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Short communication

Acute mucocutaneous toxicity following high-dose hydroxyurea

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Abstract. Three patients with advanced acute myeloid leukemia were treated with oral high-dose hydroxyurea at a dose of 10 g daily for 8–10 days. Severe acute stomatitis developed in all three patients. In addition, two of the patients developed a peculiar acute cutaneous type of toxicity associated with soreness, violet erythema, and edema of the palms and foot soles followed by intense universal hyperpigmentation of the skin. Apparently, the pronounced acute mucocutaneous toxicity was caused by the sustained high daily dose of hydroxyurea, indicating that myelosuppression may not be the dose-limiting toxicity of this drug.

Introduction

Although currently established indications for the use of hydroxyurea are limited to myeloid leukemia and the myeloproliferative syndromes, there are several potential new indications for this drug [10]. Various new dose regimens have also been explored for hydroxyurea, including so-called high-dose hydroxyurea in lung cancer [9], in chronic myelogenous leukemia [5], and in autologous bone marrow transplantation [8]. In all of these studies the dose-limiting toxicity was hematologic, whereas nonhematologic toxicity was insignificant. In one study, total doses in excess of 200 g were given in 48 days [5], and in another study, daily doses of up to 24 g were given for 2 days [9]. However, thus far, no study has combined high daily doses with a high total dose. We report some uncommon acute nonhematologic toxic effects observed in three patients treated with oral hydroxyurea at a dose of 10 g daily for 8–10 days.

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Case reports

Case 1. A 33-year-old man presented with advanced acute myeloid leukemia (AML) of the M6 type. A complete remission (CR) was obtained with one course of daunorubicin plus cytosine arabinoside (Ara C), but a relapse occurred less than 4 months after the diagnosis following one course of consolidation treatment with high-dose Ara C. The patient's disease progressed rapidly in spite of subsequent treatment with amsacrine plus etoposide. At this time, his leukocyte count was 71×10^9/l and his platelet count was 14×10^9/l. He was given one course of oral hydroxyurea at a dose of 10 g daily for 10 days without any concomitant nausea or vomiting. Nadir values were reached on day 10, with the leukocyte count being 2×10^9/l and the platelet count being 6×10^9/l, but the leukocyte value rose to 20.4×10^9/l as early as on day 12. Mild stomatitis appeared on day 6, progressing to oral ulcerations on day 12. There was no sign of cutaneous toxicity. The patient died 10 days later of a cerebral hemorrhage following treatment with mitoxantrone.

Case 2. A 40-year-old man presented with AML of the M4 type. A CR was obtained following two courses of high-dose Ara C after unsuccessful induction therapy with both daunorubicin plus Ara C and amsacrine plus etoposide. Three further courses of high-dose Ara C were given, but a relapse occurred 1 year after the diagnosis, accompanied by lymphadenopathy. At this time, the patient's leukocyte count was 22×10^9/l and his platelet count was 30×10^9/l. He was given one course of oral hydroxyurea at a dose of 10 g daily for 5 days and a similar course 2 weeks later. Following both courses, leukocyte nadir values of 2×10^9/l were reached in 1 week, with a reversal of counts to the initial values occurring within 2 weeks. None of these courses was followed by any nonhematologic toxicity, except that the patient complained of sore feet after the end of the second course.

Since posttreatment platelet counts rose to 60×10^9/l and since the lymphadenopathy subsided, it appeared that some improvement had been achieved with hydroxyurea. Accordingly, a third course of oral hydroxyurea at a dose of 10 g daily for 10 days was given 2 weeks after the second course. Neither this course nor the preceding two courses resulted in any nausea or vomiting. Following the third course, nadir values were reached in 1 week, with the leukocyte count being 0.4×10^9/l and the platelet count being 9×10^9/l. However, the patient developed stomatitis on day 7. The latter reaction progressed to the point where the patient could not swallow his own saliva and lasted for 2 weeks. On day 6 a peculiar reaction occurred in the palms and foot soles, manifesting as soreness, violet erythema, and edema. The latter reaction subsided in 10 days and was followed by pronounced scaling of the skin of the hands and feet. At the same time, an intense generalized hyperpigmentation of the skin was noted. Leukocyte and platelet counts reverted to pretreat-

ment values on day 25. The patient lived for a further 4 months, during which he received oral treatment with hydroxyurea and 6-mercaptopurine at conventional doses.

Case 3. A 42-year-old man presented with AML of the M4 type. A CR was obtained following treatment with one course of aclarubicin plus Ara C. Consolidation therapy consisting of two courses of high-dose Ara C and two courses of amsacrine plus etoposide was given, but a relapse occurred 8 months after the diagnosis. Although subsequent treatment with daunorubicin plus Ara C, novantrone, and methyl-GAG was without any effect, the disease was relatively stable. However, 17 months after the diagnosis, the patient became pancytopenic, his leukocyte count being 0.7×10^9/l and his platelet count being 7×10^9/l. At this time, a course of hydroxyurea was given at a dose of 10 g daily for 8 days. This treatment was not associated with nausea or vomiting. Stomatitis was noted on day 7, and at the same time, soreness, violet erythema, and edema of the palms and foot soles occurred. The latter manifestations disappeared in 1 week without scaling, but the stomatitis lasted for 12 days, during which the patient could not swallow food or drink. By the time these symptoms disappeared, the patient had developed intense generalized hyperpigmentation. His leukocyte count returned to pretreatment values on day 25. The patient died of infection 5 weeks later without having received further cytostatic treatment.

Discussion

Hydroxyurea therapy has been associated with mucositis, although the latter problem has been uncommon except in patients receiving concomitant radiation therapy [6]. Cutaneous toxicity has been observed in patients receiving hydroxyurea for extended periods, occurring in the form of hyperpigmentation, erythema, atrophy of the skin and nails, scaling, and violet papules [4], but the peculiar acute cutaneous toxicity we noted in cases 2 and 3, involving soreness, violet erythema, and edema of the palms and foot soles, has not previously been observed.

In patients receiving protracted-infusion chemotherapy, a palmar-plantar erythrodysesthesia syndrome occurred after a median period of 40 days in 17 patients receiving 5-fluorouracil at a dose of 300 mg/m^2 daily. Of these patients, 39% also developed stomatitis [7]; a similar reaction was noted in 1 patient receiving doxorubicin [7]. Apparently, this particular type of toxicity is similar to that noted after the administration of high-dose hydroxyurea, which suggests a stereotypic reaction to several classes of cytostatics.

In the study of Kolitz et al. [5], 25 courses of high-dose hydroxyurea were given at doses ranging from 80 g in 22 days to more than 200 g in 48 days, with only 1 case of mild mucositis and no case of cutaneous toxicity being noted. However, our three cases document that severe acute mucocutaneous toxicity may be seen at cumulative doses of hydroxyurea ranging from 80 to 100 g, provided that the dose rate is high. Thus, it appears to be unsafe to exceed a dose rate of 10 g daily for 6–7 days.

The observation that hydroxyurea is capable of reducing high leukocyte counts quickly and reliably in both acute [2] and chronic [3] myeloid leukemia suggests that the full antileukemic potential of this drug has not yet been realized. In spite of the occurrence of significant toxic effects, the use of high-dose treatment with methotrexate and Ara C appears to have resulted in some therapeutic benefit. However, on the basis of our experience, we are doubtful as to whether it might be possible to escalate the dose of hydroxyurea in a similar way without producing unacceptable nonhematologic toxicity. The statement that "myelosuppression is hydroxyurea's dose-limiting toxicity" [1] should probably be modified.

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