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European Journal of Cancer 37 (2001) 1096–1103

European Journal of Cancer

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A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma

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Received 8 December 2000; accepted 14 December 2000

Abstract

The aim of this study was to examine the strategy, feasibility and outcome of neo-adjuvant chemotherapy, with doxorubicin and ifosfamide, in adult patients with 'high-risk' soft-tissue sarcomas. Patients with 'high-risk' soft-tissue sarcomas, defined as tumours $\geqslant 8$ cm of any grade, or grade II/III tumours <8 cm, or grade II/III locally recurrent tumours, or grade II/III tumours with inadequate surgery performed in the previous 6 weeks and therefore requiring further surgery, were randomised between either surgery alone or three cycles of 3-weekly doxorubicin 50 mg/m^2 intravenous (i.v.) bolus and ifosfamide 5 g/m^2 (24 h infusion) before surgery. The type of surgery had to be planned at randomisation. Tumours were to be amenable to surgery by amputation, compartmental resection, wide or marginal excision. If chemotherapy was given, surgery had to be performed within 21 days after the last chemotherapy. Patients received postoperative radiotherapy in cases of marginal surgery, microscopically incomplete resection and no further possibility for surgery, and in cases of surgery because of local recurrence. 150 patients were entered into the study and 134 were eligible, 67 in each arm. The most frequent side-effects of chemotherapy were alopecia, nausea and vomiting (95%), and leucocytopenia (32%). One patient died of neutropenic fever after the first cycle of chemotherapy. Chemotherapy did not interfere with planned surgery and did not affect postoperative wound healing. Limb-salvage was achieved in 88%, amputation was necessary in 12% (all according to the plan at randomisation). The trial was closed after completion of phase II, since accrual was too slow to justify expanding the study into the scheduled phase III study. At a median follow-up of 7.3 years, the 5 year disease-free survival is estimated at 52% for the no chemotherapy and 56% for the chemotherapy arm (standard error: 7%) ($P=0.3548$). The 5 year overall survival for both arms is 64 and 65%, respectively (standard error 7%) ($P=0.2204$). Neo-adjuvant-chemotherapy with doxorubicin and ifosfamide at these doses and with this schedule was feasible and did not compromise subsequent treatment, surgery with or without radiotherapy. Although not powered to draw definitive conclusions on benefit, but with an at least 7 year median follow-up, the results render it less likely that major survival benefits will be achieved with this type of chemotherapy.

Keywords: Soft-tissue sarcoma; Neoadjuvant chemotherapy; Randomised study

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0959-8049/01/$ - see front matter
PII: S0959-8049(01)00083-1

1. Introduction

Patients with a 'high-risk' soft-tissue sarcoma [1] have a 50% risk of developing distant metastases with subsequent poor survival.

Several prospective randomised trials, comparing adjuvant chemotherapy after surgery to surgery alone, have produced controversial results [2]. Zalupski and colleagues [3] concluded from a meta-analysis that was performed on data from publications, that there was a statistically significant improvement in disease-free and overall survival in favour of chemotherapy. An international collaborative group [4] concluded from their meta-analysis performed on the actual study data (a more valid way of performing meta-analysis) comprising 1568 patients from 14 trials that adjuvant doxorubicin-based chemotherapy significantly increased the time to local and distant recurrence and recurrence-free survival. However, there was only a trend towards improved overall survival with the result that adjuvant chemotherapy is still not regarded by many as standard treatment.

The timing of chemotherapy as an adjuvant to surgery is a topic for ongoing debate. In several other malignancies, e.g. head and neck cancers, bladder cancer, osteosarcomas and inflammatory breast cancer, neo-adjuvant-chemotherapy preceding surgery is now preferred. Such chemotherapy is associated with better patient compliance and has no negative impact on the potential of local treatment.

In view of this the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) designed a study to investigate the feasibility and outcome of neo-adjuvant-chemotherapy in adult soft-tissue sarcomas.

As the possibility that disease progression during chemotherapy might render patients inoperable was a major concern, the study was designed as a phase II/III trial. Only if progression during chemotherapy was infrequent and accrual appeared to be appropriate would the study proceed to phase III. Due to limited accrual, however, the study was terminated at the end of phase II. Preliminary results have been presented in abstract previously [5]. This is presently still the only randomised trial of neo-adjuvant-chemotherapy in soft-tissue sarcoma and here we report the results after a median follow-up of 7.3 years.

2. Patients and methods

The design of the trial is shown in Fig. 1.

2.1. Criteria for eligibility

Patients aged 15–75 years, with a potentially radically resectable histologically proven soft-tissue sarcoma located in the limbs, head and neck, trunk or pelvis, were eligible for study. The following histological types were excluded: (extra-osseous) Ewing's sarcoma, osteo- and chondrosarcomas, Kaposi's sarcoma, embryonal rhabdomyosarcoma, malignant mesothelioma and radiation-associated sarcomas. Pathology was subject to review by a panel of expert pathologists.

Patients had to have a good World Health Organization (WHO) performance score (0–2) and appropriate bone marrow White Blood Cell (WBC) $>4.0\times10^9$/l, and platelet count $>120\times10^9$/l), cardiac, renal and hepatic function. There had to be no evidence of regional or distant metastases as shown by computed tomography (CT) scans. Patients had to meet the criteria for a 'high-risk' tumour; defined as tumours $\geqslant 8$ cm of any grade (independent of mitotic count), or grade II/III (three or more mitoses per 10 high power field; HPF), tumours <8 cm, or grade II/III locally recurrent tumours or grade II/III tumours with inadequate surgery performed in the previous 6 weeks and therefore requiring further surgery. These criteria were selected based on the results of a preceding EORTC study on adjuvant chemotherapy [1]. Patients consented to randomisation according to national or institutional regulations.

2.2. Pretreatment and follow-up investigations

At entry, the surgical oncologist and radiotherapist examined each patient. The following features were

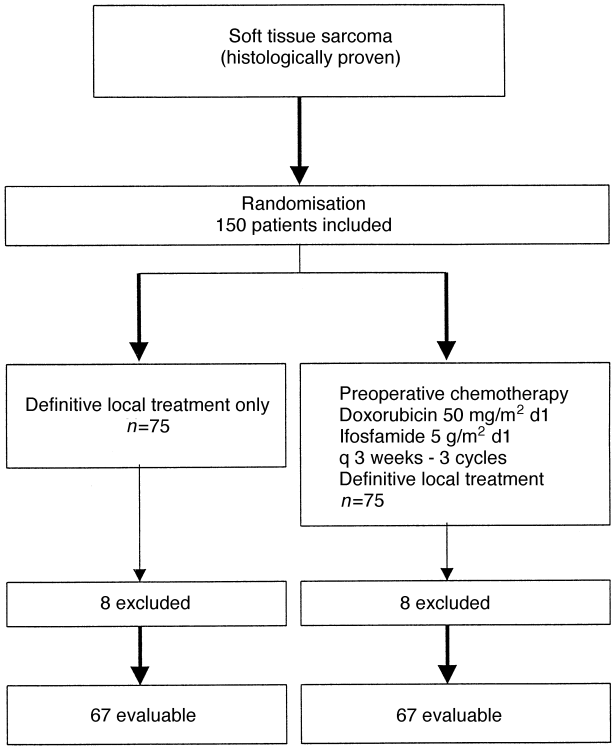

Fig. 1. The design of the trial.

assessed: history, physical examination, performance status, clinical measurement of the tumour, preferably with a photograph of the tumour, with a ruler and date, full blood count, serum-creatinine, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (gamma-GT), and lactate dehydrogenase (LDH), electrocardiogram, chest X-ray, CT scan of lungs, CT or magnetic resonance imaging (MRI) of the primary tumour and surroundings.

Before each chemotherapy cycle, physical examination with clinical tumour measurements, liver function tests and serum creatinine were repeated. Haematology was performed weekly.

For patients receiving chemotherapy the response to treatment was measured preoperatively by physical examination (with photographs) and by CT scan or MRI. During radiotherapy, blood counts were repeated weekly.

During follow-up, physical examination, blood count, liver function tests and chest X-ray were performed every 3 months during the first year, every four months in the second and third year, every 6 months in the fourth and fifth year, and yearly thereafter.

2.3. Chemotherapy

The neo-adjuvant regimen consisted of three cycles of doxorubicin at a dose of 50 mg/m^2 by intravenous (i.v.) bolus on day 1, immediately followed by ifosfamide given as a 24 h infusion at a dose of 5 g/m^2 /24 h. Ifosfamide was combined with mesna 600 mg/m^2 i.v. bolus, given at the start of the infusion, followed by 5 g/m^2/24 h infusion for a total of 36 h. Chemotherapy cycles were to be repeated every 21 days.

In cases of progression during the neo-adjuvant chemotherapy, before the completion of three cycles, chemotherapy was terminated and surgery was performed.

2.4. Dose modification

If, at the time of scheduled retreatment, the granulocyte count was $<1.5\times10^9$/l or the platelet count was $<100\times10^9$/l, chemotherapy was delayed for 1 week. If after 2 weeks (i.e. 5 weeks since last therapy), these values were not reached, the subsequent drug doses were to be reduced by 50% for residual WHO grade I toxicity, or further postponed for persisting WHO grade II toxicity. If dosages were reduced, the full dose had to be resumed at the subsequent cycle if possible. If treatment had to be postponed for more than 3 weeks, the patient had to proceed to surgery. Dose reduction for nadir counts was not applied unless neutropenic fever developed, in which case the subsequent doses of both drugs had to be reduced by 20%.

Chemotherapy was not given if serum creatinine was above 150 μmol/l or creatinine clearance was below 0.83 ml/s.

2.5. Evaluation of toxicity and response

Evaluation was performed according to the WHO recommendations for grading of acute and subacute toxic effects and response [6]. Other end-points were defined as follows:

- Early death: death due to causes other than malignant disease or toxicity.
- Early death due to malignant disease: death due to malignant disease.
- Toxic death: death occurring at any time during the study and due to drug toxicity.

The disease-free interval was calculated as the time from the date of adequate surgery to the date of first recurrence. The duration of survival was measured from the date of randomisation. All randomised patients were followed for survival.

2.6. Surgical requirements

All tumours had to be considered resectable before randomisation and the surgical procedure was planned and defined before randomisation. It consisted of marginal excision, wide excision, compartmental resection or amputation. If chemotherapy was given, surgery had to be performed within 21 days after the last cycle. The surgical procedure planned before randomisation was to be performed, unless a more radical procedure was feasible. The procedure was considered radical if a margin of $\geqslant2$ cm healthy tissue *in vivo* or $\geqslant1$ cm after fixation was obtained.

2.7. Radiotherapy

If microscopic residual disease was present at the resection-margin, or if there was less than 1 cm of healthy tissue around the tumour after fixation, radiotherapy was to be given irrespective of the study-arm. Re-excision was also an indication for radiotherapy. The radiotherapy dose was 50 Gy in 5–6 weeks in cases of marginal excision, with a boost of 10–15 Gy in the case of microscopic residual disease or a boost of 20–30 Gy in the case of macroscopically residual disease where no further surgery was possible. Radiotherapy was to start as early as possible after surgery.

2.8. Statistical considerations

The main purpose of the phase II part of the study was to assess the feasibility and the accrual to allow expansion into a phase III study. The formal statistics

related to the phase III part of the study. Since 'high-risk' patients have an anticipated median survival of 3.5 years and an overall 5 year survival of 40%, a total of 269 patients would have been required to detect an increase of 15% in 5 year survival in patients receiving preoperative chemotherapy with error rates alpha = 0.05 and beta = 0.20, using the logrank test.

2.9. Randomization

Patients were randomised centrally at the EORTC Data Center by telephone. Eligibility criteria were checked at randomisation. A dynamic random treatment allocation technique was used, stratified by centre and by risk groups. Risk groups were defined on the basis of tumour size (as described above).

3. Results

3.1. Patient characteristics

150 patients were entered into this study by 23 centres. Seventy percent of all patients were entered by five centres. The accrual rate was initially extremely low. It thereafter varied considerably over time, in some periods tending to increase to such an extent that with a further increase extension into the phase III study would have become possible. However, despite various efforts to further increase accrual, it finally dropped again to such unacceptably low rates that continuation could not be justified. The study was therefore terminated prematurely. The reason for the low accrual was not formally investigated but based on information from group members it appeared to be related to the difficulty of getting these patients referred to the specialised centres before surgery. In the last years of the study, isolated limb perfusion with TNF-alpha was a competitive factor.

75 patients were entered into each arm. Distribution according to stratification factors and the tumour site was balanced. 16 patients (11%), 8 in each arm, were considered ineligible and the reasons are listed in Table 1.

With regard to age and performance status, the 134 eligible patients were equally divided over the two arms, female patients were more frequently in the chemotherapy arm (Table 2).

3.2. Histopathology

Central histopathological review showed malignant fibrous histiocytoma to be the most frequent cell-type (29%), followed by leiomyosarcoma (16%), liposarcoma (15%) and synovial sarcoma (15%). Distribution according to histology was well balanced (Table 2).

Table 1
Patient characteristics ($n = 150$)

	No preoperative chemotherapy *n* (%)	Preoperative chemotherapy *n* (%)
Stratification according to risk factor		
< 8 cm, group II/III	18 (24)	18 (24)
> 8 cm, group I	6 (8)	6 (8)
> 8 cm, group II/III	31 (41)	33 (44)
Inadequate surgery, group II/II	13 (17)	13 (17)
Local recurrence	7 (9)	5 (7)
Distribution according to localisation		
Limbs	61 (81)	62 (83)
Head/neck	4 (5)	1 (1)
Trunk	7 (9)	10 (13)
Pelvis	3 (4)	2 (3)
Eligibility		
Eligible	67 (89)	67 (89)
Ineligible	8 (11)	8 (11)
Reasons for ineligibility		
Retroperitoneal localisation	2	–
T. category	–	1
Distant metastases	2	2
Age	–	1
Other histology	4	2
Cardiovascular disease	–	1
Grade unknown	–	1
Total	75 (100)	75 (100)

Table 2
Patient characteristics eligible patients ($n=134$)

	No preoperative chemotherapy	Preoperative chemotherapy	Total
Gender: male/female ratio	2.35	1.23	1.68
	n (%)	*n* (%)	*n* (%)
Performance status 0	52 (78)	51 (76)	103 (77)
Performance status 1	13 (19)	13 (19)	26 (19)
Performance status 2	2 (3)	3 (4)	5 (4)
Median age (years) (range)	49 (19–74)	56 (15–69)	53 (15–70)
Distribution according to histopathology			
M.F.H.	19 (28)	20 (30)	39 (29)
Fibrosarcoma	2 (3)	1 (1)	3 (2)
Liposarcoma	9 (13)	11 (16)	20 (15)
Leiomyosarcoma	10 (15)	12 (18)	22 (16)
Rhabdomyosarcoma	3 (4)	2 (3)	5 (4)
Angiosarcoma	1 (1)	0	1 (1)
Synovial sarcoma	9 (13)	11 (16)	20 (15)
Neurogenic sarcoma	8 (12)	3 (4)	11 (8)
Other sarcoma's	1 (1)	3 (4)	4 (3)
Unclassifiable sarcoma	4 (6)	2 (3)	6 (4)
Undifferentiated sarcoma	1 (1)	1 (1)	2 (1)
Unknown	0	1 (1)	1 (1)
Total	67 (100)	67 (100)	134 (100)

M.F.H., malignant fibrous histocytoma.

3.3. Preoperative chemotherapy

67 patients were randomised in the neo-adjuvant chemotherapy arm. One patient did not receive the allocated treatment; 7 patients only received one cycle (1 due to toxic death, 1 due to neurological toxicity, 4 because of progression and 1 patient was lost to follow-up), 1 patient only received two cycles, related to drug-supply problems. 58 (87%) patients received all three scheduled cycles.

Dose reductions were not applied. The second cycle was delayed eight times (delay 4–8 days) while the third cycle was delayed six times (delay 4–13 days), but only once was delay due to haematological toxicity. The achieved median dose intensity was 98%, ranging from 85 to 106%.

In general, chemotherapy was well tolerated. Leucopenia was seen in 32%, but grade 4 only occurred in 8%. One patient died of septic shock after the first course of chemotherapy. The main non-haematological side-effects were nausea and vomiting (95%) and alopecia (all patients) (Table 3).

In 18 cases, response could not be assessed: 1 patient died after the first cycle, 1 patient was lost to follow-up, 1 patient did not receive the chemotherapy, while in 15 cases there was no measurable lesion at the start of the chemotherapy.

Responses (of which 8% were complete) were seen in 29% of 49 patients assessable for response, 53% had stable disease, and only 18% progressed (Table 4). In none of the progressing patients did progression prohibit adequate surgery.

Table 3
Side-effects and toxicity of chemotherapy ($n=65$)

Side-effect	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	% toxicity	% severe
Haematological							
Leucopenia	44	10	6	5	–	32	8
Thrombocytopenia	65	–	–	–	–	–	–
Non-haematological							
Nausea/vomiting	3	13	30	18	1	95	29
Renal	62	3	–	–	–	5	–
Haematuria	64	–	1	–	–	2	–
Infection	61	2	1	–	1	6	2
Cardiotoxicity	62	1	–	1	1	2	–
Neurotoxicity	62	1	–	1	1	5	3
Other	51	8	5	1	–	21	2

Table 4
Response to chemotherapy ($n=49$)

Response	n (%)
Complete remission	4 (8)
Partial remission	10 (20)
Stable disease	26 (53)
Progression	9 (18)
Total	49

3.4. Surgery

The type of surgery was planned before randomisation and surgery was mostly performed according to the original planning (Table 5).

Planned amputations were always performed. Wide excision was changed to compartmental resections in 2 cases in the surgery alone and in 4 cases in the chemotherapy arm. Marginal excision occurred more frequently than expected. Microscopically-free margins were obtained in 89% of the operations. Preoperative chemotherapy did not, in general, increase postoperative complications (Table 5).

3.5. Radiotherapy

Postoperative radiotherapy was indicated according to protocol in 80 patients, 43 (54%) patients in the surgery alone arm and 37 (46%) patients in the chemotherapy arm. Radiotherapy was postponed or interrupted in 70% of cases in both arms, mainly due to administrative reasons, i.e. lack of facilities (47% in the surgery alone arm and 49% in the neo-adjuvant arm), or due to delayed wound-healing (23% in the surgery alone arm and 16% in the chemotherapy arm) and due to progression or loss to follow-up in 5% in the chemotherapy arm. Skin and other side-effects related to radiotherapy were seen in equal frequency in both arms.

Table 5
Surgery ($n=129$)[a]

	No preoperative chemotherapy	Preopetative adjuvant chemotherapy
Planned/performed surgery		
Amputation	6/6	9/9
Compartimental resection	22/24	13/17
Wide excision	27/24	32/28
Marginal excision	7/11	9/10
No information	3/0	1/0
Total	65/65	64/64
Microscopical radicality		
Radical	57 (88%)	58 (91%)
Irradical	8 (12%)	6 (9%)
Postoperative complications		
Superficial infection	9 (14%)	9 (14%)
Deep infection	3 (5%)	–
Vascular complication	2 (3%)	1 (2%)
Neurological	2 (3%)	2 (3%)
Skin necrosis	7 (11%)	4 (6%)

[a] The surgery on these two patients missed in the database and were not taken into these calculations.

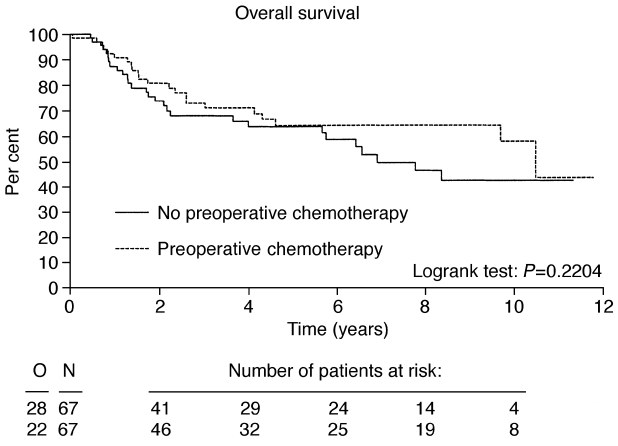

Fig. 2. Overall survival. O, observed number of deaths; N, number of patients.

3.6. Survival and time to progression

All 134 eligible patients are included in the survival and disease-free survival analyses. The median follow-up of patients is 7.3 years. A total of 50 deaths (37%) have been recorded so far, 28 in the surgery alone arm and 22 in the neoadjuvant chemotherapy arm. The 5 year survival estimate is 64% in the surgery alone arm and 65% in the neoadjuvant arm (standard error 7%, logrank $P=0.2204$) (Fig. 2).

The cause of death was soft-tissue sarcoma in 38 patients (20 in the surgery alone and 18 in the chemotherapy arm, respectively), and a second primary in 4 cases (3 and 1, respectively). One toxic death was reported in the neo-adjuvant arm. All of the seven other deaths were neither drug- nor disease-related.

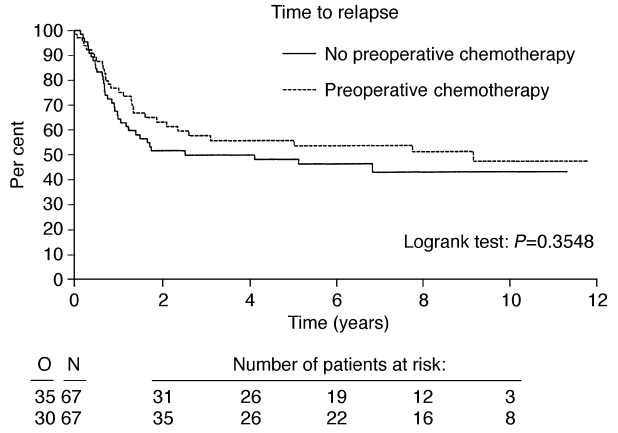

Fig. 3. Time to relapse. O, number of relapses; N, number of patients.

Relapses were observed in 65 patients (35 in the surgery alone arm, 30 in the neoadjuvant arm). The proportion of disease-free patients at 5 years is estimated at 52% in the surgery alone arm and 56% in the neoadjuvant arm (standard error of the mean: 7%, logrank $P = 0.3548$) (Fig. 3).

Most relapses were distant metastases (63%); the others involved synchronous local recurrence and distant metastases (25%) or local recurrence only (12%) equally divided over both arms.

4. Discussion

The concept of neo-adjuvant chemotherapy is a topic for ongoing debate. The outcome of non-randomised phase II studies of neo-adjuvant chemotherapy suggest that chemotherapy given at this stage of the disease gives a higher response rate than chemotherapy given for distant metastases [7–9]. This suggestion would be consistent with similar data available from treatment in tumours such as osteosarcoma, head and neck cancer, breast cancer [9,10], bladder cancer and various other types of malignancies.

In general, patients treated with neo-adjuvant chemotherapy are fitter than those with metastatic disease, and this has been suggested as one of the reasons why they tend to be better able to tolerate chemotherapy. The few published non-randomised phase II studies on neo-adjuvant chemotherapy in soft-tissue sarcomas [11,12] have used more 'aggressive' (more toxic) chemotherapy than we have used in our study, and have sometimes added concomitant radiotherapy. Obviously, the resulting toxicity in these phase II studies was more severe than observed in our study. However, in two of our recent studies [13,14] we have shown that an increase in dose and toxicity does not necessarily result in a better outcome, at least for patients with metastatic disease. In view of the latter, it can be postulated that the seemingly beneficial results of the above phase II studies are related to patient selection. In our present study, the neo-adjuvant chemotherapy was clearly found to be feasible, lacking major toxicity. Interestingly, the toxicity seemed to be less compared with our previous experience in patients with metastatic disease [15,16], but this could again well be related to patient-selection. Still, the difference in the leucopenia rate is, at the very least, remarkable.

It is important to note that the neo-adjuvant chemotherapy used in this study never prevented surgery and did not necessitate a change in planned surgery. The progression rate was only 18% which is similar to the rate in patients with metastatic disease [15,16]. Potential progression of disease, rendering the patient inoperable, was one of the prime concerns when designing the protocol.

We chose three preoperative cycles of chemotherapy because our previous experience in a large study [15] had shown that the best response to treatment with chemotherapy was usually observed within three cycles, while only 12% of the patients experienced progression during these three cycles. The results obtained in this study seem to confirm that this was an appropriate choice. Apart from not affecting the possibility of surgery, the chemotherapy also did not increase the complication rate of surgery, and did not increase the side-effects of subsequent radiotherapy.

The combination of doxorubicin and ifosfamide was selected for this study because we had, as indicated above, considerable experience with the regimen in patients with advanced disease [16]. The complete response rate of this combination in patients with metastatic disease was higher (12%) than with single agent doxorubicin (3%).

Disappointingly, complete and partial remissions were seen in only 29% of patients, which is no better than the usual response rate obtained in metastatic disease.

Over the years, we seem to have witnessed a shift in incidence of the various subtypes of soft-tissue sarcomas. It has also been argued that some subtypes are more sensitive to chemotherapy than others. Whether these arguments can serve as an explanation for the relatively disappointing objective regression rate is unknown. The number of patients in our study did not permit performance of further subset analyses.

Some may argue that grade 1 sarcomas are not 'high-risk' tumours. The larger grade 1 tumours (i.e. >8 cm.) in a previous EORTC adjuvant chemotherapy study [1], however, did prove to be 'high-risk' tumours. In the present neo-adjuvant study, only 12 patients with grade I tumours were included, evenly distributed over both arms (Table 1). Even if these patients are excluded from the analyses, the results are not different.

Even with a median follow-up of more than 7 years, the statistical analysis of this study does not appear to show a large benefit from neo-adjuvant chemotherapy, with respect to either disease-free or overall survival, but the study was only designed to measure survival in the phase III part that was not performed. Since the overall survival and progression-free survival curves for patients receiving chemotherapy were always slightly superior to those for surgery alone, it can therefore not be excluded that an extension of the study could have shown a small benefit for neo-adjuvant chemotherapy.

Unfortunately, accrual was too slow to permit expansion to a large phase III trial. The reason for the slow accrual was difficult to assess, but seemed largely related to the fact that referral of patients with these soft-tissue sarcomas to specialised centres in many parts of Europe is not as good as anticipated. This does not seem dissimilar to the situation in most other parts of

the world, perhaps with the exception of Scandinavia. Apparently, the recommendations for referral to specialised centres and the multidisciplinary design of treatment schedules have not yet resulted in a universal approach. Isolated limb perfusion with TNF-alpha also proved competitive in the last years of the study as an alternative treatment for large high-grade limb sarcomas.

In conclusion, neo-adjuvant chemotherapy does not negatively affect the ability to perform adequate surgery, and delaying the surgery does also not negatively affect the soft-tissue sarcoma patient. However, the exciting and valid question whether neo-adjuvant chemotherapy can increase overall and disease-free survival for the time being remains unanswered, and further prospective randomised trials are needed. Given the above reported experience on accrual, it would be worthwhile to explore the possibilities of performing such a study as an intergroup study. The Connective Tissue Oncology Society (CTOS) has already served as a platform that stimulated intergroup collaborations for other research questions, which may well pave the way for a further worldwide extension of sarcoma-related research.

References

1. Bramwell V, Rouesse J, Steward W, *et al*. Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma — reduced local recurrence but no improvement in survival: a study of the European Organization for Research and Treatment of Cancer. Soft tissue sarcoma group. *J Clin Oncol* 1994, **12**, 1137–1149.
2. Gortzak E, van Coevorden F. Soft tissue sarcoma: messages of completed randomized trials. *Eur J Surg Onc* 1995, **21**, 469–477.
3. Zalupski MM, Ryan JR, Hussein ME, *et al*. Defining the role of adjuvant chemotherapy for patients with soft tissue sarcoma of the extremities. In *Adjuvant Therapy of Cancer VII*. J.B. Lippincott, 1993, 385–392.
4. The Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adult: meta-analysis of individual data. *Lancet* 1997, **350**, 1647–1654.
5. Gortzak E, Rouesse J, Verweij J, *et al*. Randomised phase II study of neoadjuvant chemotherapy in soft tissue sarcomas in adults. Protocol 62874. *Eur J Cancer* 1993, **29A**, 183.
6. WHO Handbook for Reporting Results of Cancer Treatment. Geneva, WHO, 1979, 1–45.
7. Rouesse J, Friedman S, Sevin DM, *et al*. Pre-operative neo-adjuvant chemotherapy in the treatment of locally advanced soft tissue sarcomas. *Cancer* 1987, **60**, 296–301.
8. Maree D, Hocke C, Buin B, *et al*. Conservative local treatment of soft tissue sarcoma in adults after neo-adjuvant chemotherapy. *Presse Mes* 1985, **14**, 1069–1072.
9. Simon MA, Nachman J. Current concept review. The clinical utility of pre-operative therapy for sarcomas. *J Bone Joint Surg Am* 1986, **9**, 68.
10. Feldman LD, Hortobagyi GN, Buxdar AU, *et al*. Pathological assessment of response to neo-adjuvant chemotherapy in breast cancer. *Cancer Res* 1986, **46**, 2518–2578.
11. Patel SR, Vadhan-Raj S, Burgess MA, *et al*. Preoperative chemotherapy with dose-intensive adriamycin and ifosfamide for high-risk primary soft-tissue sarcomas of extremity origin. *Proc Conn Tissue Oncology Soc* 1999, **5**, 16.
12. Spiro IJ, Suit H, Gebhardt M, *et al*. Neoadjuvant chemotherapy and radiotherapy for large soft tissue sarcomas. *Proc Am Soc Clin Oncol* 1996, **15**, 5243.
13. Nielsen OS, Judson I, van Hoesel Q, *et al*. Effect of high-dose ifosfamide in advanced soft tissue sarcomas. A multicentre phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2000, **36**, 61–67.
14. LeCesne A, Judson I, Crowther D, *et al*. Randomized phase III study comparing conventional dose doxorubicin plus ifosfamide versus high dose doxorubicin plus ifosfamide plus rhGMCSF in advanced soft tissue sarcomas: an EORTC Soft Tissue and Bone Sarcoma Group trial. *J Clin Oncol*, 2001, in press.
15. Santoro A, Rouesse J, Steward W, *et al*. A randomized EORTC study in advanced soft tissue sarcomas (STS) ADM vs ADM + IFOS vs CYVADIC. *Proc Am Soc Clin Oncol* 1990, **9**, 309.
16. Schuette J, Dombernowsky P, Santoro A, *et al*. Adriamycin and Ifosfamide, a new effective combination in advanced soft tissue sarcoma; preliminary report of a phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. *Proc Am Soc Clin Oncol* 1986, **5**, 145.