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High-dose adriamycin (ADM) and *cis*-platinum (DDP) in advanced soft-tissue sarcomas and invasive thymomas

A pilot study

T. H. Klippstein, P. S. Mitrou, K. J. Kochendörfer, and L. Bergmann

Abteilung für Hämatologie/Onkologie, Zentrum Innere Medizin, Universitätskliniken, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, Federal Republic of Germany

Summary. *Eighteen previously untreated patients with advanced unresectable or metastatic soft-tissue sarcomas (STS) and two patients with locally invasive thymoma were treated with a combination of adriamycin (ADM) 80 mg/m² on day 1 and cis -platinum (DDP) 120 mg/m² on day 1. The regimen was repeated at 4-weeks intervals. In STS the overall remission rate was 44%, with 21% complete remissions. The overall survival was 15 months (3–35+), responders surviving a median of 20 months (3–35+) and nonresponders, a median of 9 months (3–20+).*

Tumor responses lasted a median of 8 months (3–35+).

Two patients with liposarcoma have now survived disease-free for at least 2 years and are potentially cured.

The two patients with thymoma experienced complete remission lasting 4+ and 20+ months.

Substantial hematologic toxicity was prominent, due to the high-doses used in this combination regimen.

Introduction

Soft tissue sarcomas (STS) are a rare group of tumors with widely ranging natural histories. Consequently there has been considerable controversy about their management. Conventional approaches rely heavily on surgery as long as an eradication of the local tumor masses is thought to be possible. But the known frequency of local recurrence [12] and invasive local growth accompanied by dissemination that cannot be cured by radical surgery leads to the necessity for more adequate methods including chemotherapy.

With the introduction of adriamycin (ADM) into clinical therapy of advanced unresectable STS, responses were seen in 20%–40% of the patients [7]. When ADM and DTIC were combined an overall response rate of 42%, with complete remissions in 11%, was reported [2, 8]. The addition of vincristine (VCR) and cyclophosphamide (CTX), which are known to be active in childhood sarcomas, resulted in the CYVADIC regimen, which has been the treatment of choice for first-line therapy in locally advanced or metastatic STS, yielding an overall response rate of 50%–60% with about 30% complete remissions (CR) [2, 21, 22]. In contrast, considerably lower remission rates of 23%–37%, or even failures, were obtained in follow-up studies [3, 9] with the same multidrug treatment.

Offprint requests to: T. H. Klippstein

Cisplatin (DDP) has shown activity in the treatment of STS. However, results vary considerably in trials in which DDP has been used as a single agent. Remission rates vary from 0 to 7% to 28% [4, 13, 19]. This discrepancy may be caused by different dosages and schedules of DDP. Therefore, we decided to combine ADM, the first-line drug, and DDP, a relatively new agent with proven activity. Both components were used in unusually high doses (ADM 80 mg/m², DDP 120 mg/m²) in a phase II clinical trial for advanced STS and thymomas.

Patients and methods

Since March 1980 eighteen patients with histologically confirmed unresectable STS and two patients with locally advanced malignant thymomas have been entered on study. To be considered evaluable patients were required to have received two complete courses of chemotherapy at least, and an adequate follow-up documentation of all clinical data was also required. Therapeutic responses were defined in the following way: CR was the disappearance of all evidence of tumor for at least 4 weeks. PR was coded when the sum of the products of the two greatest perpendicular diameters of all measurable lesions decreased by more than 50% for at least 4 weeks. A tumor regression of less than 50% was defined as stable disease or 'no change' (NC). Survival and duration of responses were recorded from the onset of treatment. The chemotherapy regimen consisted of ADM 80 mg/m² by IV bolus on day 1 and DDP 120 mg/m² IV on day 1, followed by enforced diuresis with saline 3 l/m². Treatment was repeated at 4 week intervals. Patients were considered to be evaluable for response if they had received at least two complete courses of chemotherapy. The treatment was terminated after four cycles.

The clinical characteristics of all 20 patients are outlined in Table 1. The median age was 49 years. The mean performance status according to the Karnofsky scale was 80%. Concerning the specific designation of the STS, liposarcomas (6) and fibrosarcomas (4) were the most frequent. In eight patients (45%) the STS were in the retroperitoneum (nos. 1, 2, 3, 4, 12, 13, 14, 18), in five cases in the extremities with advanced lymph node involvement or distant metastases in liver or lung (nos. 5, 7, 8, 9, 11), and in five the primary sarcoma was in lung or gut (nos. 6, 10, 15, 16, 17). The system described by Russell et al. [17] was used for staging (Table 2). All tumor types were in the advanced stages IIIb to IVb (Table 3).

Table 1. Characteristics of the patients

Total no. of patients	20
Female	6
Male	14
Age (years), median (range)	49 (19–66)
Performance status (%), median (range)	80 (40–100)
Type of tumor	
Liposarcoma	6
Fibrosarcoma	4
Malignant fibrous histiocytoma	3
Haemangiopericytoma	2
Rhabdomyosarcoma	1
Extraosseous chondrosarcoma	1
Neurogenic sarcoma	1
Thymoma	2
Pretreatment	
Irradiation	2
Chemotherapy	0

Two patients had received previous irradiation but none had had prior chemotherapy.

Toxicity. Alopecia, nausea, vomiting, and loss of appetite occurred in all patients. These subjective toxicities appeared to be tolerable. In relation to the unusually high dosage of both agents bone marrow toxicity was severe (Table 4). Eleven of 20 patients (55%) had a leukocyte nadir of $< 2 \times 10^9$/l, and the platelet nadir has $< 100 \times 10^9$/l in 13 (65%) and $< 50 \times 10^9$/l in five. In 20% of the patients transfusions were required due to a fall in hemoglobin greater than 3 g/l. Dose attenuation or prolongation of the intervals was not necessary because these disturbances were reversible within 4 weeks. There was no drug-related death. Three patients experienced serious infections and needed antibiotic therapy. A progressive fall in creatinine clearance to 40 or 50 ml/min was observed in three patients but serum creatinine did not rise above 2 mg/dl. No cardiotoxic or neurotoxic side-effects appeared.

Results

Remissions

All 20 patients entered on trial were evaluable. Two patients suffering from malignant thymoma were included because of the massive local growth in the mediastinum with infiltration of the lungs that could not be treated by surgical or radiation therapy. Moreover, cytotoxic approaches to malignant thymoma are rather uncommon, with only a few single case reports known [18] that show ADM and DDP as active drugs.

Therapeutic results are outlined in Table 3. Eight (44%) of the 18 patients with STS experienced CR (21%) or PR. In all cases entering CR or PR a significant tumor reduction occurred within the first two courses of chemotherapy. Patients who did not respond showed stable or even progressive disease during subsequent cycles of chemotherapy. Among the histological subtypes four CR were achieved in liposarcomas. PR was noted in one case each of liposarcoma, hemangiopericytoma, and rhabdomyosarcoma. In all four cases of CR, tumor regression was confirmed by 'second-look' surgery. In three of them the excised residual tumor masses contained necrotic material without evidence of viable tumor cells. In the fourth case multiple biopsies revealed fibrous tissue at the original tumor site.

One patient with liposarcoma relapsed after a CR and responded again to the same regimen, this time with a PR (patient no. 5).

Both patients with invasive thymoma achieved CR. One patient (no. 19) relapsed and entered a second remission after two cycles of ADM + DDP (Table 3).

Remission duration and survival

In STS tumor responses (CR and PR) lasted a median of 8 months (3–35+). A 15-month median survival was noted for all patients with STS. Median survival for responders was 20 months, versus 9 months for those with either stable or progressive disease. However, the difference is not statistically significant ($P = 0.07$) according to the Kaplan-Meier and

Table 2. Staging system[a] for STS according to Russel et al. [17]

Stage I Stage Ia G1T1N0M0	Grade 1 tumor less than 5 cm in diameter, with no positive regional lymph nodes or distant metastases
Stage Ib G1T2N0M0	Grade 1 tumor 5 cm or greater in diameter with no positive regional lymph nodes or distant metastases
Stage II Stage IIa G2T1N0M0	Grade 2 tumor less than 5 cm in diameter, with no positive regional lymph nodes or distant metastases
Stage IIb G2T2N0M0	Grade 2 tumor 5 cm or greater in diameter, with no positive regional lymph nodes or distant metasteses
Stage III Stage IIIa G3T1N0M0	Grade 3 tumor less than 5 cm in diameter, with no positive regional lymph nodes or distant metastases
Stage IIIb G3T2N0M0	Grade 3 tumor 5 cm or greater in diameter, with no positive regional lymph nodes or distant metastases
Stage IIIc any G1–3T1–2N2M0	Tumor of any grade or size (no invasion), with positive regional lymph nodes, but no distant metastases
Stage IV Stage IVa any G1–3T3N0–1M0	Tumor of any grade that grossly invades bone major vessel, or major nerve with or without positive regional lymph node metastases but without distant metastases
Stage IVb any GTNM1	Tumor with distant metastases

[a] T Primary tumor
T1 = Tumor less than 5 cm
T2 = Tumor 5 cm or greater
T3 = Tumor that grossly invades bone, major vessel, or major nerve

N Regional lymph nodes
N0 = No histologically verified metastases to regional lymph nodes
N1 = Histologically verified regional lymph node metastasis

M Distant metastais
M0 = No distant metastasis
M1 = Distant metastasis

Histologic grade of malignancy
G1 = Low
G2 = Moderate
G3 = High

Table 3. Staging and treatment results of the sarcomas and thymomas

Patient no.	Diagnosis	T	N	M	G	Stage	No. of treatment courses	Response (duration in months)	Survival (months)
1	Hemangiopericytoma	T2	N1	M1	G1	IVb	4	NC	9
2	Liposarcoma	T3	N0	M0	Gx	IVa	4	CR (35+)	35+
3	Neurogenic sarcoma	T2	N0	M1	G1	IVb	4	NC	18
4	Liposarcoma	T3	N0	M0	G3	IVa	4	CR (10)	18
5	Liposarcoma	T3	N1	M0	G1	IVa	4	CR (12)	
		–	–	–	–	–	2	PR (4)	27+
6	Fibrosarcoma	T2	N1	M0	G2	IIIc	2	PGR	14
7	Hemangiopericytoma	Tx	N0	M1	G2	IVb	4	PR (5)	17
8	Liposarcoma	T3	N1	M0	G1	IVa	4	PR (6)	12
9	Rhabdomyosarcoma	T3	N0	M0	G3	IVa	4	PR (3)	5
10	Fibrosarcoma	T3	N0	M1	G2	IVb	4	NC	20+
11	Fibrosarcoma	T2	N0	M0	G3	IIIb	2	PGR	3
12	Liposarcoma	T2	N0	M0	G3	IIIb	4	CR (24+)	24+
13	Liposarcoma	T3	N0	M1	G1	IVb	3	NC	9
14	Malignant fibrous histiocytoma	T3	N1	M1	G3	IVb	4	NC	17
15	Malignant fibrous histiocytoma	T2	N1	M1	G2	IVb	2	PGR	3
16	Malignant fibrous histiocytoma	T3	N0	M0	Gx	IVa	2	NC	15+
17	Chondrosarcoma	T3	N1	M1	G2	IVa	2	PGR	4
18	Fibrosarcoma	T2	N1	M0	G2	IIIc	4	NC	3+
19	Thymoma, lymphocytic	–	–	–	–	–	4	CR (12)	
		–	–	–	–	–	2	CR (8+)	20+
20	Thymoma, epithelial	–	–	–	–	–	4	CR (4+)	4+

Table 4. Side-effects of chemotherapy

	No. of patients (%)	No. of chemotherapy courses (%)
Leukocyte nadir, median ($\times 10^9$/l) 1.8		
Leukocytes $< 2 \times 10^9$/l	11 (55)	23/73 (31.5)
Leukocytes $< 1 \times 10^9$/l	3 (15)	4/73 (5.5)
Platelets nadir, median ($\times 10^9$/l) 80		
Platelets $< 100 \times 10^9$/l	13 (65)	15/73 (20.5)
Platelets $< 50 \times 10^9$/l	5 (25)	10/73 (14)
Hemoglobin decline > 3 g/dl	4 (20)	14/73 (19)
Creatinine $\geqq$ 1.5 mg/dl	3 (15)	3/73 (4)
Creatinine > 2.0 mg/dl	0	0
Bacterial infections	3 (15)	3/73 (4)

Gehan tests [6, 11]. In all, six patients with STS remain alive: three have been in CR or PR for periods ranging from 24+ to 35+ months and in three disease has been stable for 3+ to 20+ months. Two patients have been disease-free for at least 2 years (Table 3).

Discussion

It is generally accepted that ADM is the most potent drug for the treatment of STS, with an overall response rate of about 30%, although there is a wide variation in remission rates achievable with ADM-containing regimens (27%–60%) [2, 7, 9, 15, 16, 21, 22]. The dose and schedule of ADM required for optimum therapeutic effect remain undefined. However, there is some evidence that better results are obtained with a high-dose schedule, e.g., 75 mg/m^2 or more [5, 14, 16].

In recent years new cytotoxic agents have been introduced into the treatment of STS. Among these DDP appeared to be an active drug [13, 19]. Various remission rates have been reported, possibly due to different dosage and schedule of cisplatin [4, 13, 19]. Therefore, we decided to use high doses of ADM (80 mg/m^2) and DDP (120 mg/m^2).

Liposarcoma was found to be the most responsive type of STS. In six cases, four CR and one PR have been achieved, confirming the results of Bierbaum et al. [1], who reported that liposarcoma was very sensitive to chemotherapy. In general, liposarcoma, fibrosarcoma, and angiosarcoma are known to be especially responsive to cytotoxic drugs [3], while other histological types of STS seem to carry a worse prognosis (e.g., extraosseous chondrosarcoma, alveolar, rhabdo-, and leiomyosarcoma).

Despite the small number of cases, our results, with an overall response rate of 44%, including 21% CR, and responders surviving a median time of nearly 2 years, indicate that the combination of ADM and DDP is effective. Additionally it should be underlined that two patients (both with liposarcomas) have been in continuous remission for periods in excess of 2 years and are potentially curable by the regimen.

In thymomas, rare, invasively growing tumors leading to serious local complications often causing death of the patients, ADM and DDP have been described as efficient in producing complete tumor regression [10, 18, 20]. Mitrou et al. [18] have recently reviewed the literature discussing the results of combined chemotherapeutic modalities for thymomas and presenting a case report of dramatic complete tumor remission obtained with this combination regimen. In this trial two cases of invasive thymoma were seen in complete regression after ADM/DDP combined treatment.

The side-effects of our combination were severe, especially myelosupression, but the hematologic toxicity was reversible with no need to reduce the doses or extend the 4-week schedule. However, the doses of ADM and DDP needed for optimum antitumor activity in STS are still not known. There is some evidence that comparable responses may be achievable with considerably lower doses or a different schedule of both components [1]. Therefore further studies are warranted in advanced unresectable or metastatic STS and thymoma.

References

1. Bierbaum W, Bremer K, Firusian N, Higi M, Niederle N, Scheulen ME, Schmidt CG, Seeber S (1981) Chemotherapeutische Behandlungsmöglichkeiten bei fortgeschrittenen Sarkomen. Dtsch med Wochenschr 106: 1181
2. Blum RH, Corson JM, Wison RE, Greenberger JS, Canellos GP, Frei E III (1980) Successful treatment of metastatic sarcomas with cyclophosphamide, adriamycin and DTIC (CAD). Cancer 46: 1722
3. Bodey GP, Rodriguez V, Murphy WK, Burgess A, Benjamin RS (1981) Protected environment-prophylactic antibiotic program for malignant sarcomas. Cancer 47: 2422
4. Bramwell VHE, Brugordas A, Mouridsen HT, Cheix F, De Jager R, van Oosterom AT, Vendrik CP, Pinedo HM, Sylvester R, De Pauw M (1979) EORTC Phase II study of cisplatin in CYVADIC-resistant soft tissue sarcomas. Eur J Cancer 15: 1511
5. Cortes EP, Holland JF, Wang JJ, Glidewell O (1975) Adriamycin (NSC-123127) in 87 patients with osteosarcoma. Cancer Chemother Rep 6: 305
6. Gehan EH (1965) A generalized Wilcoxon test for arbitrary single-censored samples. Biometrics 52: 203
7. Gottlieb JA, Baker LH, O'Bryan RM, Sinkovics B, Hoogstraten Blumenschein GR, Saiki JH, Coltman C, Burgess MA, Sullivan P, Thigpen T, Bottomley R, Balcerzak S, Moon TE (1975) Adriamycin (NSC-123127) used alone and in combination for soft tissue and bony sarcomas. Cancer Chemother Rep [3] 6: 271
8. Gottlieb JA, Benjamin RS, Baker LH (1976) Role of DTIC (NSC-45388) in the chemotherapy of sarcomas. Cancer Treat Rep 69: 199
9. Guiliano AE, Larkin F, Eilber FR, Morton DL (1978) Failure of combination chemotherapy (CYVADIC) in metastatic soft tissue sarcomas. Implications for adiuvant studies. (Abstract C-212) Proc AACR/ASCO 19: 359
10. Jaffrey IS, Denefrio J, Chahinian C (1981) Treatment of invasive or metastatic thymoma. Cancer 47: 1752
11. Kaplan EL, Meier P (1958) Non-parametric estimation for incomplete observations. J Am Stat Assoc 53: 457
12. Karakusis CP (1982) Soft tissue sarcomas. An update. Current Surgery 39: 5
13. Karakusis CP, Holtermann OA, Hoyoke ED (1979) *cis*-Dichlorodiammineplatinum (II) in metastatic soft tissue sarcomas. Cancer Treat Rep 63: 2071
14. O'Bryan RM, Baker LH, Gottlieb JE (1977) Dose response evaluation of adriamycin in human neoplasia. Cancer 39: 1940
15. Pinedo HM, van Oosterom AT (1980) Treatment of advanced soft tissue sarcomas in adults. In: van Oosterom AT, Muggia FM, Cleton J (eds) Therapeutic progress in overian cancer, testicular cancer and the sarcomas. University Press, Leiden, p 425
16. Rosenberg SA, Suit HD, Baker LA, Rosen G (1982) Sarcomas of the soft tissue and bone. In: de Vita VT, Hellman S, Rosenberg SA (eds) Cancer. Principles and practice of oncology. Lippincott, Philadelphia Toronto, p 1037
17. Russell WO, Cohan J, Enzinger F, Hajdu SI, Heise H, Martin R, Meissner W, Miller WT, Schmitz RL, Suit HD (1977) A clinical and pathological staging system for soft tissue sarcomas. Cancer 40: 1562
18. Mitrou PS, Bergmann L, Tuengerthal S (1982) Induktion einer kompletten Remission mit Adriamycin und *cis*-Platin bei einem invasiv wachsenden Thymom. Dtsch med Wochenschr 44: 1667
19. Samson MK, Baker LH, Benjamin RS, Lane M, Plager C (1979) *cis*-Dichlorodiammineplatinum (II) in advanced soft tissue and bony sarcomas: A Southwest Oncology Group Study. Cancer Treat Rep 63: 2027
20. Shetty MR, Aurora RK (1981) Invasive thymoma treated with *cis*-platinum. Cancer Treat Rep 65: 531
21. Yap BS, Baker H, Sinkovics JG, Rivkin SE, Bottomley R, Thigpen T, Burgess MA, Benjamin RS, Bodey GP (1980) Cyclophosphamide, vincristine, adriamycin and DTIC (CYVADIC) combination chemotherapy for treatment of advanced sarcomas. Cancer Treat Rep 64: 93
22. Yap BS, Sincovics JG, Burgess MA, Benjamin RS, Bodey GP (1983) The curability of advanced soft tissue sarcomas in adults with chemotherapy (Abstract C-937). Proc Am Soc Clin Oncol 2: 239

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