheld. After withholding the drug for 6-weeks reticulocytes recovered, however she remained neutropenic. Thrombocytopenia was also noted. Platelet count dropped from 120×10^9 to $30 \times 10^9/L$. She complained of fatigue and light headedness. Examination at this time showed pallor and splenomegaly that was unchanged. Laboratory studies showed white blood count (WBC) were $2.13 \times 10^9/L$ with 19% ($0.4 \times 10^9/L$) neutrophils; Hb was 5.0 g/dl. Platelet count manual estimate was $48 \times 10^9/L$, and reticulocytes were 1.8%. Lactate dehydrogenase was 122 u/l; total bilirubin was 1.04 mg/dl. Prothrombin time and partial thromboplastin time were normal. Creatinine and blood urea nitrogen were normal. A bone marrow examination showed AML. The patient was transferred to Saudi Aramco, Dhahran Health Center for further evaluation and treatment. A bone marrow and peripheral blood examination revealed AML (FAB M1), **Figure 1**. Flow cytometry of a bone marrow aspirate showed that the gated blast population was positive for CD33, CD13, CD34, CD117, HLA-DR, and CD15, partially positive for CD56, CD38, CD19 and CD7. It was negative for CD11b, CD65, CD2, glycophorin A, and CD61. This is consistent with AML with aberrant expression of CD19 and CD7. Chromosomal analysis revealed normal female karyotype (46, XX), and no abnormal clone was apparent.

She was started on induction chemotherapy with cytarabine and idarubicin. A bone marrow examination on day 14 post-treatment showed no residual leukemic cells. Complete remission was confirmed on a day 21 bone marrow. Induction was complicated by bilateral pneumonia with cavitation, and a nasal lesion. Biopsy of the nasal lesion showed hyphae in the exudate. Bronchoalveolar lavage showed septated hyphae. She was recovering, became afebrile and had normal WBC, platelets and prothrombin time when she developed an episode of massive pulmonary hemorrhage and died. She most likely had an invasive aspergillosis, which eroded a major pulmonary vessel.

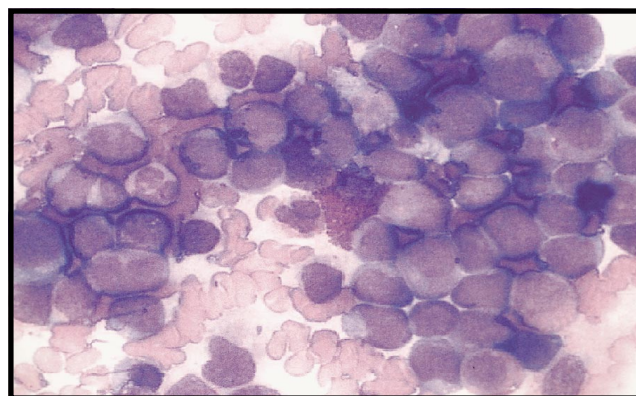


Figure 1 - A bone marrow smear showing infiltration by myeloblasts (FAB AML M1).

Discussion. Some chemotherapeutic agents are known to induce secondary leukemia, which is usually AML. Alkylating agents were used in more than 85% of patients who develop chemotherapy related leukemia. Other agents include epipodophyllotoxins especially etoposide.⁸ The leukemogenic potential of HU is uncertain. There is a general feeling that it is one of the least leukemogenic chemotherapeutic agents. Hydroxyurea was found to induce chromosomal abnormalities and DNA mutations.⁹ These abnormalities may activate some oncogenes, which may lead to leukemic transformation. Our informed consent to use HU for sickle cell disease clearly mentions this potential. Therapy related AMLs with t(8;21), inv(16), or t(8;16) are usually characterized by a short latent period with no preleukemic phase.¹⁰ Prior chemotherapy treatment in this group included exposure to drugs that directly react with DNA (alkylating agent or cisplatin), or an agent that targets topoisomerase II, or both. 17p deletions resulting in myelodysplasia and acute leukemia have been reported in patients with essential thrombocythemia treated with HU.⁵ Most of the reported HU-related secondary myelodysplastic syndrome (MDS)/AML occurred in patients with myeloproliferative disorders. These disorders are known to predispose to secondary leukemias. In benign hematological disorders in which HU was used, the leukemogenic risk is undefined. In 64 patients with cyanotic congenital heart disease treated with HU, no cases of secondary malignancy were reported.¹¹

In sickle cell disease the issue is not clear. No cases of secondary malignancy were reported in adults with SCD who were enrolled in the multicenter HU trial.¹² However 2 cases of AML have been reported since the publication of the study result, after 6 and 8 years of HU treatment in patients with SCD.^{6,7} Our patient is relatively unique in that AML developed after 2-years of use of HU. The

absence of chromosomal abnormalities, and preceding MDS; and the short latent period for the development of AML, suggest a de novo AML, but we can not rule out secondary leukemia related to HU. We shall be waiting for more reports to clarify the relationship between HU and secondary MDS/AML and to quantitate this risk. Meanwhile we believe it is prudent to restrict the use of HU to sickle cell patients with severe disease. The current indications for use of HU, of 3 painful episodes requiring hospital admission are loose, and do not reflect the severity of disease all the time. Therefore, the definition of severity of SCD should be revised on an international basis. Despite the fact that HU has been approved by United States Food and Drug Administration (FDA) for the treatment of SCD, patients should be clearly informed about the potential risk of leukemogenesis. Those who are using HU should be followed up regularly on long-term basis with regular blood counts to detect the development of MDS/AML.

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