Kinetically-based Multiple Drug Treatment for Advanced Head and Neck Cancer

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Summary

A multiple drug regimen was given to 36 patients with advanced carcinomas of the head and neck. In 19 of the 24 patients who were assessable the tumour regressed more than 50%; in one it regressed by 25%; and in four it did not respond at all. Multiple drug chemotherapy should be given much earlier in the course of these cancers, preferably as an adjuvant to surgery or radiotherapy.

Introduction

Most head and neck cancers are traditionally treated with some form of surgery preceded or followed by radiotherapy. Though most of these lesions tend to remain local and spread to a variable degree to regional nodes, cure rates for the advanced lesions, especially those with lymph node involvement, remain poor.[1] We thought that these figures might be improved by the addition of chemotherapy to a combined treatment programme. Several antitumour agents, such as methotrexate, bleomycin, adriamycin, and fluorouracil,[2] exist which individually have a partial effect in head and neck cancers. Some responses have also been observed with vinca alkaloids, hydroxyurea, and mercaptopurine.[3] In certain solid tumours—for example, breast cancers—a combination of agents will often be more effective than single drugs.[4] Accordingly, we decided to test the results of a multiple drug schedule in advanced head and neck cancer. Before adding drug therapy early in the course of the disease we had to show that multiple drug treatment was effective in these tumours. For ethical reasons we limited this trial to patients with advanced disease.

Patients and Methods

The patients were attending the head and neck unit at the Royal Marsden Hospital. All had advanced disease beyond the scope of surgery or radiotherapy. The tumour sites and histological types are shown in the table. Twenty-six patients had received radiotherapy and 19 had also received chemotherapy with various single agents. They represented, therefore, an unfavourable group in which to test a new treatment. The criteria for assessability were as follows: (*a*) all patients had to have objectively measurable disease; (*b*) at least three courses of treatment had to be given; and (*c*) no other antitumour treatment could be given concurrently. Response was defined as a 50% reduction in the tumour size compared with initial measurements.

The rationale of the multiple drug schedule was as follows: drugs were chosen which individually had some effect; the length of each course of treatment was limited to 36 hours, since combination chemotherapy is less toxic to the bone marrow when given for less than two days[5]; each drug exerted its maximum effect at a different phase of the cell cycle.[6] The drugs were also sequenced in an attempt to produce partial tumour cell synchrony.[7] The treatment cycles were repeated every three weeks and no patient was given more than six courses. The drugs were given as follows: At 0 hours, vincristine 2 mg and adriamycin 40 mg; from 6-12 hours an infusion of 60 mg bleomycin in dextrose saline; at 6, 9, and 12 hours, 100 mg of methotrexate; at 12 hours, 250-500 mg of fluorouracil; at 18 hours, hydroxyurea 2 g; and at 24 hours, mercaptopurine 200 mg. The last two drugs were given by mouth, and all the others intravenously. Starting at 30 hours, folinic acid (Calcium Leucovorin, Lederle) 21 mg was given intramuscularly six-hourly for four doses to prevent methotrexate toxicity. If the patient showed evidence of impared renal function the fluorouracil dose was reduced to 250 mg and six doses of folinic acid were given.

Sites and Histological Types of Tumours

Tumour Site	No. of Cases	Histological Differentiation
Carcinoma of larynx	9	Well differentiated (3), moderately differentiated (3), poorly differentiated (2) unknown (1)
Carcinoma of nasopharynx	5	Poorly differentiated (3), polygonal cell (2)
Carcinoma of tonsil	4	Poorly differentiated (3), unknown (1)
Carcinoma of maxilla	5	Moderately differentiated (3), poorly differentiated (1), adenoid cystic (1)
Carcinoma of tongue	5	Well differentiated (2), poorly differentiated (3)
Carcinoma of floor of mouth	4	Moderately differentiated (3), unknown (1)
Carcinoma of middle ear	1	Moderately differentiated
Carcinoma of external auditory meatus	1	Moderately differentiated
Carcinoma of pinna	1	Moderately differentiated
Secondary carcinoma (primary unknown)	1	Poorly differentiated

Results

Twelve patients could not be assessed because they were moribund when referred and died before adequate treatment could be given (five cases), were operated on before three courses had been completed (four), were lost to follow-up (one), or did not have adequately measurable lesions (two). Of the 24 assessable patients, four did not respond, one had a tumour regression of only 25%, and 19 had tumour regressions greater than 50%.

Side Effects.—Only two patients had a fall in total white count to less than 1×10^9/l. The peripheral platelet and white cell count invariably returned to pretreatment levels within 21 days. There were no drug-induced deaths. Six patients developed evidence of peripheral neuropathy, the earliest after the fourth course. The dose of vincristine was reduced to 1 mg in these patients. All patients who completed two or more courses developed alopecia. Eight patients experienced lassitude and anorexia between courses. Nausea and vomiting occurred during the treatment cycles, but were well controlled by antiemetics. No cardiac toxicity occurred.

Discussion

Our results seem superior to those achieved using other drug combinations[8-12] and indicate that multiple drug therapy can be effective in advanced head and neck cancers. This finding suggests that the role of antitumour drugs in these tumours should be reassessed. Since these agents are more effective when

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the number of tumour cells is small[13] we are conducting a trial using local treatment plus adjuvant chemotherapy versus local treatment alone in patients at high risk for relapse to see if the addition of drugs early in treatment improves the prognosis in this group. Randomized studies are also under way to see if the number of drugs in the combination can be reduced without loss of therapeutic effect, and we are investigating the use of chemotherapy instead of radiotherapy preoperatively. If effective, the normal tissue would be undamaged at operation, which would be an advantage for the surgeon. Radiotherapy could be given later.

Our results also show that it is preferable to give antitumour drugs over short periods—for example, about 36 hours. The theoretical basis for this approach has been known for some time,[14] the clinical application has been outlined,[15 16] and it has been shown to work in practice.[5 17] This approach has the advantages of a considerable reduction in bone marrow toxicity, a shorter stay in hospital for the patient, and a drastic reduction in the need for intensive supportive systems such as platelet transfusions and antisepticaemia regimens. The traditional practice of automatically administering antitumour drugs over five days or longer should be reconsidered. These initial results lead us to agree with Bertino *et al.*'s prediction that the increasing application of newer concepts of tumour cell kinetics and the addition of drug therapy to surgery and radiotherapy may lead to an improved outlook for these patients in the next few years.[18]

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Diarrhoea in Thyroid Medullary Carcinoma: Role of Prostaglandins and Therapeutic Effect of Nutmeg

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Summary

In a patient with medullary carcinoma of the thyroid with pulmonary metastases who presented with diarrhoea and steatorrhoea large amounts of prostaglandin-like material were present in peripheral blood, and some was extracted from the tumour. The diarrhoea which persisted after thyroidectomy responded to treatment with nutmeg.

Introduction

Medullary carcinoma of the thyroid is a rare member of the group of endocrine tumours which may secrete polypeptide or amine hormones. The tumour, which arises in the thyroid C cells,[1] contains and secretes large amounts of calcitonin.[2] Large quantities of material similar to prostaglandins E_2 and $F_2\alpha$ have also been found in these tumours and in the venous blood draining them.[3] 5-Hydroxytryptamine has been isolated from the C cells,[4] and increased blood and urinary levels of 5-hydroxyindole acetic acid found in patients with medullary carcinoma of the thyroid.[5]

Diarrhoea occurs in about 30% of patients with this disease and may be associated with large fluid, electrolyte, and weight loss and steatorrhoea; a combination of hormonal factors may be responsible.[4 6] Calcitonin does not seem to affect gut motility,[7] but prostaglandins can cause diarrhoea,[8] and other agents present in these medullary tumours including 5-hydroxytryptamine,[5] histaminase, and kallikrein[9] may be partly responsible for diarrhoea.

Case Report

A 41-year-old woman complained of watery diarrhoea and a weight loss of 13 kg over two years. She noticed frequent borborygmi and passed about five foul-smelling stools each day with urgency and occasionally incontinence. Her diarrhoea had been partially controlled with codeine and diphenoxylate with atropine (Lomotil). There was evidence of recent weight loss, and a hard irregular fixed mass was found in the left lobe of the thyroid. Several hard matted lymph nodes occurred in the left jugular chain and one in the left supraclavicular fossa. Frequent loud abdominal borborygmi were heard.

Investigations showed mild steatorrhoea (8 g fat daily) and a serum carotene level of 0·242 μmol/l (13 μg/100 ml). A thyroid scan showed no uptake of ^{125}I over the left lobe. The gastrointestinal tract appeared structurally normal on barium meal and follow-through examination, but the transit time was rapid: barium reached the rectum in just over one hour. Chest *x*-ray examination showed miliary mottling of both lungs, suggesting the presence of disseminated carcinoma. The total prostaglandin-

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