advances that are being made in both breast-conserving techniques and adjuvant therapy must not be emasculated by inadequacies of surgical technique.

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Papers

Desmoid Tumours Treated with Triphenylethylenes

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Desmoids are uncommon mesenchymal tumours that occur at single or multiple anatomical sites, occasionally in association with polyposis coli. This paper describes the use of the triphenylethylene tamoxifen, and a new chlorinated analogue, toremifene, in 20 patients with progressive desmoid disease. Clinical responses ranging from stabilisation of disease to complete resolution were observed in 65% of cases. The antitumour activity of this group of drugs has been attributed to their anti-oestrogenic behaviour. However, desmoids provide a clinical model of a purely mesenchymal tumour which appears to respond despite having generally low levels of hormone receptor. This emphasises the significance of the stroma within breast (and other) tumours, in particular how the stroma may regulate the response to these drugs regardless of receptor status.
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INTRODUCTION

TAMOXIFEN, A triphenylethylene traditionally described as an 'antioestrogen', is used widely in the treatment of early and advanced breast cancer. It is thought that its mode of action is via oestrogen receptors within the tumour cells [1]. This hypothesis obtained credence from trials of tamoxifen in women with advanced breast cancer, where a response was seen in approximately 60% of those women with tumours rich in oestrogen receptor (ER). In ER poor or negative tumours, responses were in the order of 10% [2]. Such a strong correlation was absent, however, from trials of adjuvant systemic tamoxifen for early breast cancer. The Nolvadex Adjuvant Trial Organisation (NATO) study demonstrated that although the presence of ER was a good prognostic indicator, the survival after 2 years on tamoxifen was identical for women with ER rich and ER poor tumours [3]. An overview of similar adjuvant tamoxifen studies confirmed a response independent of ER status [4]. A new or additional hypothesis for the mode of action of the triphenylethylenes is required to explain these findings. We propose that the tumour stromal fibroblasts themselves respond to these drugs and in turn influence the growth of adjacent

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epithelial cells, in a manner independent of ER following the induction of growth factors such as transforming growth factor beta (TGF β) [5].

Desmoid tumours, are purely mesenchymal, and therefore provide a clinical model for studying the effect of drugs on fibroblasts away from the influence of epithelial elements. Desmoid tumours or 'fibromatoses' are subdivided anatomically into extra-abdominal, abdominal and intrabdominal types [6]. Strictly they are benign tumours which do not metastasise and primary treatment is surgical excision, but recurrence is common due to incomplete excision or multicentricity. Second line treatments described include radiotherapy and a variety of chemotherapeutic agents such as vitamin C, non-steroidal anti-inflammatory drugs and tamoxifen [7–9].

The pathogenesis of desmoids is unclear. Some series have reported tumours in association with traumatic or surgical scars [10]. Abdominal wall desmoids appear to have a predilection for women during or following pregnancy, which implies either a hormonal or traumatic aetiology. However this does not account for others with the disease, in particular adult males and children of both sexes. Spontaneous regression of desmoid tumours has been reported.

Of increasing importance clinically are desmoid tumours associated with polyposis coli. Desmoid disease is now the second commonest neoplastic cause of death after periampullary carcinoma in patients with familial adenomatous polyposis.

Toremifene has similarities to the parent compound tamoxifen, but also has important differences in toxicity and antitumour activity which suggest that it may be preferential in this clinical setting. At low doses (0.3–30 mg/kg) tamoxifen and toremifene have similar statistically significant antitumour effects on chemically induced breast cancers in female rats but at doses above 45 mg/kg, tamoxifen is toxic to all rats whereas toremifene continues to produce significant antitumour activity in a dose-dependent fashion up to 200 mg/kg without ill effect. In addition, toremifene has been shown to have activity against ER-ve mouse uterine sarcomas [11].

Toxicity studies in rats have demonstrated similar uterine and ovarian atrophy with tamoxifen and toremifene, but at high doses only tamoxifen produced hyperplastic and neoplastic liver nodules and eye changes.

Toremifene is presently being studied for its use in breast cancer where it has produced clinical regression in tumours that have escaped tamoxifen control [12].

PATIENTS AND RESULTS

Patient details and results of treatment appear in Tables 1 and 2. Selected case histories of interest are given below.

Patients were referred usually after failed primary excisional surgery often followed by chemotherapy or radiotherapy. Triphenylethylene therapy was either with tamoxifen or toremifene or, in 1 case clomiphene. Initial toremifene dose was 200 mg per day and in most cases this was maintained. In some cases of tumour progression, higher doses were given (400–600 mg per day). Response rates were graded by the clinical and/or radiological findings at review. As all tumours were progressive at the time of referral, stabilisation of the disease (static disease [SD]) is considered a useful response. Increasing grades of response are partial and complete tumour necrosis [noted by clinical softening of the tumour and radiological changes on computed tomography (CT)] and decrease in tumour size [partial response (PR)], and clinical and radiological resolution [complete response (CR)]. Tumour necrosis was often accompanied by tumour pain.

When tamoxifen was used as first-line treatment (8 patients), progressive disease (PD) occurred in 62.5% (5 patients), and a

Table 1. Desmoid patients (not with Gardner's syndrome)

Patient No.	Age	Sex	Site	Previous surgery	Drug (months on drug)	Response
1	34	F	Breast, abdomen	No	Tamoxifen (19) Clomiphene (8) Toremifene × 2 courses	CR SD PR Tumour necrosis Died from sepsis
2	21	F	Pelvis	No	Toremifene (20)	CR
3	25	F	Chest	No	Toremifene (6)	SD
4	24	F	Abdomen	No	Toremifene (3)	PR Partial tumour necrosis
5	55	M	Abdomen, pelvis	No	Toremifene (2)	Partial necrosis then PD. Died
6	32	F	Leg	No	Toremifene (2)	SD
7	19	M	Abdomen	Yes	Tamoxifen (1) Toremifene (6)	PD PR Necrosis and discharge
8	28	F	Buttock	No	Toremifene (2)	SD

Clinical with or without radiological responses. PD = progressive disease, SD = static disease, PR = partial response, CR = complete response. Previous surgery = surgery previous to first appearance of desmoid.

Table 2. Desmoid patients (with Gardner's syndrome)

Patient No.	Age	Sex	Site	Previous surgery	Drug (months on drug)		Response
9	70	F	Abdomen	Yes	Toremifene	(23)	PR
10	41	M	Chest, abdomen	No	Tamoxifen	(3)	PD
					Toremifene	(15)	PR then PD (PR polyps) Died
11	30	F	Abdomen	No	Tamoxifen	(3)	PD
					Toremifene	(12)	SD abdomen PR rectus
12	30	F	Abdomen	Yes	Tamoxifen	(3)	PD
					Toremifene	(2)	PD Died
13	28	F	Abdomen	No	Toremifene	(1)	Blurred vision
					Tamoxifen	(12)	CR PD within 3/12 of stopping
14	38	F	Abdomen	No	Toremifene	(2)	PR Partial necrosis
15	51	F	Abdomen	Yes	Toremifene	(3)	PR
16	24	M	Abdomen	Yes	Toremifene	(3)	SD
17	39	F	Abdomen	Yes	Toremifene	(1)	PR Symptom relief
18	42	F	Pelvis	Yes	Toremifene	(6)	SD
19	26	M	Abdomen	Yes	Toremifene	(6)	PR Partial necrosis
20	18	F	Abdomen, pelvis	Yes	Tamoxifen	(2)	PD
					Toremifene	(2)	PD

Abbreviations as for Table 1.

response in 37.5% (2 CR, 1 PR). With toremifene as first line (12 patients), PD was seen in 8.3% (1 patient), and a response in 91% (1 CR, 5 PR, 5 SD). Toremifene as second-line or third-line triphenylethylene therapy (6 patients) gave a response rate of 50% (2 PR, 1 SD). The overall response rate (CR, PR, and SD) was 65%.

Side effects

Side effects were infrequent and generally mild. 1 patient (patient 13) had blurred vision that settled after stopping toremifene (200 mg per day) and changing to tamoxifen (40 mg per day).

Patient 12 experienced severe premenstrual symptoms on tamoxifen. Her periods were unaffected. 2 years later on toremifene she experienced similar symptoms although onset did not coincide with the start of the treatment nor subside at the end.

Case histories

Patient 1. The first patient in the study was a white woman who between the ages of 26 and 31 had recurrent abdominal and chest wall desmoid tumours excised. A further abdominal wall mass was treated with 40 mg tamoxifen with complete resolution in 2 months. 17 months later she developed obstruction due to a large tumour involving the pancreas, stomach and duodeno-jejunal flexure. She was treated by gastro-jejunostomy and 9 days later commenced on toremifene 200 mg/day. 3 weeks later she was admitted with peritonitis and at laparotomy large amounts of necrotic retroperitoneal and abdominal wall tumour material were evacuated. Over the subsequent 2 years she received intermittent courses of tamoxifen then toremifene, but soon after developed recurrent obstruction. Laparotomy revealed a huge abdominal wall tumour involving the small bowel. After a further bypass procedure she was started on clomiphene. At 3 months there was CT evidence of a decrease in tumour size but growth of pelvic masses. Indomethacin was added, and follow up CT 6 weeks later suggested slight reduction in tumour bulk. Ater an episode of PV bleeding treatment was halted pending further investigation. 2 months later, there was a visible increase in abdominal distension and toremifene was restarted at 200 mg/day, increasing to 400 mg after 1 month. Subsequent CT revealed almost complete resolution of the pelvic tumour but an increase in abdominal tumour bulk. 1 month after a further increase of toremifene to 600 mg/day she was readmitted with abdominal pain and sepsis. Barium studies demonstrated fistulae between small and large bowel and the large tumour mass, which had necrosed and cavitated. She died of sepsis 2 months later.

Patient 9. The second case was the mother of the first patient. At the age of 59 she had a total colectomy and ileorectal anastomosis after a 4 year history of recurrent colonic polyps. 9 years later she developed subacute small bowel obstruction

due to a desmoid in the small bowel mesentery. An entero-enterostomy was performed and the mass increased in size over the next 12 months, until she was administered toremifene 200-mg per day. One week later she experienced acute abdominal pain and the passage of altered blood per rectum. She was treated conservatively and over the following 2 months there was a gradual softening and shrinkage of tumour size to an ill defined area of induration in the left iliac fossa which has since remained static (18 months).

Patient 2. A young white woman of 19 presented with a swollen left leg and a left sided pelvic mass. Biopsy revealed fibromatosis and she was anticoagulated. 5 months later she underwent tumour debulking and a left oophrectomy. One year later she required a further debulking procedure together with arterial reconstruction for recurrent pelvic tumour, followed by radiotherapy. 7 months later she developed left ureteric obstruction. Chemotherapy was commenced (etoposide, bleomycin, cisplatin) after which there was some resolution of the hydronephrosis, but no change in tumour size. Her main symptoms at the time were intermittent claudication and moderately severe abdominal discomfort and hind-quarter amputation was considered. She was started on toremifene 200 mg per day. Within 1 month her claudication distance was improving but she still had considerable tumour pain. After 2 months there was further symptomatic improvement and CT evidence of necrosis within the tumour bulk. 6 months after the start of treatment the symptoms had resolved. At 20 months she remains free of symptoms and of clinical signs of recurrent disease.

Patient 10. A white man of 41 with a strong family history of Gardner's syndrome presented with large rapidly progressing chest and abdominal wall desmoid tumours. He had a past history of osteomas, skin cysts, supernumary teeth and was known to have multiple polyps throughout the colon and duodenum. His desmoid disease had previously been treated by thoracotomy, radiotherapy, interferon, cytotoxics, ibuprofen and a short course of tamoxifen. In addition, the fungating chest wall tumours required repeated surgical debulking, and he had received a short course of radiotherapy to the abdominal wall. He started on 200 mg per day of toremifene and over the next 5 months the abdominal wall tumours liquified, facilitating repeat aspirations of these masses. The chest wall lesions continued to grow unabated and he later died. Whilst on toremifene it was noticed at colonoscopy that there was a marked reduction in the number and size of his colonic polyps compared with appearances prior to treatment with toremifene.

DISCUSSION

It appears that the triphenylethylenes, particularly toremifene, do have a clinically useful effect on desmoid tumours and toremifene is now given in preference to tamoxifen to new patients entering the study. As all patients here had progressive disease refractory to other treatment regimens, a 'worthwhile' response includes stabilisation of disease and relief of symptoms regardless of tumour size. The treatment is relatively non-toxic even at higher doses. An interesting finding which may be of significance is the reduction in size and number of colonic polyps in familial adenomatous polyposis and further study of this phenomenom is suggested. A number of other questions become apparent: Firstly, how long should treatment continue?

The initial response is seen at any time from 1 week to 6 months after the commencement of treatment, and some patients are being maintained with quiescent disease at nearly 2 years. The long-term complications of tamoxifen are presently the subject of clinical trials. Weighed against the possibility of debility from chronic use of these drugs is the likelihood of accelerated tumour growth on cessation of treatment. Indeed this seems to have happened in patients 1 and 13. The choice may be made by the patient themselves as with patient 2 who wishes to continue indefinitely. She will be monitored by bone densitometry and serum biochemistry in the meantime.

The second question refers to the most appropriate clinical setting for the use of these drugs. Tamoxifen was found to be of benefit first in advanced breast cancer and thereafter as an adjuvant in early disease. This may also be true for desmoid tumours where recurrence rates for 'resectable' disease are up to 68% [9].

There are also questions about our alternative hypothesis of a fibroblast mediated mechanism for triphenylethylene mode of action. There is no doubt that toremifene and its parent compound do modify the natural history of these tumours, sometimes in a spectacular fashion producing tumour lysis and that desmoid tumours are in general ER poor [13, 14]. Tumour response however is not uniform and tumour heterogeneity exists between patients and within the same patient. There are several examples in this series of widely varying responses in multicentric tumours. Tamoxifen and toremifene are both known to stimulate the production of TGFβ from breast epithelial cells and fibroblasts [8, 15]. This polypeptide factor is a potent growth inhibitor of both immature fibroblasts and epithelial cells. It does not cause cell death as we seem to be observing here which suggests other growth factors are involved, perhaps akin to tumour necrosis factor.

The inference that these drugs influence fundamental mechanisms of cell growth suggest a role in the treatment of other neoplasms, particularly soft tissue malignancy. Perhaps the inappropriate emphasis on hormone receptor status in selecting patients for 'antioestrogen' therapy, has in the past, delayed or inhibited other promising areas of clinical investigation.

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A Single-Blind Study of the Efficacy and Safety of Intravenous Granisetron Compared with Alizapride Plus Dexamethasone in the Prophylaxis and Control of Emesis in Patients Receiving 5-day Cytostatic Therapy

Karl Bremer on behalf of the Granisetron Study Group*

200 cancer patients who were due to receive fractionated chemotherapy (cisplatin ≥ 15, ifosfamide ≥ 1.2 or etoposide ≥ 120, all mg/m² per day) for 5 days, entered a multicentre study. Patients were randomised single-blind to receive either prophylactic intravenous granisetron (40 μg/kg) or alizapride (4 mg/kg followed by 4 mg/kg at 4 and 8 h post-treatment) plus dexamethasone 8 mg. Granistron was superior to the combination in preventing nausea and vomiting (54% vs. 43% complete responders). The differences were in the cisplatin-treated group. The time to first episode of moderate to severe nausea was significantly longer in the granisetron group ($P = 0.03$). Dosing with granisetron was more simple, with over 85% of patients requiring only a single prophylactic dose. Fewer patients receiving granisetron experienced adverse events (48% vs. 62%, $P = 0.047$). The frequency of constipation was, as expected, significantly higher in the granisetron group. Extrapyramidal effects, which were not noted by any granisetron patient, occurred in 5.3% of comparator patients.
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INTRODUCTION

TREATMENT OF malignant diseases with cytostatic agents leads to a number of unwanted side-effects. Cytostatic drug-induced nausea and vomiting occur in the majority of patients. This presents an important clinical problem as not only does it reduce the patient's quality of life but it may cause the patient to refuse further cycles of chemotherapy [1]. There is thus a considerable need for effective antiemetic treatment for this group of patients.

Fractionated chemotherapy regimens have been developed for a variety of tumour types. The rationale behind these regimens is primarily focused on the reduction of toxic effects such as bone-marrow depression, neuropathy, nephropathy and emesis.

Combination treatments such as alizapride/dexamethasone are commonly used to prevent emesis [2]. Alizapride is a substituted benzamide, which in low doses blocks central dopamine D_2 receptors, but in high doses may be a 5-HT_3 antagonist [1]. Unfortunately, high dosage is also associated with extrapyramidal side-effects such as restlessness (frequently severe) [3]. Thus it is often used in conjunction with dexamethasone and benzodiazepines leading to enhanced anti-emetic efficacy and sedation [2].

Granisetron is a new antiemetic which is a potent and highly selective 5-HT_3 receptor antagonist free from dopamine D_2 receptor antagonist properties [4]. In the majority of patients receiving highly emetogenic cytostatic regimens, a single dose of granistron (40 μg/kg) has been shown to be effective in preventing or controlling nausea and vomiting during the subsequent 24 h [5]. The aim of this study was to compare the efficacy and safety of granisetron with the combination alizapride/dexamethasone in patients receiving cytostatic therapy for malignant disease on each day of a 5-day treatment period.

PATIENTS AND METHODS

Patients

This study was carried out at 25 centres in Belgium, France and Germany. Each patient was over the legal age of consent, had a Karnofsky index score of 60% or more [6], was naïve to chemotherapy and was due to receive moderately emetogenic cytostatic therapy for malignant disease (cisplatin ≥15 mg/m² or ifosfamide ≥1.2 g/m² or etoposide ≥120 mg/m²) on each day for 5 days. The patient had to receive the same main cytostatic agent on each day of treatment. Patients were excluded from the study if they had marked hepatic dysfunction, renal dysfunction,