6. Chemotherapy in advanced soft tissue sarcomas

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With local recurrence rates of 40%–80% [1] and most of these relapses occurring within 3 years [2], soft tissue sarcomas have always been a difficult tumor type for adequate local treatment. Although sophisticated surgical techniques and the addition of postoperative high-dose radiotherapy have considerably reduced the number of local recurrences in extremity lesions [2–5], the inability to apply the necessary high doses of irradiation precluded a decrease in local recurrence in truncal lesions by using the combination of surgery and radiotherapy. Besides, soft tissue sarcomas metastasize by (apparently early) hematogeneous spreading, most frequently to the lungs, which can only partly be prevented by optimal local control of the primary tumor. Therefore, distant metastases still occur in a considerable number of patients, for whom systemic treatment with chemotherapy will be considered.

This chapter summarizes previous achievements in the chemotherapy of advanced soft tissue sarcomas and discusses in detail some new developments and future topics.

Single-agent chemotherapy (Table 1)

Doxorubicin

The first drug identified as active single agent in the treatment of adult soft tissue sarcomas was doxorubicin (DX) [6], which, after this first report, has now been studied in almost 1200 patients [7, 8], yielding an overall response rate of 22% in nonpretreated patients, while preliminary data from a study by the European Organisation on Treatment and Research of Cancer (EORTC) also suggest activity of the drug in pretreated patients. A dose–response relationship has been established for DX, with doses of 60 mg/m^2 or more producing higher response rates than doses of 50 mg/m^2 or less [1, 9], when the drug is given every 3–4 weeks. The intermittent high-dose treatment schedule was generally assumed to be the most effective, but limited possibilities of combining DX with other myelosuppressive drugs and introduced the problem of cardiotoxicity. These limitations have stimulated studies on alterna-

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Table 1. Active single agents

Drug	Previous chemotherapy	No. of patients	Response rate (%)		Ref.
			Overall	Range	
Doxorubicin	No	1192	22	15–30	7, 8
DTIC	Yes	95	17	17–17	14, 15
Ifosfamide	No	93	24	23–25	20, 21
	Yes	117	36	7–65	16–21

tive schedules of DX administration, as well as research on less cardiotoxic anthracycline analogs.

Although previous studies suggested that weekly DX administration was equally as myelotoxic as one administration of DX every 3 weeks [10, 11], the recently reported Eastern Cooperative Oncology Group (ECOG) study randomizing DX 15 mg/m^2 weekly after an initial loading course, with DX 70 mg/m^2 every 3 weeks and with DX–DTIC (dacarbazine) [8], strongly indicates the opposite. The weekly DX administration resulted in more stomatitis (not significant) and less hematologic toxicity ($p > 0.05$) than did one administration of DX every 3 weeks. The weekly DX administration was as active (16% responses) as the administration of DX once every 3 weeks (18% responses), but this is a disappointing response rate for both.

One reason that the majority of soft tissue sarcoma patients do not respond to anthracyclines may be an overexpression of P-glycoprotein, as suggested by Gerlach et al. [12]. P-glycoprotein is a cell-surface glycoprotein involved in the active cellular outward transport of a.o. anthracyclines, and is overexpressed in association with the multidrug-resistant (MDR) phenotype. In six of 25 sarcoma patients, this MDR phenotype was found. Another alternative DX administration may be continuous infusion, which is thought to be less cardiotoxic [13]. However, its single-agent activity rate is unknown due to the absence of a phase II study.

The reasons for evaluating DX analogs in soft tissue sarcomas are obvious. Presently, DX is the most active single agent in this disease, while DX analogs are considered to have a more favorable therapeutic index as compared with the parent drug, mainly because of the expression of lesser degrees of myelosuppression and cardiac toxicity. The results of recently performed clinical trials with DX analogs and mitoxantrone are summarized in Table 2. Studies containing adequate numbers of patients are as yet limited. The EORTC Soft Tissue and Bone Sarcoma Group evaluated two DX analogs, carminomycin and epirubicin, respectively. Both drugs were compared in a randomized phase II trial with the parent drug, DX. Importantly, both studies were performed in patients without previous chemotherapy, which offered the new drugs an optimal chance to express significant antitumor activity.

Carminomycin [14] was shown to be inactive, while epirubicin [15] had

Table 2. Activity of doxorubicin analogs and mitoxantrone in advanced soft tissue sarcoma

Drug	No. of evaluable patients	No. of responders			Response rate (%)	Ref.
		CR	PR	Total		
Epirubicin	21 (20)	0	0	0	0	16
Epirubicin	84	4	11	15	18	15
vs						
doxorubicin	83	6	15	21	25	
Carminomycin	33	0	1	1	3	14
vs						
doxorubicin	38	1	10	11	29	
Aclarubicin	23	0	1	1	4	17
Idarubicin	35 (24)	1	1	2	6	19
Esorubicin	20 (1)	0	1	1	5	18
Mitoxantrone	46 (33)	0	0	0	0	20
Mitoxantrone	61 (61)	0	1	1	1.5	21

CR, complete remission; PR, partial remission; and ( ), number of patients with prior chemotherapy.

antitumor activity comparable to that of DX. The response rate (25%) to DX was slightly better than the response rate (18%) to epirubicin, but this difference was statistically not significant. On the other hand, toxicity of epirubicin was significantly less than that of DX, especially with respect to myelosuppression. These observations might be due to the fact that equimolar doses of both drugs were used. When doses of both drugs were used producing equal myelosuppression, it would not be surprising when epirubicin and DX were fully comparable in the treatment of soft tissue sarcoma, both with respect to efficacy and toxicity. However, a trial taking this into account has not been performed as yet. The only other study on epirubicin [16] was done in patients with prior chemotherapy, mainly consisting of DX-containing regimens. Not surprising, no responses were obtained. It seems highly unlikely that a significant number of DX-resistant patients will respond to subsequent treatment with epirubicin, due to cross resistance between epirubicin and DX. The occasional observation that cross resistance between both drugs may not be complete, as was suggested in the EORTC study [15], does not justify the use of epirubicin after resistance to the parent drug. The other DX analogs have been investigated to only a limited extent. Aclarubicin [17] and esorubicin [18] seem to have been evaluated in an adequate number of non-pretreated patients to conclude that both drugs are inactive in advanced soft tissue sarcoma. However, idarubicin [19] has mainly been studied in patients resistant to DX. Thus, a definite conclusion as to the efficacy of idarubicin is presently not possible.

Mitoxantrone, an anthraquinone derivative structurally related to DX, at present has been studied mainly in DX-resistant patients [20, 21], with

minimal to absent antitumor activity. However, its value in nonpretreated patients is not known.

DTIC

The second drug with single-agent activity is DTIC. The first phase II study on this drug resulted in a 17% response rate in 53 patients [22]. Based on this single report, the drug was incorporated into combination chemotherapy. Only recently could the data be confirmed by a phase II study conducted by the EORTC Soft Tissue and Bone Sarcoma Group. Using DTIC at a dose of 1.2 g/m^2 by short-term infusion every 3 weeks, they achieved one complete and six partial remissions in 42 evaluable patients [23], with relatively limited toxicity.

Ifosfamide

The third active drug in the treatment of soft tissue sarcomas is ifosfamide (IFOS). Although the initially reported response rate of 65% [24] has never been confirmed, the compilation of all presently available reports indicates that the drug has activity comparable to that of DX (Table 1) [25–29]. Using the drug in a daily ×3–5 schedule appears to result in similar response rates as using the 24-h infusion once every 3 weeks. The optimal total dose of IFOS to be administered is 5 g/m^2. In pretreated patients, the overall response rate was 36% [24–29], while it was 24% in nonpretreated patients [28, 29], a difference mainly caused by the inclusion of the never-confirmed initial data in pretreated patients. The results of the two studies in nonpretreated patients are practically identical and offer a firm base for the conclusion that this drug has activity in the treatment of soft tissue sarcomas. On the other hand, the results obtained in nonpretreated patients clearly indicate that a truly active drug in soft tissue sarcomas will also be discovered by phase II studies in pretreated patients, a conclusion confirmed by the recent EORTC DTIC data [23]. Based on all IFOS studies, no single histological subtype has shown a preferential sensitivity for the drug, although it is interesting that four of eight patients with mixed mesodermal sarcomas, included in the EORTC study, responded [29].

Cyclophosphamide

Without the availability of single-agent data, cyclophosphamide has previously been incorporated into combination chemotherapy regimens. One of the important findings of the EORTC study randomizing IFOS versus cyclophosphamide was that cyclophosphamide cannot be considered to be a drug with interesting activity [29]. Even using a high dose of 1.5 g/m^2, the EORTC Soft Tissue and Bone Sarcoma Group achieved an overall response rate of only 8%: 13% for 38 nonpretreated patients and 0% for 29 pretreated patients.

Mixed mesodermal sarcoma may be the only histological subtype for which this cannot be concluded, because two of five patients did respond [29]. However, IFOS achieved similar results in this tumor type [29].

Other phase II studies

A variety of established and new antineoplastic agents have recently been studied in advanced soft tissue sarcoma. The results of the recently performed phase II studies on these drugs are summarized in Table 3. Of course, almost all of the patients in these trials had been pretreated with standard chemotherapy regimens. With one exception, disappointingly low response rates ranging from 0 to 6% were achieved in all of these studies. As a consequence, these drugs, inactive in pretreated patients, do not warrant testing up front. CDDP (cisplatin) is the only exception among the drugs listed in Table 3.

In a study by Sordillo et al. [38] of 26 nonpretreated patients, CDDP at a conventional dose of 120 mg/m^2 every 3–4 weeks did not show significant antitumor activity with a response rate of only 4%, confirming previous reports. In contrast, a study conducted by the Southwest Oncology Group (SWOG) [39] yielded a remarkable response rate of 24%. In this study, CDDP was used at a high dose of 40 mg/m^2 on 5 consecutive days, every 4 weeks. Moreover, all patients were heavily pretreated, while one patient had failed on a standard-dose CDDP regimen. Obviously, these data have to be confirmed by others before meaningful conclusions can be drawn, while the

Table 3. Activity of various established and new drugs in advanced soft tissue sarcoma

Drug	No. of evaluable patients	No. of responders			Response rate (%)	Ref.
		CR	PR	Total		
Methyl-GAG	18 (18)	0	0	0	0	30
Piperazinedione	19 (18)	0	1	1	5	31
Bleomycin	32 (32)	0	0	0	0	32
Chlorozotocin	37 (37)	0	1	1	3	32
MGBG	36 (36)	0	1	1	3	32
Bruceantin	34 (34)	0	0	0	0	32
Diaziquone	31 (31)	0	0	0	0	33
Bisantrene	17 (17)	0	0	0	0	34
Mitomycin C	16 (12)	0	1	1	6	35
Homoharringtonine	16 (16)	0	0	0	0	36
Cisplatin	19 (19)	1	0	1	5	37
Cisplatin	26 (0)	0	1	1	4	38
Cisplatin (high-dose)	17 (17)	0	4	4	24	39
TGU	19 (19)	0	0	0	0	40
VP-16	26 (24)	0	1	1	4	41
Fludarabine	20 (20)	0	0	0	0	42

CR, complete remission; PR, partial remission; and ( ), number of patients with prior chemotherapy.

Table 4. Activity of single-agent cisplatin in advanced mixed mesodermal sarcoma of the uterus

Dose/schedule	No. of evaluable patients	No. of responders			Response rate (%)	Ref.
		CR	PR	Total		
50 mg/m^2 i.v. q 3 weeks	28 (25)	2	3	5	18	45
75–100 mg/m^2 i.v. q 4 weeks	18 (7)	1	4	5	28	46

CR, complete remission; PR, partial remission; and ( ), number of patients with prior chemotherapy.

toxicity of such an approach also has to be taken into account. In contrast to other tumor types, data on biological response modifiers in the treatment of soft tissue sarcomas are very sparse.

In the recent literature, only two studies on interferon have been reported. In the first study [43], beta-interferon was evaluated in 20 patients, of whom 15 had received previous chemotherapy. One partial response was observed in a patient with fibrosarcoma. Gamma-interferon was studied by Edmonson et al. [44] in 16 patients with advanced soft tissue sarcomas; 14 patients had received prior chemotherapy. No objective responses were obtained. As for most other tumor types in advanced stages, interferons appear to be of little, if any, benefit to soft tissue sarcoma patients. The role of other biological response modifiers has presently not been tested in soft tissue sarcoma.

In contrast to the other types of soft tissue sarcoma, mixed mesodermal sarcoma of the uterus is sensitive to CDDP as was recently reported by Thigpen et al. [45] and Gershenson et al. [46] (Table 4). Of note, there were also responders among patients with prior chemotherapy. The relative insensitivity of mixed mesodermal sarcomas of the uterus to DX further distinguishes this disease from other soft tissue sarcomas as was recently reported by Morrow et al. [47].

VP-16 (etoposide) single-agent therapy has also recently been evaluated in this disease with a negative outcome [48]. In this study, 31 patients, 29 of whom had received previous chemotherapy, were treated with VP-16 at a dose of 100 mg/m^2 on days 1, 3, and 5, every 4 weeks. Only two patients experienced a short-term partial response.

In conclusion, in recent years, except for IFOS, no new antineoplastic agents or other treatment modalities have been developed for advanced soft tissue sarcomas. It is unlikely that epirubicin has a better therapeutic index as compared with DX in this disease, while the other DX analogs are probably inferior to the parent drug. Mitoxantrone has still to be evaluated in adequate numbers of nonpretreated patients. Definite results of high-dose CDDP should be awaited, as a preliminary report was promising. In mixed mesodermal

sarcoma of the uterus, CDDP has shown definite activity, so incorporation of this drug into combination chemotherapy should be evaluated.

Combination chemotherapy

After having noted efficacy in preliminary reports on DX and DTIC single-agent treatment, and based upon suggested synergism in preclinical studies, the SWOG initiated a study, utilizing DX 60 mg/m^2 on day 1 and DTIC 250 mg/m^2/day on days 1–5, repeated every 3 weeks. This regimen is known as ADIC [Adriamycin (doxorubicin)–DTIC] [49]. Because of an initial responses rate of 42%, ADIC has also been studied by other groups, and recently interesting results using this combination have been published.

The ECOG has performed a randomized trial comparing DX 70 mg/m^2 i.v. bolus on day 1 every 3 weeks, with DX 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 DX 60 mg/m^2 i.v. bolus on day 1 plus DTIC 250 mg/m^2/day on days 1–5 repeated every 3 weeks [8]. This trial thus questioned the influence of the dosing schedule of DX and the value of the addition of DTIC. Regarding activity, the single-agent DX regimens resulted in comparable response rates (18% and 16%, respectively), while the addition of DTIC significantly ($p < 0.02$) increased the response rate to 30%, mainly by increasing the number of partial remissions. Unfortunately, the higher response rate of the combination was not reflected in an increased overall survival.

Although the combination was more toxic than the single-agent DX treatments, especially regarding gastrointestinal toxicity, this did not result in a lower treatment compliance, indicating that the combination side effects in general appear tolerable.

The Gynecologic Oncology Group (GOG) performed a quite similar trial in uterine sarcomas [50], comparing DX 60 mg/m^2 on day 1 every 3 weeks with the same dose of DX plus DTIC 250 mg/m^2/day on days 1–5 every 3 weeks. A response was achieved in 13 (16%) of 80 DX-treated patients and in 16 (24%) of 66 ADIC-treated patients. This difference in response rate is not significant in this subset of patients.

Two other randomized trials also questioned the value of the addition of other drugs to DX. The ECOG previously studied DX 70 mg/m^2 every 3 weeks, versus DX 50 mg/m^2 plus cyclophosphamide (CTX, or Cytoxan) 750 mg/m^2 plus vincristine (VCR) 1.4 mg/m^2 all by i.v. bolus on day 1 every 3 weeks, versus CTX 750 mg/m^2 plus VCR 1.4 mg/m^2 plus actinomycin-D (DACT, or dactinomycin) 0.4 mg/m^2 i.v. bolus on day 1 every 3 weeks [51]. In a total of 200 patients, response rates were 27%, 19%, and 11%, respectively. The difference between the first and the latter regimens was significant ($p = 0.03$) in terms of response but not in terms of survival. This study strongly suggests that CTX and VCR do not add activity to DX, while replacing DX DACT with DX results in significantly decreased activity in such a way that one might

expect VCR, CTX, and DACT to have very limited value in the treatment of soft tissue sarcomas.

The GOG [52] randomly compared DX 60 mg/m^2 every 3 weeks, with DX 60 mg/m^2 plus CTX 500 mg/m^2 every 3 weeks in a total of 104 patients with uterine sarcomas. Both regimens resulted in a 19% response rate, again indicating that CTX does not add to DX.

The data above suggest that combination chemotherapy only results in improved response rates in comparison with single-agent DX if DX is combined with DTIC.

The ADIC regimen was tested against the same regimen plus either CTX or DACT in a SWOG study [53]. Patients were randomized to receive DX 60 mg/m^2 on day 1 plus DTIC 250 mg/m^2/day on days 1–5 every 3 weeks (the ADIC regimen), or ADIC plus CTX 500 mg/m^2 on day 1 every 3 weeks, or ADIC plus DACT 1.2 mg/m^2 on day 1 every 3 weeks. A total of 276 patients were evaluated. There was no statistically significant difference in response rates of 33%, 34%, and 24%, respectively. Also, median durations of response and survival were not significantly different. Toxicities from each of the treatment arms were equivalent. These data confirm the earlier mentioned ECOG study indicating the very limited value of CTX and DACT in the treatment of adult soft tissue sarcomas.

In an effort to lessen toxicity of the ADIC regimen, the SWOG initiated a study using a different schedule of DTIC administration [54]. The regimen consisted of DX 60 mg/m^2 i.v. on day 1 and DTIC 750 mg/m^2 as a 45-min infusion on day 1. Courses were administered at 21-day intervals. With 10 complete and 17 partial remissions in 114 evaluable patients, the overall response rate was 24%. Indeed, this regimen appeared to be very well tolerated with only moderate myelosuppression and moderate nausea and vomiting.

Recently, the SWOG presented the preliminary data from a randomized trial comparing the effectiveness of bolus versus continuous infusion administration of DX and DTIC [55]. The toxicity appeared to be reduced by the infusion regimen (104 evaluable patients) as compared with the bolus regimen (112 evaluable patients), while response rates were 22% and 23%, respectively.

Since 1972, the SWOG has reported several studies including the original ADIC regimen. A remarkable observation is the constant decrease in response rate over the years, starting with 42% and now at 23%. This might be related to the improvement in diagnostic techniques enabling a better evaluation of true responses.

Although the earlier discussed ECOG, GOG, and SWOG studies on combination chemotherapy regimens [51–53] and the single-agent data generated by the EORTC [29] at the moment do not support the inclusion of CTX in combination chemotherapy regimens, this drug together with VCR was incorporated with ADIC, resulting in the CYVADIC regimen [cyclophosphamide (Cytoxan)–vincristine–Adriamycin (doxorubicin)–DTIC] originally studied in M.D. Anderson Hospital and afterward adapted by several other groups.

The original CYVADIC regimen consisted of CTX 500 mg/m^2 i.v. on day 1, VCR 1.5 mg/m^2 i.v. on days 1 and 5, DX 50 mg/m^2 i.v. on day 1, and DTIC 250 mg/m^2/day i.v. on days 1–5 [56]. In the initial 125 patients studied, 21 complete remissions (CRs) (17%) and 42 partial remissions (PRs) (34%) were achieved. The median duration was 9½ months for CR and 7 months for PR. In subsequent follow-up reports including more patients, the response rate did not change [57, 58]. One of the important observations within this study was that the CR rate was much higher in patients <50 years of age than in those >50 [57]. Also, after having treated 331 patients with CYVADIC, the investigators could stress 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 [58]. Finally, also patients in PR who could be converted to CR experienced long-term survival, suggesting cure [58].

The only randomized study including CYVADIC that has been completed was reported by Pinedo et al. [59] on behalf of the EORTC group. It compared CYVADIC (CTX 500 mg/m^2 i.v. on day 1, VCR 1.5 mg/m^2 on day 1, and DX 50 mg/m^2/day on days 1–5 every 4 weeks with a schedule alternating VCR/CTX and ADIC in similar doses as used with CYVADIC, at 4-week intervals. With CYVADIC, 17% CRs and 21% PRs were achieved in 84 patients while, in the cycling arm, a significantly lower response rate of 5% CR and 9% PR was achieved in 78 patients ($p = 0.001$), reflecting the lower activity of CTX/VCR as compared with ADIC, which suggests that patients with soft tissue sarcomas do not benefit from alternating non-cross-resistant combinations of the currently known drugs, confirming results of earlier trials [60, 61]. Moreover, the EORTC results indicate that DX should be administered every 3 or 4 weeks instead of every 8 weeks [59].

Other studies have confirmed the activity of CYVADIC [62–64]. The regimen induces nausea and/or vomiting in almost all patients, as well as alopecia. Also leukocytopenia and thrombocytopenia appear to be substantial, but the regimen nevertheless is considered tolerable. The disadvantage of both the original ADIC and CYVADIC regimens is the necessity of hospitalization. To reduce the required number of treatment days and in an effort to reduce toxicity, shorter schedules have been studied [54, 64] (EORTC study 62851). Response rates and toxicity of these shortened treatments appear comparable to those of the original regimens (Table 5), but proof from a randomized trial is not available.

After confirmation of the activity of IFOS in soft tissue sarcomas [29], this drug was combined with DX. The Royal Marsden Group has treated 50 patients with DX 40–60 mg/m^2 i.v. on day 1 plus IFOS 5–8 g/m^2 by 24-h infusion on day 1 with mesna uroprotection [28], with courses repeated every 3 weeks. In 57 evaluable patients, they achieved 6 CRs (11%) and 11 PRs (19%) for an overall response rate of 30%. The optimal doses for the combination appeared to be DX 50 mg/m^2 and IFOS 5 g/m^2. Using that schedule, the EORTC Soft Tissue and Bone Sarcoma Group performed a phase II trial [65]. In 178 evaluable patients, 16 CRs (9%) and 47 PRs (26%) were noted

Table 5. Various schedules of DTIC infusion in ADIC and CYVADIC combination chemotherapy

Regimen	DTIC (days of treatment)	Total DTIC dose (mg/m^2)	No. of evaluable patients	Response rate (%)			Ref.
				CR	PR	Overall	
ADIC	1–5	1250	237	11	24	35	8, 23, 26, 27
	1	750	114	9	15	24	27
CYVADIC	1–5	1250	314	16	26	42	30, 32, 35, 36
	1–3	1200	60	7	42	49	37

Table 6. Combination chemotherapy: most extensively studied combinations

Drugs	No. of evaluable* patients	Response rate (%)			Ref.
		CR	PR	Overall	
DX–DTIC	351	10	21	31	8, 23, 26, 27
DX–DTIC–CTX–VCR	374	14	29	43	32, 35–37
DX–IFOS	235	9	25	34	38, 39

* Cumulative data.

for an overall response rate of 35%, in fact confirming the Royal Marsden data. The major toxicities were leukopenia, nausea and vomiting, and alopecia, all of which were manageable. Currently, the EORTC group is conducting a randomized trial comparing the DX–IFOS regimen with single-agent DX 75 mg/m^2 i.v. on day 1 every 3 weeks, and with CYVADIC administered 1 day every 3 weeks.

Other combinations have been studied, but none appeared to be superior to ADIC, CYVADIC, or DX–IFOS [66], and it is difficult to conclude which of these three is the best. Therefore, the results of the ongoing EORTC study are awaited with interest. In the meantime, it seems justified to use CYVADIC as standard regimen in patients treated outside of trials because, despite the absence of single-agent CTX and VCR activity, the reported studies indicate the highest overall response rate and, even more important, the highest CR rate with this regimen (Table 6). The CR patients may potentially be cured by chemotherapy [58], so it appears important to aim at achieving CR.

With the conclusion that DX, IFOS, and DTIC are the only active single agents in the treatment of soft tissue sarcomas, it seems logical to combine these three drugs. Indeed, at Dana Farber Cancer Institute, the first results of the use of such a combination are now available. A phase I study indicated that the maximum tolerated dose was DX 60 mg/m^2, DTIC 900 mg/m^2, and IFOS 7500 mg/m^2 per course when all were given together as a 72-h continuous infusion every 3 weeks [67]. Dose-limiting toxicity was leukopenia.

With antiemetics, Grade-3 nausea and vomiting were infrequent. Other toxicities were remarkably mild. Using this regimen in a phase II study of 62 evaluable patients [68], 6 CRs (10%) and 26 PRs (42%) were achieved. Several other study groups have recently started phase II studies with modified schedules of this three-drug combination.

Prognostic factors

With several study reports available that deal with the three major combination chemotherapy regimens that appear to be comparable as far as response rates are concerned, it becomes possible to obtain further insight into factors predicting the outcome of chemotherapy.

Although several authors indicate that some tumor types may be more responsive than others, Table 7, combining all data of studies with ADIC-based regimens, indicates the opposite. There is no evidence of one histological subtype with a better prognosis.

Regarding other factors with a possible influence on achievement of response there is certainly no consensus on age, sex, and bone marrow reserve. The most important prognostic factor for response appears to be the performance score [8, 57, 59, 64], which may be partly related to a favorable influence of a <5% weight loss [8, 30]. Another important observation from virtually all studies concerns the time necessary to achieve response. The median time varies from 7 to 10 weeks [8, 50, 56, 59, 65], but it is even more important to realize that treatment periods as long as 32 [56], 56 [8], or 101 [59] weeks may be required to achieve response, indicating that soft tissue sarcomas respond rather slowly to chemotherapy.

Mixed mesodermal sarcomas

As has been indicated, cisplatin (CDDP, or *cis*-diamminedichloroplatin) can be considered an inactive single agent for the treatment of soft tissue sarcomas, which has been confirmed by the absence of an additive effect of CDDP when combined with active drugs [63, 69–71]. In contrast to these general data, mixed mesodermal sarcomas (MMS) appear to respond to some extent to CDDP. In a phase II trial with single-agent CDDP at a dose of 50 mg/m^2 every 3 weeks as second-line chemotherapy, five (18%) of 28 patients achieved a response [45] and, at a higher dose, Gershenson et al. even achieved a 28% response rate [46] (Table 4). These data in MMS appear to be confirmed by limited data on combination chemotherapy including CDDP. Piver et al. [72] combined DTIC and different dosages of CDDP, achieving three responses (27%) in 11 patients. Although DX appears to be less active in MMS than in other histological subtypes [47, 50], others have combined DX and CDDP. Seltzer et al. [73] applied 50 mg/m^2 DX plus 50 mg/m^2 CDDP both i.v. on

Table 7. Response rates in histological subtypes of soft tissue sarcomas

Histology	Regimen														Total	
	ADIC						CYVADIC									
	[8][a]		[26]		[27]		[29]		[32]		[35]		[37]			
	n[b]	(%)[c]	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Leiomyosarcoma	27	(44)	73	(33)	27	(19)	31	(58)	35	(20)	18	(22)	6	(17)	217	(33)
MFH	24	(25)	43	(21)	13	(54)	—		29	(34)	5	(40)	6	(67)	120	(32)
Schwannoma	9	(22)	—		—		—		—		—		2	(50)	11	(27)
Liposarcoma	7	(14)	16	(19)	—		12	(41)	15	(33)	5	(40)	4	(25)	59	(29)
Fibrosarcoma	4	(0)	—		6	(50)	21	(48)	19	(37)	2	(50)	9	(56)	61	(43)
Synoviasarcoma	3	(0)	10	(33)	2	(0)	2	(50)	7	(28)	—		9	(67)	30	(33)
Angiosarcoma	—		12	(25)	—		5	(60)	7	(14)	—		—		26	(26)
Neurosarcoma	—		12	(33)	10	(20)	13	(69)	6	(17)	—		—		41	(39)
Rhabdomyosarcoma	—		14	(29)	8	(25)	13	(54)	4	(25)	5	(40)	9	(44)	53	(38)

[a] [ ], reference.
[b] n, number of evaluable patients.
[c] (%), response rate.

day 1 every 3 weeks, achieving 3 CRs and 2 PRs in six patients. The Toronto group [74] treated 15 patients with MMS of the ovary with either CAP [CTX, Adriamycin (DX), and Platinol (CDDP)] or CYVADIC achieving a 60% response rate. Jansen et al. [75] achieved five remissions in six patients, with a combination of cyclophosphamide, hexamethylmelamine, doxorubicin, and cisplatin (CHAP-5). Of course, for the latter two studies, we should also consider the possible role of CTX, because this drug may also be active in MMS [29]. In the near future, the role of CDDP as well as CTX in this rare, but less-DX-responsive, sarcoma subtype should be explored.

Induction chemotherapy

The value of preoperative chemotherapy in the treatment of locally far-advanced soft tissue sarcomas is one of the important issues of investigation in the present decade. Intra-arterial chemotherapy is discussed in Chapter 8 by Huth and Eilber. As for other tumor types, there is also increasing interest in systemic induction chemotherapy for which only limited data are yet available, usually as case reports. However, Rouëssé et al. [76] recently reported a series of 34 patients with locally far-advanced, but nonmetastatic, sarcomas treated with either DX–CTX–CDDP–DTIC–vindesine (DCPAV), CYVADIC, or DX–IFOS, achieving 38% remissions: 24 patients underwent surgery after 2–7 cycles of chemotherapy, which in 12 proved to be radical. Patients who did not undergo radical operation were irradiated postoperatively. While 2-year survival was only 18% in those patients who never achieved CR, it was 80% in patients who achieved CR after chemotherapy + surgery + radiotherapy, a figure at least suggesting a benefit of preoperative systemic chemotherapy (Fig. 1). Also, at Dana Farber Cancer Institute, some patients were

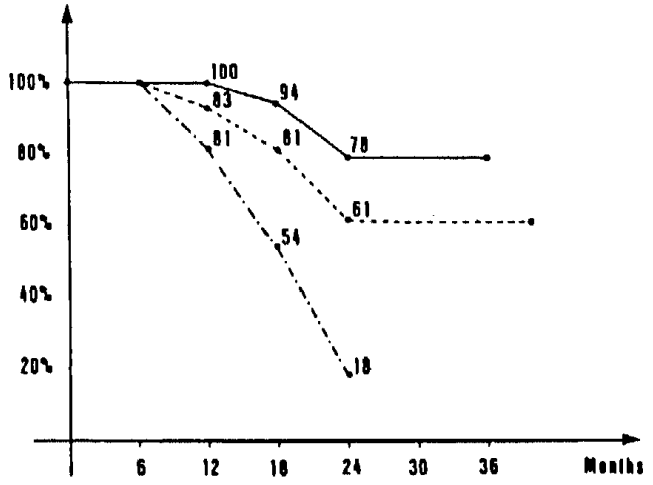

Figure 1. Survival of patients responding to systemic preoperative chemotherapy versus those not responding: (—) patients with CR, $n = 22$; (----) total number of patients, $n = 34$; and (—·—·) patients without a CR, $n = 12$. Reproduced from Rouëssé et al. [76], with permission.

treated with DX–IFOS–DTIC preoperatively [68]. During the 1987 ASCO meetings, there were preliminary reports of an 82% response rate in a limited number of patients. Clearly this type of treatment should be further explored.

Conclusion

The last few years have shown a trend toward consensus in the chemotherapeutic approach of soft tissue sarcomas. Three active single agents—DX, IFOS, and DTIC—are available. CTX and CDDP may also be considered active in the treatment of mixed mesodermal sarcomas. The ECOG study comparing DX with ADIC indicates that combination chemotherapy yields higher response rates than does single-agent chemotherapy, although other studies applying inactive combination regimens previously suggested the opposite. Therefore the results of the ongoing randomized EORTC study are awaited with interest. At this moment, there is no proof that combination chemotherapy also yields improved survival when compared with single-agent treatment.

Although it is not clear which combination chemotherapy is the best, three regimens emerge as most interesting: ADIC, CYVADIC, and DX–IFOS. Although the addition of CTX and VCR to ADIC still can be debated, nonrandomized studies suggest that CYVADIC yields the highest CR rate, which may be important because of indications that these patients may potentially be cured. The future years will highlight investigations on the combination DX–IFOS–DTIC.

The role of systemic preoperative chemotherapy will also have to be further outlined, because preliminary data indicate high response rates. However, regarding this topic, survival will be more important than response.

Clearly there is still a need for new active drugs and therefore the continuous search through phase II trials should be encouraged.

References

1. Enneking WF, Spanier SS, Malawer MM: The effect of the anatomic setting on the results of surgical procedures for soft-part sarcomas of the thigh. Cancer 47:1005–1022, 1981.
2. Lindberg RD, Martin RG, Ramsdahl MM: Surgery and postoperative radiotherapy in the treatment of soft tissue sarcomas in adults. AJR Ther Nucl Med 123:123–129, 1975.
3. Gerson R, Shiu MH, Hajdu SI: Sarcoma of the buttock: a trend toward limb-salvage resection. J Surg Oncol 19:238–242, 1982.
4. Leibel SA, Tranbaugh RF, Wara WM, et al.: Soft tissue sarcomas of the extremities: survival and patterns of failure with conservative surgery and postoperative irradiation compared to surgery alone. Cancer 50:1076–1083, 1982.
5. Suit HD, Mankin HJ, Wood WC, Proppe KH: Preoperative, intraoperative, and postoperative radiation in the treatment of primary soft tissue sarcoma. Cancer 55:2659–2667, 1985.
6. Bonadonna G, Beretta G, Tancini G, et al.: Adriamycin (NSC-123127) studies at the Instituto Nazionale Tumori, Milan. Cancer Chemother Rep 6:231–245, 1975.

7. Verweij J, van Oosterom AT, Pinedo HM: Melanomas, soft tissue and bone sarcomas. Eur J Cancer Clin Oncol [Suppl] 4:75–85, 1985.
8. Borden EC, Amato DA, Rosenbaum Ch, et al.: Randomized comparison of three adriamycin regimens for metastatic soft tissue sarcomas. J Clin Oncol 5:840–850, 1987.
9. O'Bryan RM, Luce JK, Talley RW: Phase II evaluation of adriamycin in human neoplasma. Cancer 32:1–8, 1973.
10. Mitts DL, Gerhardt H, Armstrong D, et al.: Chemotherapy for advanced soft tissue sarcomas: results of phase I and II cooperative studies. Tex Med 75:43–47, 1979.
11. Chlebowski RT, Paroly WS, Pugh RP: Adriamycin given as a weekly schedule without a loading course: clinically effective with reduced incidence of cardiotoxicity. Cancer Treat Rep 64:49–51, 1980.
12. Gerlach JH, Bell DR, Karakousis C, et al.: P-glycoprotein in human sarcoma: evidence for multidrug resistance. J Clin Oncol 5:1452–1460, 1987.
13. Benjamin RS, Yap BS: Infusion chemotherapy for soft tissue sarcomas. In: Baker LH (ed), Soft tissue sarcomas. Boston: Martinus Nijhoff, 1983, pp 109–116.
14. Bramwell VHC, Mouridsen HT, Mulder JH, Somers R, van Oosterom AT, Santoro A, Thomas D, Sylvester R, Markham D: Carminomycin vs adriamycin in advanced soft tissue sarcomas: an EORTC randomized phase II study. Eur J Cancer Clin Oncol 19:1097–1104, 1983.
15. Mouridsen HT, Bastholt L, Somers R, Santoro A, Bramwell V, Mulder JH, van Oosterom AT, Buesa J, Pinedo HM, Thomas D, Sylvester R: Adriamycin versus epirubicin in advanced soft tissue sarcomas: a randomized phase II/phase III study of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer Clin Oncol 23:1477–1483, 1987.
16. Bodey GP, Yap BS, Ajani J: Clinical trials of 4'-epidoxorubicin. In: Proceedings of the 13th international congress on chemotherapy 215:23–26, 1983.
17. Bertrand M, Multhauf P, Bartolucci A, Ellison D, Gockerman J: Phase II study of aclarubicin in previously untreated patients with advanced soft tissue sarcoma: a South-Eastern Cancer Study Group trial. Cancer Treat Rep 69:725–726, 1985.
18. Raymond V, Magill GB, Wissel PS, Cheng EW, Ochoa M, Young CW: Phase II trial of deoxydoxorubicin in patients with soft tissue sarcoma. Proc Am Soc Clin Oncol 5:146, 1986.
19. Wissel PS, Magill GB, Raymond V, Well S, Sordillo P, Cheng E: 4'Demethoxydaunorubicin in advanced soft tissue sarcomas: an update with emphasis on patients without prior doxorubicin. Proc Am Soc Clin Oncol 3:259, 1984.
20. Presant CA, Gans R, Bartolucci AA: Treatment of metastatic sarcomas with mitoxantrone. Cancer Treat Rep 68:813–814, 1984.
21. Bull FE, von Hoff DD, Balcerzak SP, Stephens RL, Panetierre FJ: Phase II trial of mitoxantrone in advanced sarcomas: a South-West Oncology Group study. Cancer Treat Rep 69: 231–233, 1985.
22. Gottlieb JA, Benjamin RS, Baker LH, et al.: Role of DTIC (NSC-45338) in the chemotherapy of sarcomas. Cancer Treat Rep 60:199–203, 1976.
23. Buesa J, Mouridsen H, van Oosterom AT, Steward WT, Verweij J, Thomas D: High-dose DTIC in advanced soft tissue sarcoma of the adult: a phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. Proc ECCO 4:235, 1987.
24. Hoefer-Janker H, Scheef W, Gunther U, et al.: Erfahrungen mit der fraktionierten Ifosfamid-Stoss Therapie bei generalisierten malignen Tumoren. Med Welt 26:972–979, 1977.
25. Klein HO, Wickramanayake PD, Coerper CL, et al.: High-dose ifosfamide and mesna as continuous infusion over five days: a phase I/II trial. Cancer Treat Rev 10:167–173, 1983.
26. Czownicki A, Utracka-Hutka B: Contribution to the treatment of malignant tumours with ifosfamide. In: Burkert H, Voight HC (eds), Proceedings of the international Holoxan symposium. Düsseldorf: ASTA-Werke, 1977, pp 109–111.
27. Antman KM, Montella D, Rosenbaum Ch, Schwen M: Phase II trial of ifosfamide with mesna in previously treated metastatic sarcoma. Cancer Treat Rep 69:499–504, 1985.
28. Wiltshaw E, Westbury G, Harmer C, McKinna A, Fisher C: Ifosfamide plus mesna with and without adriamycin in soft tissue sarcoma. Cancer Chemother Pharmacol [Suppl 2] 18:

S10–12, 1986.
29. Bramwell VHC, Mouridsen H, Santoro A, Blackledge G, Somers R, Verweij J, Dombernowsky P, Onsrud M, Thomas D, Sylvester R, van Oosterom AT: Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. Eur J Cancer Clin Oncol 23:311–321, 1987.
30. Sordillo PP, Magill GB, Welt S: Phase II trial of methylglyoxal-bis-guanylhydrazone (methyl-GAG) in patients with soft-tissue sarcomas. Am J Clin Oncol (CCT) 8:316–318, 1985.
31. Thigpen JT, Blessing JA, Homesley HD, Hacker N, Curry SL: Phase II trial of piperazinedione in patients with advanced or recurrent uterine sarcoma: a Gynecologic Oncology Group Study. Am J Clin Oncol (CCT) 8:350–352, 1985.
32. Amato DA, Borden EC, Shiraki M, Enterline HT, Rosenbaum C, Davis HL, Paul AR, Stevens CM, Lerner HJ: Evaluation of bleomycin, chlorozotocin, MGBG, and bruceantin in patients with advanced soft tissue sarcoma, bone sarcoma, and mesothelioma. Invest New Drugs 3:397–401, 1985.
33. Chan C, Bartolucci A, Brenner D, Presant C, Davila E, Carpenter J, Greco A, Clamon G, Moore J: Phase II trial of diaziquone in anthracycline-resistant adult soft tissue and bone sarcoma patients: a South-Eastern Cancer Study Group trial. Cancer Treat Rep 70:427–428, 1986.
34. Cowan JD, Gehan E, Rivkin SE, Jones SE: Phase II trial of bisantrene in patients with advanced sarcoma: a South-West Oncology Group study. Cancer Treat Rep 70:685–686, 1986.
35. Wissel P, Magill G, Sordillo P, Cheng E, Hakes T, Applewhite A: A phase II trial of mitomycin C in advanced soft tissue sarcomas. Proc Am Soc Clin Oncol 5:146, 1986.
36. Ajani JA, Dimery I, Chawla SP, Pinnamaneni K, Benjamin RS, Legha S, Krakoff IH: Phase II studies of homoharringtonine in patients with advanced malignant melanomas, sarcoma, and head and neck, breast and colorectal carcinomas. Cancer Treat Rep 70:375–379, 1986.
37. Thigpen JT, Blessing JA, Wilbanks GD: Cisplatin as second-line chemotherapy in the treatment of advanced or recurrent leiomyosarcoma of the uterus: a phase II trial of the Gynecologic Oncology Group. Am J Clin Oncol (CCT) 9:18–20, 1986.
38. Sordillo PP, Magill GB, Brenner J, Cheng EW, Dosik M, Yagoda A: A phase II evaluation of cisplatin in previously untreated patients with soft tissue sarcomas. Cancer 59:884–886, 1987.
39. Budd GT, Balcerzak S, Mortimer J, Fletcher W: SWOG 8465: high-dose cisplatin for advanced sarcomas. Proc Am Soc Clin Oncol 6:137, 1987.
40. Rouëssé JG, van Oosterom AT, Capellaere P, Kerbrat P, van Groeningen CJ, Thomas D, Benshahar D: Phase II study of 1,2,4-triglycidyl urasol (TGU) in advanced soft tissue sarcoma: a trial of the EORTC Soft Tissue and Bone Sarcoma Cooperative Group. Eur J Cancer Clin Oncol 23:1413–1414, 1987.
41. Dombernowsky P, Buesa J, Pinedo HM, Santoro A, Mouridsen HT, Somers R, Bramwell V, Onsrud M, Rouëssé J, Thomas D, Sylvester R: VP-16 in advanced soft tissue sarcoma: a phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer Clin Oncol 23:579–580, 1987.
42. Zalupski M, Pazdur R, Samson M, Baker L: Phase II clinical evaluation of fludarabine in soft tissue and osteosarcomas. Proc Am Soc Clin Oncol 6:135, 1987.
43. Harris J, Das Gupta T, Vogelzang N, Badrinath K, Bonomi P, Desser R, Locker G, Blough R, Johnson C: Treatment of soft tissue sarcoma with fibroblast interferon (beta-interferon): an American Cancer Society/Illinois Cancer Council study. Cancer Treat Rep 70:293–294, 1986.
44. Edmonson JH, Long HJ, Creagan ET, Frytak S, Sherwin SA, Chang MN: Phase II study of recombinant gamma-interferon in patients with advanced non-osseous sarcomas. Cancer Treat Rep 71:211–213, 1987.
45. Thigpen JT, Blessing JA, Orr JW, DiSaia J: Phase II trial of cisplatin in the treatment of patients with advanced or recurrent mixed mesodermal sarcomas of the uterus: a Gynecologic Oncology Group study. Cancer Treat Rep 70:271–274, 1986.

46. Gershenson DM, Kavanagh JJ, Copeland LJ, Edwardo CL, Stringer CA, Wharton JT: Cisplatin therapy for disseminated mixed mesodermal sarcoma of the uterus. J Clin Oncol 5:618–621, 1987.
47. Morrow CP, Bundy BN, Hoffman J, Sutton G, Homesley H: Adriamycin chemotherapy for malignant mixed mesodermal tumor of the ovary: a Gynecologic Oncology Group study. Am J Clin Oncol (CCT) 9:24–26, 1986.
48. Slayton E, Blessing JA, DiSaia PJ, Christopherson WA: Phase II trial of etoposide in the management of advanced or recurrent mixed mesodermal sarcomas of the uterus: a Gynecologic Oncology Group study. Cancer Treat Rep 71:661–662, 1987.
49. Gottlieb JA, Baker LH, Quagliana JM, Luce JK, Whitecar JP, Sinkovics JG, Rivkin SE, Brownlee R, Frei E: Chemotherapy of sarcomas with a combination of adriamycin and dimethyl triazeno imidazole carboxamide. Cancer 30:1632–1638, 1972.
50. Omura GA, Major FJ, Blessing JA, Sedlacek TV, Thigpen JT, Creasman WT, Zaino RJ: A randomized study of adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. Cancer 52:626–632, 1983.
51. Schoenfeld DA, Rosenbaum Ch, Horton J, Wolter JM, Falkson G, De Conti RC: A comparison of adriamycin versus vincristine and adriamycin and cyclophosphamide versus vincristine, actinomycin-D and cyclophosphamide for advanced sarcoma. Cancer 50:2757–2762, 1982.
52. Muss HB, Bundy B, DiSaia PJ, Homesley HD, Fowler WC, Creasman W, Yordan E: Treatment of recurrent or advanced uterine sarcoma: a randomized trial of doxorubicin versus doxorubicin and cyclophosphamide (a phase III trial of the Gynecologic Oncology Group). Cancer 55:1648–1653, 1985.
53. Baker LH, Frank J, Fine G, Balcerak SP, Stephens RL, Stuckey WJ, Rivkin S, Saiki J, Ward JH: Combination chemotherapy using adriamycin, DTIC, cyclophosphamide and actinomycin-D for advanced soft tissue sarcomas: a randomized comparative trial—a phase III Southwest Oncology Group study (7613). J Clin Oncol 5:851–861, 1987.
54. Saiki JH, Baker LH, Rivkin SE, Shahbender S, Fletcher WS, Athens JW, Balcerak SP, Bonnet JD: A useful high-dose intermittent schedule of adriamycin and DTIC in the treatment of advanced sarcomas. Cancer 58:2196–2197, 1986.
55. Baker LH, Green S, Ryan J, Rosenberg B, Balcerak S: SWOG 8024: combind modality therapy for disseminated soft tissue sarcoma, phase III. Proc Am Soc Clin Oncol 6:138, 1987.
56. Yap BS, Baker LH, Sinkovics JG, Rivkin SE, Bottomley R, Thigpen T, Burgess MA, Benjamin RS, Bodey GP: Cyclophosphamide, vincristine, adriamycin and DTIC (CYVADIC) combination chemotherapy for the treatment of advanced sarcomas. Cancer Treat Rep 64: 93–98, 1980.
57. Yap BS, Burgess MA, Sinkovics JG, Benjamin RS, Bodey GP: A 5-year experience with cyclophosphamide, vincristine, adriamycin and DTIC (CYVADIC) chemotherapy in 169 adults with advanced soft tissue sarcoma. Proc Am Soc Clin Oncol 22:534, 1981.
58. Yap BS, Sinkovics JG, Burgess MA, Benjamin RS, Bodey GP: The curability of advanced soft tissue sarcomas in adults with chemotherapy. Proc Am Soc Clin Oncol 2:239, 1983.
59. Pinedo HM, Bramwell VHC, Mouridsen H, Somers R, Vendrik CPJ, Santoro A, Buesa J, Wagener Th, van Oosterom AT, van Unnik JAM, Sylvester R, de Pauw M, Thomas D, Bonadonna G: CYVADIC in advanced soft tissue sarcoma: a randomized study comparing two schedules. Cancer 53:1825–1832, 1984.
60. Dalley DN, Levi JA, Nesbitt RA, Tattersall MHM, Woods RL, Fox RM, Aroney RS: Cyclical combination chemotherapeutic regimen in adult soft tissue sarcoma. Cancer Clin Trials 4:163–165, 1981.
61. Presant CA, Lowenbraun S, Bartolucci AA, Smalley RV, the Southeastern Cancer Study Group: Metastatic sarcoma: chemotherapy with adriamycin, cyclophosphamide and methotrexate alternating with actinomycin-D, DTIC and vincristine. Cancer 47:457–465, 1981.
62. Karakousis CP, Rao U, Park HG: Combination chemotherapy (CYVADIC) in metastatic soft tissue sarcomas. Eur J Cancer Clin Oncol 18:33–36, 1982.
63. Kerzel W, König HJ, Walter M, Arnold I: Zytostatische Kombinationsbehandlung fort-

geschrittener Sarkome: Ergebnisse einer prospektiv angelegten Studie. Tumor Diagn Ther 6:180–184, 1985.
64. Bui NB, Chauvergne J, Hocke C, Durand M, Brunet R, Coindre JM: Analysis of a series of sixty soft tissue sarcomas in adults treated with a cyclophosphamide–vincristine–adriamycin–dacarbazine (CYVADIC) combination. Cancer Chemother Pharmacol 15:82–85, 1985.
65. Schuette J, Mouridsen H, Santoro A, Steward W, van Oosterom AT, Somers R, Blackledge G, Verweij J, Rouëssé J, Green JA, Pinedo HM, Kaye SB, Kerbrat H, Wagener T, Thomas D, Sylvester R: Adriamycin and ifosfamide, a new effective combination in advanced soft tissue sarcoma. Proc ECCO 4:232, 1987.
66. Pinedo HM, Verweij J: The treatment of soft tissue sarcomas with focus on chemotherapy: a review. Radiother Oncol 5:193–205, 1986.
67. Elias AD, Antman KH: Doxorubicin, ifosfamide and dacarbazine (AID) with mesna uroprotection for advanced untreated sarcoma: a phase I study. Cancer Treat Rep 70:827–833, 1986.
68. Elias AD, Ryan L, Aisner J, Antman KH: Doxorubicin, ifosfamide and DTIC (AID) for advanced untreated sarcomas. Proc Am Soc Clin Oncol 6:134, 1987.
69. Klippstein TH, Mitrou PS, Kochendörfer KJ, Bergmann L: High-dose adriamycin and cisplatinum in advanced soft tissue sarcomas and invasive thymomas: a pilot study. Cancer Chemother Pharmacol 13:78–81, 1984.
70. Hartlapp JH, Münch HJ, Illinger HJ, Wolter H, Jensen JC: Alternatives to CYVADIC combination therapy of soft tissue sarcomas. Cancer Chemother Pharmacol [Suppl 2] 18: S20–S23, 1986.
71. Edmonson JH, Hahn RG, Schutt AJ, Bisel HF, Ingle JN: Cyclophosphamide, doxorubicin and cisplatin combined in the treatment of advanced sarcomas. Med Pediatr Oncol 11:319–321, 1983.
72. Piver MS, Lele SB, Patsner B: Cis-diamminedichloroplatinum plus dimethyl-triazenoimidazole carboxamide as second- and third-line chemotherapy for sarcomas of the female pelvis. Gynecol Oncol 23:371–375, 1983.
73. Seltzer V, Kaplan B, Vogl S, Spitzer M: Doxorubicin and cisplatin in the treatment of advanced mixed mesodermal uterine sarcoma. Cancer Treat Rep 68:1389–1390, 1984.
74. Moore N, Fine S, Sturgeon J: Malignant mixed mesodermal tumors of the ovary: the Princess Margaret Hospital experience. Proc Am Soc Clin Oncol 5:114, 1986.
75. Jansen RLH, van der Burg MEL, Verweij J, Stoter G: Cyclophosphamide, hexamethylmelamine, adriamycin and cisplatin combination chemotherapy in mixed mesodermal sarcoma of the female genital tract. Eur J Cancer Clin Oncol 23:1131–1133, 1987.
76. Rouëssé JG, Friedman S, Sevin DM, Le Chevalier Th, Spielmann ML, Contesso G, Sarrazin DM, Genin JR: Preoperative induction chemotherapy in the treatment of locally advanced soft tissue sarcomas. Cancer 60:296–300, 1987.