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INTRODUCTION

SOFT TISSUE sarcomas are rare diseases comprising only 1% of all malignant tumours. As a consequence, the personal experience of physicians is usually limited with these tumours and treatment by multidisciplinary teams in specialised centres is therefore warranted. Studies have shown that multidisciplinary team discussions prior to the initial treatment of patients with soft tissue sarcomas result in a better treatment strategy and improved treatment outcome. Soft tissue sarcomas have a tendency to early haematogenous spreading and to control these distant metastases we obviously need effective systemic therapy. However, in view of the above mentioned team-dependent results of treatment as well as for other reasons, various single-centre studies may well result in a markedly different outcome. Firm conclusions on treatment strategies and projecting these to the world of common practice can only be based on multicentre studies of a large sample size. Bearing this in mind, the following will review the results of chemotherapy for metastatic soft tissue sarcomas.

STANDARD-DOSE SINGLE-AGENT CHEMOTHERAPY (TABLE 1)

Doxorubicin (DOX) was the first single agent found to be active in the treatment of metastatic soft tissue sarcomas, yielding response rates of 15–35% [1–6] in different studies. The most recent studies suggest a response rate to DOX of ± 20% when given as first-line chemotherapy.

In an attempt to reduce the toxicities related to DOX without reducing the activity, there has been extensive research on anthracycline analogues such as epirubicin. At equimolar doses the response rate to DOX (25%) was better than the response rate to epirubicin (18%) [7], but myelosuppression with epirubicin was less compared to DOX. All other anthracycline analogues and structurally related drugs unfortunately have been found to be inactive in soft tissue sarcomas.

One reason that most of soft tissue sarcoma patients do not respond to anthracyclines may be an overexpression of P-glycoprotein in association with the multidrug-resistant (MDR) phenotype [8, 9]. This observation limits the potential of high-dose anthracycline treatments in this disease.

The second active single agent in the treatment of soft tissue sarcomas is ifosfamide (IFOS). Initial studies with this drug were hampered by improper study designs but more recent phase II studies have proven the drugs' activity. IFOS given at a dose of 5 g/m^2 as 24 h infusion with concomittant mesna uroprotection yielded a response rate of 24% in non-pretreated patients [10, 11] while cyclophosphamide in this patient population was significantly less active [11]. The third

Table 1. First-line single-agent activity

Drug	Response rate
Doxorubicin	20%
Ifosfamide	20%
Dacarbazine	17%

drug commonly considered to be active is dacarbazine (DTIC), yielding a 17% response rate [12, 13]. However, the responses observed with DTIC were all extremely short and thus we might have to reconsider the actual role of this drug in the treatment of soft tissue sarcomas.

STANDARD-DOSE COMBINATION CHEMOTHERAPY

In an effort to improve the results of chemotherapy in metastatic disease, different combination chemotherapy regimens have been studied. In general, DOX has been the backbone in most of these regimens. In the early 1970s the SouthWest Oncology Group (SWOG) initiated a study combining DOX 60 mg/m^2 on day 1 with DTIC 250 mg/m^2/day on days 1–5, a regimen known as ADIC [14]. It yielded a response rate of 42% in the first study performed. Since 1972, the SWOG has performed several studies with the same ADIC regimen, observing a gradual decrease in response rate over the years, starting with 42% and most recently falling to 17% [15]. This observation might relate to the improvement in diagnostic techniques enabling a better evaluation of true responses and is another argument against the use of historical controls. However, in view of the latter response rate, we might also question the value of combining DTIC and DOX.

The Gynecologic Oncology Group (GOG) performed a study comparing 3-weekly DOX with ADIC in patients with uterine sarcomas [16]. In these patients the response rates were not significantly different (16% and 24%, respectively).

In 1987, the ECOG reported a randomised trial comparing DOX 70 mg/m^2 i.v. bolus on day 1 every 3 weeks with DOX 20 mg/m^2 i.v. bolus on days 1, 2 and 3 and 15 mg/m^2 i.v. bolus on day 8 and weekly thereafter; and with ADIC [5]. This study thus questioned the value of the different dosing schedules of DOX already discussed. Single-agent DOX yielded response rates of 18 and 16%, respectively, while the addition of DTIC increased the number of partial remissions, resulting in a significantly ($P < 0.02$) increased response rate of 30%. Unfortunately, the higher response rate was not reflected in an improved survival.

The value of adding drugs to DOX has further been assessed in several randomised trials. The ECOG studied 3-weekly DOX 70 mg/m^2, versus DOX 50 mg/m^2 plus cyclophosphamide and vincristine, versus cyclophosphamide, vincristine and actinomycin-D [1]. The response rates were 27, 19 and 11%, respectively. This study shows that cyclophosphamide and vincristine do not add activity to DOX, while replacing DOX with actinomycin-D results in significantly decreased activity. Apparently these drugs have very limited value in the treatment of soft tissue sarcomas. In addition, the data suggest that a lower dose of DOX to enable its combination with other drugs reduces the response rate.

By adding cyclophosphamide (CTX) and vincristine (VCR) (despite the fact that their single-agent activity was unknown) to the ADIC regimen, the so-called CYVADIC regimen was developed. The initial response rate reported was 51%, with a response duration of 9.5 months for CR and 7 months for PR [17]. After treating 331 patients with CYVADIC, the investigators stressed the importance of achieving CR because 21% of those patients had remained disease free for more than 5 years and have been potentially cured by chemotherapy [18]. Many other studies have shown a tailing of survival curves at approximately the 5% level, further supporting this observation. This means that trying to achieve CR is of utmost importance.

A randomised study of the EORTC compared CYVADIC with a schedule alternating VCR/CTX and ADIC at similar doses, at 4-week intervals [19]. With CYVADIC, 17% CRs and 21% PRs were achieved in 84 patients, while with the alternating schedule the response rate was significantly lower with 5% CR and 9% PR in 78 patients ($P = 0.001$). These data indicate that DOX should be administered every 3 or 4 weeks instead of every 8 weeks and lend further support to the earlier mentioned DOX dose–response relationship [1].

After confirmation of the activity of IFOS in soft tissue sarcomas, this drug was combined with DOX. The optimal doses for the combination appeared to be DOX 50 mg/m^2 and IFOS 5 g/m^2 [20] and overall response rates varied from 30 to 35% [20, 21]. Subsequent to their phase II study, the EORTC Soft Tissue and Bone Sarcoma Group performed a randomised trial comparing single-agent DOX 75 mg/m^2 i.v. on day 1 with the DOX/IFOS regimen and with a CYVADIC schedule. All regimens were repeated every 3 weeks. A total of 663 eligible patients were entered, of whom 605 could be evaluated for response [22]. The response rates were similar at 23, 28 and 28%, respectively and median duration (10 months) and median survival (12 months) data also did not differ. Toxicity profiles were in favour of single-agent DOX. While DOX/IFOS resulted in more leucocytopenia, CYVADIC was much more emetogenic, resulting in early closure of this treatment arm of the study.

Similarly, an ECOG study compared single-agent DOX at a dose of 80 mg/m^2 repeated every 3 weeks, with DOX 30 mg/m^2 i.v. on day 1 + 2 plus IFOS 3.75 g/m^2 i.v. over 4 h on days 1 + 2 every 3 weeks and with mitomycin C 8 mg/m^2 plus DOX 40 mg/m^2 and cisplatin 60 mg/m^2 all on day 1 every 3 weeks [23]. The latter regimen might seem peculiar in view of the reported inactivity of mitomycin C and cisplatin in the treatment of soft tissue sarcomas and the low dose of DOX applied, but a preceding phase II study had shown some interesting activity. Actually, in the phase III study the latter was confirmed [23], which may suggest some form of additive effect. The respective response rates were 20% (90 patients), 34% (88 patients) and 32% (84 patients). The DOX/IFOS regimen was significantly more myelotoxic than the other two regimens. This is undoubtedly related to the relatively high dose used for both drugs. Unfortunately, as in the previous ECOG study [5], the higher response rates for the combination regimens were not associated with an improved survival.

In view of the four studies now reported comparing single-agent DOX with different combination chemotherapy regimens [1, 5, 22, 23], we can safely conclude that at standard doses single-agent DOX is as effective as combination chemotherapy in terms of survival. Higher response rates may sometimes be achieved by combination chemotherapy, but

most of these responses are partial and this does not contribute to an improved survival.

DOSE–RESPONSE RELATIONSHIPS

In an attempt to reduce toxicities and to determine whether lower doses of DOX could be given over longer periods without loss of efficacy, O'Bryan and associates designed a study administering DOX at different doses [2]. Patient grouping was based on the opinion of the investigator. Obviously this design biased the outcome of the study. Nevertheless, the results are interesting. In 98 evaluated good risk patients receiving 75 mg/m^2, 60 mg/m^2 or 45 mg/m^2 DOX every 3 weeks, the remission rates achieved were 37%, 20% and 18%, respectively. The data strongly suggest that for DOX given as single agent every 3 weeks, a response relationship, with doses of 75 mg/m^2 producing higher response rates than doses of 60 mg/m^2 or less, confirming previously mentioned studies [1, 19].

Hoekman and associates [14] administered high-dose DOX to 35 patients. Nine patients received a dose of 90 mg/m^2 and 26 patients received 110 mg/m^2 repeated every 3 weeks. GM–CSF 250 μg/m^2/d by continuous infusion (CI) or subcutaneously was used as myeloprotector and given from days 2–12 after the first cycle with related bone marrow toxicity (white blood cells $< 1\times10^9$/l and platelets $< 50\times10^9$/l). Only haematological data relating to GM–CSF given by CI (25 patients) were analysed. DOX 90 mg/m^2 and 110 mg/m^2 resulted in response rates of 33 and 31%, respectively, in this limited and uncontrolled study. When administering 90 mg/m^2 DOX every 3 weeks without GM–CSF, grade 4 neutropenia lasting 7 days after the first cycle occurred in 8 patients. At both DOX doses combined with GM–CSF, grade 4 neutropenia lasting 7 days was first seen after the fourth chemotherapy cycle. At the dose of 110 mg/m^2 DOX, GM–CSF grade 4 thrombocytopenia became dose limiting after the fourth cycle. Clearly, GM–CSF is able to accelerate the recovery of neutrophils following high-dose chemotherapy, but this effect is not maintained when chemotherapy is continued.

As previously stated, the optimal dose of single-agent DOX without growth factor support is 70–75 mg/m^2 every 3 weeks [1, 2, 19], while equivalent doses of epidoxorubicin are slightly less active, although it appears that higher doses of epidoxorubicin could be applied [25, 26]. Investigators from Belgrade used the very high dose of epirubicin of 60 mg/m^2/day, days 1–3, combined with the, in this disease, hardly active cisplatin, repeated every 4 weeks. In 35 patients the response rate was as high as 57% including 20% CRs. Myelotoxicity included grade 4 leucocytopenia in 63% of patients with neutropenic fevers in 51%, while 37% of patients had (uncomplicated) grade 4 thrombocytopenia. The authors suggested that epidoxorubicin should be tested in soft tissue sarcomas at a single-agent dose of at least 150 mg/m^2 per cycle. The latter two studies, apart from addressing the question of the relevance of epidoxorubicin dose intensity, also addressed the question of the relevance of dose scheduling. In view of these and previous studies, the EORTC initiated a phase II study randomising DOX 75 mg/m^2 i.v. bolus day 1 versus Epi–DOX 160 mg/m^2 i.v. bolus day 1 versus Epi–DOX 60 mg/m^2 i.v. bolus days 1–3, cycles to be repeated every 3 weeks [27]. However, after a total of 30 patients had been entered in this study, the latter two schedules were changed into 150 mg/m^2 i.v. bolus day 1 and 50 mg/m^2/day i.v. bolus days 1–3 because of unacceptable toxicity observed at the higher doses. Three hundred and thirty-four patients were entered in total, and 305 could be evaluated for response. There was absolutely no difference in response rates between the arms and, although not statistically different, time to progression was highest in the standard-dose doxorubicin arm. Survival data were similar in the three arms, but toxicity was significantly more pronounced in both epidoxorubicin arms. This study indicates that further use of epirubucin in this disease cannot be justified.

Also for IFOS there may be a dose–response relationship, although the available data are inconsistent (Table 2). Using the 24 h infusion schedule, the dose of 8 g/m^2 was not found to be beneficial over the dose of 5 g/m^2 [21]. Using a daily times 4 schedule of 4 h infusions, Antman and associates [10] were able to administer 2–2.5 g/m^2/day (course dose 8–10 g/m^2) in patients failing doxorubicin-based chemotherapy, yielding a response rate of 28% in 28 patients with soft tissue sarcomas. Of note, all responses were partial and the median duration was only 4 months, although this was achieved in pretreated patients.

In a phase II study, Le Cesne and associates [28] showed that high-dose ifosfamide (HDI) was able to circumvent resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. On 3 consecutive days they administered 4 g/m^2/day IFOS by continuous intravenous infusion with an equivalent dose of Mesna, every 4 weeks. Thirty-six patients were evaluable for response, 12 achieved a PR (33%) lasting 6–13+ months, 8 had stable disease (SD) and 16 progressed (PD). Eleven of the 12 responders had previously received standard-dose IFOS, 5 of whom were truly refractory to this treatment. Toxicity was mainly haematological and was considered manageable. There were 76% grade 3–4 neutropenias including 12 (8%) febrile neutropenic episodes requiring hospitalisation, 20% grade 3–4 thrombocytopenias and 25% grade 3–4 anaemias. Non-haematological toxicities were substantial and mainly renal with this continuous infusion schedule. Four patients developed irreversible renal failure, 2 developed renal Fanconi's syndrome. All but 3 patients had serum electrolyte or urinalysis abnormalities, with metabolic acidosis in 67%. Clearly the antitumour activities in pretreated patients are of interest, but they will have to be balanced against the side-effects. Exploring this schedule in non-pretreated patients is recommended.

Table 2. High-dose ifosfamide: results of phase II studies

Drugs	Dose (mg/m^2) + schedule	Interval (weeks)	Growth factor	No. of evaluable patients	Responses CR	Responses PR	Response rate (%)	Ref.
Ifosfamide	10 000 Days 1–4	3	None	28	1	11	28	[10]
Ifosfamide	12 000 Days 1–3 (CI)	4	None	36	0	12	33	[28]
Ifosfamide	14 000 Days 1–5	3	GM–CSF	11	0	6	55	[29]
Ifosfamide	12 000 Days 1–4 (CI)	2	G–CSF	7	0	2	28	[30]

Similar to Le Cesne [28], Cerny and associates [29] also suggested a dose–response relationship for IFOS. They combined HDI with GM–CSF in 15 patients, 8 of whom had been pretreated with standard-dose IFOS. The first 4 patients received IFOS 2.4 g/m^2/day on days 1–5, without GM–CSF every 3 weeks. All had grade ≥ 3 leucopenia. There were five episodes of infection in 22 cycles. The subsequent 11 patients received 2.8 g/m^2 IFOS on days 1–5 with GM–CSF (5 μg/kg s.c. on days 7–16). In this group there were only two episodes of infection in 25 cycles. Out of 8 patients no longer responding to standard-dose IFOS (< 8 g/m^2/cycle), 4 achieved a PR.

Christman and associates [30] administered IFOS with a starting dose of 10 g/m^2/cycle on 4 consecutive days by continuous intravenous infusion every 2 weeks. In addition, G–CSF was given subcutaneously 5 μg/kg on days 5–12 of each cycle. At these doses, 87% of cycles were administered on schedule. 4 of 9 patients received at least three cycles of IFOS every 2 weeks without delay, with hospitalisation for toxicity or progression. However, the authors also reported that within individual patients, the duration and depth of myelosuppression increased with each cycle. At a dose of 12 g/m^2 of IFOS, thrombocytopenia was dose limiting. Of the 7 patients in this study with measurable disease, 2 achieved a PR and 1 had a minor response.

The above-mentioned studies not only leave us with the still burning question of the relevance of dose of ifosfamide, but also with the uncertainty of the importance of schedule. Only randomised studies will provide the answer to these questions. It is for this reason that the EORTC initiated a randomised study comparing the optimal dose of 24 h infusion of ifosfamide (5 g/m^2) with the optimal dose of a 3 day course of daily 4 h infusions (course dose 9 g/m^2). The results of this study are awaited with interest. A follow-up study should involve the best schedule of the two, at least compared to the 72 h infusion at the dose of 12 g/m^2 and should preferably also include the standard dose of 75 mg/m^2 of DOX.

DOSE-INTENSIFIED COMBINATIONS

Besides increasing the dose in single-agent treatment, it also appeared worthwhile to study treatment intensification with combinations of drugs. Antman and associates [15] performed a study in 374 patients to determine if medium high-dose IFOS added to DOX and DTIC (MAID) significantly affected toxicity, response rate and survival. Patients were randomised to receive ADIC (DOX 60 mg/m^2 and DTIC 900 mg/m^2) or MAID (DOX 60 mg/m^2, DTIC 1000 mg/m^2 and IFOS 7500 mg/m^2), with Mesna 10 000 mg/m^2 over 3 and 4 days, all cycles to be repeated every 3 weeks. Because of unacceptable myelosuppression, the IFOS dose was reduced to 6000 mg/m^2 after the first 154 patients were accrued. Ultimately, 339 patients were fully assessable. The response rate was significantly higher in the MAID group compared to the ADIC group, 32% versus 17% ($P < 0.005$), but although there was a longer time to progression for patients treated with the MAID regimen of 6 versus 4 months ($P < 0.2$), the overall survival was not significantly different (12 versus 13 months, $P < 0.04$). In the MAID group, 8 patients (5%) died of treatment-related toxicity. This death rate was unacceptably high and overall the MAID regimen was much more toxic than the ADIC regimen. In view of the lack of any survival benefit and the observed toxicities, the MAID regimen cannot be recommended for general treatment. By adding G–CSF to this regimen, it appeared feasible to maintain dose-intensity for only 2 cycles [32], after which cumulative thrombocytopenia became dose limiting. Of concern is that the response rate in 48 non-pretreated patients was only 23%, with only 1 (2%) complete response, lending further support to the above conclusion.

The highest feasible dose of doxorubicin in combination with 24 h infusion of 5 g/m^2 IFOS without the use of growth factor appears to be 60 mg/m^2. This combination is complicated by a high percentage of neutropenic infections (Table 3). The EORTC [33] entered 111 patients with advanced soft tissue sarcoma in a study, administering the combination of DOX 75 mg/m^2 i.v. bolus day 1 with IFOS 5 g/m^2 24 h continuous intravenous infusion day 1 and rh-GM–CSF 250 μg/m^2/d s.c. days 3–17. 52 patients received rh-GM–CSF as a once-daily subcutaneous injection and 59 patients received the same total dose of rh-GM–CSF as divided doses every 12 h. Chemotherapy was repeated at 3-week intervals up to a maximum of seven cycles or to two cycles beyond documentation of CR, whatever came first. The regimen resulted in a 45% objective response rate with 10% CRs. The median survival of responders was 15 months and the median duration of remission was 9 months. The toxic death rate was 2%. Comparison of blood counts for the two schedules of rh-GM–CSF did not show a significant difference in the depth or duration of neutropenia or thrombocytopenia. The median duration of neutropenia less than 0.5×10^9/l (grade 4, according to Common Toxicity Criteria) was only 3 days after course 1 and 6 days after course 6. The median platelet nadir after cycle 6 was 37×10^9/l. Toxicities related to rh-GM–CSF were mild and of short duration.

Questioning whether this high-dose regimen was actually superior to a regimen with standard doses, the EORTC performed a randomised study involving 334 patients [34]. The response rates were similar in both treatment arms (20% for standard doses and 21% for high dose), and there were no differences in complete remission rates, time to progression and overall survival. Although the toxicities were also not different due to the inclusion of GM–CSF in the high-dose arm, this study highlights that phase II study results may be overinterpreted and should first be confirmed in phase III studies before being implemented into common practice. The same statement can be made for the interesting results obtained by the Scandinavian Sarcoma Group with a regimen involving medium–high-dose etoposide [35], a drug other-

Table 3. Doxorubicin dose in combination with 5 g/m^2 ifosfamide relative to myelotoxicity and infection

Group	DOX dose (mg/m^2)	GM–CSF	No. of patients	Leucopenia	Infection (%)	Ref.
Royal Marsden	60	–	27	45% Grade 4	55	[20]
EORTC	50	–	400	34% Grade 4	6	[21]
Indiana	60	–	42	Median nadir 1.3	43	[31]
EORTC	75	+	104	100% Grade 3 + 4	14	[33]

wise inactive in soft tissue sarcomas. The role of this drug in soft tissue sarcomas remains unclear [36].

PROGNOSTIC FACTORS

Although many data are now available on different schedules of chemotherapy resulting in comparable response rates, there is still no consensus on possible factors predicting the outcome of chemotherapy and these factors may also largely contribute to differences between studies. The most important prognostic factor for response, on which there is agreement throughout all studies, is the performance score [5, 18, 37]. In a multivariate analysis on 1474 patients from the EORTC–STBSG database, treated with doxorubicin-based chemotherapy, the performance score was found to be an independent prognostic factor for survival [38]. The absence of liver lesions, presence of lung lesions and young age were independent prognostic factors for response. Although several authors indicated that some tumour types may be more responsive than others, combining all literature data on studies with ADIC-based regimens suggests the opposite [39]. The existence of prognostic factors for response is a major argument only to base conclusions on high-dose chemotherapy on properly designed randomised phase III studies.

CONCLUSION

Trying to achieve complete remissions appears the only way to improve survival in metastatic soft tissue sarcomas. The suggestions for the existence of a dose–response relationship in soft tissue sarcomas are several-fold, but all come from non-controlled phase II studies. Anthracyclines, still the backbone of combination chemotherapy in soft tissue sarcomas, are limited in their potential for dose intensification in view of their side-effects. Moreover, this approach rapidly leads to cumulative myelotoxicity. Based upon the available data, there appears to be no justification for further use of epidoxorubicin in this disease. Also, ifosfamide data on dose and schedule are far from consistent.

Data on very high doses of chemotherapy supported by autologous bone marrow rescue or peripheral stem cell transplantation are scanty for soft tissue sarcomas and in view of the above can therefore not be considered as conclusive evidence for the value of this approach. The above-mentioned EORTC study [34] does not lend support to over optimistic expectations on the efficacy of such a schedule.

Administration of combination chemotherapy and dose intensification in the treatment of soft tissue sarcomas have both sometimes produced higher response rates, but this strategy never resulted in significantly longer overall survival. Until results of phase III studies show any improvement of high-dose chemotherapy over standard-dose chemotherapy, high-dose chemotherapy for soft tissue sarcomas should be considered as investigational.

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Arbiter

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SOFT TISSUE sarcoma of adults is not highly responsive to chemotherapy. Doxorubicin is the best single agent, but a dose of 60–75 mg i.v. every 3 weeks produces a response rate only of the order of 20% (15–35%) and change in the schedule of administration has not resulted in improvement [1]. The analogue epirubicin has been evaluated in a large randomised trial by the EORTC but no advantage over doxorubicin has been demonstrated [2]. Other analogues have also been shown to have limited activity. Ifosfamide is also of value in treating patients with advanced sarcoma and is capable of producing tumour responses in patients previously treated with doxorubicin. Its use as a single agent produces responses of a similar magnitude to doxorubicin [3, 4]. Other alkylating agents have limited or no activity in adult patients with sarcoma. The case for dacarbazine (DTIC) having useful activity is less convincing, but the agent when used singly has been reported in the early literature to be accompanied by a response rate of 17% [5]. A large number of other single agents have been evaluated in phase II trials but no useful response rates have been observed, although these drugs have usually only been tested in previously treated and refractory patients. The agents we have available provide only modest benefit and new more effective agents are urgently required.

The evidence for combination chemotherapy being more effective than full-dose single-agent doxorubicin therapy is rather weak and, although some randomised trials have shown a beneficial effect associated with the addition of ifosfamide or DTIC to doxorubicin in terms of response rate, survival has not been improved [1, 6, 7]. Other randomised studies have shown no such benefit [8–10], although the results may have been compromised by the addition of relatively ineffective drugs (cyclophosphamide and vincristine) in the first two studies and the use of a lower dose of doxorubicin in the group of patients receiving combination chemotherapy in the EORTC study [10].

Some evidence that the dose and dose intensity of doxorubicin is important in improving the response rate is available [11], but no studies have been carried out with an appropriate randomised design to confirm this. However, two randomised studies comparing different dose intensities of the CYVADIC combination have shown an advantage for the higher dose intensity [12, 13], although the higher dose intensity was the standard approach and the alternative schedule was of lower intensity. It is difficult to increase the dose intensity of doxorubicin to levels providing a realistic chance of improving the complete response rate and survival for adults with sarcoma. A 5-fold increment in dose intensity has been obtained using G-CSF but the doses of 100–150 mg every 2 weeks × 3 were accompanied by unacceptable toxicity [14].

Relatively modest increases in the dose intensity of single-agent ifosfamide (up to 3-fold) have produced responses in patients shown to be refractory to standard-dose therapy [15, 16]. The response rate associated with the higher doses, 28–55%, seems promising but this apparent advantage requires confirmation using a randomised study.

Single-agent studies suggest that a dose-intensive combi-