Chemotherapy of advanced soft-tissue sarcomas in adults†

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Introduction

Primary mesenchymal tumors with localization outside the skeleton, parenchymatous organs, or hollow viscera are generally referred to as soft-tissue sarcomas. These tumors have become an increasing problem to medical oncologists in the past decade.

The classification of soft-tissue sarcomas has led to considerable confusion. In many reports the histological type is not specified. A good description of the different types of soft-tissue has been given by Stout (96–98). Although one would like to assign every tumor to a well-defined category, this is not always possible because of the multipotential capacities of the mesenchyme and the appearance of several elements in the same tumor. The terms spindle cell and round cell sarcoma do not accurately reflect the histological picture of the tumor type. Tumors classified under these terms should be placed in the undifferentiated group.

The histological types to be discussed in this review are indicated in Table 1. Kaposi's sarcoma is not included, because it has a different natural history and a rather divergent sensitivity to chemotherapy (74, 110). Mesothelioma, although not a sarcoma, shares some of the characteristics of these tumors and is generally included in most studies and will therefore be dealt with here.

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Experience has shown that simple excision or enucleation of the primary tumor is followed by local recurrence in 40–80% of the cases (11, 22, 23, 52, 62, 75, 76, 96–98), and the prognosis for the majority of the patients depends to a high degree on whether there is local recurrence. Two-thirds of the patients who develop distant metastases do so only concomitantly with or after a local recurrence.

Table 1. Sarcomas of the soft tissues of the trunk and extremities (11)

Type of sarcoma	No. of patients	Percentage
Unclassified	200	25.6
Liposarcoma	135	17.2
Rhabdomyosarcoma	113	11.0
Fibrosarcoma	110	14.0
Synovial cell sarcoma	104	13.3
Neurofibrosarcoma	47	6.0
Embryonal rhabdomyosarcoma	28	3.6
Hemangiopericytoma	11	1.2
Angiosarcoma	7	0.9
Extra osseous osteogenic sarcoma	5	0.6
Leiomyosarcoma	2	0.3
Alveolar soft parts sarcoma	2	0.3
Total	784	100

In general, one recurrence means a slight predisposition to further recurrence. The high recurrence rate is due to the absence of encapsulation of the tumor, which spreads along fascial planes and nerve trunks, and possibly also to a multifocal origin. The available data on the influence of the site of the tumor on local recurrence are somewhat conflicting (11, 111). In the extremities, Cantin *et al.* found that lesions located distal to the knee and elbow recur slightly more frequently than those situated proximally from these joints. Suit *et al.* (97) found only 3 recurrences in 59 cases with the localization in the distal extremities and 12 recurrences for tumors in the thigh or upper arm. Radical surgery (radical resection or amputation) has reduced local recurrence to 25–30% (62).

Fibrosarcoma, neurofibrosarcoma, and synovial cell sarcoma seem to have the highest local-recurrence rate, but the histopathological type seems less important in this respect than the histological grade and the size of the primary lesion (97). In cases of moderately advanced sarcomas the frequency of local recurrence can be reduced to approximately 15% (99, 100) by combining non-radical surgery with high-dose radiation therapy (82–84). Even with this approach, however, metastases will occur as a result of unsuccessful treatment of the primary tumor and in cases in which the diagnosis is made in a very advanced stage of the disease.

It should be borne in mind that 5- and 10-year survival rate (from the time of diagnosis) may be considerably higher for certain histological types of soft-tissue sarcomas, e.g. fibrosarcoma. Thus, the importance of stratification of histological types in clinical trials is obvious. In one series the 5- and 10-year survival rate for fibrosarcoma was 82% and 73%, respectively (24), whereas other authors report 60% and 43%, respectively (44). The survival rate for rhabdomyosarcoma is lower, and there are even differences between the three histological subtypes of this tumor (24). Enzinger (23) reported a series of 110 cases of alveolar rhabdomyosarcomas in which the 5-year survival was only 2%. The bad prognosis of leiomyosarcoma has been stressed, the mortality rate being surpassed only by that of rhabdomyosarcoma (44). Synovial-cell sarcoma (61) and the other sarcomas (24, 64,

87) have an intermediate 5-year survival rate i.e., between these extremes. For each histological type hematogeneous spread, local recurrence, and disease-free survival times are determined predominantly by the mitotic index, for instance a mitotic index above 12 in fibrosarcoma correlating with 100% metastasis (97, 98, 115). For soft tissue sarcomas of the lower extremities distant metastases were the direct cause of death in 90% of the cases (91). Despite their hematogeneous spread metastasis to the cerebral hemispheres is extremely rare (27).

Chemotherapy in advanced disease

In the data to be discussed, a response usually means a decrease of more than 50% in the sum of the products of the two largest perpendicular diameters of all measurable lesions. Under complete response is understood disappearance of all measurable lesions as well as of all symptoms for at least a month. Patients whose disease remains stable or whose lesions regress less than 50% are considered stable patients. When different criteria were applied in a particular study, this will be mentioned. Although both single-drug therapy and combination chemotherapy were tried prior to the adriamycin era, responses were observed almost exclusively in childhood sarcomas. The difference between childhood and adult sarcomas is most evident in the treatment of rhabdomyosarcomas (79). Whereas cyclophosphamide, vincristine, and actinomycin D give a 27–62% response rate in children (26, 41, 46, 57, 102–104), the response rate in adults seems to be below 20% (46, 57, 103–105). However, these agents have not been studied extensively in adults (Table 2). Thus, published results can only be interpreted if the ages of the patients are mentioned (35, 79).

Table 2. Single-drug treatment in children and adults

Drug	Children			Adults		
	No. of cases	Response rate (%)	Refs.	No. of cases	Response rate (%)	Refs.
Vincristine	20	50	82, 83, 104	10	0	53, 119
Cyclophosphamide (i.v.)	42	62	26, 41, 82, 83	14	14	4, 54
Actinomycin D	38	27	82, 83	6	3/6†	67, 114

† No definition of tumor response, all 3 patients showed "improvement".

In this review we have excluded all data referring to the treatment of childhood sarcomas. Some of the older data on the effects of vincristine, actinomycin D, and cyclophosphamide will be presented first. The list of single agents will be extended by more recent data on methyl-CCNU (MeCCNU), dimethyl triazeno imidazole carboxamide (DTIC), and adriamycin. The section on single agents will be followed by one on combination chemotherapy. We will also mention on-going trials and a few suggestions for future trials.

The significant improvement in the treatment of adult soft-tissue sarcoma has in all probability been effected solely by the acquisition of adriamycin. This drug, whose action is not restricted to mesenchymal tumors, can induce remission and has shown its greatest

value when combined with DTIC, this combination being called ADIC. Agents found to be effective in childhood sarcomas have been added to the latter combination.

The treatment considered most effective for adult soft-tissue sarcoma at present is a regimen combining cyclophosphamide, vincristine, adriamycin, and DTIC (CYVADIC). This combination was developed by the late Jeffrey Gottlieb after several years of experience with two-drug (ADIC) and three-drug (VADIC) combination treatments (31, 39). However, the difference between the remission rates and duration of survival of responding patients on ADIC and CYVADIC are, if any, very small.

Single-agent treatment

Most of the data on single-drug treatment of soft-tissue sarcomas with vincristine, actinomycin D, or cyclophosphamide have already been reviewed (5, 57, 113). Remission rates of 52% (cyclophosphamide), 47% (vincristine) and 24% (actinomycin D) have been reported for these drugs (4, 41). However, most of the studies referred to in these reviews were done in children. Other studies do not mention the ages of the patients (30). The few reports on the effects of vincristine (53, 119), actinomycin D (67, 114), and cyclophosphamide (4, 54) in adults concern very small groups of patients (Table 2).

Vincristine. Several adult patients (5 leiomyosarcomas, 1 hemangiopericytoma, 1 hemangioendotheliosarcoma) were given a weekly schedule of vincristine (7.5–50 $\mu\text{g/kg/week}$) (53). No response was observed.

Whitelaw *et al.* (119) administered vincristine to 3 patients in doses of 0.05–0.08 mg/kg intravenously. This was repeated at first twice weekly and then weekly. The drug was withheld if the white blood count fell too low, and was discontinued if neurologic symptoms proved intolerable to the patients. A patient with rhabdomyosarcoma, one with angiosarcoma, and a third with an undifferentiated sarcoma showed no objective response.

Actinomycin D. Two single-agent studies with actinomycin D comprised a total of only 6 patients. In one of these studies (67), one of the 2 patients concerned showed a remission of less than 4 weeks. The second study (114) concerned 3 leiomyosarcomas and 1 liposarcoma. One of the 3 leiomyosarcoma patients showed improvement for 2 weeks, and the liposarcoma patient had a 3-month remission. The other data in the literature also usually concern a very small number of patients. Response rates for these types of tumor never exceeded 20%, and the rare cases of remission were of very short duration, with little or no clinical benefit to the patients. This is in marked contrast with the results obtained in childhood sarcomas.

Cyclophosphamide. In children, cyclophosphamide has been reported to be effective in sarcomas originating not only in bone, but also in soft tissue. A large weekly intravenous dose was distinctly more effective (103) than daily doses in children with soft-tissue sarcomas (16, 80). A recent and extensive review on cyclophosphamide makes no mention of data on the effect of single-agent treatment with this drug in adult soft-tissue sarcomas (46). However, some data on this subject have been published. A clinical trial reported by Bergsagel *et al.* in 1970 (4) included 6 evaluable adult patients. Two of these patients showed an objective response. The definition of partial remission used by these authors includes responses seen in cases with 30% or more regression, however. Korst *et al.* (54) treated 2 patients with intravenous doses and saw no response.

Adriamycin. Initial experimental toxicity studies on adriamycin were done *in vitro* by Di Marco *et al.* (19) and Kim *et al.* (51) and the distribution and metabolism of the drug were

studied by Di Fronzo *et al.* (18). The investigations were soon followed by several clinical studies which showed the anti-tumor activity of the drug in man (8, 9, 66, 89).

The toxic effects of adriamycin consist of bone-marrow depression (in the first 2 weeks of therapy), alopecia and stomatitis. Cardiac toxicity has been a rare occurrence when the total dose did not exceed 600 mg/m² (9, 65, 106, 112).

Adriamycin, now the backbone of combination chemotherapy in soft-tissue sarcomas (Table 3), has given remission rates as low as 9% (43) and as high as 70% (118) (Table 4). The response rates of the different histological types are shown in Table 5. Despite the encouraging results obtained with adriamycin as a single agent, there is little,

Table 3. Completed protocols for metastatic sarcomas in adults

Protocol/Center	Period of trial study	Drug	Regimen applied under adequate marrow reserve
SWOG-434	1969-70	DTIC	250 mg/m ² /d, days 1-5†
SWOG-442	1971-72	ADM	75 mg/m ² †
SWOG-7206	1973-74	ADM	45-75 mg/m ² †
SWOG-445	1971-72	ADM	60 mg/m ² , day 1†
		DTIC	250 mg/m ² , days 1-5
MILAN	1971-75	ADM	60 mg/m ² , day 1†
		DTIC	250 mg/m ² /d, days 1-5
SWOG-7210	1972-73	VCR	1.5 mg/m ² (max. 2 mg), days 1 and 5‡
		ADM	60 mg/m ² , day 1
		DTIC	250 mg/m ² /d, days 1-5
DT-7302	1973-74	CPA	500 mg/m ² , day 1 (i.v.)†
		VCR	1.5 mg/m ² (max. dose 2 mg) days 1 and 5
		ADM	50 mg/m ² , day 1
		DTIC	250 mg/m ² /d, days 1-5
SWOG-7402	1974-76	CPA	500 mg/m ² , day 2 (i.v.)†
		VCR	1.5 mg/m ² (max. 2 mg), day 1 and weekly ×7
		ADM	50 mg/m ² , day 2
		DTIC	250 mg/m ² /d, days 1-5
SWOG-7402	1975-76	CPA	500 mg/m ² , day 2 (i.v.)†
		VCR	1.5 mg/m ² (max. 2 mg), day 1 and weekly ×7
		ADM	50 mg/m ² , day 2
		ACD	0.3 mg/m ² /d (max. 0.5 mg/day) days 3-5
Roswell Park	1973-74	ACD	10 µg/kg/d, days 1-5‡
		VCR	1.5 mg/m ² , days 1, 5
		ADM	25 mg/m ² , days 29, 30, 31
MILAN	1971	CPA	1 g/m ² , day 1†
		VCR	1.4 mg/m ² , days 1 and 8
		MTX	20 mg/m ² , days 1 and 8
Mayo Clinic	1974-76	DTIC	250 mg/m ² /d, days 1-5§
		ADM	50 mg/m ² , day 3
		VCR	1.2 mg/m ² (max. 2 mg), days 1 and 5
Mayo Clinic	1974-76	ACD	325 µg/m ² /d, days 1-5§
		CPA	250 mg/m ² /d, days 1, 3, 5 (i.c.)
		VCR	1.2 mg/m ² (max. 2 mg), days 1 and 5
Mayo Clinic	1974-75	Me-CCNU	200 mg/m ² (p.o.)§

† Repeated at 3-week intervals if blood count had recovered.

‡ Repeated at 7-week intervals.

§ Repeated at 5-week intervals

Table 4. Adriamycin in advanced cases of sarcoma

Histologic type	Age group	No. evaluable cases	Response rate (%)	Reference
Soft tissue sarcomas†	adults	357	27	Gottlieb <i>et al.</i> (33)
		56	16	Krakoff (55)
		15	47	Benjamin <i>et al.</i> (2)
Soft tissue sarcomas	unspecified	50	22	Bonadonna <i>et al.</i> (7)
		17	70	White <i>et al.</i> (118)
"Majority of soft tissue sarcomas"	unspecified	44	32	Gerhardt <i>et al.</i> (28)
Unspecified sarcomas†	unspecified	351	25	Wasserman <i>et al.</i> (113)
		97	31	Gottlieb <i>et al.</i> (38)
		22	9	Hahn <i>et al.</i> (43)

† Review of literature.

or no statistically significant difference in survival time between responders (8–9 months) (33, 73) and non-responders (4 months) (33). Whereas most patients in the SWOG-442 protocol (31% responses) had had previous treatment (32), the response rate reported by Benjamin *et al.* (47%) was obtained in a group in which the majority of the patients had had no previous treatment (2). The dosage schedules in these last two studies were equivalent to 60–75 mg/m² every 3 weeks. A detailed review of 357 patients treated with adriamycin showed a response rate of 27% (31).

Investigation of different schedules of administration (72) and the dose-response relationship (73) for adriamycin (SWOG-7206) indicated that patients treated with 60–75 mg/m² tend to respond better than patients given lower dosages. The duration of response is short, amounting to about 4 months (33). In a small series Kukuksu *et al.* (56) investigated 5 patients with mesothelioma treated with adriamycin (50 mg/m² i.v. every 3 weeks). It is of interest that 2 of these patients went into complete remission, the other 3 showing partial responses. The two complete responders remained in remission for 7 and 19 months, the partial responders for 2, 6, and 9 months, from the start of treatment. These 5 patients were not included in Table 2, because of the smallness of the series.

Table 5. Single-drug therapy with adriamycin in the various histologic types of metastatic sarcoma; literature review (33)

Diagnosis	No. of patients	No. of responses	Response rate (%)
Rhabdomyosarcoma	79	21	27
Fibrosarcoma and neurofibrosarcoma	38	9	24
Leiomyosarcoma	37	12	32
Synovial cell sarcoma	22	7	32
Liposarcoma	19	6	32
Angiosarcoma	16	7	44
Undifferentiated sarcoma	16	3	19
Unspecified and miscellaneous sarcomas	130	31	24
Total	357	96	27

Bonadonna *et al.* (7) obtained 2 complete responders among 8 patients. Further evaluation in larger series is clearly required.

Dimethyl triazeno imidazole carboxamide (DTIC). The mode of synthesis and the biological activity of DTIC and other imidazole derivatives have been reviewed extensively (90). The first pharmacological study on DTIC in man dates from 1968 (58), and preliminary clinical trials with DTIC were published between 1968 and 1971 (59, 60, 92, 111). In contrast to vincristine, cyclophosphamide, and actinomycin D, there are few reports on the effect of this drug in childhood sarcomas (25). Data on the use of DTIC as a single agent in the treatment of adult patients with sarcomas were collected from various studies (Table 6). Leiomyosarcoma, one of the more common sarcomas, shows a relatively high response rate (25); fibrosarcoma seems to be the least responsive. The mean response rate of all sarcomas to DTIC amounts to 16%. It may be mentioned that Kaposi's sarcoma, which is not included in this review, has shown a 50% response rate to DTIC in small series (110).

Table 6. DTIC in sarcomas; literature review† (36)

Histologic type	No. of patients			Total remission rate (%)
	Treated	CR	PR	
Leiomyosarcoma	24	1	5	25
Fibrosarcoma	18	—	1	6
Rhabdomyosarcoma	5	—	1	20
Liposarcoma	7	—	1	14
Unspecified	4	—	—	—
Mesothelioma	1	—	1	—
Synovial cell sarcoma	1	—	—	—
Angiosarcoma	1	—	—	—
Total	61	1	9	16

† All childhood sarcomas and unspecified sarcomas excluded.

Nausea and vomiting are more pronounced with DTIC than with adriamycin, but there is a tendency for the nausea to diminish during the 5-day course. Other side effects attributable to this agent are a rare flu-like syndrome and some accumulation of myelo-suppressive toxicity expressed especially in thrombocytopenia.

Other agents. Data on single-agent chemotherapy are available for a number of other drugs, usually in publications not mentioning the type of sarcoma (whether soft tissue or osseous) or the age of the patients (children or adults). Mithramycin, hexamethylmelamine, and streptozotocin have a very limited activity (113). A response rate of 23% was reported for 1,3-bis-2-chloroethyl-1-nitrosourea (BCNU) in a recent review (93) but some of the responses were in Ewing's sarcoma. Exclusion of the certain cases of Ewing's sarcoma reduced the response rate to 17%. The other nitrosoureas, CCNU and methyl-CCNU, have virtually no activity in soft-tissue sarcomas (17, 93, 109, 121), even when methylCCNU is given intravenously (13).

A derivative of daunorubicin and adriamycin, i.e. duborimycin (20798 RP), was given to 23 patients with bone and soft-tissue sarcomas. Only one partial response was observed (15). It is worth mentioning that in a phase I study with the oral form of the epipodophylotoxin derivative VP-16-213, a partial remission was obtained in one patient with an ab-

dominal liposarcoma and in one patient with lung metastases of a uterine sarcoma among 5 cases with soft tissue sarcoma (71).

Combination chemotherapy

Vincristine + actinomycin D. In one study, which was probably performed in adults, a combination regimen of vincristine and actinomycin D was applied in 14 patients with different types of sarcomas (12). Six out of the 12 evaluable patients responded, the median duration amounting to 5.3 months. However, the definition of response (25% reduction of all measurable lesions) differed from the one generally applied. Furthermore, the group included a disproportionately high number of cases of mesothelioma (5/14) and 2 cases of osteogenic sarcoma (one response).

Vincristine + actinomycin D + cyclophosphamide. This combination has proven to be very effective in advanced embryonal rhabdomyosarcoma of childhood. Wilbur *et al.* (120) reported 10 out of 16 patients doing well without evidence of recurrence since the initial treatment (median time 65 months). Jacobs (48) found that adults with soft-tissue sarcomas also respond to this combination. He treated 17 patients with a regimen consisting of vincristine 0.025 mg/kg/week i.v.; actinomycin D, 2 mg/week, i.v.; and cyclophosphamide, 2 mg/kg/day orally, and saw a response in 8 of 17 patients. However, only the ages of the responders in this report are mentioned. If one excludes the 3 patients with sarcoma originating in bones 14 patients with soft-tissue sarcomas can be evaluated. He also observed 5 responders (tumor reduction greater than 50%) among this series (1CR + 4PR), giving a response rate of 29%. It should be mentioned, however, that 2 responders were 17-year-old boys with rhabdomyosarcomas. Of the other 3 responders, 2 patients had a long-term remission: a complete remission lasting 26 months in a case of rhabdomyosarcoma (female, 46 years old) and a partial remission lasting 12 months in a female with a hemangiopericytoma.

In a recently completed randomized study the same combination of vincristine, actinomycin D, and cyclophosphamide was compared with a regimen comprising vincristine, adriamycin plus DTIC (VADIC). The drugs were administered over a 5-week period. The low response rate observed for both regimens (8% and 11%, respectively) is probably ascribable to the long intervals between doses (17).

Vincristine + cyclophosphamide + methotrexate + 5-fluorouracil. Four patients with mesothelioma were given the following combination treatment: cyclophosphamide 300 mg on days 1 and 5; vincristine 0.025 mg/kg on days 2 and 5; methotrexate 0.5 mg/kg on days 1 and 4; and 5-fluorouracil 10 mg/kg on days 1 to 5 (56). In this group one complete response and 2 partial responses were seen, lasting 19, 3 and 7 months, respectively. Because of the very small numbers, further investigation is required. With the same four drugs given according to a different schedule, no objective response was seen by Gerner and Moore (29) among 10 patients with different types of soft-tissue sarcoma.

Adriamycin + DTIC (ADIC). Studies performed at the Southern Research Institute in rodents bearing sarcoma 180, B16 melanoma, or C3H breast adenocarcinoma have shown that the toxicity of adriamycin and DTIC given in combination is not additive and that almost the full doses of each drug can be used in combination (40). The drugs do not appear to be cross resistant.

Because definite activity was observed with both adriamycin and DTIC, Gottlieb initiated a broad study (SWOG-445) with these 2 drugs in combination (32, 35). Most of the

patients were treated according to the following schedule: adriamycin, 60 mg/m² on day 1, and DTIC 250 mg/m² dissolved in 150 ml 5% dextrose in water given intravenously over a 30-min period on each of days 1 through 5. In general this regimen does not lead to severe leucopenia (Table 7). For patients with an inadequate marrow reserve due to extensive previous chemotherapy and/or radiotherapy, a lower dose-regimen was used: adriamycin 45 mg/m² day 1 and DTIC 200 mg/m² on day 1 to 5. None of the drugs were given from day 6 through 21, and the entire regimen was repeated starting on day 22. The dosage in subsequent courses was modified on the basis of the degree of myelosuppression achieved with the preceding course. If a patient's white blood cell count had not fallen below 3000 and his platelet count had not fallen below 100,000/mm³ during the preceding course, the dosage in the next course was increased by 15 mg/m² for adriamycin and 50 mg/m²/day $\times$ 5 for DTIC. For patients developing a white blood cell count below 2000/mm³ or a platelet count below 50,000 per mm³, the dose of adriamycin and DTIC was decreased by 15 mg/m² and 50 mg/m²/day, respectively. In patients whose lowest count fell between 2000 and 3000 for the white blood cells and between 50,000 and 100,000 for platelets, the dosages was not changed. If on the 22nd day of a course of therapy, the white blood cell count was still below 3000 and/or the platelet count still below 75,000/mm³, the start of the next course was delayed until these levels had been reached. Therapy was given every 3 weeks until disease progression or substantial toxicity precluded further treatment.

Table 7. Leukopenia induced by adriamycin plus DTIC (31)

Adriamycin (mg/m ² , day 1)	DTIC (mg/m ² d, days 1-5)	Wbc ($\times 10^3$ /mm ³)	Neutrophils ($\times 10^3$ /mm ³)	Median day of nadir
45	200	3.7	2.5	15
60	250	3.4	1.9	14
75	300	3.1	0.8	13
90	350	1.5	0.4	13

To avoid cardiac toxicity, adriamycin therapy was, as is usually done, discontinued at a cumulative dose of 600 mg/m², after which DTIC was continued alone. The response rate for this regimen calculated from cumulative data in the literature is shown in Table 8. ADIC had a total response rate of 47% for all histologic types. With this combination

Table 8. Responses (CR + PR) to adriamycin + DTIC, according to histologic subgroups in soft tissue sarcomas (3, 33)

Histologic type	No. of evaluable patients	Response rate (%)
Undifferentiated	26	58
Fibrosarcoma	31	42
Leiomyosarcoma	39	51
Liposarcoma	20	45
Rhabdomyosarcoma	20	40
Synovial cell sarcoma	11	45
Angiosarcoma	9	33
Neurofibrosarcoma	27	48
Mesothelioma	9	44
Total	192	47

complete remissions had been observed in rhabdomyosarcoma, undifferentiated sarcoma, and liposarcoma, and partial remissions in all types of soft-tissue sarcoma. Besides the increased remission rate, a slight increase in the duration of remission had been observed for ADIC as compared with both adriamycin alone and DTIC treatment. DTIC has contributed not only to improvement of the response rate but also to the survival duration (31). The "no-change" patients under this regimen had a significantly ($P < 0.01$) better survival rate than patients classified as having progressive disease, whose median survival from the start of chemotherapy was 6 months (32).

Responders tend to be somewhat younger and to have had less prior chemotherapy or radiotherapy. The response rate is lower when the primary tumor is located in the gastrointestinal tract or in the pelvis and trunk. Brain metastases respond very poorly (33).

The over-all tolerance of this regimen is excellent. Nausea and vomiting are often severe on the first day, but less than 5% of the patients require withdrawal of treatment because of this side effect. Stomatitis occurs in the second week in 15% of patients, but is usually mild. Fever was seen on day 1 in 6% of the patients. Furthermore, each of the two drugs may cause toxicity when given as single agent. Most patients are able to support this treatment on an out-patient basis. The median day of the white blood cell count nadir falls at the end of the second week, with rapid recovery and often with a rebound at the end of the third week. A few patients show prolonged reduction of the platelet counts due to DTIC. The response rate is slightly higher in previously untreated patients than in treated patients, which suggests that this therapy may be even more effective if used earlier in the course of the disease.

Adriamycin + DTIC + vincristine (VADIC). Vincristine has been added to ADIC because of its known activity as a single agent in soft-tissue sarcomas, specifically in children (82, 83, 104). Of 86 patients evaluated with this regimen (33), 8 achieved a complete remission and 32 a partial remission, giving an over-all response rate of 47% (Table 9). The response rate thus appeared to equal that of ADIC. There are indications that in e.g. fibrosarcoma, rhabdomyosarcoma, and undifferentiated sarcoma vincristine may play a small additive role. The only important difference is that the percentage of patients with progressive

Table 9. Response according to diagnosis in VADIC and CYVADIC I† (33)

Diagnosis‡	VADIC			CYVADIC I		
	No. of evaluable patients	Response rate (%)		No. of evaluable patients	Response rate (%)	
		CR	CR + PR		CR	CR + PR
Angiosarcoma	7	0	57	5	0	80
Fibrosarcoma	10	10	60	23	17	57
Leiomyosarcoma	22	22	36	28	7	68
Liposarcoma	15	15	47	10	10	60
Mesothelioma	6	0	0	6	0	33
Neurofibrosarcoma	3	33	33	13	23	62
Rhabdomyosarcoma	9	22	67	15	40	67
Synovial cell sarcoma	2	0	50	3	0	67
Undifferentiated sarcoma	12	33	59	15	13	40
Total	86	9	47	118	15	59

† Not randomized.

‡ Sarcomas of bones excluded.

disease is lower (17%) for VADIC than for ADIC (25%) ($P < 0.04$) (33). There is no difference between VADIC and ADIC as to survival duration. Myelosuppression is identical for the 2 regimens, and neuropathy due to vincristine has been negligible.

Adriamycin + DTIC + vincristine + cyclophosphamide (CYVADIC). The most effective combined chemotherapeutic regimen for soft-tissue sarcoma is formed by cyclophosphamide, vincristine, adriamycin and DTIC (1, 33, 37). Cyclophosphamide was added because it was known to have some activity as a single drug (4, 53), its addition to the VADIC regimen required reduction of the adriamycin dose to 50 mg/m². The cyclophosphamide dose and schedule initially used by the South Western Oncology Group was 500 mg/m² on day 1, the dose of DTIC and vincristine being kept unchanged. This 4-drug regimen (SWOG-7302) will be indicated here as CYVADIC I to distinguish it from a more recent protocol (SWOG-7402) with a modified schedule (CYVADIC II). In the first 12-month period in which SWOG-7302 was applied, 118 patients with soft-tissue sarcoma were evaluable; 18 (15%) of these showed complete and 52 (44%) partial remissions, resulting in an over-all response rate of 59% (excluding sarcoma in bones) (33). From the data presented it is impossible to calculate the exact percentage of patients with soft-tissue sarcoma whose disease remained stable or improved slightly, but in a group of 136 patients including those with sarcoma of the bones, only 22% showed progression of the disease on this CYVADIC I regimen (33). In a more recent protocol (SWOG-7402) comparing CYVADIC II with CYVADACT (Table 10) cyclophosphamide and adriamycin have been given on day 2, and in addition, the schedule and dosage of vincristine have been changed by giving the drug weekly for 7 weeks (Table 3 and 10) (1, 33). As will appear in the next section the remission rate obtained with the CYVADIC II regimen was lower than that obtained with CYVADIC I (52% and 59% respectively). The patients achieving complete response on CYVADIC I tend to have had less prior chemotherapy and to be younger. It should be emphasized once again that for both combination regimens and single-agent treatment, there are indications (73) that the dose of adriamycin should not be lower than 50 mg/m², and the treatment-free period should not be prolonged more than 3–4 weeks.

Table 10. CYVADIC II versus CYVADACT (SWOG 7402) (33)

Drug	Regimen used with:	
	Adequate marrow reserve	Inadequate marrow reserve
CYVADIC II†		
Cyclophosphamide	500 mg/m ² , day 2 (i.v.)	400 mg/m ² , day 2 (i.v.)
Vincristine	1.5 mg/m ² (top dose 2 mg), day 1 and weekly ×7	1.5 mg/m ² , (top dose 2 mg), day 1 and weekly ×7
Adriamycin	50 mg/m ² , day 2	40 mg/m ² , day 2
DTIC	250 mg/m ² /d, days 1–5	200 mg/m ² , days 1–5
CYVADACT		
Cyclophosphamide	500 mg/m ² , day 2 (i.v.)	400 mg/m ² , day 2 (i.v.)
Vincristine	1.5 mg/m ² (top dose 2 mg), day 1 and weekly ×7	1.5 mg/m ² (top dose 2 mg), day 1 and weekly ×7
Adriamycin	50 mg/m ² , day 2	40 mg/m ² , day 2
Actinomycin D	0.3 mg/m ² /day (top daily dose 0.5 mg), days 3–5	0.2 mg/m ² /day (top daily dose 0.3 mg), days 3–5

† All patients stratified by histologic cell type and marrow reserve status prior to randomization, regimen repeated at 3-week intervals if blood counts have recovered.

In one study (17) a modified CYVADIC regimen given at 5-week intervals resulted in a response rate as low as 10%.

As already mentioned, the additive effect of adriamycin and DTIC should be exploited. Adriamycin and its metabolites are eliminated over a period of several days, and therefore the high tissue levels of the drug persist for several days. The most logical schedule is to give adriamycin on day 1, followed by DTIC for several days. It remains to be seen whether the total dose of DTIC can be given over 3 instead of 5 days. Also, the effectiveness of a second dose of vincristine on day 5 (SWOG-7302), the weekly dose given in SWOG-7402, and even the dose of vincristine on day 1, remains to be demonstrated.

Addition of cyclophosphamide to the VADIC regimen does result in a significantly greater myelosuppression; about 25% of the patients achieve an absolute granulocyte count of less than 500 cells/mm³ at some time during the course of the chemotherapy (Table 11). In general, however, the duration of myelosuppression is short, few infectious episodes occur, and lethal complications are extremely rare.

Table 11. Myelosuppression in patients given DT 7302 (cyclophosphamide, vincristine, adriamycin, and DTIC) (33)

Response	Number of patients with:					
	Absolute granulocyte nadir			Platelet nadir		
	<1000	500-1000 (cells/mm ³)	<500	<100	50-100 (cells × 10 ³ /mm ³)	<50
Complete	6	5	8	13	5	1
Partial	25	20	11	44	9	3
Stable	14	6	11	24	4	3
Progression	15	9	6	26	4	0
Total	60 (44%)	40 (29%)	36 (27%)	107 (79%)	22 (16%)	7 (5%)

In a small number of patients, CYVADIC was used in a protected environment in combination with a prophylactic antibiotic program, and the chemotherapy dose was escalated at each subsequent course regardless of the bone-marrow toxicity if no severe infections occurred during the preceding course (6). Among 7 patients thus treated, the dosage was escalated in 6 with only one severe infection. There were 5 partial remissions.

It is clear that the CYVADIC I combination regimen has greatly improved the remission rate as compared with the rate obtained with adriamycin alone. Complete responses increased from 4 to 15%, and the over-all response rate from 27 to 59% (Table 9).

The increase in the duration of remission and the median survival of patients on chemotherapeutic regimens including adriamycin has led to an increased incidence of cerebral metastases in the group relapsing after a prolonged response (27).

Adriamycin + actinomycin D + vincristine + cyclophosphamide GYVADACT. Used alone, actinomycin D seems to be superior to DTIC (20, 67, 114). Although evaluation of a combination treatment in which DTIC is replaced by actinomycin D would seem logical, experimental data on a possible additive effect between adriamycin and actinomycin are not available. On the contrary, there are indications that these two drugs are mutually antagonistic.

The afore-mentioned recently terminated trial (SWOG-7402) included the CYVADACT regimen (cyclophosphamide, vincristine, adriamycin, and actinomycin D) (Table 10). Patients with inadequate marrow reserve due to extensive prior radiation or who were older than 65 years received only 80% of the doses of the myelosuppressive drugs. This was a controlled clinical trial with randomization of the patients who were to receive either CYVADIC II or CYVADACT.

In this study 14% of the patients on CYVADIC II achieved a complete remission, 52% either a complete or a partial remission, and 72% at least stability, the corresponding figures for CYVADACT being 12, 40, and 72%. The over-all remission rate for this group of patients is significantly better for CYVADIC II than for CYVADACT ($P < 0.02$).

The duration of remission is significantly longer on CYVADIC II than on CYVADACT ($P < 0.03$). The median duration of complete remission on CYVADACT was only 5.5 months; the median duration on CYVADIC II has not yet been reached in this trial but is tentatively projected at 14 months. The median remission duration for the partial responders did not differ significantly between CYVADIC II and CYVADACT, being 5 and 4 months, respectively. The values of this group are expected to increase slightly. Survival for patients with at least a partial remission was significantly better for CYVADIC than for CYVADACT ($P < 0.05$), i.e. 19 as against 12 months. The median duration of survival for complete responders has not yet been reached in this SWOG-7402 study, but is projected at 18 months for CYVADIC II and at 14 months for CYVADACT. The hematologic toxicity of the 2 regimens is comparable.

Table 12. 4-drug combination regimen (EORTC Soft Tissue Sarcoma Working Party)

Cyclophosphamide	400–500 mg/m ² , day 1
DTIC	150–250 mg/m ² , day 1–5 40 mg/m ² , day 1
Adriamycin	40 mg/m ² , day 1
Actinomycin D	200 µg/m ² , days 1–5 or 600 µg/m ² , days 1, 2

Adriamycin + DTIC + cyclophosphamide + actinomycin D. In view of the limited contribution of vincristine and the unacceptable 18% incidence of severe neurotoxicity in the earlier published studies, we performed a collaborative pilot study (unpublished) in the Soft-Tissue Sarcoma Working Party of the Organization on Research and Treatment of Cancer (EORTC), using actinomycin D instead of vincristine. The treatment is indicated in Table 12. As could be expected this regimen led to an unacceptable toxicity. Of a

Table 13. 4-drug combination ADM-DTIC-CPA-ACD. Response according to histologic type (EORTC Soft Tissue Sarcoma Working Party)

Histologic type	Number of patients			
	Evaluable	With CR/PR	With no change	With progression
Leiomyosarcoma	6		2	4
Rhabdomyosarcoma	6	0/2	1	3
Fibrosarcoma	8	1/0	3	4
Liposarcoma	3		2	1
Total	23	1/2	8	12

group of 33 patients, 23 were evaluable. The remission rate in this small group was 13% (Table 13), showing once again that simultaneous administration of adriamycin and actinomycin D may lead to antagonistic effects.

Table 14. Combinations used in advanced sarcoma (combinations without adriamycin)

Drugs	Histologic type or origin of sarcoma	No. of evaluable patients	Response rate (%)	References
VCR-ACD	Soft tissue and bone	12	"50"†	(12)
VCR-ACD-CPA	Soft tissue	13	31	(48)
VCR-CPA-MTX	Soft tissue	28	15	(3)
VCR-CPA-MTX-5FU	Mesothelioma	4	1 CR, 1 PR	(56)
	Soft tissue	10	0	(29)
VCR-BCNU	Soft tissue	33	9	(95)
VCR-mitomycin C-melphalan	Soft tissue	10	"30"	(70)
CPA-MeCCNU	Unspecified	6	0	(69)
L-Asparaginase-MTX	Unspecified	11	18	(86)
Ara-C‡-MTX	Unspecified	8	0	(117)
DDP§-CPA	Unspecified	7	"14"	(77)

† Objective response: $\geq 25\%$ decrease

‡ Cytosine arabinoside

§ Cis-dichlorodiammineplatinum(II)

Alternating administration of adriamycin and vincristine + actinomycin D. Douglass and Karakousis (21) treated 11 patients with soft-tissue sarcoma by a regimen consisting of actinomycin D and vincristine in alternation with adriamycin, administered in such a way that full doses of all 3 agents (Table 3) could be applied. A 7-week cycle was used. The history and pretreatment of the patients varied widely from patient to patient and only a few cases of each histological type were included. Furthermore, one patient received immunotherapy as well. Consequently, this heterogeneous group of patients is difficult to evaluate. Although 3 patients showed a partial response, the remission rate is of the same order of that of adriamycin alone, indicating that compared with the established regimens, this regimen offers no favourable additional effects.

Cyclophosphamide + vincristine + methotrexate (CPA-VCR-MTX). One of the few published randomized trials (3) compared ADIC with cyclophosphamide, vincristine, and methotrexate. The doses of adriamycin and DTIC were identical to those applied in SWOG-445 (Table 3).

The remission rate with CPA-VCR-MTX was 15% as against 57% in the ADIC group. In addition, the authors observed stabilization of disease in 26% of the patients on ADIC. Although the remission rate for ADIC was significantly higher than in CPA-VCR-MTX, the median survival times for complete and partial responders were similar in the 2 groups. It might be useful to investigate the effect of giving vincristine a day before cyclophosphamide, since the sequential use of these 2 drugs was found to be more effective than simultaneous administration in L1210 leukemia (85).

Other combinations. Many other combinations have been investigated, and these are included in Tables 14 and 15, together with the results of the combinations already mentioned above. The response rates are poor when adriamycin is not included in the regimen. Most of the combinations including adriamycin but not DTIC do not seem to be superior to adriamycin-

Table 15. Combination chemotherapy for advanced sarcoma (combinations with adriamycin)

Drugs	Histologic type or origin of sarcoma	No. of evaluable patients	Response rate (%)	References
ADIC†	Soft tissue	192	47	(33)
		21	57	(3)
VADIC†	Soft tissue	86	47	(33)
CYVADIC†	Soft tissue	118	59	(1)
		193	52	(1)
CYVADACT†	Soft tissue	199	40	(1)
ADM-DTIC-CPA-ACD	Soft tissue	23	13	EORTC Working Party
ADM, alternating with VCR-ACD	Soft tissue	11	"27"	(21)
ADM-MTX	Soft tissue and bone	67	16	(10)
ADM-Streptozotocin	Unspecified	10	"20"	(14)
ADM-VCR, weekly	Soft tissue and bone		64	(102)
ADM-VCR, loading dose	Soft tissue and bone	35	45	(102)
ADM-VCR-CPA	Soft tissue and bone		27	(102)
ADM-VCR-MTX‡	Unspecified	15	7	(50)
ADM-MeCCNU-VCR	Soft tissue	39	23	(55)
ADM-VCR-ACD-MTX‡	Soft tissue	11	"45"	(55)

† For abbreviations, see text.

‡ Methotrexate followed by folinic acid rescue.

cin alone. This holds particularly for adriamycin combined with methotrexate (102), streptozotocin (14), vincristine and cyclophosphamide (102), vincristine followed by methotrexate (50), or vincristine and methylCCNU (55), all of which give a response rate lying below 30%. As we have already seen, the introduction of actinomycin D into a combination containing adriamycin seems to reduce the percentage of objective responses.

A study has recently been undertaken at the M. D. Anderson Hospital to investigate treatment including both adriamycin and actinomycin D but using a short interval (several days) between the doses, in an attempt to avoid any antagonistic effects between adriamycin and actinomycin D.

Because of the relatively short duration of remission obtained with CYVADIC, we recently initiated a cooperative randomized trial in the EORTC based on alternation of ADIC and vincristine-cyclophosphamide at 4-week intervals. This schedule is being compared with CYVADIC (78).

Adjuvant chemotherapy and immunotherapy

There are several reports showing the value of adjuvant chemotherapy and immunotherapy in the treatment of malignancies (68). The survival of children with rhabdomyosarcoma (20, 120), osteogenic sarcoma (49), or Ewing's sarcoma (47, 81) has improved with the use of post-operative adjuvant chemotherapy. As for adjuvant therapy, the number of studies done on adult sarcomas is limited.

Some preliminary data indicate that surgical adjuvant combination chemotherapy may be of benefit in patients with adult soft-tissue sarcomas (108). These authors used a regimen comprising adriamycin and high-dose methotrexate with citrovorum factor rescue. However, this series includes both skeletal and soft-tissue sarcomas, and gives no

further indication of the number of cases of each of the histological types. Thirty-five patients with localized disease were evaluated. Of the 16 patients given post-operative adjuvant therapy, 11 (68%) have remained free of recurrent disease (mean follow-up 9.3 months), but only 5 out of 19 patients (23%) have remained free of metastases. The treatment was tolerated well, but more information from this study is needed.

Adjuvant chemotherapy with isolation-perfusion has been applied for the treatment of soft-tissue sarcomas of the extremities, followed by local excision and/or radiotherapy. Melphalan and actinomycin D were used in combination (63, 94), sometimes together with hyperthermia (94). Since these trials were not controlled, the value of the perfusion itself is difficult to assess. The 5-year survival (61%) is the same for these 2 studies, and the local recurrence rate is similar to that after radical surgical resection (62) or simple wide excision and post-operative radiotherapy (100).

Chemotherapy was utilized as an adjuvant to radiotherapy of lung metastases by Ryall *et al.* (88). The drug, i.e. ICRF 159, was chosen because it had been found experimentally to potentiate the effects of radiation. The small number of cases and the absence of a randomized controlled series does not permit reliable evaluation of the effect of the drug. The same criticism holds for another trial concerning the combined treatment of lung metastases by irradiation and chemotherapy with vincristine, actinomycin D, and cyclophosphamide (116). The complete and partial remission rates for these trials are 12/14 and 3/5, respectively. Long-term survivors are rare, and the survival data are not statistically significant when compared with the results obtained in patients treated by radiotherapy or chemotherapy alone.

As far as we know, results of the combination of chemotherapy and immunotherapy have not been published. Preliminary results of adjuvant immunotherapy with BCG and allogenic tumor cell vaccine after surgery are significantly better than those obtained in the control group treated by surgery alone (107).

Current studies

Because of the results obtained with CYVADIC, similar schedules are being tested in an adjuvant setting for patients at high risk with respect to recurrence. At the M. D. Anderson Hospital, the value of non-radical surgery (no amputations) and radiotherapy plus adjuvant combination chemotherapy is under investigation. In the latter protocol adriamycin, cyclophosphamide, and vincristine are given at the same time as radiotherapy to the surgical bed. The study is limited to histological grades II and III (high mitotic index).

At present, at the National Cancer Institute Rosenberg *et al.* are studying the effect on soft-tissue sarcomas of combined modality therapy. Soft-tissue sarcomas of the extremities and those of the head, neck, and trunk, are being studied separately in 2 randomized trials, but using the same protocols for the combined modality therapy. The study in sarcomas of the extremities has 3 categories: (1) radical surgery (amputation), (2) conservative surgery with chemotherapy, and (3) conservative surgery with chemo-immunotherapy. Thus, immunotherapy in combination with chemotherapy is compared with chemotherapy alone, as modalities capable of delaying or preventing the development of metastatic soft-tissue sarcoma. The second study on sarcomas of the trunk has 2 categories. The treatment groups consist of either (1) surgery, radiotherapy, and chemotherapy, or (2) surgery, radiotherapy, and chemotherapy plus immunotherapy. In the EORTC we are on the point of initiating a surgical adjuvant chemotherapeutic regimen with the al-

ternating schedule mentioned for the treatment of advanced disease. This regimen will be studied with and without immunotherapy.

Conclusions

The most effective regimen now available for the treatment of metastatic soft-tissue sarcoma is the combination of cyclophosphamide, vincristine, adriamycin, and DTIC. However, adriamycin plus DTIC may prove to be as effective and is much less toxic. These two regimens should be studied in a controlled randomized trial.

From the review of the various studies, a few interesting points have emerged:

1. Soft-tissue sarcomas are much less responsive to chemotherapy in adults than in children.
2. The most effective treatment developed so far for metastatic soft-tissue sarcomas is probably the CYVADIC regimen.
3. The first major step forward in the chemotherapy of these tumors was achieved with the combination of adriamycin and DTIC.
4. Since there is an additive effect of adriamycin and DTIC, DTIC should be started simultaneously with adriamycin on day 1.
5. There seems to be an antagonistic effect between adriamycin and actinomycin D when given simultaneously, which might be related to similar findings made in animal studies on advanced P-388 leukemia performed at the Southern Research Institute.
6. Patients should be considered evaluable if they have received a minimum of 2 cycles of any treatment regimen, since a remission can occur after the second cycle.
7. Surgical adjuvant combination chemotherapy has been giving very promising results in the treatment of patients with soft-tissue sarcoma, making it possible to reduce the extent of surgical resection required to achieve permanent local control and possibly also eradicating a number of sub-clinical metastases.
8. The role of immunotherapy as surgical adjuvant therapy remains to be investigated.

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