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Erythema and Swelling of Ears After Treatment with Cytarabine for Leukemia

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COMMON side-effects of cytarabine plus an anthracycline for acute myelogenous leukemia (AML) include bone marrow depression, gastrointestinal symptoms, alopecia, fever and rashes [1–3]. Burgdorf *et al.* described an acral erythema in a patient receiving high-dose chemotherapy [4]. The syndrome consists of pain and dysesthesia of palms and soles, erythematous discoloration, bulla formation and desquamation [5–9]. Clinical and histopathological features are consistent with a toxic eruption [8].

Over a 3 year period, eight patients with acute myelogenous leukemia treated with combination chemotherapy had painful erythema and swelling of the ears (Table 1). Infectious causes could be ruled out. The symptoms subsided spontaneously within a week. Consolidation therapy with the same drugs had no skin complications, except in patient 7.

Table 1. Details of patients

Patient	Cytostatic drugs	Day of symptoms
1 (38/F)	Cytarabine 100 mg/m² Vincristine 2 mg 1 day Doxorubicin 45 mg/m²	6
2 (64/F)	Cytarabine 200 mg/m² Doxorubicin 30 mg/m²	5
3 (59/F)	Cytarabine 200 mg/m² Doxorubicin 45 mg/m²	7
4 (50/F)	Cytarabine 200 mg/m² Doxorubicin 45 mg/m²	4
5 (43/F)	Cytarabine 200 mg/m² Doxorubicin 45 mg/m²	8
6 (47/F)	Cytarabine 2 g/m² *m*-Amsacrine 120 mg/m²	7
7 (58/M)	Cytarabine 1 g/m² *m*-Amsacrine 120 mg/m²	18*
	Cytarabine 4 g/m²	3
8 (52/M)	Cytarabine 200 mg/m² Doxorubicin 45 mg/m²	6

Cytarabine, doxorubicin and *m*-amsacrine for 7, 3 and 3 days, respectively, except in patients 6 (cytarabine for 6 days) and 7 (cytarabine for 6 days and then for 4 days at higher dose during second consolidation cycle). Patients 2, 3 and 5 also had erythema of the trunk, legs, hands and/or face.
*Erythema of face.

All our patients had been treated for AML with cytarabine in combination with either daunorubicin or *m*-amsacrine. All patients received alimentary tract decontamination with neomycin, polymyxin B, amphotericin B and nalidixic acid or pipemidic acid [10]. Allopurinol and sodium bicarbonate were administered routinely during cytostatic treatment. During or soon after cytostatic treatment, both ears were red and swollen. Because the earlobes were also involved, this condition could be distinguished from acute perichondritis. All the patients had a normal temperature. Because of the risks of bleeding and secondary infection, biopsies were not done. Patients 3 and 4 received high-dose corticosteroids prophylactically. The side-effect is probably the result of a toxic reaction because in patients 2, 3, 5 and 7, other parts of the body were also involved.

It is most likely that cytarabine was responsible for this reaction although drugs such as nalidixic acid or allopurinol might have been involved.

Although corticosteroids may be therapeutic and prophylactic in cytarabine-induced skin toxicity [2, 3], their value is not established. Cytarabine can be re-instituted with little hazard; in our group, consolidation therapy induced the same side-effect in only one patient.

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Mitoxantrone in Advanced and/or Recurrent Endometrial Carcinoma

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DOXORUBICIN is the most active single drug in endometrial cancer and is more effective than cyclophosphamide. Other drugs of interest in this disease are 5-fluorouracil, hexamethylmelamine and cisplatin [1]. Mitoxantrone is one of several aminoanthraquinones that bind to DNA and inhibit nucleic acid synthesis. In animals, this compound is less cardiotoxic than doxorubicin. In phase I and II trials myelosuppression was dose-limiting [2]. Several schedules have been studied especially, in solid tumors, with a single dose of 12–14 mg/m^2 every 3 weeks. We summarize the experience of the EORTC Gynecological Cancer Cooperative Group with mitoxantrone used as first-line therapy in patients with advanced and/or recurrent endometrial cancer in a phase II study.

Patients with histologically confirmed adenocarcinoma of the uterine corpus entered this trial. Eligibility criteria included: age 80 or below, life expectancy 2 months or more, and no previous chemotherapy. Hormone therapy and radiotherapy had to be stopped for at least 4 weeks before the start of mitoxantrone. Patients had to have measurable and/or evaluable disease outside previously irradiated areas as well as documented progression, and 4 × 10^9/l or more white cells, 100 × 10^9/l or more platelets, and adequate cardiac and hepatic function.

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Table 1. Patients' characteristics

Evaluable patients	17
Median age (range)	65 (54–74)
Performance status (WHO/ECOG)	
0	6
1	8
2	3
Tumor site	
Local recurrence	3
Distant metastases	11
Both	3
Previous:	
Surgery	17
Radiotherapy	11
Hormonal therapy	5

Treatment consisted of mitoxantrone 14 mg/m^2, given intravenously every 3 weeks. Patients were evaluable for toxicity if they had completed one treatment cycle and for response after two cycles. Toxicities and responses were defined according to WHO criteria [3]. Early death due to progressive disease was evaluable as treatment failure.

Twenty patients entered the study. For one patient no forms or data were obtained. Two patients were not evaluable: one refused further treatment after the first cycle and the other died after cerebral stroke 10 days after the first course. Thus 17 patients were evaluable for response and toxicity (Table 1). A median of four treatment cycles (range 2–27) was given. No complete or partial responses were observed. In seven patients the disease remained stable for 15–105 weeks or longer, and 10 patients had progressive disease from the start. The treatment was well tolerated with only mild toxicity. Two patients had grade 2 and one patient grade 3 nausea and vomiting; one patient had grade 3 diarrhea and three patients had grade 1 hair loss. Cardiotoxicity was not observed. The major side-effect was leukopenia (4 × 10^9/l or below) in all patients. The median while cell nadir, 14 days after the first day of therapy, was 3.2 × 10^9/l. Grade 3 or 4 leukopenia occurred in six patients. Thrombocytopenia (100 × 10^9/l or below) was not observed. Dose modifications were necessary in six patients.

Our results agree with two earlier negative reports on the activity of mitoxantrone in endometrial carcinoma [4, 5]. However, contrary to these studies, our patients had not received any previous chemotherapy, which indicates even more strongly that mitoxantrone has no activity in this disease.

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