Early onset life-threatening myelosuppression after low dose of intravesical thiotepa

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Summary

Intravesical instillation of thiotepa is a popular treatment for localized bladder carcinoma. The drug can enter the systemic circulation, and such absorption may be enhanced by extensive tumour infiltration or by a recent tumour resection. A case is reported of early onset life-threatening pancytopenia following an unusually low dose of the drug in a patient who had undergone a recent tumour resection.

Introduction

The efficacy of intravesical instillation therapy with thiotepa (N-N'-N"-thiethylene-thiophosphoramide), a poly-functioning alkylating agent, against bladder carcinoma was first reported by Jones and Swinney (1961). Subsequently, many clinical evaluations of this therapy have been performed regarding the direct destruction of and prophylaxis against bladder carcinoma (Abbassian and Wallace, 1966; Wescott, 1966; Drew and Marchall, 1968; Veenema, Dean and Uson, 1969; Pavone-Macaluso, Caramia and Rizzo, 1971; Tomiyama, 1972). At present, thiotepa remains a popular agent for the treatment of localized bladder carcinoma. Reduction in the extension of tumour or even complete eradication may be obtained in about one-third of the patients if they are treated with instillations of thiotepa (Prout, 1974).

The chief disadvantage of this therapy is the absorption of thiotepa into the circulating blood through the bladder wall. As with other alkylating agents, dose-related myelosuppression is a well-known toxic effect, regardless of the route of administration. We report here a case of early onset life-threatening pancytopenia following an unusually low dose of the drug.

Case report

A 68-year-old male was treated with 30-min intravesical instillations of thiotepa, 20 mg weekly for 6 weeks, starting 20 days from resection of localized malignant vesical papilloma. Before thiotepa treatment the patient had a normal blood cell count. White blood cell (WBC) and platelet counts performed before each weekly dose remained normal. Five days after the sixth instillation, the patient complained of fever, epistaxis, gingival bleeding, multiple petechiae and ecchymoses, and at this point he was referred to our hospital.

Admission laboratory data showed a haematocrit value of 17%, a platelet count of $8 \times 10^9/l$ and a WBC count of $0.7 \times 10^9/l$, with a differential count of 2% neutrophils and 98% lymphocytes. Careful haemostatic examinations excluded disseminated intravascular coagulation. Bone marrow aspirate and biopsy showed marrow aplasia. Chest X-ray showed bilateral pneumonia. Platelets and red cell concentrates were infused every day during the first week. Although antibiotic therapy was promptly started, fever disappeared only after 8 days when the WBC count began to rise. Twenty days after admission, the WBC count was $2.7 \times 10^9/l$ with 52% neutrophils, and the platelets $140 \times 10^9/l$; the patient was discharged.

Discussion

Myelosuppression has long been recognized as a consequence of intravesical instillation of thiotepa for bladder carcinoma. Nevertheless, this side effect is often underestimated because of the erroneous idea that intravesical thiotepa is a topical therapy rather than a systemic one.

Acute myelosuppression by intravesical thiotepa is dose related. The recommended dosage is usually 60 mg thiotepa in 60 ml distilled water instilled once weekly. Two fatal cases of pancytopenia following

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such a treatment schedule have been reported by Abbassian and Wallace (1966) and an additional case has been reported by Bruce and Edgcomb (1967). Prout (1974) reduced both drug and diluent by 50% and observed salutary effects while decreasing the hazard of toxicity. Hollister and Coleman (1980), in a recent review of the haematological side effects of intravesical thiotepa therapy for bladder carcinoma, have suggested a guideline to minimize such toxicity. They recommended an initial treatment schedule averaging 90 mg/month and reported that only one of their 29 patients suffered pancytopenia with this dosage during the first three months. We have observed another case of early onset life-threatening pancytopenia following such a treatment schedule. In our patient, thiotepa therapy was started 20 days after resection of a localized malignant vesical papilloma. Absorption of thiotepa is greater in highly vascular tumours and through bladders in which there has been a recent resection (Koontz, 1979). The aforementioned data of Hollister and Coleman (1980) are incomplete regarding the extension of tumour and previous treatment.

In our opinion patients who have undergone a recent resection should be treated, at least for the first three months, with thiotepa doses lower than 90 mg/month and watched for signs of early toxicity. Frequent checks of blood cell count are mandatory, but they do not shelter the patient, as in the case we report, from early onset myelosuppression.

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