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The treatment of soft tissue sarcomas with focus on chemotherapy: A review

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Summary

Radical surgery remains the most effective treatment of soft tissue sarcomas. The postoperative addition of radiotherapy appears to reduce local recurrence in extremity lesions. To date, there are still only two drugs with major activity as a single agent in the treatment of soft tissue sarcomas: doxorubicin (DX) and ifosfamide (IFX). Doxorubicin should be administered preferably as 3-weekly bolus injections at doses higher than 60 mg/m² because of its dose-response relationship. In combination chemotherapy ADIC and CYVADIC are probably the best choice. Although there are no definite data on increased activity with the addition of cyclophosphamide (CTX) and vincristine (VCR) to ADIC, we prefer CYVADIC because of the higher reported complete response rate. A limited number of patients with soft tissue sarcomas achieving a complete response with chemotherapy, will probably be cured, and for this reason it is important to aim at achieving a complete response. Preoperative intraarterial chemotherapy in locally advanced soft tissue sarcomas may further improve survival results, but before definite conclusions can be drawn, this technique should be investigated in randomized studies. Postoperative adjuvant chemotherapy should still be considered investigational, as no advantage has been observed in head, neck and trunk lesions, while data on extremity lesions are still conflicting.

Introduction

Soft tissue sarcomas are malignant tumors that arise from supportive tissues from mesenchymal origin. These tissues account for over 50% of the body weight, but still only 1% of all malignant tu-

mors are soft tissue sarcomas. They may be found anywhere in the body, but are most frequently located in the legs and the trunk [67].

Although the multipotential capacities of the mesenchyme, and the appearance of several elements in the same tumor do not always allow the assignment of a tumor into a well-defined category, the classification proposed by Stout [84], based on the tissue of origin, is very useful. The introduction

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of electron microscopy added an important tool for subtyping. Although a wide variation in the incidence of the various subtypes characterizes the reported series, malignant fibrous histiocytoma, rhabdomyosarcoma, liposarcoma, synovial sarcoma and undifferentiated sarcoma appear to emerge as the most frequent types [53,87]. The diversity in histologic types has been a factor producing confusion in understanding the natural history of this tumor, as survival may vary widely among the histologic subtypes.

However, even more important prognostic criteria are the histologic grade [89] and the size of the primary tumor [80]. Histologic grade emerges as the most important factor to allocate stage. Although previously, grade was badly defined, recent reports indicate that tumor differentiation, number of mitosis and tumor necrosis, are the most important criteria of grade [10,25]. While Costa et al. [25] score the extent of tumor necrosis in a well-defined way, Boddaert et al. [10] do the same for all three parameters. Using such scores, grading will be facilitated. This now offers the possibility of a more intensive use of grade as a parameter for comparing the results of clinical trials. For the present report we are unable to state with certainty whether or not the reviewed reports on the results of treatment deal with high grade sarcomas, because grade was often not mentioned.

The stages in the AJC-staging system [72], have been shown to correlate well with survival [73]. This staging system is based on the TNM-classification, but also takes grade into account as a main prognostic criterium.

Surgery remains the main treatment of soft tissue sarcomas. Although the addition of postoperative radiotherapy has reduced the initially high incidence of local recurrence after surgery [1,34,44,67], local recurrence, almost always occurring within 3 years after surgery [46] still is a problem and besides a lot of patients develop distant metastases, most frequently in the lungs. These facts have stimulated the research on chemotherapy, in particular after the identification of doxorubicin (DX) as an active drug in soft tissue sarcomas [11]. Besides chemotherapy in metastatic disease, this treatment modality

is now also applied in a pre- or postoperative way for primary tumors. This report will review the treatment of soft tissue sarcomas with emphasis on chemotherapy.

Surgery

Surgical ablation remains the main treatment of soft tissue sarcomas. The type of surgery to be used will depend on staging as well as on the site of the primary tumor.

Wide surgical excision of the primary tumor or amputation of the extremity are the choices for treatment. The surgeon must weigh the results of a complete resection in relation to the structures present, so as to find functional results. However, the judgement of the surgeon during surgery will be hampered by the absence of true encapsulation of the tumor, the presence of a misleading pseudomembrane consisting of a zone of compressed normal and neoplastic cells, and the possibility of a multifocal origin of this tumor. Partly because of this, soft tissue sarcomas were previously characterized by a high incidence of local recurrence (40–80%) after surgery [58]. Nowadays, the addition of pre- and/or post-operative radiotherapy and/or chemotherapy appear to reduce the incidence of local recurrence or to increase the operability of the primary tumor. These techniques will be discussed separately, but they offer the surgeon the possibility of less disabling surgery.

Radiotherapy

The concept that soft tissue sarcomas are radioresistant was based on reports from 1920 to 1930 [70]. However, because of the changing concepts in treatment and the introduction of multimodality treatment, the role of radiotherapy in the treatment of soft tissue sarcomas has changed.

Concerning the treatment of localized soft tissue sarcomas by radiation therapy alone using conventional modalities and techniques there is still little chance for cure, but some patients will benefit pal-

liatively [47]. The role of new techniques such as fast neutron therapy or high linear energy transfer radiotherapy is still under investigation. However, the use of radiotherapy as a supplement to surgery has been shown to reduce the number of local recurrences after surgery [1,34,44,67] and to allow the introduction of limb-sparing surgical techniques [69]. Radiation therapy is usually started within 3 to 4 weeks postoperatively when wound-healing is complete, and covers the surgical field with generous margins. The effectiveness of this kind of treatment may be related with the reduced volume of tumor, by the preceding surgery. Still the dose should be high (50–70 Gy) which may limit the application of effective radiotherapy in truncal lesions, because of the amount of healthy tissues included in the radiation field.

More recently, preoperative radiotherapy has been introduced into clinical trials for inoperable tumors. The preliminary results appear to be encouraging [47]. This technique is now also studied in combination with preoperative chemotherapy.

Chemotherapy

For a long time, the role of chemotherapy in the treatment of soft tissue sarcomas has been a very modest one, because of the absence of active drugs. However, since the introduction of DX some 15 years ago, chemotherapy has become more important. However, the interpretation of the results of chemotherapy may be influenced by the absence of stratification for histological subtypes grade and tumor size in clinical trials.

Single agent chemotherapy (Table I)

Doxorubicin was introduced into clinical trials in 1972. It appeared to be an active drug in the treatment of soft tissue sarcomas [11]. During the last decade, more than a thousand patients have been treated with the drug in connection with several reported studies. The cumulative response rates in these non-pretreated patients is 23% [91]. More recently, activity in pretreated patients has been sug-

TABLE I

Soft tissue sarcomas: active single agents.

Drug	No. of evaluated patients	Response rate (%)
Doxorubicin	1010	23 ^a
Ifosfamide	155	40 ^a
DTIC	53	17

^a Cumulative data.

gested in an ongoing EORTC trial (unpublished data). In soft tissue sarcomas DX was found to have a dose-response relationship. Doses of 50 mg/m² or less gave lower response rates than doses of 60 mg/m² or more, given every 3 to 4 weeks [55,58]. This high dose intermittent schedule is generally assumed to be the most effective administration. The possibilities to combine DX with other myelosuppressive drugs are limited by the relatively high-dose of DX required for activity. Moreover, this dose faces us with the problem of cardiotoxicity. For this reason research on alternative ways of administration and on the development of less cardiotoxic anthracyclines has been stimulated. Borden et al. [3] have randomly compared a dose of 70 mg/m² every 3 weeks with a weekly dose of 15 mg/m², achieving comparable response rates. Although weekly administration appears to be less cardiotoxic, the results concerning myelosuppression are inconsistent [6,13,52]. Another approach was the use of continuous infusion of DX, which method is thought to be less cardiotoxic. This method has not been studied with DX as a single drug, but combined with DTIC and/or cyclophosphamide (CTX) continuous infusion of DX appears to be equally effective as compared to single doses [6]. Recently, the EORTC Soft Tissue and Bone Sarcoma Group conducted two randomized phase II trials comparing the analogs carminomycin and 4'-epidoxorubicin with DX [17,54]. The activity of high dose DX (75 mg/m² every 3 weeks) was confirmed in both studies, with response rates of 29 and 25% respectively. Carminomycin only resulted in

a 3% response rate [17], quite contradictory to a previously reported 27% response rate [57]. The response rate to 4'-epidoxorubicin was 15% which was not significantly different compared with the response to DX, but still this does not appear to render the drug as an attractive alternative for DX although one should consider that non-equivalent doses were used [54]. Nevertheless, leukocytopenia was significantly reduced with 4'-epidoxorubicin compared to DX. The study did not permit the evaluation of cardiotoxicity at high cumulative dose levels.

A third analog, 4'-demethoxydaunorubicin was studied by Raymond et al. in 22 mainly pretreated patients, achieving 1 partial remission and 5 S.D. [64]. This drug is now under investigation in non-pretreated patients.

A second active drug in the treatment of soft tissue sarcomas appears to be ifosfamide (IFX). The initial nonrandomized studies had shown response rates of 38–67% in over a 100 patients [37,79,85], but those trials already indicated the phenomenon of a decreasing response rate with an increasing number of studies. For this reason and because of scarce data on the activity of cyclophosphamide in adult soft tissue sarcomas, the EORTC performed a randomized phase II trial comparing CTX with IFX. In this trial activity of IFX was confirmed, the response rate being approximately 25% in non-pretreated patients (unpublished data). Cyclophosphamide appeared to be minor activity.

The third drug with known moderate activity as a single agent is the commonly used DTIC which achieved a response rate of 17% in 53 patients [36]. Because the response rate of the combination of DX plus DTIC was much higher as compared with either one of these two drugs alone [35], DTIC has not been studied further as a single agent.

At present there are no other active drugs available for the treatment of soft tissue sarcomas. Vincristine (VCR) and actinomycin (DACT), active drugs in childhood sarcomas, have hardly been studied in adults. Methotrexate (MTX) and *cis*-platin (CDDP) are inactive [15,19,21,38,41,76] although for both drugs the initial studies had suggested some activity [39,86]. As a possible excep-

tion, mixed mesodermal uterine sarcomas are more responsive to CDDP, with a response rate of 18%.

Previously, Bakers' antifol, dianhydrogalactitol, pyrarofurin, cycloleucine, chlorozotocin, DCNU, CCNU, methyl-CCNU, AMSA, 5-azacytidine, hexamethylmelamine, mitomycin C, piperazine-dione, vindesine, cytembena, metoprime, VM-26 and VP-16-213 were found to be inactive [90]. Since 1982, PALA [16], dibromodulcitol [12], ICRF-159 [12], Maytansine [12,28], prednimustine [42], gallium nitrate [74], Vinblastin [95] and low-dose mitoxantrone [63] could be added to this list.

Combination chemotherapy

Because DX still is considered to be the most active single agent in soft tissue sarcomas, most combination chemotherapy regimens include DX. Moreover, because the combination of DX + DTIC was the first to achieve a relatively fair response rate of 35% [35], this so-called ADIC combination became the basis for many of the other combinations studied. In several studies, ADIC achieved a 30–47% response rate with 4–11% complete remissions [7,13,35,58]. The SWOG group subsequently added VCR and CTX to the original ADIC regimen, thus creating the CYVADIC regimen, which has become the regimen studied most extensively. The initial SWOG response rate reached up to 59%, more recently dropping to 49% [93,94]. Various other groups have reported studies with the same regimen achieving somewhat lower response rates. The EORTC recently reported a randomized trial [59] comparing CYVADIC (CTX 500 mg/m² i.v. day 1, VCR 1.5 mg/m² day 1, DX 50 mg/m² day 1 and DTIC 250 mg/m²/days 1–5) with a schedule alternating ADIC and VCR/CTX in similar doses as used with CYVADIC at 4-week intervals. The overall response rate in the latter, cycling arm was 14% compared to 38% (17% CR and 21% PR) for CYVADIC. This reflects the lower activity of CTX/VCR as compared with that of ADIC. Moreover, it indicates that DX should be administered every 3 to 4 weeks, instead of 8-weekly.

Karakousis et al. [43] found a 27% response rate on CYVADIC, while Bui et al. [22] giving DTIC

during 3 days found a 52% response rate. All these studies indicate the importance of several prognostic factors as well as the heterogeneity of these tumors. Piver et al. [60] treated 26 extensively pretreated patients with sarcomas of the genital tract, achieving a 23% response rate, indicating that even in pretreated patients, CYVADIC may be active. Finally, in an attempt to reduce toxicity, Bernard et al. [8] applied a single high dose of DTIC within the CYVADIC regimen in a small number of patients. While toxicity was similar as in the original regimen, activity appeared to drop.

Other modifications of the CYVADIC regimen have been studied in clinical trials as well. However, CTX/DX/DTIC [9], CI-CYADIC [6] applying the same three drugs but with continuous infusion of ADIC, and CYOMAD (CTX/VCR/MTX/DX) [48] had worse response rates and/or significant toxicity as compared to CYVADIC. A new regimen with possible activity was reported by Spielman et al. [83]. They utilized DX/DTIC adding CTX/VDS

and CDDP, the latter three drugs being inactive as single agents. Surprisingly, response rate was 51% in 57 evaluable patients, but the data have to be confirmed by others before this regimen can be advised in clinical practice. The activity of CDDP in mixed mesodermal uterine sarcomas was more or less confirmed in a very small study in only six patients receiving DX/CDDP, achieving five responses [81].

All other combinations tested in more than 20 patients (Table II) could not show any advantage over single agent treatment with DX or combination therapy with ADIC or CYVADIC. It appears from those studies that VCR and DACT do not add much to the effect of DX or ADIC, so these two drugs may be considered inactive.

The randomized EORTC study on CYVADIC [59] included an arm alternating VCR/CTX with ADIC. In this alternating arm, the response rate achieved was only 14%, which was significantly lower ($p = 0.001$) than the response rate of the

TABLE II

Soft tissue sarcomas: combination chemotherapy^a.

Drugs	No. of evaluated patients	Response rate (%)			Ref.
		CR ^c	PR ^d	Overall	
DX/DACT	22	10	18	28	18
DX/DTIC ^b	442	11	25	36	13, 35, 57, 75
DX/DTIC/CTX ^b	165	12	31	47	6, 9, 57
DX/DTIC/CTX/VDS/CDDP	57	12	39	51	83
DX/DTIC/VCR	80	10	40	50	35
DX/DTIC/VCR/CTX ^b	317	16	28	44	22, 43, 59, 94
DX/DTIC/DACT	92	9	15	24	57
DX/CTX/VCR	62	3	16	19	78
DX/CTX/VDS	27	22	15	37	20
DX/CTX/MTX ^b	229	—	—	23	61, 62
DX/CTX/MTX/AMFB	46	0	10	10	62
DX/VCR/HDMTX/DACT	34	—	—	44	49
DX/VCR/HDMTX/DACT/DTIC/CLB	33	—	—	27	49
DX/Me-CCNU	41	7	42	49	65
DX/Me-CCNU	42	—	—	26	49
VCR/CTX/DACT	57	2	9	11	78

^a Only series with more than 20 patients.

^b Cumulative data.

^c CR = complete remission.

^d PR = partial remission.

original CYVADIC regimen. Dalley et al. [26] alternated DX/CTX with DTIC/DACT, also only achieving a 20% response rate. These data indicate that alternating non-cross resistant combinations of the currently available drugs do not benefit the adult with a soft tissue sarcoma.

The EORTC found a median of 8 weeks, necessary to achieve response, but with wide ranges [59]. Sometimes even more prolonged treatment will lead to response [59,93] reflecting the slow regression of some soft tissue sarcomas. It appears that patients with inoperable primary tumors are more likely to respond than patients with advanced metastatic disease [87,93], while patients with bone or liver metastases do worse than patients with soft tissue disease [59,93].

In the EORTC study [59], the median survival following complete response was 130 weeks, following partial response 54 weeks, for stable disease 56 weeks and for progressive disease 23 weeks. Thus there appears to be a survival benefit in patients achieving a complete response. Maybe even more important, Yap et al. [96] reported a disease-free survival of 5 years or more in 21% of their patients achieving a complete response. This indicates that patients with advanced soft tissue sarcomas may potentially be cured with chemotherapy, and that chemotherapy should aim at achieving complete response. As CYVADIC appears to achieve more complete responses than ADIC, although these two regimens have not been directly compared in a randomized trial, we prefer to use CYVADIC.

Another important conclusion from the EORTC study [59] was, that the achievement of response mainly depended on a good performance score (PS). In fact, PS was the single most important prognostic factor. This observation may explain some of the controversy in reported response rates, and stresses once more the necessity of stratification for PS in future trials. Age less than 60 years, weight loss of less than 5% and female sex appear to be other prognostic factors related with a high incidence of response and long survival [57,59,65]. Old patients probably respond worse because of their generally poorer physical condition and the necessity of dose reduction [55].

Combined modality treatment

Preoperative chemotherapy

One of the problems in the treatment of soft tissue sarcomas is the development of local recurrence after surgery. Experience with various types of surgical procedures all have shown local failures. Nevertheless, the introduction of postoperative radiotherapy offered the possibility of limb-sparing surgery with relatively effective local control [1,67,69]. However, local failures still occur, and it is important to stress that a truly radical limb-sparing procedure may leave as much functional disability as amputation [90].

Secondly, soft tissue sarcomas often present as very large lesions, while these tumors can extend along fascial planes for long distances, posing problems in terms of surgical excision of all gross tumor. For these reasons, the option of preoperative chemotherapy is interesting.

Several investigators studied the effects of regional intraarterial isolation-perfusion chemotherapy. The basic premise of this treatment is to deliver a high concentration of drug into an extremity that has been excluded from the systemic circulation by a tourniquet technique. In this way, also the risk for systemic side effects of the drug, in particular myelosuppression, can be reduced.

McBride was the first to report results of this technique in soft tissue sarcomas, achieving a 57% 5-year survival in 79 patients [50]. These patients had local excision, 6 weeks after chemotherapy. After some pilot studies, the UCLA group began to treat patients with DX 30 mg/day by continuous infusion over 3 days, immediately followed by radiotherapy in a dose of 3.5 Gy/day for 10 treatment days over a 2-week period, followed by radical en bloc resection of the tumor [31]. After a median follow-up of 32 months they observed only 2 local and 22 distant relapses in 65 patients [30]. However, it should be noted that almost half of their patients also received adjuvant chemotherapy with DX/HDMTX. Thus it is impossible to interpret survival results or the incidence of distant metastases reduction as a result of the local treatment

[32]. Their complication rate was acceptable, with wound slough, lymphedema and fractures of adjacent bone emerging as the most frequent complications. Still, one should remember that far more serious complications related to this technique have been reported previously, for which reason we believe that this technique should only be applied in specialized centers.

Karakousis et al. [40] using a similar technique but infusing adriamycin (ADM) and MTX, had comparable results.

The Milan group treated their patients with preoperative continuous intraarterial infusion of ADM or ADM/CDDP for 8 consecutive days. One of their observations was the fact that histologic response (necrosis of the tumor) does not coincide very frequently with clinical reduction of tumor size [4,5].

The effectivity of preoperative intraarterial chemotherapy for soft tissue sarcomas has also been suggested by results of other, small studies [14,77], but the absence of randomized studies that include a group of patients without preoperative chemotherapy makes further investigation concerning this approach necessary.

Only limited data are available on systemic preoperative chemotherapy in local bulky disease. The option of such an approach is to determine the sensitivity of the tumor to chemotherapy, to change an initially inoperable tumor into a surgically resectable one, and to eliminate possible micrometastases. The only published report on this topic came from the Institute Gustave-Roussy [71]. They used CYVADIC or other combinations preoperatively, achieving resectability of the tumor in approximately half of their patients. However, because of the absence of further data, this approach should still be considered investigational, and only be applied in clinical trial.

Postoperative radiotherapy

The most important combined modality treatment is the addition of radiotherapy after surgery. This combination has already been discussed in the paragraph on Radiotherapy, p. 194.

Adjuvant chemotherapy

Patients with soft tissue sarcomas are at high risk for the development of metastatic disease. Because of the fairly good responses to chemotherapy achieved in patients with advanced soft tissue sarcomas and a high performance status, there appears to be a basis to study adjuvant chemotherapy, which aims at the eradication of possible micrometastases. The first study drawing attention to adjuvant chemotherapy came from the NCI [66]. They investigated the possibility to prevent local recurrence with postoperative local irradiation, but also applied adjuvant chemotherapy with DX 50–70 mg/m² and CTX 500–700 mg/m² followed by high-dose MTX with leucovorin rescue after a cumulative dose of 550 mg/m² of DX had been reached. Patients with extremity lesions who had received adjuvant chemotherapy experienced an increased survival compared to historical controls (Table III). These results stimulated these investigators to initiate a randomized study using the same adjuvant chemotherapy regimen in one arm, but including a control group not receiving adjuvant chemotherapy. The 5-year disease-free survival in patients with soft tissue sarcomas of the extremities was 71% for the 37 patients in the chemotherapy group as compared with 46% for the 28 control patients (Fig. 1) ($p = 0.008$) (Table IV). The 5-year overall survival was 86% and 51% respectively ($p = 0.01$) (Fig. 2) [69]. The improvement in survival was also noted in patients who had had limb-sparing surgery. As opposed to these results in extremity lesions, adjuvant chemotherapy did not result in improvement of disease-free or overall survival in head, neck and truncal lesions. This may be due to differences in the ability to achieve local control, because in head, neck and truncal lesions complete surgical tumor removal is more complicated and it is difficult to apply adequate high-dose postoperative radiotherapy. One of the problems arising in this study was the high incidence of cardiomyopathy caused by DX. Fourteen percent of the patients developed cardiac failure and an additional 52% had abnormal ejection fractions [69]. For these reasons, NCI now compares in a randomized way the original

TABLE III

Non-randomized studies on adjuvant chemotherapy in soft tissue sarcomas in adults.

Treatment	Site	No. of evaluated patients	Follow-up (mths)		Survival (%)		Ref.
			Median	Range	DFS ^a	Overall	
DX/CTX/HDMTX	Limb	26	60	–	68	84	69
DX/CTX/HDMTX	H/N ^b	23	60	–	42	52	69
DX/VCR/HDMTX	Limb	62	30	6–70	65	61	30
DX/DTIC	All	113	24	–	74	–	27
DX/CTX/VCR/MDMTX	All	12	–	36–84	75	91	51
DX/VCR/HDMTX/DTIC/CLB/DACT	All	64	50	28–71	70	88	82

^a DFS = disease-free survival.^b H/N = head and neck.

18-month schedule with a 5-month regimen of DX 70 mg/m² + CTX 700 mg/m² in patients with extremity lesions. Although follow-up of the latter study is too short to draw definite conclusions, the 26 months actuarial survival rates are similar in both groups [69].

Another randomized study alternating adjuvant

VCR/CTX/DACT with VCR/DX/DTIC at 6-week intervals for 48 weeks, was performed in 61 patients in the Mayo Clinic [29]. After a median follow-up of 64.3 months the estimated 5-year disease-free survival is 68% for patients receiving adjuvant chemotherapy and 62% for those not receiving such treatment. However, early adjuvant chemoth-

TABLE IV

Randomized studies on adjuvant chemotherapy in soft tissue sarcomas in adults.

Treatment	Site	No. of evaluated patients	Follow-up (mths)		Survival (%)		Ref.
			Median	Range	DFS ^a	Overall	
DX/CTX/HDMTX	Limb	37	54	–	71	86	69
Controls		28	54	–	46	51	
DX/CTX/HDMTX	H/N ^b	28	35	–	53	59	69
Controls		28	35	–	42	53	
VCR/CTX/DACT alternating VCR/DX/DTIC	All	30	64	–	68	70	29
Controls		31	64	–	64	70	
DX	All	17	19	0–50	54	87	3
Controls		19	19	0–50	64	68	
DX	All	16	30	2–50	–	–	45
Controls		16	30	2–50	–	–	
DX	Uterus	77	–	–	62	–	56
Controls		82	–	–	51	–	

^a DFS = disease-free survival.^b H/N = head and neck.

Fig. 1. Actuarial analysis of disease-free survival in patients with soft tissue sarcomas of the extremities (Reproduced with permission of Rosenberg [69].)

erapy in this study did reduce the requirement for salvage surgical excision of metastases, but not for local recurrence.

In this study, the use of inactive agents in one of the alternating regimes and the administration of ADIC at only 12-week intervals may have influenced

Fig. 2. Actuarial analysis of overall survival in patients with soft tissue sarcomas of the extremities (Reproduced with permission of Rosenberg [69].)

the observed absence of survival advantage after adjuvant chemotherapy. The good local control and survival rate for both study groups, may also be attributable to the application of an aggressive surgical salvage program.

Three groups are randomly comparing single agent adjuvant DX and no adjuvant chemotherapy (Table IV). Antman et al. from Boston [3] applied 90 mg/m² every 3 weeks for a total of five courses in 17 patients and compared their results with a no-treatment control group of 19 patients. Only a nonsignificant survival advantage was found for extremity lesions. ECOG [45] is comparing DX 70 mg/m² every 3 weeks for a total of seven courses, versus nothing. In their most recent report, 44 patients had entered the study and for 32 patients median follow-up results at 30 months were available. They only stated that no significant difference was noted concerning survival. The third study concerns an Intergroup Adult soft tissue sarcomas study, but no report has been published to date.

Finally, the EORTC Soft Tissue and Bone Sarcoma Group is still running a randomized trial comparing 8 cycles of adjuvant CYVADIC with no adjuvant chemotherapy. Stratification for localization of the primary tumor and postoperative concurrent administration of local radiotherapy are also included in this study. Over 300 patients have been entered and there still appears to be no reason to stop entry.

In uterine sarcomas, Omura [45] conducted a randomized study using DX 60 mg/m² every 3 weeks in 77 patients. No improvement of survival was seen as compared with survival in 82 patients who did not receive adjuvant chemotherapy. In all these studies it was common use to start chemotherapy within 6 to 12 weeks following surgery and after completion of postoperative irradiation.

Several non-randomized studies on adjuvant chemotherapy have been performed [2,27,32,51,82] (Table III). However, the selection of patients due to modern diagnostic techniques such as lung tomography and CT-scanning will influence results of comparisons with historical control groups. Moreover, the application of postoperative radiotherapy and secondary salvage surgery nowadays will also

influence survival results. In this context, the observation of Rosenberg [68] that patients in the no-treatment arm in their randomized study survived significantly better than the patients in the historical control group in their pilot study, emphasizes the need to perform prospective randomized trials. Non-randomized trials on adjuvant chemotherapy should be considered to be of very limited value.

Chemotherapy and hyperthermia

A new interesting approach may be the combination of chemotherapy with hyperthermia. Artificially induced temperatures between 41 and 43°C have demonstrated a lethal effect on neoplastic cells both in vitro and in vivo. Combining cytotoxic drugs and heat, has produced evidence suggestive of antitumor synergism. In a small number of nine patients with advanced soft tissue sarcomas, Gerad et al. [33] observed two complete remissions and two partial remissions with use of the combination of DX/CTX plus whole body hyperthermia. Cavaliere et al. applied the combination of DX plus hyperthermic antineoplastic infusion for primary tumors prior to surgery, with very good survival results [23]. However, these results have only been published in abstract form. Further studies on this topic are awaited with interest.

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