These results indicate that the differential in acquisition price between ondansetron and metoclopramide was compensated for by the superior efficacy, lower incidence of adverse events, lower antiemetic administration costs and lower nursing staff and material costs associated with treatment with ondansetron. Moreover, the acquisition price of ondansetron, in this study, was based on three 8 mg intravenous doses. In patients receiving cisplatin (50–120 mg/m^2) containing chemotherapy, two recent studies have demonstrated that a single 8 mg intravenous dose is effective in controlling acute emesis [3, 4], thereby shifting the cost-effectiveness calculations positively in favour of ondansetron.

From a strictly economic viewpoint embracing all potential resource costs and therapeutic outcomes associated with the use of ondansetron and metoclopramide, the present study shows that the NHS would neither lose nor gain by selecting one of the antiemetic agents in preference to the other. However, the analysis does not take into account the very real benefits to patients of avoiding emesis, the side-effect identified by many individuals as the most distressing of those caused by cytotoxic chemotherapy. In this respect the findings of the present study indicate that ondansetron offers significant advantages over metoclopramide: patients receiving the former agent have a probability of successfully avoiding significant emesis that is more than twice that for individuals given metoclopramide.

Furthermore, analysis of the group of patients who experienced significant emesis with or without adverse events indicates that the ondansetron-treated patients experienced emesis to a lesser extent than the metoclopramide group: the median number of emetic episodes suffered by the ondansetron "failures" was only three compared with five for the "failed" metoclopramide cases.

Although conducted in a relatively small sample of patients, the present study has reiterated the need to assess the costs of different treatment options in the light of the outcomes they achieve if NHS resources are to be used efficiently.

Specifically, the study has shown that ondansetron and metoclopramide emerge as equally cost-effective antiemetic options when all utilisation costs and outcomes are taken into account, even though ondansetron carries a higher basic NHS price.

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Marginal Surgery and Postoperative Radiotherapy in Soft Tissue Sarcomas

The Scandinavian Sarcoma Group Experience

Tom A. Wiklund, Thor A. Alvegård, Henning T. Mouridsen, Anders Rydholm and Carl P. Blomqvist

In a randomised Scandinavian Sarcoma Group study (n=240) on the effect of postoperative adjuvant doxorubicin in high grade adult soft tissue sarcoma, 26 patients were treated with marginal surgery and postoperative radiotherapy. The protocol dose was 51 Gy in 17 fractions, or equivalent. Local recurrence occurred in 6 patients. Two local failures were geographical misses. Salvage treatment was ultimately successful in 3 of 4 attempted cases. 15 patients had complications, which in 3 cases necessitated amputation. These 3 patients had received the protocol fractionation and doxorubicin. However, other factors possibly responsible for the complication were also present.
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INTRODUCTION

CONSERVATIVE SURGERY combined with radiotherapy has been increasingly used in the management of soft tissue sarcomas (STS). Local control is achieved in 80–95% [1–3].

We report on a well-defined group of patients, included in a trial on adjuvant chemotherapy in high grade STS conducted by the Scandinavian Sarcoma Group (SSG) [4]. Patients with marginal surgical margins received postoperative radiotherapy. The recommended target dose was 51 Gy in 17 fractions over 24 days, or an equivalent dose based on CRE (cumulative radiation effect) formalism. This formula takes into account the total dose, the number of fractions and the total time of the radiotherapy.

The higher than conventional radiation dose per fraction was

based on the radiobiological knowledge at the time this trial was initiated [5, 6], and a need for an early start of the chemotherapy.

MATERIALS AND METHODS

From 1981 to 1986, 240 patients were entered into a randomised, multicentre trial of adjuvant, postoperative chemotherapy. Eligibility was restricted to adult patients with a previously untreated, localised, resectable, and histologically confirmed STS of grade III or IV [7].

The surgical margins, and the histopathological type and grade have been reviewed, without knowledge of the clinical course [8, 9].

Postoperative radiotherapy was recommended in case of marginal surgery. Surgery was marginal if the knife cut close to the tumour, through the pseudocapsule or reactive zone, or if during an operation the tumour was exposed, or if histological examination revealed that the margin was inadequate. No macroscopic residual tumour was left, however, histological evidence of tumour cells at the resection margin was accepted.

Radiotherapy was to start as soon as the wound had healed. The target volume should include the entire tumour-involved anatomical structure, surgical scars, and drainage canals with appropriate margins. Irradiation of the entire circumference of an extremity was to be avoided. The recommended protocol target dose was 51 Gy/17 fractions/24 days or CRE equivalent. For retroperitoneal sites it was 42 Gy/17 fractions/24 days.

The patients were randomised to doxorubicin or control after the radiotherapy. The dose was 60 mg/m^2 intravenously (i.v.) at 3 week intervals (total cumulative dose 540 mg/m^2), starting 1 week after the conclusion of the radiotherapy.

Out of 34 randomised patients given radiotherapy, 6 patients with either non-sarcoma histology, visceral sarcomas, or gross tumour at start of radiotherapy were excluded. 3 patients ineligible for the randomised study, but included in this analysis presented with resectable solitary metastases (2 patients), or the tumour was regraded to grade 2 (1 patient). Moreover, in 2 patients the surgical margins were reclassified to wide and radical, respectively. These 2 patients were included only in the toxicity analysis. 15 patients were randomised in the doxorubicin arm, 14 received the drug.

The number of surgical procedures (excluding incisional biopsy) were one in 20 patients and two in 8 patients. The surgical procedure was aimed at compartmental excisions in 6 patients. Delayed wound healing, postoperative wound infection or seroma was detected in 4 patients. In 1 of these patients the wound had not healed completely when the radiotherapy was initiated.

Median time to start of radiotherapy was 29 days (range 15–84). The longest delay was recorded in a patient who had a wound infection postoperatively. The radiotherapy schedule followed the protocol recommendations in 14 patients, and 5 additional patients had accepted adjustments. 8 of the 9 patients who had non-protocol adjustments were extremity tumours. All but one of these 8 patients received a total dose above 48 Gy (range 48–54 Gy), with daily fractions of 1.8–2.6 Gy. The last patient received 42 Gy in 2.5 Gy daily fractions. Both patients with retroperitoneal tumours received radiotherapy in 2 Gy fractions. The treatment of extremity tumours was delivered through opposed anteroposterior fields (15 of 22 tumours), opposed oblique fields (one of 22 tumours), or one anterior field (6 of 22 tumours). Individual isodose planning was utilised in 2 patients with extremity tumours. Opposed fields were treated at the same fraction, except for 2 patients in whom the fields were treated on alternate days. The treatment volume encompassed the whole surgical area with wide margins, and was decreased in 2 patients at the end of the treatment. The whole circumference of an extremity was irradiated in 4 patients. The treatment was delivered with cobalt (8 patients), or high energy photons (20 patients).

In patients randomised to the doxorubicin arm chemotherapy was started between 1 and 3 weeks after the radiotherapy was finished in all but 2 patients.

Minimum follow-up for surviving patients was 62 months. Complications to radiotherapy were graded; major (amputation, persisting wound, ankylotic joint), moderate (persistent oedema, moderately decreased strength or joint mobility), minor (transient oedema, induration) and none.

RESULTS

14 males and 14 females were included, the mean age was 52 years (range 18–78). The most common histological subtypes were malignant fibrous histiocytoma ($n=10$), and synovial sarcoma ($n=6$). Twenty-two lesions were in the extremities (10 in the thigh), one in the chest wall, three were head and neck tumours, and two were retroperitoneal. There were 18 tumours larger than 5 cm.

Local control

6 patients experienced local failures. Three- and 5 years local control rates for patients with a marginal margin on review were 79% and 73%, respectively (life-table analysis) (Table 1). Salvage therapy was attempted in all of the patients with local failure only ($n=4$). No salvage amputations were performed.

Toxicity

15 patients had some complication. 9 were moderate or worse (30% at 1 year, and 35% at 3 years; life-table analysis) (Table 2). Two amputations were performed within 1 year, and a third after 3 years. 20 patients with extremity tumours survived for

Table 1. *Characteristics of patients with local failure*

Location	Dose	Infield	Time to local recurrence/ metastasis (months)	Current status (survival, months)
Knee	3 Gy × 16	No	11/11	DOD, Local failure (19)
Pharynx	3.1 Gy × 17	Yes	19	DOD, Local failure (74)
Lower leg	1.8 Gy × 27	Yes	7/6	DOD, Local failure (11)
Lower leg	3 Gy × 17	Yes	36	Alive, Local control (77)
Thigh	1.85 Gy × 30	Yes	42	Alive, Local control (94)
Chest wall	3 Gy × 17	No	12	Alive, Local control (55)

DOD: dead of disease.

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Table 2. Characteristics of the moderate, and major complications

Location of primary	Complication	Dose	DOX†	Size of treatment field (cm)	Comments‡
Thigh	Ankylosis, seroma, infection, amputation	3 Gy × 17	+	8–11 × 45	Comp
Thigh	Surgery for chronic infection, profuse bleeding, amputation	3 Gy × 10 + 3.5 Gy × 6	+	14.5 × 34	Comp
Lower leg	Surgically treated traumatic wound (including bone resection), fracture, amputation*	3 Gy × 17	+	14 × 44	Comp circum
Lower leg	Erysipelas, surgically treated traumatic wound	3 Gy × 17	−	5 × 32	
Inguinal	Oedema, fibrosis, decreased motion	2.75 Gy × 19 (given dose 3 Gy × 19)	+	13 × 25	
Elbow	Oeema, fibrosis, complete loss of motion	3 Gy × 17	−	19 × 26	Circum
Chest wall	Oedema, induration*	3 Gy × 17 (given dose)	−	11 × 16	
Lower leg	Oedema	2.25 Gy × 26 (one field/day)	−	9 × 36	
Lower leg	Oedema, decreased sensibility, strength, and function	2.5 Gy × 6 + 3 Gy × 12 (one field/day)	+	9–10.5 × 40.5	Comp, circum

*These patients also experienced local recurrence, both were salvaged.
†Adjuvant doxorubicin.
‡Comp; compartmentectomy, Circum; the whole circumference of the extremity was irradiated.

more than 1 year. All but 3 received a dose per fraction larger than 2 Gy, and 11 had 3 Gy or more, and all received total doses above 42 Gy. 8 experienced moderate to major late complications. Of these complicated cases, 7 had received a dose per fraction $\geq$ 2.7 Gy, in three the whole circumference of the extremity was irradiated, 5 received doxorubicin, and in 7 the treatment field was larger than 300 cm^2.

DISCUSSION

Our results in terms of local control are within the limits of previously reported large single institution series [1–3].

The rate of complications was, however, much higher than usually reported [1–3]. This may be due to the higher than conventional dose per fraction. According to the linear quadratic model our schedule equals 60–62 Gy in 2 Gy fractions as for long term damage [10]. This dose was delivered without field reductions, now commonly employed [11]. In a previous study on hypofractionated radiotherapy (6.6 Gy once weekly for 2–7 weeks), the rate of complications was also high [12]. In that study, field sizes were reduced after four fractions. In addition, the radiation technique was not optimised in all our patients. The whole circumference was irradiated in 4 patients, and computerised treatment planning was not standard at the time of the study, as was not immobilisation. Moreover, the 28 patients studied were treated at 12 different institutions. Thus experience accumulated slowly in the treatment of these uncommon tumours. The treatment policy varied between the participating institutions, some consequently followed the protocol, whereas other consequently followed the practice of the individual institution.

The role of adjuvant doxorubicin is unclear. The rate of wound breakdowns after postoperative radiotherapy has in some studies been increased with adjuvant chemotherapy whereas it has not been in others [13, 14]. No increase has been demonstrated for long term local complications [14].

We conclude that our treatment schedule produced an acceptable local control, but was accompanied with a high rate of late complications. These were probably in part due to the high dose per fraction, however, with good technique and small treatment volumes some patients with extremity STS retained excellent function. The need for centralisation of these patients is thus emphasised.

Currently our treatment policy includes multidisciplinary preoperative evaluation of the patients, and frequent use of reconstructive surgery. Radiotherapy is recommended after marginal surgery. The radiotherapy treatment volume encompasses the whole surgical area with wide margins, and in case of extremity tumours the whole muscle compartment. The total dose to this volume is 50 Gy in 25 fractions over 5 weeks, whereafter a boost dose is given to areas at high risk, when pertinent (10–20 Gy in 5–10 fractions over 1 to 2 weeks). Individualised treatment planning is the routine, and immobilisation essential.

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A Randomised Cross-over Trial of Antiemetic Therapy for Platinum-based Chemotherapy. Improved Control With an Intensive Multiagent Regimen

Michael Findlay, R. John Simes, Keith Cox, Kim Carmichael, Tien Chey, Ed McNeil and Derek Raghavan

In a partially blinded randomised cross-over trial, 78 patients receiving cisplatinum based chemotherapy were assigned to receive two forms of antiemetic therapy: SAD, a regimen composed of serenace (haloperidol), ativan (lorazepam), and dexamethasone followed by low dose maxolon (metoclopramide) and STADMAX, a regimen composed of scopolamine (hyoscine), tavegyl (clemastine), ativan, dexamethasone and high dose maxolon. Each antiemetic regimen was given in random order, with the first and second cycles of cytotoxic chemotherapy. 66 (85%) patients completed both cycles of antiemetic therapy and were available for the cross-over comparison. Significantly less acute vomiting, as assessed by nurse observer ($P < 0.0001$), and less delayed vomiting, as assessed by patient diary ($P = 0.03$), were seen with STADMAX. In the first 18 h, complete control of vomiting (no episodes) was achieved in 30 (45%) patients with STADMAX compared with 10 (15%) receiving SAD. Overall, major control of emesis (≤ 2 episodes) was achieved in 56 (85%) patients with STADMAX compared with 35 (53%) receiving SAD. Vomiting was also better controlled on STADMAX in the week after this initial 18 hour period based on the 7 day patient diary with no vomiting episodes in 18/65 (28%) on STADMAX vs. 13/65 (20%) on SAD. However, no significant differences in appetite, nausea or vomiting were found when based on linear analogue self assessment (LASA) scales recorded by patients. Significant differences in side effects of the two antiemetic regimens were noted on LASA scales with more dry mouth ($P = 0.01$), blurred vision ($P = 0.03$) and diarrhoea ($P = 0.04$) associated with STADMAX and more restlessness ($P = 0.002$) associated with SAD. Significantly, no episodes of dystonic reactions were seen among patients on either regimen. In the 68 patients who completed both cycles and were in a position to express a preference, 46 (68%) preferred STADMAX compared with only 20 (29%) who preferred SAD ($P = 0.001$), while 2 patients expressed no preference. It is concluded that STADMAX is the preferred regimen to SAD for the control of cisplatinum-related emesis. It has a role, both where specific serotonin 3 antagonists are not available and as a model for building more effective combinations where these agents are available.
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INTRODUCTION

CURRENTLY, NO antiemetic therapy offers patients receiving cytotoxic drug treatment, total freedom from nausea and vomiting [1, 2]. Subjectively, these side effects are amongst the worst experienced by patients having chemotherapy [3]. The use of metoclopramide in high doses [4] has made a significant impact on cytotoxic drug-induced emesis, especially when due to *cis*-dichlorodiammine platinum (cis-DDP). Studies using serotonin 3 receptor antagonists as a single agent have also provided encouraging results [5, 6], however, they have also not achieved total antiemetic control with platinum based chemotherapy. While no single agent antiemetic offers ideal control, various combinations have given better prevention of emesis [2, 7]. Work by Borison and colleagues has lead to a better understanding of the anatomy and physiology of the vomiting reflex [8, 9] although the exact location of the vomiting centre is still not certain. It has been postulated that simultaneous blockage of histamine, muscarinic cholinergic and dopamine receptors, found in high density in the emetic pathway, would lead to increased control of vomiting [10]. Multiple blockade regimens