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Prevention of doxorubicin-induced alopecia by scalp hypothermia: relation to degree of cooling

Although doxorubicin is extremely effective in treating carcinoma of the breast, many clinicians are reluctant to use it because of the almost certain alopecia that ensues.¹ The hair loss, which is usually complete, is particularly disadvantageous if the drug is part of adjuvant systemic treatment after mastectomy.

Because of the rapid clearance of doxorubicin from the circulation scalp hypothermia has been used to limit the amount of drug reaching the hair follicles, preventing hair loss. This is particularly effective when total doses are below 50 mg,²⁻⁴ but with higher doses results are less certain. We investigated the relation of the scalp skin temperature obtained with hypothermia to the degree of hair loss.

Patients, methods, and results

Scalp cooling was undertaken in 24 patients with breast carcinoma. Of these, 18 were receiving chemotherapy for advanced disease and six adjuvant systemic treatment for primary tumours. Results of liver function tests were normal in all cases. The same drug regimen was used in all 24 patients. Doxorubicin 40 mg/m² (average dose 60-70 mg) and vincristine 2.0 mg were given intravenously on days 1 and 8 of a four-week cycle. Prednisolone 10 mg was given by mouth for the first 14 days of the cycle.

Scalp temperature was measured with a thermocouple constructed from a hypodermic needle, which was introduced into the scalp to a depth of 1-2 mm to be at the approximate level of the hair follicles and remained in place throughout the cooling procedure. To cool the scalp frozen cryogel packs were moulded on to the head and held in place with a plastic helmet.

Typical scalp cooling curve.

Cooling was maintained until the lowest temperature was reached and doxorubicin then injected. Cooling continued for a further 30 minutes.

Hair loss was categorised as slight, moderate, severe, or complete at the patient's third cycle of chemotherapy.

Scalp temperature in the 24 patients varied from 18.5°C to 28.5°C. In each individual patient, however, a consistent temperature was obtained on repeated measurement. Maximal cooling occurred after 20-30 minutes of hypothermia, which was maintained for 30-40 minutes (figure).

Ten of the 24 patients (42%) receiving high-dose doxorubicin showed satisfactory hair retention. All these patients suffered slight hair loss but not sufficient for them to require a wig.

The degree of alopecia was temperature dependent. In 19 patients in whom temperature was measured during two cycles of chemotherapy that reached in women who showed good hair retention was significantly lower ($p < 0.001$) than that reached in those with alopecia (20.8°C v 24.2°C). To prevent alopecia scalp temperature had to be reduced to 22°C or below.

Comment

Altogether 42% of patients showed appreciable hair preservation, compared with 5% before scalp cooling was introduced. When frequent pulses of high-dose doxorubicin are used it appears that the scalp temperature must be reduced below 22°C before injection and this temperature maintained for 20 minutes to prevent alopecia. Vincristine contributes to the alopecia, which will not, because of this drug's prolonged clearance, be prevented by hypothermia.

These results compare favourably with those reported by other groups using high-dose regimens.⁵ The improvement in this study was probably due to the delay in administering the chemotherapy until maximal cooling had been obtained—that is, 20-30 minutes after the initiation of hypothermia. In other studies injection was given after five to 10 minutes of cooling. The degree of alopecia is undoubtedly drug-dose dependent,^{2,5} with a much higher proportion of hair preservation occurring at lower dosage regimens of less than 40 mg/m².

The large variation in scalp temperature between patients could not be explained by differences in hair thickness or density of scalp tissue. The degree of cooling obtained in each woman, however, was remarkably consistent at each recording, and differences between patients were therefore not due to changes in procedure.

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Tamoxifen-induced tumour regression associated with dermatomyositis

Carcinoma of the breast is the commonest tumour associated with dermatomyositis and precedes the rash in only 20% of cases. When the tumour is controlled with surgery, radiotherapy, chemotherapy or hormone treatment there may be improvement of the dermatomyositis.¹ No cases have been described in which the tumour was regressing with treatment when dermatomyositis started. We describe three

patients whose carcinomas responded completely or partially to tamoxifen and who developed dermatomyositis or polymyositis within three months of tumour regression.

Case reports

Dermatomyositis, polymyositis, or polymyositis-systemic sclerosis overlap syndrome were diagnosed as definite by the criteria of Bohan *et al.*² Results of investigations are shown in the table. In all our cases muscle biopsies gave results compatible with inflammatory polymyositis and tumour recurrences were confirmed histologically.

Case 1—A 50-year-old woman had a left mastectomy in 1972. In September 1976 she developed a mass in the right supraclavicular fossa and enlarged mediastinal nodes. The recurrent tumour responded completely to radiotherapy and six courses of combination chemotherapy. In June 1979 tumour recurred in the left supraclavicular fossa. Tamoxifen 10 mg twice daily was started, and by August the nodes had completely regressed but she had developed muscle aches and stiffness. In September she had swelling of both arms, proximal muscle weakness, and the characteristic rash of dermatomyositis. She was treated with prednisolone 60 mg daily and tamoxifen was stopped. Dermatomyositis progressed rapidly, however, and she died. Necropsy showed bronchopneumonia and dermatomyositis but no evidence of carcinoma of the breast.

Case 2—A 46-year-old woman had a right lumpectomy and postoperative radiotherapy for breast carcinoma in 1973. In April 1977 she had a right axillary recurrence. Tamoxifen 10 mg twice daily was given and the nodes regressed completely, but over the next three months she developed general muscle weakness, dysphagia, Raynaud's phenomenon, and increased skin pigmentation and induration. Tamoxifen was stopped in January 1979. The weakness improved after three weeks but progressed again when tamoxifen was restarted. Tamoxifen was again stopped, but the weakness did not improve. In July a tumour recurrence in the right breast was excised. She developed perioral telangiectasia. In October she was treated with prednisolone 30 mg daily and methotrexate 15 mg by mouth weekly. Her strength gradually improved.

Case 3—A 60-year-old woman presented in September 1979 with a mass in the left supraclavicular fossa. Biopsy showed a poorly differentiated mucus-secreting adenocarcinoma. Chest radiography showed probable secondary deposits in the left lower lobe. Tamoxifen 10 mg twice daily was given for presumed secondary carcinoma from an undetected breast primary. By January the nodes had partially regressed (from 4 × 3 to 2 × 2 cm), with no change on the chest x-ray picture. Three months later she developed aches in her knees, elbows, and hands. In July she had a scaly pruritic rash on her fingers and aches in her thighs. In September she had dysphagia, proximal muscle weakness, cardiomegaly with left bundle-branch block, and the characteristic rash of dermatomyositis. Tamoxifen was stopped. She was given prednisolone 60 mg/day, with initial improvement in muscle weakness, but she died from progressive dermatomyositis in December. Necropsy showed a necrotic mucus-secreting adenocarcinoma in the lung, but the primary site was unknown. Dermatomyositis was confirmed.

Investigations in three patients with dermatomyositis or polymyositis associated with malignancy

Investigation	Case No		
	1	2	3
Creatinine phosphokinase (normal < 50 IU/l)	580	145	2146
Alanine transaminase (normal < 17 IU/l)	77	21	45
RA latex test	Negative	Positive	Negative
Anti-double-stranded DNA antibody (normal < 28 × 10 ³ units/l)	10	7	Not done
Erythrocyte sedimentation rate (mm in first hour)	104	63	47
Electromyography	Not done	Negative	Not done
Muscle biopsy	Negative	Negative	Negative
Cine swallow	Neuromuscular inco-ordination	Dilated, inert	Dilated, inert
Antinuclear factor	Negative	Positive	Negative
		Speckled nucleolar 1/60	
Electron microscopy	Endothelial microtubular particles	Not done	Not done
Immune complexes (normal (IgG) < 100 mg/l)	Not done	71.9	153.6
C3 (normal range 840-1652 mg/l)	Not done	1921	1559
Lymphocyte count	2.13 × 10 ⁹ /l	1.9 × 10 ⁹ /l	2.7 × 10 ⁹ /l

Comment

The cause of dermatomyositis is unknown. Possible mechanisms include autoantibodies³ and cell-mediated reactions to muscle.⁴ Viral-like endothelial microtubular particles have also been seen on electron microscopy,⁵ as in case 1.

Tamoxifen may possibly interact with cell components—for ex-

ample, oestrogen receptors—that on release from dying cells induce an immunological cross-reaction with similar components in connective tissue.

Although tamoxifen was stopped in all the patients, two died from dermatomyositis before complete clearance of tamoxifen could be expected, because of the long plasma half life. If patients develop muscle aches and pains while receiving tamoxifen consideration should be given to the possibility of myositis rather than assuming the symptoms to be non-specific or signs of bone metastases.

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Hormone replacement treatment and benign intracranial hypertension

Benign intracranial hypertension is an uncommon condition associated with many drugs, including oral contraceptives. I report the first case of benign intracranial hypertension associated with hormone replacement treatment.

Case report

A 58-year-old woman was admitted to hospital with constant headache of eight days' duration, dizziness, vomiting, deteriorating visual acuity with transient obscurations, and generalised weakness. Intermittent headaches of increasing frequency and severity over the past three years had correlated chronologically with the start of hormone replacement treatment with Menophas (mestranol and norethisterone).

Examination showed her to be distressed and obese with bilateral papilloedema, mild paresis of the lateral recti, and intact visual fields on confrontation testing. Full investigations including chest radiography, haematological and biochemical screening, and barium series of the gastrointestinal tract showed no abnormality apart from mild diverticular disease of the colon. An isotope brain scan gave normal results and a computed tomogram showed ventricles of normal size. Lumbar puncture yielded clear colourless cerebrospinal fluid under increased pressure (greater than 300 mm cerebrospinal fluid) with normal protein and cell contents.

Benign intracranial hypertension was diagnosed. Hormone replacement treatment was stopped, and she was treated with dexamethasone and later tapering doses of oral prednisolone. This resulted in prompt cessation of headaches, restoration of normal vision, and gradual clearance of papilloedema. She was maintained on decreasing doses of prednisolone over the subsequent six months; on withdrawal there was no recurrence of papilloedema.

Comment

Hormone replacement is widely used in the treatment of acute menopausal symptoms, and the duration of treatment has become increasingly prolonged in many instances for various reasons, including potential prevention of osteoporosis.¹ Conventional combined oral contraceptives have been reported in rare instances to cause benign intracranial hypertension.^{2,3} The occurrence with hormone replacement treatment is, however, surprising in view of the pseudo-physiological nature of the dosage, which in the case of Menophas would account for less than 20% of that of the oestrogen and proges-