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Painful Oral Ulcers with Hydroxyurea Therapy

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ABSTRACT

Five patients treated with hydroxyurea for various haematological malignancies developed multiple painful oral ulcers. Their neutrophil counts were either normal or elevated. The ulcers disappeared with cessation of hydroxyurea. Oral ulcers recurred when hydroxyurea was resumed in one of the patients. As the patients were unable to tolerate this painful side effect, hydroxyurea had to be discontinued. Appearance of painful oral ulceration seems to be independent of dosing rate or total cumulative dose of hydroxyurea.

Keywords: adverse effect, polycythaemia, essential thrombocythaemia, chronic myeloid leukaemia

INTRODUCTION

Hydroxyurea is known for many years but its anti-tumour activity was not recognised until the late 1960's. It is an anti-metabolite and inhibits DNA synthesis by inhibiting ribonucleoside reductase. Its use has been establised for the treatment of chronic myeloid leukaemia (CML) and myeloproliferative disorders[1]. The side-effects of hydroxyurea include myelosuppression which is dose related. Other non-haematological complications are cutaneous toxicity and mild gastrointestinal toxicity resulting in nausea and vomiting. Mucositis is a rare complication notably seen in patients receiving concomitant radiation therapy[2]. We report 5 patients who developed painful oral ulcers while on hydroxyurea only. Three received less than 70g and the other two had more than 250g of hydroxyurea when the ulcers appeared.

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Case 1

A 25-year-old Malay lady presented with easy bruising, pallor and hepatosplenomegaly. She was anaemic (Hb 9g/dL), had leucocytosis (390 x 10^9/L, neutrophils 49%, lymphocytes 32%, monocytes 4%, immature granulocytes 15%) . Peripheral blood film showed marked shift of white blood cells to the left. Her platelet count was 180 x 10^9/L. Neutrophil alkaline phosphatase (NAP) score was 0 . She was diagnosed to have CML. She was started on hydroxyurea 2.5g twice a day and the dosage was adjusted according to the white cell response. She was receiving about 500-2,500 mg of hydroxyurea daily. Eight months after therapy with hydroxyurea (total dose 264g), she developed sorethroat, painful lower lip ulceration and tonsillitis. She continued to have recurrent painful ulcers over the lips and buccal mucosa. She noted that the ulcers disappeared when she stopped the hydroxyurea. During the occurrence of the ulcers, her cell counts and neutrophils were normal or high (8.5, 12.5, 19.5, and 11.3 x 10^9/L with more than 50% neutrophils). Reduction of dose did not improve her condition and hydroxyurea was discontinued.

Case 2

A 68-year-old Chinese man was diagnosed to have polycythaemia rubra vera (PRV) 7 years ago, when he was noted to have persistent elevation of haemoglobin (Hb > 20g/dL) and leucocytosis (20 x 10^9/L). A bone marrow examination showed proliferation of all 3 cell lines . A red cell mass study supported the diagnosis. He was venesected periodically to maintain a haematocrit of between 42-45. He had a dose of radioactive phosphorus in November 1988 when he required frequent venesections. Thereafter, he did not undergo venesection for 2 years. Unfortunately, his PRV recurred later and needed venesections. When hydroxyurea became available in 1992, he was started on 1g of hydroxyurea daily. Two months later, he was noted to have hyperpigmented nails. About a year after treatment, his counts were (Hb 13.4g, haematocrit 40, white cell count 21.2 x 10^9/L with 55% neutrophils, platelet 281 x 10^9/L), however, he developed painful ulcers over the base of the tongue. By then, he had already received 340g of hydroxyurea at an average dose of 1.5g daily. The ulcers disappeared after 2 days of cessation of hydroxyurea. On reintroduction of hydroxyurea, the painful ulcers recurred and hydroxyurea had to be discontinued.

Case 3

A 56-year-old Chinese man presented with pallor and gross hepatosplenomegaly. His initial leucocyte count was 116.4 x 10^9/L of which 11.6% were blasts. NAP score was 0. He was diagnosed to have CML. He was started on 1g of hydroxyurea daily and allopurinol 100 mg three times daily. On follow-up a month later, the total leucocyte count was 3.9 x 10^9/L (40%

neutrophils), platelet 284 x 10^9/L, Hb 10g/dL. He was noted to have painful mouth blisters which later burst to become painful ulcers. Hydroxyurea was immediately stopped with resolution and disappearance of the ulcers.

Case 4

A 48-year-old Malay man with PRV was treated with 1g of hydroxyurea daily. His initial counts were Hb 19.8g/dL, Hct 58.4%, wbc 39.4 x 10^9/L, platelet 738 x 10^9/L. He was not compliant with treatment and took hydroxyurea intermittently. After one and a half months of therapy, he was noted to have hyperpigmentation of the face, hands, and nails. After receiving about 60g of hydroxyurea over a span of 3 months, he developed painful oral ulcers. His leucocyte counts then were Hb12.8g/dL, wbc 34.8 with neutrophils 45%, platelet 358 x 10^9/L. He was taken off hydroxyurea and the oral ulcers disappeared.

Case 5

A 16-year-old Malay boy was referred to the Haematology Clinic for further investigation of incidental findings of thrombocytosis. He had moderate hepatosplenomegaly. His leucocyte counts were Hb 14.9g/dL, wbc 10.8 x 10^9/L with 59% neutrophils, platelet of 1,030 x 10^9/L. Bone marrow biopsy confirmed that he had essential thrombocythaemia. He was started on hydroxyurea 500 mg twice a day and inteferon alpha 3 MU three times a week. At follow-up three weeks later, he was noted to have painful oral and tongue ulcers of one week's duration. His blood count showed Hb 13.1 g/dL, wbc 4.3 x 10^9/L (neutrophils 50%) and platelet 832 x 10^9/L. Hydroxyurea was stopped and there was complete disappearance of ulcers within a week. Subcutaneous alpha interferon was continued as the treatment of thrombocytosis.

DISCUSSION

Mucositis associated with hydroxyurea is uncommon[2]. It was reported to occur in patients receiving concomitant chemotherapy and radiotherapy, in whom the adverse effect of both modalities seem to be magnified. Oral mucosal ulceration occurs commonly in neutropaenic patients[3] because neutropaenia affects growth of epithelial cells. In all of our patients, the neutrophil counts were normal or high indicating that neutropaenic state was not the cause of oral ulcers. There was rapid recovery from oral mucositis with withdrawal of hydroxyurea implicating this drug as the aetiological factor. This is further supported by case 2 where recurrence of ulcers happened on reintroduction of hydroxyurea. Brincker and Christensen[4] documented the occurance of acute mucocutaneous toxicity with painful ulceration in 3 patients following cumulative doses of hydroxyurea ranging from 80-100g at a high dosage (10g daily), and suggested that a dosage of 10g daily for 6-7 days appeared to produce the side effect. Three of our patients (cases 3, 4, 5) developed oral ulcers even though they were given a low dosage (0.5-1g daily). They had a cumulative dose of less than 70g. Although cases 1 and 2 developed oral ulcers after receiving high cumulative doses of hydroxyurea (340g and 264g respectively), the dosage was only about 1-1.5g daily. This is in contrast to the high dosage (10g) prescribed by Brincker and Christensen. Thus, painful ulceration may be caused by hydroxyurea regardless of its dosage or total cumulative dose. This may be due to a different pharmacokinetics of the drug in the Asian population. This mechanism of disease needs further elucidation. Hydroxyurea is a very useful drug in controlling the proliferation of cells in patients with CML and other myeloproliferative diseases, however, the distressing side effect of painful oral ulceration necessitated withdrawal of the treatment.

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