Cancer Chemother Pharmacol (1985) 14:81–82

Cancer Chemotherapy and Pharmacology

Short communication

Induction of remission in acute promyelocytic leukemia with mitoxantrone

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Summary. *Two patients with acute promyelocytic leukemia in first relapse received mitoxantrone 12 mg/m²/day for 5 days. Both patients received IV heparin with replacement of platelets and coagulation factors for control of disseminated intravascular coagulopathy. Both have achieved a complete remission after one course of treatment. We conclude that mitoxantrone is active in patients with acute promyelocytic leukemia and that these patients should also be included in the planned prospective randomized trials comparing daunorubicin and mitoxantrone in combination with cytarabine in previously untreated patients with acute nonlymphoblastic leukemia.*

Introduction

The administration of intensive therapy with either daunorubicin [4] or amsacrine [2] and control of disseminated intravascular coagulopathy [7] have led to improved response rates in acute promyelocytic leukemia. Mitoxantrone [8] is an anthraquinone with cytotoxic activity similar to that of the anthracyclines and amsacrine. Since it may be less cardiotoxic than the anthracyclines it is important to determine whether, as in the case of amsacrine [1], it can effectively replace the anthracyclines in the treatment of patients with the subtypes of acute leukemia, including acute promyelocytic leukemia.

Case Reports

Patient no. 1. This 52-year-old man presented in April 1982 with weakness, fever, and hemoptysis. On physical examination he had adenopathy and petechiae. The WBC was 34.4×10^9/l; hemoglobin 11.3 g/dl; and platelets 120×10^9/l. The WBC differential included mostly promyelocytes and myelocytes. A bone marrow aspirate was hypercellular, with 15% blasts and 70% promyelocytes. Auer rods were seen and the cells were peroxidase-positive. Cytogenetic study revealed a deletion of chromosome 17. He received induction chemotherapy with daunorubicin, cytarabine, and thioguanine. His course was complicated by disseminated intravascular coagulopathy, which was controlled with heparin and replacement with platelets and coagulation factors, and he achieved remission. He received maintenance chemotherapy through May 1983. In July 1983 he complained of gingival bleeding and a bone marrow aspiration revealed relapse. He was admitted to hospital with a WBC of 2.7×10^9/l; hemoglobin 14 g/dl; platelet count 52×10^9/l. He received mitoxantrone 12 mg/m² daily for 5 days and appropriate treatment for disseminated intravascular coagulopathy. A bone marrow aspiration on 15 August 1984 indicated remission, and blood counts on 1 September 1983 indicated a WBC of 3×10^9/l; hemoglobin 11.9 g/dl, and platelet count 240×10^9/l. The WBC differential was normal. He received no further therapy and remained in complete remission until 13 January 1984.

Patient no. 2. This 22-year-old man was well until April 1983, when he noted increased bruising. This became progressively more noticeable and he was admitted to the hospital on 6 May 1983. On physical examination he had multiple areas of ecchymosis on his trunk and extremities. He also had left periorbital and subconjunctival hemorrhages. His WBC was 5.2×10^9/l; hemoglobin 10.1 g/dl; platelets 12×10^9/l. The WBC differntial included 23 neutrophiles, 49 lymphocytes, eight monocytes, seven metamyelocytes, 10 myelocytes, and three promyelocytes. The serum fibrinogen was 96 mg/dl. The bone marrow aspiration was characteristic of acute promyelocytic leukemia and he was treated with a combination of daunorubin with cytarabine and thioguanine, IV heparin, and transfusion of platelets and cogulation factors. Following two courses of induction therapy he achieved remission and was discharged from hospital on 17 June 1983. He received one additional course of postinduction intensification therapy in August 1983, following which he was observed while receiving no therapy.

On 10 November 1983 routine blood counts showed a WBC of 3.6×10^9/l; hemoglobin 12.6 g/dl, and platelets $114{,}000 \times 10^9$/l. A bone marrow aspirate confirmed relapse of acute promyelocytic leukemia and beginning on 11 November 1983 he received mitoxantrone 12 mg/m²/day for 5 days and appropriate treatment for disseminated intravascular coagulopathy. Following 1 month of pancytopenia he achieved a complete remission and is currently receiving no therapy.

Discussion

Mitoxantrone is effective in metastatic breast cancer [12] and in lymphomas [6]. Recent studies have indicated that mitoxantrone is also effective in acute lymphoblastic leukemia and acute nonlymphoblastic leukemia [3, 5, 9–11]. In the largest series [3] mitoxantrone 12 mg/m²/day for 5 days induced remission in nine of 22 patients with ANLL in first relapse. In this series, the side-effects included some nausea and vomiting (75%), stomatitis (33%), and in less than a third of the patients, minor hepatic dysfunction and rare instances of

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cardiac dysfunction. Our own patients with promyelocytic leukemia tolerated the drug well and all were discharged from hospital in complete remission after only one course of therapy.

Previous studies had suggested a unique responsiveness of promyelocytic leukemia to anthracyclines and as a result daunorubicin, adriamycin, or rubidazone have been considered the drugs of choice for treatment [4]. We have recently seen that patients with APL who receive amsacrine achieve a remission rate and a remission duration that is comparable to that achieved with anthracyclines [2]. Future trials have been proposed to compare mitoxantrone and daunorubicin in combination with cytarabine in previously untreated patients with acute myelogenous leukemia. In view of the responsiveness of APL to mitoxantrone documented here, patients with this disease should not be excluded from these planned prospective trials.

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Received January 25, 1984/Accepted July 5, 1984