Soft Tissue Sarcomas

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Soft tissue sarcomas are rare malignant mesenchymal tumors (43). Usually they are classified according to their parent tissue of origin (52), but it is not always possible to subtype every tumor, despite important new diagnostic procedures such as electron microscopy and immunohistochemistry. Malignant fibrous histiocytoma, rhabdomyosarcoma, liposarcoma, synovial sarcoma, and undifferentiated sarcoma appear to be the most frequently occurring subtypes (30,54). Although histologic subtyping has prognostic relevance, the histologic grade (50) and the size of the primary tumor (55) were found to be more important prognostic criteria. Indeed histologic grade is the most important prognostic factor, and it has been included in the American Joint Committee (AJC) staging system, as has tumor size (47). The stages in this system have been shown to correlate well with survival (46). Unfortunately, grading has been poorly defined for a long time, which has prevented widespread use of this parameter. However, two reports (12,13) have indicated that the extent of necrosis within the tumor, the number of mitoses, and the differentiation of the tumor are the most important determinants of grade. Both reports define subgrades of each of these parameters, which allow more standardized grading. Hopefully this will initiate more frequent inclusion of these parameters into future studies.

Surgery continues to be the main treatment modality of soft tissue sarcomas. Depending on the localization of the primary, as well as the possibility of additional treatment, amputation or wide excision of the primary tumors should be performed. However, local recurrence rate after surgery alone is as high as 40 to 80% (38), with most relapses occurring within 3 years (25). The presence of a misleading pseudomembrane consisting of compressed cells and the possibility of a multifocal origin are probably responsible for the high local recurrence rate.

Combining surgery with high-dose irradiation has been found to reduce the frequency of local recurrence (1,18,24,43) in extremity lesions, but distant metastases still occur frequently. They develop mainly by hematogenous spread, and in many instances their first site of appearance is the lung. The high dose of irradiation necessary for effective treatment of soft tissue sarcomas precludes adequate application of this technique to abdominal lesions.
The frequent development of advanced disease has provided the rationale for the use of chemotherapy, and over the past few years results have improved slowly. Doxorubicin (DOX) was found to be the most active drug (7), and the addition of DTIC (dacarbazine) further improved the results. At present, complete remission is achieved in only a small number of patients, but there is some evidence that a limited number of these complete responders have a chance of cure (61). The results of chemotherapy in advanced disease have stimulated studies on pre- and postoperative chemotherapy. Stratification for histologic types within such studies, because of observed differences in incidence, rate of dissemination, and survival for different histologic subtypes, would allow more proper interpretation of the results of treatment. Unfortunately, such trials seem hardly possible.

This chapter focuses on the results of randomized clinical trials in adult soft tissue sarcomas. We only briefly mention results of nonrandomized trials as far as they are thought to be of importance for proper interpretation of the present state of the art concerning treatment of soft tissue sarcomas.

**SINGLE-AGENT CHEMOTHERAPY**

In adult soft tissue sarcomas DOX remains the most effective single agent. In more than 1,000 reported patients the cumulative response rate was 23% (57). A dose of 60 to 75 mg/m² or more every 3 weeks has been found to be much more effective than a dose of 50 mg/m² or less with the same interval (33,38). This relatively high dose of DOX required for activity in soft tissue sarcoma limits the opportunities of combining the drug with other myelosuppressive agents and presents, in addition, the problem of cardiotoxicity. These facts have triggered studies of alternative scheduling and research on less cardiotoxic anthracycline analogs. Borden et al. (8) have randomly compared a dose of 70 mg/m² every 3 weeks with a weekly dose of 15 mg/m². Both schedules resulted in a similar response rates: 19% and 16%, respectively (Table 1). The reason for these relatively low response rates remains unclear. Toxicity was found to be less with weekly administration, but this has not been a consistent finding (11,29). The EORTC Soft Tissue and Bone Sarcoma Group conducted two randomized phase II trials comparing DOX with the analogs carubicin (carminomycin, CMM) and epirubicin (4'-epidoxorubicin; epiDOX) (9,32) (Table 1). Both studies confirmed the activity of DOX 75 mg/m² every 3 weeks in soft tissue sarcomas, with response rates of 29% and 25%, respectively. Carubicin at a dose of 20 mg/m² every 3 weeks was inactive with a response rate of only 3% in 33 patients (9) in contrast to the 27% response rate in a previously reported nonrandomized study (36). With epirubicin a 15% response rate was achieved in 79 patients, which was not statistically different when compared with the response to DOX. Epirubicin (32) was found to cause significantly less leukocytopenia and was slightly less toxic in regard to nausea and
vomiting. Other toxicities were not decreased. The study did not permit the evaluation of cardiotoxicity at high cumulative dose levels. Although the response rate with epirubicin does not statistically differ from that with DOX, the results do not appear to promote epirubicin as an interesting alternative to DOX, but one should consider that nonequivalent doses were used. Trials to decrease cardiotoxicity by administering DOX as a continuous intravenous infusion have not been performed in a randomized way.

A second interesting drug in the treatment of soft tissue sarcomas appeared to be ifosfamide (IFX). Initial nonrandomized studies had shown response rates of 38 to 67% with a cumulative mean of 46% in more than 100 patients (57). However, also for this drug the phenomenon of decreasing response rates with an increasing number of studies could be observed. For this reason and because of scarce data on the activity of cyclophosphamide (CTX) in adult soft tissue sarcomas, the EORTC Soft Tissue and Bone Sarcoma Group has initiated a randomized phase II trial comparing CTX 1.5 g/m² every 4 weeks with IFX 5 g/m² every 4 weeks, both with mesna for prophylaxis against bladder toxicity (Table 1). In this ongoing trial overall response rates are 8% in 36 patients treated with CTX and 12% in 40 patients treated with ifosfamide (unpublished data). However, in nonpretreated patients response rates are 13% and 20%, respectively. Thus it seems that single-agent CTX may be considered to have minor activity in adult soft tissue sarcomas, and ifosfamide is much less active than initially thought, although its response rate in nonpretreated patients still compares favorable to most other single agents. Thus it may still be an interesting drug, particularly because of the manageable minor toxicities. For this reason

### Table 1. Randomized trials of single-agent chemotherapy for soft tissue sarcomas

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/m²)</th>
<th>No. of patients</th>
<th>Response (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOX</td>
<td>70 q 3 weeks</td>
<td>93</td>
<td>CR 6</td>
<td>PR 13</td>
</tr>
<tr>
<td>DOX vs.</td>
<td>15 q 1 week</td>
<td>92</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>DOX</td>
<td>75 q 3 weeks</td>
<td>38</td>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMM</td>
<td>20 q 3 weeks</td>
<td>33</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>DOX</td>
<td>75 q 3 weeks</td>
<td>84</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EpiDOX</td>
<td>75 q 3 weeks</td>
<td>79</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>DOX</td>
<td>60 q 3 weeks</td>
<td>79</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclol.</td>
<td>200–300a × 8 q 4 weeks</td>
<td>81</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CTX</td>
<td>1.5b q 4 weeks</td>
<td>36</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFX</td>
<td>5b q 4 weeks</td>
<td>40</td>
<td>0</td>
<td>12</td>
</tr>
</tbody>
</table>

a Milligrams per kilogram.

b Grams per square meter.

c EORTC unpublished data.
the EORTC group has started a phase II study using DOX 50 mg/m² plus ifosfamide 5 g/m² every 4 weeks.

The only other commonly used drug with some known activity as a single agent is DTIC, which achieves a response rate of 16%. However, this drug has not been studied in randomized trials. This may be because of the observed increase response rate with the combination of DOX plus DTIC (20) compared with either one of these two drugs. Data on the other drugs active in childhood sarcomas, especially vincristine (VCR) and actinomycin D, are not available for adult soft tissue sarcomas. All other drugs tested may be considered inactive (56); this judgment also applies to cycloleucine (cyclol.), which was compared to DOX in a large randomized trial (Table 1). Response rate was only 7% in 81 patients (48).

COMBINATION CHEMOTHERAPY

The combination of DOX plus DTIC (ADIC) remains the basis for many other combinations used for soft tissue sarcomas. The response rates achieved with ADIC varies from 30 to 47% with 4 to 11% complete remissions (6,20,38). These results have been confirmed in a randomized trial by ECOG (8) comparing DOX with ADIC (Table 2). Whereas DOX as a single agent gave 16 to 19% responses depending on schedule (see above), the combination of DOX 60 mg/m² on day 1 plus DTIC 250 mg/m² on days 1 to 5 every 3 weeks resulted in a 30% response rate, with 4% complete responses. However, the combination was far more toxic, and median survival did not differ. A similar trial on uterine

<table>
<thead>
<tr>
<th>Combination</th>
<th>No. of patients</th>
<th>CR</th>
<th>PR</th>
<th>Overall</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOX</td>
<td>93</td>
<td>6</td>
<td>13</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOX/DTIC</td>
<td>95</td>
<td>4</td>
<td>26</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOX</td>
<td>80</td>
<td>6</td>
<td>10</td>
<td>16</td>
<td>35</td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYVADIC</td>
<td>66</td>
<td>11</td>
<td>13</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCR/CTX alternating DOX/DTIC</td>
<td>78</td>
<td>5</td>
<td>9</td>
<td>14</td>
<td></td>
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<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOX</td>
<td>57</td>
<td>8</td>
<td>21</td>
<td>29</td>
<td>48</td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOX/VCR/CTX</td>
<td>62</td>
<td>3</td>
<td>16</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DACT/VCR/CTX</td>
<td>57</td>
<td>2</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOX/CTX/MTX</td>
<td>41</td>
<td>4</td>
<td>34</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOX/CTX/MTX/amfot.B</td>
<td>46</td>
<td>0</td>
<td>10</td>
<td>10</td>
<td></td>
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</tbody>
</table>
sarcomas was reported by Omura et al. (35), achieving a 16% overall response rate (five complete and eight partial responses) with DOX 60 mg/m² every 3 weeks in 88 patients and a 24% overall response rate with ADIC in 66 patients (seven complete and nine partial responses). Dose and schedule of ADIC were the same as those used by ECOG. Again no survival advantage was observed. Although these results are somewhat disappointing compared with previous studies mainly because they did not show any survival advantage, they still confirm higher response rates achieved with ADIC than with DOX as a single agent.

Triggered by the additive effect of DOX and DTIC, Gottlieb developed the combination of CTX, vincristine (VCR), DOX and DTIC (CYVADIC), which has become the regimen studied most extensively. Initially the SWOG reported response rates up to 59% for this combination, but this response rate dropped to 49% in their updates (59,60). Other nonrandomized studies have more or less confirmed the activity of this combination, achieving a 27 to 53% response rate with 7 to 18% complete responses (10,22,37) by using the original schedule or minor modifications. Only one randomized trial of CYVADIC in advanced soft tissue sarcomas was performed (39) (Table 2). This EORTC study compared CYVADIC (CTX 500 mg/m² i.v. on day 1, VCR 1.5 mg/m² on day 1, DOX 50 mg/m² on day 1, and DTIC 250 mg/m² on days 1–5) with a schedule alternating ADIC and VCR/CTX (in doses similar to those used with CYVADIC) at 4-week intervals. The overall response rate achieved with CYVADIC in 84 patients was 38%, with 17% complete responses and 21% partial responses, whereas in 78 patients in the cycling arm a response rate of only 14% was achieved (p = 0.001) reflecting the lower activity of CTX/VCR compared with that of ADIC. These results suggest that alternating noncross-resistant combinations of the currently known cytotoxic drugs do not benefit the adult soft tissue sarcoma patients (14,39). Moreover, it indicates that DOX should be given every 3 or 4 weeks as in the original ADIC and CYVADIC schedules, instead of every 8 weeks. Another very important observation within this EORTC study is the fact that response rate was much higher in patients with good performance scores (PSs). In fact, the PS was the single most important prognostic factor, which may explain part of the variability in reported response rates. It appears that stratification for PS is essential in future studies on soft tissue sarcomas. The observation that old patients appear to be less responsive is probably related to the necessity of dose reduction as well as their generally poorer PS (39).

The SWOG has reported a randomized trial comparing CTX, DOX, and DTIC—in fact, a CYVADIC modification with ADIC and with DOX, DTIC, and DACT (actinomycin D). Among 243 patients, response rates were 33%, 22%, and 25%, respectively (5).

The ECOG (49) reported a randomized trial comparing 3-weekly DOX 70 mg/m² with DOX 50 mg/m² on day 1, VCR 1.4 mg/m², and CTX 750 mg/m² on day 1 every 3 weeks; this regime was compared with DACT 0.4 mg/
m² on day 1, VCR 1.4 mg/m² on day 1, and CTX 750 mg/m² on day 1 every 3 weeks as well. The problem in interpreting their results is the fact that early death and nonevaluable patients as well as patients with bone sarcomas appear to be included in their results. DOX achieved a 29% response rate, whereas the combinations achieved only 19% and 11% responses, respectively. These and previously mentioned SWOG results (5,46) may suggest that DACT is an inactive agent in adult soft tissue sarcomas and that VCR does not add much to the activity of DOX.

The SECSG has treated 188 patients with soft tissue sarcomas with DOX 60 mg/m² on day 1, CTX 600 mg/m² on day 1, and methotrexate (MTX) 25 mg/m² on day 1 every 3 weeks (ACM) followed by randomization to receive either ACM, DACT 1 mg/m² on day 1, DTIC 250 mg/m² on day 1, and VCR 1.4 mg/m² on day 1 weekly (ADV) or a regimen alternating ACM and ADV (41). Of these 188 patients, 37 achieved a response, but these data have not been specified. Of the total group of 232 patients, including those with bone sarcomas and mesotheliomas, 16% achieved a remission after the initial two ACM cycles, whereas only an additional 4% achieved a remission during maintenance treatment. These results indicate the minor activity of ACM, although the high number of leiomyosarcoma patients entered in the study may have influenced these results negatively to a certain extent. This again stresses the necessity for stratification for histologic subtypes. ACM and ADV appeared to be cross-resistant schedules, and in fact ADV should be considered ineffective. Maintenance treatment using these regimens did not increase duration of response or survival.

In a second randomized study the SECSG compared ACM with ACM + amphotericin B (40) (Table 2). The latter drug was given because of a postulated membrane-permeabilizing effect which was thought to increase cellular uptake of antitumor drugs. However, although the response rate on ACM was higher than in the previous study (38% in 41 patients), the result of adding amphotericin B in 46 patients was a response rate of only 10% (p < 0.05). This indicates that the addition of amphotericin B does not provide therapeutic advantage, although a part of the decreased response rate to the combination ACM + amphotericin B may be explained by the decreased doses of DOX, CTX, and MTX compared with the original schedule. Moreover, this study again reported the uselessness of ACM maintenance treatment.

All other studies of combination chemotherapy for adult soft tissue sarcomas have been nonrandomized. None was able to show advantage over single-agent therapy with DOX or combination chemotherapy with ADIC, either because of decreased response rates or because of unfavorable toxicity (56). Moreover, some of these studies appear to confirm that VCR and/or DACT, and possibly also CTX, do not add much to the effect of ADIC. Still, one may not conclude that CYVADIC has no advantage at all over ADIC because the number of complete responses achieved with CYVADIC is usually higher. Especially for some of these complete response patients, the administration of chemotherapy
may appear to be worthwhile, as YAP et al. (61) reported 21% of them to be alive and free of disease after 5 years or more. This indicates that patients with advanced soft tissue sarcomas may potentially be cured with chemotherapy.

The time necessary to achieve a response may vary greatly (39,59). In the EORTC study with CYVADIC the median time to response was 8 weeks (39), but more prolonged intervals have also been reported, reflecting the occasional slow regression of soft tissue sarcomas. Not only may complete response patients potentially be cured, but many studies indicate that any form of response appears to increase survival compared to nonresponders (26,39,41,53,59). However, the results of other studies seem conflicting concerning this subject (8,35). Interestingly, there are some indications that conversion of a partial remission after chemotherapy to a complete response by surgery may improve prognosis. As relapse is particularly likely to occur at the site of the primary tumor, perhaps future studies should consider adjuvant surgery or radiotherapy after achieving a response with chemotherapy.

**ADJUVANT TREATMENT MODALITIES**

Pre- and postoperative chemotherapy as well as pre- and postoperative irradiation have been applied as adjuvant treatment modalities in soft tissue sarcomas. Of these, the postoperative addition of radiotherapy appears to be the most important gain. Before the use of postoperative irradiation soft tissue sarcomas were characterized by a tendency to develop local recurrence after surgery in as many as 40 to 80% of cases (38). The combination of wide surgical excision or amputation followed by high-dose irradiation has been shown to reduce the frequency of local recurrence (1,18,24,43). However, randomized studies on this subject have not been performed, and application of radiotherapy seems useful only in extremity lesions, as head and neck and trunk localizations may limit the administration of high doses because of the risk of serious toxicity.

Although postoperative radiotherapy reduces the frequency of local recurrence, distant metastases still develop in an important number of cases. Because of the fairly good responses to chemotherapy achieved in patients with advanced soft tissue sarcomas and a high performance status, as well as the encouraging results obtained in osteosarcomas, studies on preoperative chemotherapy seem justifiable. The aims of such treatment are reduction of tumor size, thereby allowing less complicated surgery, and the irradiation of possible micrometastases. Preoperative chemotherapy may be given intraarterially or systemically, but data on the latter route are equivocal. No randomized studies on preoperative intraarterial chemotherapy have been performed, but the results of several non-randomized studies (4,17,19,21,23,27,31,58) suggest that this technique facilitates surgery, decreases local recurrence rates, and increases survival. However, we believe that the technique should be applied only in specialized centers because of the risk of serious complications such as tissue necrosis, sepsis, and even
death. Furthermore, randomized studies on this subject, including a group of patients not receiving preoperative chemotherapy, are required before more definite conclusions can be drawn.

The first study drawing attention to adjuvant chemotherapy came from the National Cancer Institute (NCI). Rosenberg et al. (42), investigating the possibility of preventing local recurrence with postoperative local irradiation, also applied adjuvant chemotherapy with DOX 50 to 70 mg/m² and CTX 500 to 700 mg/m², followed by high-dose MTX with leucovorin rescue after a cumulative DOX dose of 550 mg/m² was reached. They observed an increased disease-free and overall survival in patients with extremity lesions who had received adjuvant chemotherapy compared to historical controls. For head, neck, and truncal sarcomas, this improvement did not appear (44). These results prompted the same investigators to initiate a randomized study using the same adjuvant chemotherapy regimen in one arm but including a control group not receiving adjuvant chemotherapy. The 3-year actuarial disease-free survival in patients with soft tissue sarcomas of the extremities was 92% for the 37 patients in the chemotherapy group compared with 60% for the 28 patients in the control group (Table 3) (45). The 3-year actuarial overall survivals were 95% and 74%, respectively. For extremity lesions, the type of surgery did not influence the results; however, the difference in the effect of adjuvant chemotherapy in patients with soft tissue sarcomas of the extremities, compared with the effect of the same chemotherapy in lesions of head, neck, and trunk, may be due to differences in the ability to achieve local control.

In another randomized study alternating adjuvant VCR/CTX/DACT with VCR/DOX/DTIC at 6-week intervals (Table 3), investigators from the Mayo Clinic (16) reported a 4-year disease-free survival of 70% in patients receiving adjuvant chemotherapy and 60% in those not receiving adjuvant chemotherapy. The overall survival at 4 years was 92% and 82%, respectively. However, the use of inactive agents in one of the alternating regimens and the administration of ADIC at only 12-week intervals may have influenced the observed absence of advantage of adjuvant chemotherapy. The good local control and survival rate for both groups may also be attributed to the use of an aggressive surgical program.

Antman et al. (3) have performed a small randomized study comparing 17 patients receiving DOX 90 mg/m² every 3 weeks for a total of five courses with 19 patients not receiving adjuvant chemotherapy (Table 3). The actuarial disease-free survival at 30 months is 54% in the treated group and 64% in the control group, and the actuarial overall survival is 87% versus 68%. A nonsignificant advantage was found for extremity lesions.

Currently the EORTC Soft Tissue and Bone Sarcoma Group is running a large randomized trial comparing eight cycles of adjuvant CYVADIC with no adjuvant chemotherapy. The study also includes stratification for localization of the primary tumor and postoperative concurrent administration of local radiotherapy. Over 300 patients have been entered already, but no significant difference between the two arms has been observed to date (unpublished data).
Omura et al. (34) reported a randomized study using DOX 60 mg/m² every 3 weeks in 77 patients with uterine sarcomas (Table 3). No improvement of survival was seen compared with survival in 82 patients who did not receive adjuvant chemotherapy.

Adjuvant chemotherapy in these studies is usually started after completion of postoperative irradiation, within 6 to 12 weeks following surgery. Although the results of some nonrandomized studies (2,15,28,51) suggested that there is a place for adjuvant chemotherapy in soft tissue sarcomas, the investigations should be considered to be of limited value because of the selection of patients due to the modern diagnostic techniques such as lung tomography and computed tomography scanning. Because of the application of these techniques, some patients who would previously have been considered to be free of clinical detectable dissemination, are now ineligible for adjuvant studies. In this context the observation of Rosenberg et al. (45) that patients in the no-treatment arm in their randomized study survived significantly better than those in the historical control group who did not receive chemotherapy in their nonrandomized study deserves special attention and emphasizes the need to perform prospective randomized trials.

**CONCLUSIONS**

Surgery remains the cornerstone of treatment of soft tissue sarcomas, and postoperative radiotherapy appears to decrease the local recurrence rate in extremity lesions. Although the results of chemotherapy for patients with advanced
soft tissue sarcomas have improved, DOX remains the most active single agent. Based on present data we advocate 3-weekly bolus administrations at doses higher than 50 mg/m². The less myelotoxic analog epirubicin merits further study in combination chemotherapy but should not yet be considered to be as active as DOX. Although the initial enthusiasm has been tempered, ifosfamide remains an interesting drug that should be incorporated in combination chemotherapy for further study.

For combination chemotherapy ADIC or CYVADIC is probably the best choice. Although definite data on increased activity with the addition of CTX and VCR are lacking, we tend to prefer CYVADIC because of the slightly higher reported complete response rate.

Adjuvant chemotherapy should not be considered standard treatment. The data are conflicting in extremity soft tissue sarcomas, and no advantage has been observed in head and neck or in trunk lesions. Preoperative intraarterial chemotherapy in locally advanced inoperable soft tissue sarcomas may offer further improvement in survival but must be studied in a randomized fashion before further conclusions can be drawn.

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