Hiroshima J. Med. Sci.
Vol.42, No.3, 109~115, September, 1993
HIJM 42-14

Adjuvant Chemotherapy for Patients with Soft Tissue Sarcoma

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ABSTRACT

Forty patients with soft tissue sarcoma (Enneking's stage I and II) were treated in our department between 1965 and 1992. We administered VACA regimen (composed of vincristine, actinomycin-D, cyclophosphamide, and doxorubicin) to 14 of 40 patients. Among 40 patients, the 5-year survival rate was 56% in 14 patients with chemotherapy and 39% in 26 without chemotherapy ($p<0.02$). In 32 patients of Stage II, the 5-year survival rate was 40% in 11 patients with chemotherapy and 31% without chemotherapy ($p<0.05$). The improvement of the survival rate was due to delay in the development of lung metastases (chemotherapy group: 21.2 months after first visit, non-chemotherapy group: 9.4 months) and prolongation of the survival period after metastases (chemotherapy group: 26 months, non-chemotherapy group: 7.4 months).

Key words: *Soft tissue sarcoma, Chemotherapy, Survival*

In recent years, the prognosis of patients with malignant bone tumors such as osteosarcoma and Ewing's sarcoma has improved because of the widespread use of intensive chemotherapy[10-12]. However, the efficacy of chemotherapy against soft tissue sarcomas excluding certain histological types remains controversial[13]. There are no highly effective drugs, and surgical resection is still the primary treatment. Since 1983, we have administered chemotherapy (VACA regimen) composed of vincristine (VCR), actinomycin-D (ACT-D), cyclophosphamide (CPM), and doxorubicin (ADR), to patients with soft tissue sarcoma. This regimen was designed for Ewing's sarcoma[12]. In this study, we evaluated the effect of the chemotherapy to soft tissue sarcomas treated in our department.

PATIENTS AND METHODS

Forty-six patients with soft tissue sarcoma were treated in our department between 1965 and 1992. We evaluated all cases histologically, and corrected the diagnosis in several cases. As none of the 6 patients with pulmonary metastasis at the initial visit received chemotherapy and since their outcome was significantly poorer than that of the other patients, these patients were excluded from the study.

Table 1 shows the characteristics of 40 patients and the morphological classification according to Rosen's method[15]. The surgical stage and treatment of patients with chemotherapy is summarized in Table 2. Thirteen cases were administered VACA regimen, one case (Case 13) was treated with T-11 protocol[15]. The surgical stage and treatment of patients without chemotherapy is summarized in Table 3.

Anti-cancer drugs were administered postoperatively, in principle, using the VACA regimen (Fig. 1). In all patients receiving chemotherapy, the total dose of ADR was more than 400mg, and chemotherapy according to the initial schedule was possible for 4 months or more. The dosage was reduced in the children. One case of extraskeletal Ewing's sarcoma was performed T-11 protocol[15], and 2 cases of Ewing's sarcoma with metastasis after treatment for primary tumor was administered ifosfamide and etoposide.

The effect of chemotherapy was assessed by dividing patients into 2 subgroups: no chemotherapy group and chemotherapy group. Preoperative chemotherapy was performed only in a patient with synovial sarcoma and two with extraskeletal Ewing's sarcoma. Therefore, evaluation of chemotherapy was estimated by the cumulative survival rate. The survival rate was calculated by the Kaplan-Meier's method[8] and analyzed by the generalized-Wilcoxon method[5].

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Table 1. Patient characteristics

Number of patients		40
Male/Female		16/24
Mean age (range, yrs.)		43.9 (16–82)
Mean follow-up periods (range, mos.)		37.8 (2–213)
Histology	Subtype	
Malignant fibrous	Ordinary	9
histiocytoma	Myxoid	2
	Inflammatory	1
Synovial sarcoma	Biphasic	5
	Monophasic	7
Malignant shwannoma	Ordinary	5
Liposarcoma	Well diffe.[a)]	2
	Myxoid	3
	Pleomorphic	1
Extraskeletal		3
Ewing's sarcoma		
Leiomyosarcoma		1
Hemangioendothelioma		1
Site		
Thigh		18
Lower leg		5
Buttock		4
Upper arm		3
Forearm		3
Knee		2
Back		1
Abdominal wall		1
Foot		1
Morphological Claasification[b)]		
Spindle cell sarcoma		
Low grage		8
High grage		28
Pleomorphic sarcoma		1
Small cell sarcoma		3

a: Well differentiated.
b: Morphological classification by Rosen[14)].

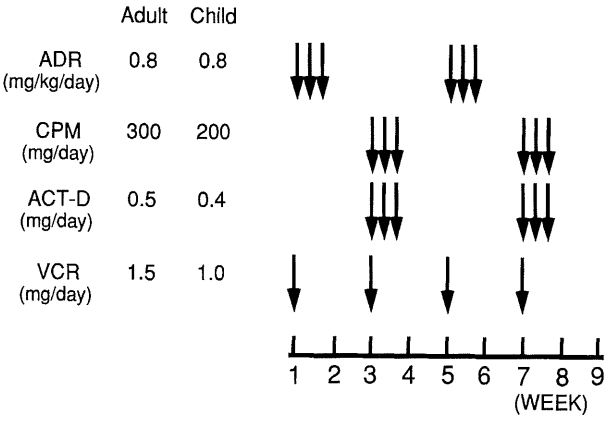

Fig. 1. VAC-A regimen. ADR: doxorubicin (adriamycin), CPM: cyclophosphamide, ACT-D: actinomycin-D, and VCR: vincristine. We administered these drugs intravenously every other day (3 days a week), and every other week. This protocol is published in 1993[12)].

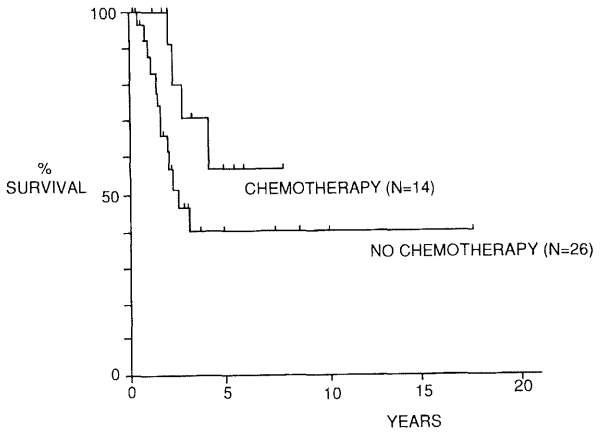

Fig. 2. Cumulative survival curve (Enneking's stage I and II).

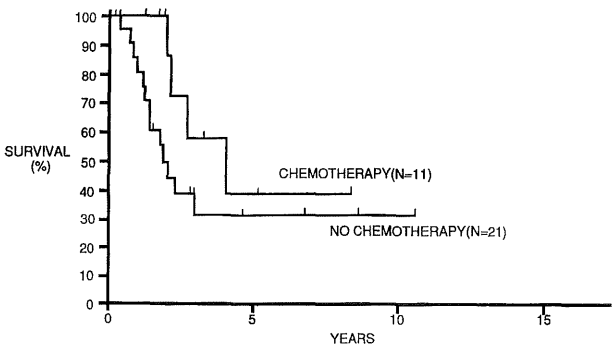

Fig. 3. Cumulative survival curve (Enneking's stage II)

RESULTS

Concerning the cumulative 5-year survival rate in 40 patients of Enneking's stage I and II, the 5-year survival rate was 56% in 14 patients receiving chemotherapy, but 39% in 26 patients without chemotherapy ($p<0.02$) (Fig. 2). In the 32 patients of Enneking's stage II (high grade malignant tumor), the 5-year survival rate in 11 patients receiving chemotherapy was 39% and 31% in the 21 patients without chemotherapy ($p<0.05$) (Fig. 3).

Table 2. Summary of treatment in chemotherapy cases

Case	Diagnosis	Sybtype	Age	Sex	Site	Surgical stage[a]	Radiation[b] therapy	Resection margin[c]	Local recurrence	Metastasis	Treatment after relapse	Prognosis
1	MFH[d]	ordinary	40	F	lower leg	IIB	—	curative wide	—	gingiva (26)[h] mamma (26)	radiation (49 Gray), surgery	DOD[j] (32)[i]
2	MFH	ordianry	53	M	thigh	IIA	—	wide	—	—		CDF[k] (60)
3	MFH	ordinary	45	F	thigh	IIB	—	marginal	+(12)[g]	lung (22)	—	DOD (25)
4	MFH	myxoid	36	F	thigh	IA	—	wide	—	—		CDF (54)
5	Synovial sarcoma	biphasic	26	F	thigh	IIB	—	wide	—	lung (37)	surgery	NED[l] (97)
6	Synovial sarcoma	biphasic	47	M	thigh	IIB	—	curative wide	—	—		CDF (38)
7	Synovial sarcoma	biphasic	57	F	thigh	IIB	+	wide	—	—		CDF (23)
8	Synovial sarcoma	monophasic	23	F	lower leg	IIA	—	wide	+(8)	—	radiation (40 Gray), surgery, ifosphamide	NED (20)
9	Liposarcoma	myxoid	24	F	thigh	IB	—	wide	—	—		CDF (64)
10	Liposarcoma	myxoid	51	F	thigh	IA	—	marginal	—	—		CDF (38)
11	Extra. Ewing[e]		21	M	thigh	IIB	—	curative wide	—	lung (13)	surgery	DOD (48)
12	Extra. Ewing		19	M	upper arm	IIB	—	wide	+(3)	lymph node (8)	ifosphamide, surgery, radiation (30 Gray)	DOD (24)
13	Extra. Ewing[f]		40	F	thigh	IIB	—	intralesional	—	—		CDF (2)
14	Leiomyosarcoma		40	F	thigh	IIB	—	intralesional	—	—		CDF (14)

a: Enneking's surgical stage[4]. b: pre or postoperative radiation therapy. c: evaluation method of surgical margin for musculo-skeletal sarcoma by JOA musculo-skeletal tumor committee (18). d: malignant fibrous histiocytoma. e: extraskeltal Ewing's sarcoma. f: treat with T-11 protocoal (15). g,h: months. i: follow-up periods. j: dead of disease. k: continous disease free. l: no evidence of disease.

Table 3. Summary of treatment in non-chemotherapy cases

Case	Diagnosis	Sybtype	Age	Sex	Site	Surgical stage[a]	Radiation therapy[b]	Resection margin[c]	Local recurrence	Metastasis	Treatment after relapse	Prognosis
15	NFH[d]	ordinary	42	M	thigh	IIB	—	curative wide	—	—		CDF[i] (101)[h]
16	MFH	ordinary	47	F	buttock	IIB	—	marginal	+(4)[f]	—	radiation (40 Gray)	DOD[j] (27)
17	MFH	ordinary	80	M	fore arm	IIB	—	curative wide	—	axilla (12)[g]		DOD (24)
18	MFH	ordinary	29	F	bittpck	IIB	—	intralesional	+(8)	—	radiation (40 Gray)	DOD (15)
19	MFH	ordinary	80	F	thigh	IIB	—	wide	—	—		CDF (17)
20	MFH	ordinary	82	F	lower leg	IIB	—	wide	—	—		CDF (4)
21	MFH	myxoid	80	F	thigh	IB	—	marginal	—	—		CDF (6)
22	MFH	inflammatory	75	M	abdomen	IIB	—	wide	—	—		CDF (32)
23	Synovial sarcoma	biphasic	30	F	forearm	IIB	—	curative wide	—	lung (13)	surgery	DOD (21)
24	Synovial sarcoma	biphasic	16	F	forearm	IIB	—	wide	—	—		CDF (125)
25	Synovial sarcoma	Monophasic	40	F	knee	IIA	—	curative wide	—	lung (10)	—	DOD (14)
26	Synovial sarcoma	monophasic	31	M	knee	IIB	—	curative wide	—	lung (6)	—	DOD (12)
27	Synovial sarcoma	monophasic	39	M	thigh	IIB	—	marginal	+(5)	lung (12)	surgery radiation (60 Gray)	DOD (35)
28	Synovial sarcoma	monophasic	52	F	foot	IIB	—	curative wide	—	—		CDF (79)
29	Synovial sarcoma	monophasic	60	M	thigh	IIB	—	curative wide	—	lung (3)	—	DOD (9)
30	Synovial sarcoma	monophasic	17	M	buttock	IIB	—	marginal	+(6)	—	surgery	DOD (17)
31	Mal. schwannoma[e]	ordinary	34	F	buttock	IIB	—	marginal	+(1)	lung (4)	—	DOD (5)
32	Mal. schwannoma	ordinary	29	M	lower leg	IIB	—	wide	+(8)	—	—	DOD (17)
33	Mal. schwannoma	ordinary	64	M	upper arm	IIB	—	curative wide	—	lung (8)	—	DOD (10)
34	Mal. schwannoma	ordinary	41	M	thigh	IIB	—	wide	+(19)	—	surgery	AWD[k] (54)
35	Mal. schwannoma	ordinary	25	M	upper arm	IIB	—	marginal	—	—		CDF (34)
36	Liposarcoma	well diffe.[l]	56	F	lower leg	IB	—	marginal	—	—		CDF (213)
37	Liposarcoma	well diffe.	68	F	thigh	IA	—	marginal	—	—		CDF (6)
38	Liposarcoma	myxoid	57	F	thigh	IA	—	wide	—	—		CDF (23)
39	Liposarcoma	pleomorphic	19	F	back	IIB	—	marginal	+(6)	lung (17)	surgery	DOD (22)
40	Hemangioendo-thelioma		42	M	upper arm	IB	—	marginal	—	—		CDF (40)

a: Enneking's surgical stage[4]. b: pre or post operative radiation therapy. c: evaluation method of surgical margin for musculo-skeletal sarcoma by JOA Musculo-skeletal tumor committee (18). d: malignant fibrous histiocytoma. e: malignant schwannoma. f: and g: months. h: follow-up periods. i: continous diesease free. j: dead of disease. k: alive with disease. l: well differentiated.

The local recurrence rate in these cases was evaluated (Table 4). The local recurrence rate was 0% in the stage I cases. There was no considerable difference of local recurrence in stage II cases with or without chemotherapy. In the patients of Enneking's stage I, there was no local recurrence in the patients who had undergone wide marginal or marginal resection. However, local recurrence was observed in 36% of the stage II patients who had undergone wide marginal resection, and 75% of patients with marginal resection.

The relationship between chemotherapy and lung metastasis was evaluated in patients in stage I and II (Table 5). No lung metastasis was observed in patients of stage I. However, in stage II patients, lung metastases occurred in 45.5% of patients with chemotherapy and 42.9% in the patients without chemotherapy (Table 3). Lung metastases appeared 21.2 months after the first visiting in the chemotherapy group, but 9.4 months after in the non-chemotherapy group. The survival period after the development of lung metastasis was longer in the chemotherapy group.

DISCUSSION

The effect of chemotherapy on soft tissue sarcomas has been a source of considerable controversy. Edomonson et al[1] and Eilber et al[3] reported basically the same survival rate for patients with soft tissue sarcoma in the extremities with or without chemotherapy. Rosenberg et al[16], on the other hand, reported a significant difference between the with or without chemotherapy groups.

There are many kinds of soft tissue sarcomas. However, there are few cases in each subtype in this study. It is impossible, therefore, to compare the survival rate in each histological subtype of soft tissue sarcomas. We think it significant to compare the survival rate in the group according to Enneking's staging system, because this system is the most popular staging of bone and soft tissue sarcomas. The histological grade was divided into 2 grades (low and high), so it is simple and many another kind of tumors were able to evaluated under one criterion. From this evaluation, we can predict the effect of chemotherapy on soft tissue sarcomas.

Table 4. Local recurrence in cases

surgical margin[a]	local recurrence			
	Enneking's stage I		Enneking's stage II	
	with chemotherapy	without chemotherapy	with chemotherapy	without chemotherapy
curative wide	—	—	0% (0/3)	0% (0/8)
wide	0% (0/2)	0% (0/1)	40% (2/5)	33% (2/6)
marginal	0% (0/1)	0% (0/4)	50% (1/2)	83% (5/6)
intralesional	—	—	0% (0/1)	100% (1/1)
Total	0% (0/3)	0% (0/5)	27% (3/11)	38% (8/21)

a: surgical margin[18]

Table 5. Metastasis of cases

	Enneking's stage I		Enneking's stage II	
	with chemotherapy	without chemotherapy	with chemotherapy	without chemotherapy
metastasis rate	0% (0/3)	0% (0/5)	45.5% (5/11)	42.9% (9/21)
time of metastasis after first visit (mean)	—	—	21.2 mos.	9.4 mos.
survival rate after metastasis	—	—	20% (1/5)	0% (0/9)
mean survival periods after metastasis	—	—	26 mos.	7.4 mos.

The cumulative 5-year survival rate in the chemotherapy group was slightly higher than that in the non-chemotherapy group in this study. We analyzed these results from the local recurrence rate and metastasis. The local recurrence rate gradually decreased, according to whether the margin was marginal to curative wide. The local recurrence rate of each resection margin was reported 4 % in curative wide, 22 % in wide, 60 % in marginal[9]. We had no local recurrence in stage I cases with wide or marginal margin, so we might resect tumors in stage I with marginal margin. However, in stage II, more extensive resection is needed to prevent local recurrence[4,19]. There is no significant difference of local recurrence between the chemotherapy or non-chemotherapy groups. One intralesional resected case without local recurrence was the leiomyosarcoma case.

Metastasis rate was almost the same whether with (45.5%) or without chemotherapy (42.9%). But lung metastasis was delayed in the chemotherapy group (21.2 mos.) compared to non-chemotherapy group (9.3 mos.). We assumed that our VACA was mild regimen, however, by reducing the activity of micrometastatic lesions in lung, appearance of metastasis was delayed. The survival period after the development of lung metastasis was also longer in the chemotherapy group (24.7 mos) than non-chemotherapy group (8 mos.). Thus, the chemotherapy group showed a delay in the development of lung metastasis and prolongation of the mean survival period after its development. The prolongation of the survival periods after metastasis is mainly effected by the long survival cases of small cell sarcoma with chemotherapy. This is resulted in a higher survival rate of the chemotherapy group than the non-chemotherapy group.

Table 6. Morphologic-therapeutic classification of soft tissue sarcoma

tumor type	chemotherapy	
	with	without
small cell sarcoma	3	0
pleomorphic sarcoma	0	1
spindle cell sarcoma		
high grade	7	21
low grade	4	4
total	14	26

VACA regimen is composed of 4 drugs, and these drugs are also composed of CAVADACT regimen[2]. Most regimen have used mainly doxorubicin alone or combination regimens with other agents. Benjamin et al[2] reported that the effective rate of CYVADACT was 35 %. On the other hand, the effective rate of CYVADIC was 44 %. In our cases, preoperative chemotherapy was performed in one synovial sarcoma and two extraskeletal Ewing's sarcoma. The effective rate of these 3 cases was 66%. As our protocol was mild, serious side effect was rarely experienced. We could not use granulocyte colony-stimulating factor (G-CSF) because of it was not for sale, so leukopenia sometimes appeared, at the bottom, usually over 1000/mm^3.

In 1987, Rosen morphologically and therapeutically classified soft tissue sarcomas and reported that chemotherapy is needed for both small cell sarcomas and high grade spindle cell sarcomas, but not always for low grade spindle cell sarcomas[14,15]. We performed chemotherapy not only in patients with small cell sarcomas or high grade spindle cell sarcomas, but also in 4 of 8 patients with low grade spindle cell sarcoma (Table 6). All eight patients with low grade spindle cell sarcomas belonged to Enneking's stage I. Small cell sarcomas, pleomorphic sarcomas, and high grade spindle cells sarcomas belonged to stage II. Chemotherapy for low grade sarcomas may be unnecessary. However, in 32 tumors in Enneking's stage II (3 small cell sarcomas, 1 pleomorphic sarcoma, and 28 high grade spindle cell sarcomas), lung metastasis appeared in 14 patients (42.4%). Thus effective chemotherapy is essential for patients with stage II tumors.

Gherinzoni et al reported the survival rate of chemotherapy group was 79.1% and 54.3 % in the non adjuvant chemotherapy group, which had significant difference. Sudo et al[17] reported the 5-year survival rate in high grade sarcoma (Enneking's stage II) was 56.5% with chemotherapy and 30.3% without chemotherapy. They used mainly doxorubicin and the result was better than ours. They noted that intensive chemotherapy would be an influential factor in the favorable prognosis of soft tissue sarcomas[17]. The sensitivity of soft tissue sarcomas to anti-cancer drugs and radiotherapy is considered to be low. However, in this study, postoperative chemotherapy alone is expected to affect soft tissue sarcomas to some degree. As these data were obtained from neither a randomized study nor multivariate analysis, no definite conclusions could be drawn. We thought, however, that even our mild chemotherapy is influential factor in favorable prognosis. We cannot be satisfied with this survival rate. We needed to reflect on these results (poor effect of chemotherapy) and investigate more effective treatment.

ACKNOWLEDGMENT

The authors are greatly obliged to Dr. K. Taguchi (Department of Pathology, Okayama University Hospital) for making the diagnosis of tumors

in this study.

(Received January 25, 1993)
(Accepted July 7, 1993)

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