Myelodysplasia and acute myeloid leukaemia following adjuvant chemotherapy for breast cancer using mitoxantrone and methotrexate with or without mitomycin

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Summary

Background: Secondary acute myeloid leukaemia/myelodysplasia (t-AML, t-MDS) may occur following adjuvant chemotherapy for breast cancer and has been most frequently associated with alkylating agents. This complication is now being associated with an expanding list of chemotherapeutic agents including topoisomerase II poisons. Mitoxantrone is an agent with potential to cause t-AML and t-MDS and which is being used increasingly in the treatment of breast cancer.

Patients and methods: Fifty-nine patients who received mitoxantrone as part of adjuvant chemotherapy for breast cancer between 1986 and 1992 were studied to determine the incidence of t-AML and t-MDS.

Results: With a median follow-up of 72 months, 2 cases of t-AML and 1 of t-MDS have occurred.

Conclusions: This 5% incidence of t-AML and t-MDS is high and likely related to mitoxantrone. Whereas this agent is effective and has acceptable toxicity in advanced disease, its incorporation into adjuvant treatment regimens cannot be recommended based on this experience.

Key words: adjuvant chemotherapy, breast cancer, mitoxantrone, t-AML, t-MDS, topoisomerase II

Introduction

Data suggest that the risk of secondary acute myeloid leukaemia (t-AML) or myelodysplastic syndrome (t-MDS) among patients receiving standard-dose, cyclophosphamide-containing, adjuvant chemotherapy for breast cancer is not much greater than that in the general population [1,2].

In the treatment of breast cancer new regimens, if effective in advanced disease, are frequently used as adjuvant therapy and a further approach being tested is high-dose chemotherapy with haematopoietic rescue as adjuvant therapy in patients with high recurrence risk. An agent used in these settings is mitoxantrone, an anthracenedione and topoisomerase II poison most frequently combined with methotrexate (2M) or methotrexate and mitomycin (3M) in patients with metastatic disease or with cyclophosphamide and etoposide as high-dose chemotherapy (HD-CNV) with haematopoietic rescue for metastatic breast cancer [3].

Topoisomerase II poisons are associated with t-AML with a short (< 3 years) post-treatment interval and cytogenetic alterations such as t(8;21) inv (16), t(15;17) and balanced translocations to 11q23. A short pre-leukaemic phase is reported and response rates to therapy and prognosis may be similar to de novo AML [4]. Cases of t-AML have been described following 2M or 3M in patients with advanced breast cancer but short survival may not allow enough time for this complication to develop.

We report our experience with regimens containing mitoxantrone showing a high level of t-AML and t-MDS when this drug is used in the adjuvant setting.

Patients and methods

Fifty-nine premenopausal women with early breast cancer were treated with adjuvant regimens containing mitoxantrone between 1986 and 1992 in a single-institution, pilot study to assess toxicity and efficacy. Patients had a performance status (WHO) of 2 or less and gave informed consent. Initially 3M was used but with the acceptance that, in advanced disease 2M was equally effective to 3M, mitomycin was later omitted. Planned doses in 3M were mitomycin 8 mg/m² every 6 weeks and mitoxantrone 8 mg/m² with methotrexate 30 mg/m² every three weeks, all given intravenously. For 2M planned doses were mitoxantrone 12 mg/m² and methotrexate 35 mg/m² given intravenously every three weeks. With both regimens 24 weeks' therapy was planned with projected total doses per m² of mitomycin 8 mg/m² every 6 weeks and mitoxantrone 8 mg/m² with methotrexate 30 mg/m² every three weeks, all given intravenously. For 2M planned doses were mitoxantrone 12 mg/m² and methotrexate 35 mg/m² given intravenously every three weeks. With both regimens 24 weeks' therapy was planned with projected total doses per m² of mitomycin 32 mg, methotrexate 240 mg and mitoxantrone 64 mg in 3M and methotrexate 280 mg and mitoxantrone 96 mg in 2M. Standard criteria were used for dose modification in the face of haematologic and other toxicities. Full blood counts, biochemical profiles, physical examination and patient assessment were performed every three weeks or more frequently where required. Best supportive care was provided. Median age at diagnosis was 42 years (range 32-54). Eight patients were treated following an isolated local recurrence without systemic disease and the remaining 51 patients received adjuvant chemotherapy following definitive local therapy: 30 received 3M and 29 received 2M. Eleven patients received local radiation therapy, either as part of their primary treatment following limited surgery or following an isolated local recurrence.
yet transfusion dependent and active therapy has not been introduced.

Bone marrow shows progression to RAEB with tri-lineage dysplasia and 12% blasts suggesting possible progression to M4EO as in patient 1. Cytogenetic analysis shows monosomy 7 and trisomy 21. Gum biopsy shows an infiltrate similar to that in the bone marrow. She is not yet transfusion dependent and active therapy has not been introduced.

Results

Percentage of projected dose given was 89% for mitomycin, 93% for methotrexate and 96% for mitoxantrone. With a median follow-up of 72 months three cases of t-AML/t-MDS have occurred. All three patients received 2M.

Patient 1 (45 years) received 400 mg of methotrexate and 144 mg of mitoxantrone. Twelve months following commencement of chemotherapy she developed metastatic disease in soft tissue and then bone metastases. Local radiation therapy was given and tamoxifen 20 mg daily commenced. At 18 months severe pancytopenia developed. This was initially felt to be related to metastatic disease affecting bone marrow but marrow examination revealed acute leukaemia, M4EO (FAB classification). A cytogenetic abnormality was not detected. She refused active treatment and died six days later.

Patient 2 (41 years) received 360 mg of methotrexate and 120 mg of mitoxantrone, 75% of the projected course. Because of severe nausea and vomiting, persistent neutropenia and an unstable mental state chemotherapy was stopped and tamoxifen 20 mg daily introduced. She developed t-MDS after 8 months. This progressed over four months to refractory anaemia with excess blasts (RAEB) and with 15% blasts and heavy dependence on red cell and platelet transfusions she was treated with daunorubicin, cytosine arabinoside and thioguanine (DAT). She entered complete remission and consolidation courses of DAT x 1 and mAMSA, cytosine arabinoside and etoposide (MACE) x 1 were given. Autologous bone marrow was harvested and further consolidation with mitoxantrone and cytosine arabinoside (MIDAC) given. Prolonged pancytopenia followed with a hypocellular bone marrow. After 5 months AML was diagnosed with M2 morphology and 69% blasts. A cytogenetic abnormality was not detected. She was treated with myeloablative doses of busulphan and cyclophosphamide and her stored marrow was reinfused. Pancytopenia and leukaemia persisted until she died 3 months later.

Patient 3 (49 years) received 435 mg of methotrexate and 157.5 mg of mitoxantrone. Tamoxifen 20 mg daily had been prescribed by the referring surgeon and she continued to take this until she developed t-MDS at 36 months. Two years later progressive pancytopenia has developed with gum bleeding and easy bruising. Bone marrow shows progression to RAEB with tri-lineage dysplasia, an increase in eosinophil precursors and 12% blasts suggesting possible progression to M4EO as in patient 1. Cytogenetic analysis shows monosomy 7 and trisomy 21. Gum biopsy shows an infiltrate similar to that in the bone marrow. She is not yet transfusion dependent and active therapy has not been introduced.

Discussion

A 5% incidence of t-MDS and t-AML causes serious concern and the use of mitoxantrone seems to increase the risk significantly [5, 6]. It may be relevant that patient 2 developed frank leukaemia following a second exposure to mitoxantrone during therapy for t-MDS. Methotrexate appears to have little or no leukaemogenic potential as evidenced by reports of its use in regimens to treat breast cancer and as a single agent in non-malignant conditions such as rheumatoid arthritis [7]. A possible interaction between methotrexate and mitoxantrone cannot be excluded but the major suspicion must fall on mitoxantrone. This experience should strike a note of caution with regard to its use as adjuvant therapy. The cytogenetic findings in case 3 and cases reported elsewhere [5] support the view that cytogenetic abnormalities may not be as specific as has been thought in t-AML/t-MDS following the use of different chemotherapeutic agents [8].

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References


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