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Contrasting Prognostic Implications of Platelet-Derived Growth Factor Receptor-β and Vascular Endothelial Growth Factor Receptor-2 in Patients with Angiosarcoma

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ABSTRACT

Background. Angiosarcoma is an extremely rare tumor among sarcomas and comprises a heterogeneous group of high-grade vascular malignancies. Our study aimed to examine the correlations between 6 immunohistochemical biomarkers—stem cell factor receptor (KIT), platelet-derived growth factor receptor (PDGFR)-α, PDGFR-β, vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3—and overall survival (OS) in patients with angiosarcomas.

Methods. Immunohistochemical analyses for the 6 biomarkers were performed by using tumor specimens obtained from 34 patients with angiosarcomas. Correlations between biomarkers were examined by Fisher's exact test. For each biomarker, the correlation between the immunohistochemical score and OS was examined by the log-rank test and Cox regression analysis.

Results. The percentages of angiosarcoma patients with positive expressions (immunohistochemical score > 0) of KIT, PDGFR-α, PDGFR-β, VEGFR-1, VEGFR-2, and VEGFR-3 were 14.7%, 11.8%, 88.2%, 61.8%, 94.1%, and 100.0%, respectively. No statistically significant correlations between any 2 biomarkers were observed. Cox regression analysis demonstrated a significant positive correlation between short OS and the immunohistochemical score for PDGFR-β and between long OS and the immunohistochemical score for VEGFR-2.

Conclusion. Increased expression of PDGFR-β may be a statistically significant prognostic factor for poor OS, while increased expression of VEGFR-2 may be a favorable prognostic factor for patients with angiosarcoma.

Angiosarcomas comprise a heterogeneous group of high-grade vascular malignancies of presumed endothelial cell origin. These tumors are extremely rare, accounting for less than 1% of all soft tissue sarcomas. Angiosarcomas may originate from any anatomical site in the body, but they are most commonly found in the scalp, skin of the neck, and in the breast.[1] Previous irradiation, toxic chemical exposure, and chronic lymphedema have been identified as specific risk factors for angiosarcoma.[2,3] For patients amenable to complete resection, a multidisciplinary therapeutic approach combining surgery with radiation and/or systemic chemotherapy is generally advocated. Despite these treatments, angiosarcoma has a high rate of local and systemic recurrence, exhibits clinically aggressive behavior, and is associated with short median survival times.[4,5]

Agents with effective antitumor activity against soft-tissue sarcomas in adults are limited. The most effective known agents are doxorubicin and ifosfamide. These agents produce response rates of 15–40% when used as

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single agents or in combination with other agents for treating advanced soft tissue sarcomas. Recently, molecularly targeted drugs, such as imatinib, sunitinib, and sorafenib, have been investigated as novel agents for treatment of soft-tissue sarcomas.[6,7] Some of these agents inhibit various receptor-type tyrosine kinases, such as stem cell factor receptor (KIT), platelet-derived growth factor receptor (PDGFR), the epidermal growth factor receptor family, the vascular endothelial growth factor receptor (VEGFR) family, and insulin-like growth factor-1 receptor. These kinases are involved in cell proliferation, adhesion, migration, angiogenesis, and survival.[6] Further advances in our understanding of both the genetic and biological nature of soft-tissue sarcomas may lead to clinical trials aimed at the development of new molecularly targeted drugs.

To explore promising molecular targeting agents with antiangiogenic effects, we examined the immunohistochemical expression of the primary targeted molecules of tyrosine kinase inhibitors, including KIT, PDGFR-α, PDGFR-β, VEGFR-1, VEGFR-2, and VEGFR-3, Additionally, we evaluated associations between these immunohistochemical markers and overall survival.

MATERIALS AND METHODS

Patients

The present retrospective study included patients with histologically confirmed angiosarcomas who had been treated in the Departments of Breast and Medical Oncology, Orthopedic Surgery, and Dermatology at the National Cancer Center Hospital in Japan from January 1982 to March 2005, and from whom adequate tumor tissue samples were available. Clinical information was collected from patient charts. This study was approved by the National Cancer Center Hospital institutional review board.

Our study included 34 patients with angiosarcomas, and the median age at the time of diagnosis was 68 years (range, 16–88 years). Patient characteristics are shown in Table 1. Past medical histories relevant to carcinogenesis for angiosarcoma were evaluated, with the following findings: 6 patients had received adjuvant abdominal radiotherapy for treatment of gynecological cancer; 4 patients had been treated for head injuries; 1 patient had received adjuvant radiotherapy for treatment of breast cancer; 1 patient had undergone repeated surgeries for a congenital lymph cyst; and 1 patient had undergone repeated surgeries for Ollier disease. The median Eastern Cooperative Oncology Group performance status (PS) at the time of diagnosis was 0 (range, 0–1). The median tumor size was 4.0 cm (range, 1.0–30 cm.). Twenty-six patients had localized disease, whereas 8 patients had metastatic disease; the median number of disease sites was 1 (range, 1–3). Among the 26 patients with localized disease treated with surgical resection, complete and incomplete resection was performed for 14 and 7 patients, respectively. For the remaining 5 patients, information on the completeness of resection was unavailable. After surgical resection, 10 patients received adjuvant radiotherapy, 4 patients were administered adjuvant interleukin-2 immunotherapy, and 1 patient received adjuvant chemotherapy (CyVADIC regimen). Among the 8 patients with metastatic tumors, 6 patients were treated with surgical resection, 3 patients were administered interleukin-2 immunotherapy, 2 patients

TABLE 1 Patient characteristics ($N = 34$)

Characteristic	Value
Age (years)	
Median age	68
Range	16–96
Gender	
Male	9 (26%)
Female	25 (74%)
Performance status at diagnosis	
0	29 (85%)
1	5 (15%)
Primary site	
Skin	21 (62%)
Soft tissue	11 (32%)
Bone	1 (3%)
Liver	1 (3%)
Status at diagnosis	
Primary	26 (76%)
Metastatic	8 (24%)
Metastatic site	
Soft tissue	5 (15%)
Lung	2 (6%)
Lymph node	2 (6%)
Liver	1 (3%)
History of radiotherapy	
Yes	7 (21%)
No	27 (79%)
History of lymphedema	
Yes	5 (15%)
No	29 (85%)
Tumor size	
<5 cm	19 (56%)
≥5 cm	15 (44%)
Tumor sample	
Primary tumor	22 (65%)
Recurrent tumor	11 (32%)
Metastatic tumor	1 (3%)

received radiotherapy, 1 patient was administered thermotherapy, and 1 patient received best supportive care. The median overall survival time was 26.7 months (range, 0.3–152.6 months).

Tissue Samples and Immunohistochemical Staining and Evaluation

Tissue samples were obtained from core-needle biopsy samples or surgical specimens. All hematoxylin-and-eosin-stained surgical specimens were reviewed by experienced pathologists (K.T., T.H.), and the tissue samples were confirmed to contain adequate amounts of cancer tissue for use in the present study.

Formalin-fixed, paraffin-embedded tissue samples were sectioned (4 μm thick) and mounted on charged slides. All tissue sections were then heat-treated with an antigen retrieval solution (Target Retrieval Solution Low pH; Dako, Carpinteria, CA), except for the sections used for anti-podoplanin staining. Immunohistochemical staining for KIT (polyclonal A4502; Dako), PDGFR-α (polyclonal sc-338; Santa Cruz Biotechnology, Inc., Santa Cruz, CA), PDGFR-β (polyclonal sc-339; Santa Cruz), CD34 (clone QBEnd10; Dako), and podoplanin (clone D2–40; Dako) were performed by using the polymer method (EnVision FLEX system; Dako). Immunohistochemical staining for VEGFR-1 (polyclonal AF321; R&D Systems, Minneapolis, MN), VEGFR-2 (clone 55B11; Cell Signaling Technology, Danvers, MA), and VEGFR-3 (polyclonal AF349; R&D Systems) were performed by using an enhanced polymer method combined with a linker reagent (EnVision FLEX+ system; Dako).

Pathological and immunohistochemical examinations were conducted by experienced pathologists (K.T., T.H.) who were unaware of the clinical courses of the patients. Staining for immunohistochemical markers for tumor cells was evaluated with regard to intensity and proportion. The intensity of immunohistochemical marker staining of tumor cells was evaluated by a sliding scale from 0 to 3+ (0 = negative staining, 1+ = weak, 2+ = intermediate, 3+ = strong). The percentage of each intensity score was determined (0–100%). For each marker, p_0, p_1, p_2, and p_3 ($p_0 + p_1 + p_2 + p_3 = 100$ and $0 \leq p_0, p_1, p_2, p_3 \leq 100$) were defined as the percentages of immunohistochemical intensity scores of 0, 1+, 2+, and 3+, respectively. A total score $t = p_0 \times 0 + p_1 \times 1 + p_2 \times 2 + p_3 \times 3$ was then calculated. On the basis of the calculated total score, each patient was categorized into one of the following groups: group 0, $t = 0$; group 1, $0 < t \leq 100$; group 2, $100 < t \leq 200$; and group 3, $200 < t \leq 300$. For example, the total score was 0 when $p_0 = 100\%$, while the total score was 300 when $p_3 = 100\%$; therefore, the range of total scores was 0–300. This method was adapted from a previous study.[8]

Statistical Analysis

Correlations among the 6 markers and between the 6 biomarkers and clinical variables (age, gender, PS, primary site, status at diagnosis, previous history of radiation, history of lymphedema, and tumor size) were examined by Fisher's exact test. Overall survival (OS) was defined as the time from diagnosis of angiosarcoma to the time of death due to any cause and was estimated by the Kaplan–Meier method. OS among the 4 groups was compared by the log-rank test. For each biomarker, multivariate Cox regression analyses on the basis of the patient categories, and the total score were performed. The clinical factors that were included were as follows: age (< 65 vs. ≥ 65), gender (female vs. male), PS (0 vs. 1), primary site (skin vs. other), status at diagnosis of angiosarcoma (primary vs. metastatic), previous history of radiation (no vs. yes), history of lymphedema (no vs. yes), and tumor size (< 5 cm vs. ≥ 5 cm). For the log-rank test and multivariate Cox regression analyses for PDGFR-α, KIT, and VEGFR-3, we categorized the patients into 2 groups to avoid groups with small numbers of patients. A 2-sided $P < 0.05$ was considered statistically significant. All analyses were performed by SAS software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Table 2 shows the frequency distributions of the 4 groups for KIT, PDGFR-α, PDGFR-β, VEGFR-1, VEGFR-2, and VEGFR-3 expression (Fig. 1). The percentages of patients with positive expression (i.e., patients in groups 1–3) for each biomarker were 14.7%, 11.8%, 88.2%, 61.8%, 94.1%, and 100.0%, respectively.

Table 3 shows the contingency table for group 0 and groups 1–3 for pairs of biomarkers and the P value based on Fisher's exact test. As shown in Table 3, no statistically significant correlations were observed between any 2 biomarkers. Table 4 shows correlations between biomarker expression and clinical variables. No significant correlations were observed between the biomarkers and clinical variables, other than a correlation between PDGFR-α and age.

Figure 2 shows the Kaplan–Meier curve for OS for each biomarker and the P value based on the log-rank test. Significance differences were observed in OS among the 4 groups for VEGFR-2 and VEGFR-3. For each biomarker, the hazard ratio (HR) and the 95% confidence interval (CI) were estimated by multivariate Cox regression analysis

TABLE 2 Immunohistochemical expression in angiosarcoma

Marker	Group	*n* (%)
KIT	0	29 (85.3)
	1	1 (2.9)
	2	4 (11.8)
	3	0 (0.0)
PDGFR-α	0	30 (88.2)
	1	3 (8.8)
	2	1 (2.9)
	3	0 (0.0)
PDGFR-β	0	4 (11.8)
	1	11 (32.4)
	2	11 (32.4)
	3	8 (23.5)
VEGFR-1	0	13 (38.2)
	1	11 (32.4)
	2	4 (11.8)
	3	6 (17.7)
VEGFR-2	0	2 (5.9)
	1	10 (29.4)
	2	5 (14.7)
	3	17 (50.0)
VEGFR-3	0	0 (0.0)
	1	1 (2.9)
	2	7 (20.6)
	3	26 (76.5)

including clinical variables (Table 5). A statistically significant positive correlation was observed between OS and the total score for PDGFR-β, and a significant negative correlation was observed between OS and the total score for VEGFR-2. Furthermore, as the total score increased, the HR for PDGFR-β significantly increased ($P = 0.017$, contrast test), while the HR for VEGFR-2 significantly decreased ($P = 0.006$, contrast test).

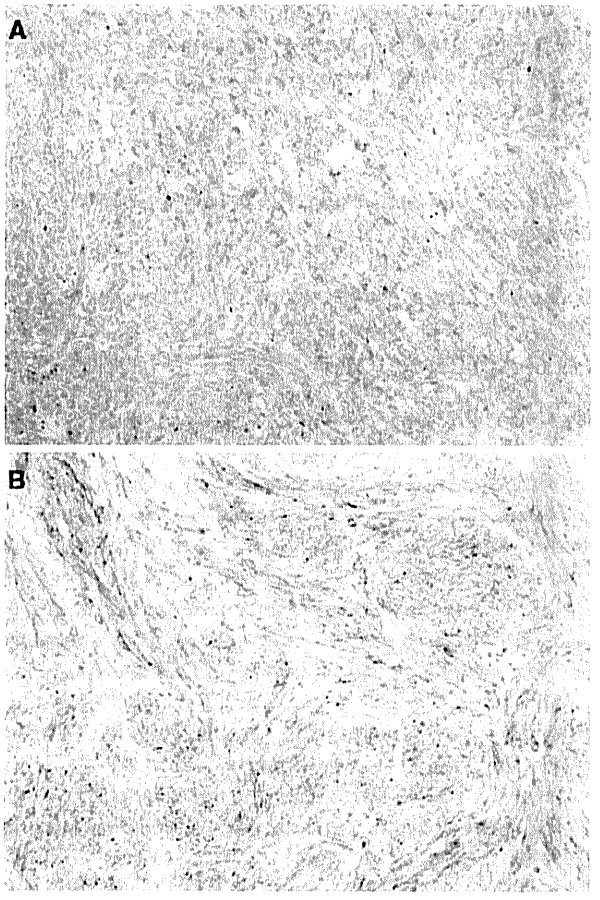

FIG. 1 Immunohistochemical pattern of PDGFR-β and VEGFR-2 expression in angiosarcoma. Diffuse strong staining of both PDGFR-β (**a**) and VEGFR-2 (**b**) in the cytoplasm of a tumor cell (original magnification, 100×)

DISCUSSION

The results of our study suggest that increased immunohistochemical expression of PDGFR-β is correlated with shorter OS, while that of VEGFR-2 is correlated with longer OS in patients with angiosarcoma. However, the present study has some limitations that should be noted. Because the sample size in our study was relatively small, and biomarker evaluation is exploratory and not yet standardized, the results of the statistical analyses may contain uncertainties. Additionally, the multiple biomarker evaluations conducted as part of the Cox regression analysis should also be considered in interpreting our study. We were unable to use the primary tumor for all test samples because of the small amount of the tumor blocks. Thus, further studies may be valuable to examine these biomarkers in a larger number of patients with primary tumor samples and to examine the expression profile changes in these biomarkers between primary, recurrent, and metastatic disease. Such studies would reveal the importance of these biomarkers more clearly in patients with angiosarcoma.

The present study and previous reports have described the individual frequencies of positive immunohistochemical expression for biomarkers in patients with angiosarcoma. Most studies have included small numbers of patients, ranging from 2 to 60, because angiosarcoma is an extremely rare tumor even among sarcomas; therefore, the reported positive frequencies of these biomarkers vary considerably. The individual frequencies of positive immunohistochemical expression of KIT, PDGFR-β, VEGFR-1, VEGFR-2, and VEGFR-3 in angiosarcoma have been reported to be 17–66%, 100%, 94%, 65–100%, and 50–100%, respectively.[5,9–19] However, there have been

TABLE 3 Contingency table for group 0 and groups 1–3 for biomarker pairs

	PDGFR-α			PDGFR-β			VEGFR-1			VEGFR-2			VEGFR-3		
	Group 0	Groups 1–3	*P*	Group 0	Groups 1–3	*P*	Group 0	Groups 1–3	*P*	Group 0	Groups 1–3	*P*	Group 0	Groups 1–3	*P*
KIT															
Group 0	26	3	0.488	4	25	1.000	12	17	0.627	2	27	1.000	0	29	–
Groups 1–3	4	1		0	5		1	4		0	5		0	5	
PDGFR-α															
Group 0				4	26	1.000	12	18	1.000	1	29	0.225	0	30	–
Groups 1–3				0	4		1	3		1	3		0	4	
PDGFR-β															
Group 0							2	2	0.627	0	4	1.000	0	4	–
Groups 1–3							11	19		2	28		0	30	
VEGFR-1															
Group 0										1	12	1.000	0	13	–
Groups 1–3										1	20		0	21	
VEGFR-2															
Group 0													0	2	–
Groups 1–3													0	32	

– not evaluated

no previous reports regarding the immunohistochemical expression of PDGFR-α in patients with angiosarcoma. The variations in the frequencies of positive expression of these biomarkers may have been caused by varying sample sizes, immunohistochemical staining methods (including the antibodies that were used), evaluation methods for immunohistochemical staining, or cutoff levels for positive or negative expression of these biomarkers. However, the frequencies noted in the present study were consistent with the results of most of the previous studies with regard to VEGFRs; i.e., high expression of the VEGFR family kinases was observed in patients with angiosarcoma.

Previous studies have reported that expression of VEGFR family kinases, including VEGFR-2, in tumor cells was a statistically significant poor prognostic factor for various malignancies.[20–22] However, the present study demonstrated that in patients with angiosarcoma, higher expression of VEGFR-2 was significantly associated with a more favorable OS. Interestingly, a previous study comprising 34 patients with angiosarcoma reported similar results; i.e., patients expressing low or no VEGFR-2 had a significantly unfavorable prognosis according to a log-rank test and multivariate analysis, whereas VEGFR-1 and VEGFR-3 were not significantly associated with prognosis.[14] A previous study also demonstrated that both VEGF and VEGFR-2 were highly expressed in patients with angiosarcoma, and their expression was correlated with cell proliferation.[15] In addition, serum VEGF and VEGF-D protein levels have been noted to increase with advancing tumor stages in patients with angiosarcoma.[23] Therefore, the results of these studies suggested that VEGF/VEGFR-2 signals and VEGF-C and D/VEGFR-3 signals contribute to cell proliferation and tumor progression as autocrine and paracrine signals.[15] According to our present results and those of previous studies, the expression of VEGFR-2 may indicate cell differentiation and maturation in angiosarcoma; it may thus play different biological roles than in other malignancies, with correspondingly different prognostic implications.

The present study also revealed that the expression of PDGFR-β was statistically significantly associated with shorter OS. Platelet-derived growth factor (PDGF) and PDGFR play a role in the invasion, metastasis, and proliferation of solid tumors. Expression of PDGF and PDGFR has been observed in various tumors, such as osteosarcoma, Ewing sarcoma, and chondrosarcoma; it has also been correlated with poor prognosis.[24–26] Our results demonstrated that the PDGFR and VEGFR family had no statistical correlations with each other. On the basis of current knowledge, it is difficult to hypothesize why the receptors PDGFR-β and VEGFR-2, both of which are related to angiogenesis, had contrasting prognostic implications in patients with angiosarcoma.[14,24–26] Thus, these biomarkers should be further investigated for possible breakthroughs in understanding of the nature and treatment of angiosarcoma.

Taxanes are cytotoxic agents classified in the microtubule-damaging category; on the basis of a preclinical study, they currently appear to be the most potent antiangiogenic agents.[27] A phase II trial for patients with unresectable

TABLE 4 Correlations between biomarker expression and clinical variables

	Age (years)			Gender			PS			Primary site			Status at diagnosis			Previous radiation			History of lymphedema			Tumor size (cm)		
	<65	≥65	*P*	Female	Male	*P*	0	1	*P*	Skin	Other	*P*	Primary	Metastatic	*P*	No	Yes	*P*	No	Yes	*P*	<5	≥5	*P*
KIT																								
Group 0	10	19	0.348	21	8	1.000	26	3	0.146	12	17	0.627	22	7	1.000	24	5	0.268	26	3	0.146	17	12	0.634
Groups 1–3	3	2		4	1		3	2		1	4		4	1		3	2		3	2		2	3	
PDGFR-α																								
Group 0	9	21	0.015	21	9	0.554	25	5	1.000	12	18	1.000	23	7	1.000	23	7	0.559	25	5	1.000	18	12	0.299
Groups 1–3	4	0		4	0		4	0		1	3		3	1		4	0		4	0		1	3	
PDGFR-β																								
Group 0	1	3	1.000	3	1	1.000	4	0	1.000	1	3	1.000	2	2	0.229	3	1	1.000	3	1	0.488	2	2	1.000
Groups 1–3	12	18		22	8		25	5		12	18		24	6		24	6		26	4		17	13	
VEGFR-1																								
Group 0	7	6	0.168	9	4	0.704	12	1	0.627	7	6	0.168	12	1	0.116	11	2	0.682	12	1	0.627	9	4	0.296
Groups 1–3	6	15		16	5		17	4		6	15		14	7		16	5		17	4		10	11	
VEGFR-2																								
Group 0	1	1	1.000	1	1	0.465	2	0	1.000	0	2	0.513	1	1	0.421	2	0	1.000	2	0	1.000	2	0	0.492
Groups 1–3	12	20		24	8		27	5		13	19		25	7		25	7		27	5		17	15	
VEGFR-3																								
Group 0	0	0	–	0	0	–	0	0	–	0	0	–	0	0	–	0	0	–	0	0	–	0	0	–
Groups 1–3	13	21		25	9		29	5		13	21		26	8		27	7		29	5		19	15	

– not evaluated

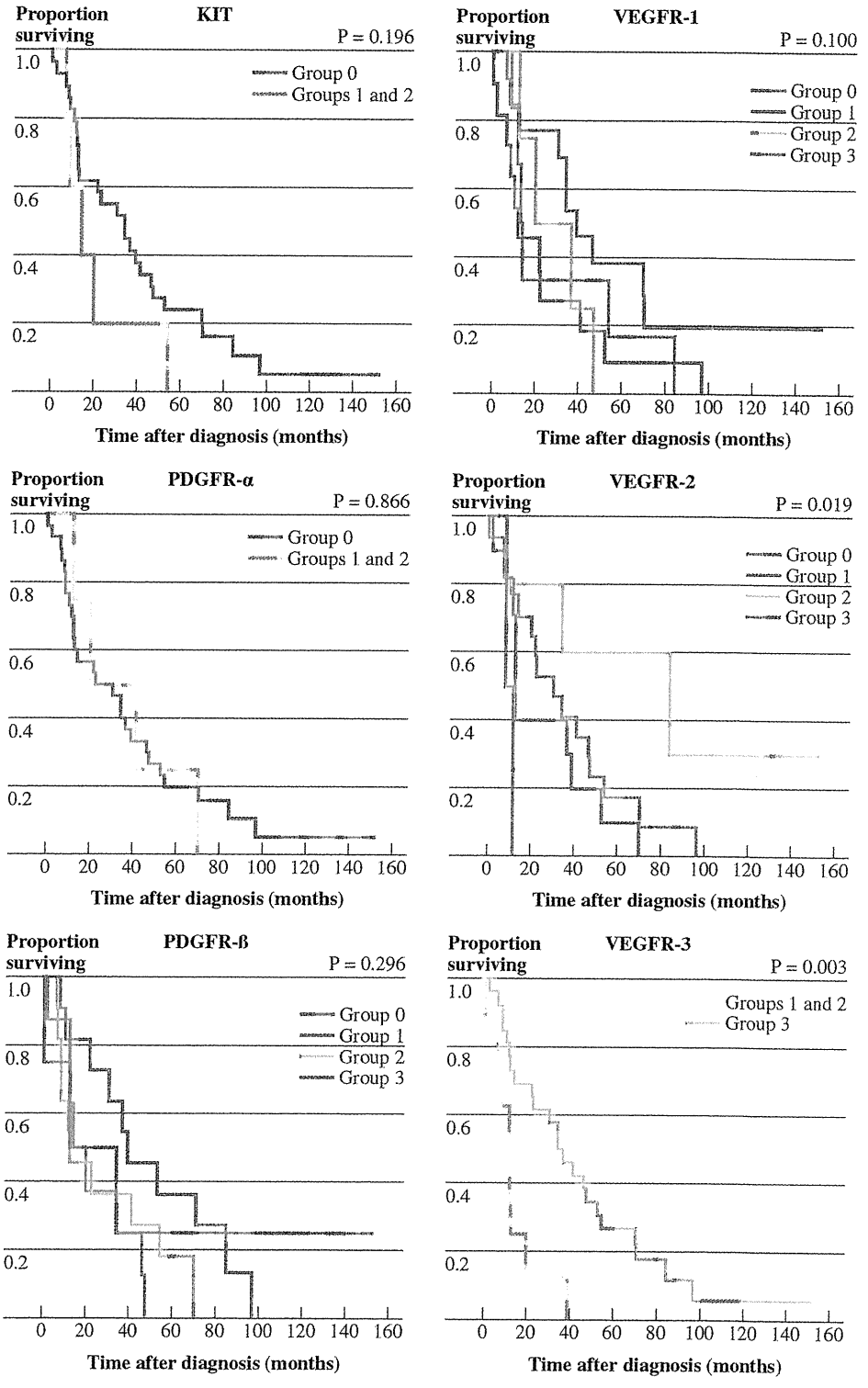

FIG. 2 Kaplan–Meier curves for OS for each biomarker

angiosarcomas reported a response rate of 18% for paclitaxel, with a time to progression of 4 months.[28] Recently, molecularly targeted drugs have shown modest activity in a phase II trial of patients with metastatic sarcoma. For sorafenib, the overall response rate was 5% (n = 6/122) in patients with metastatic or recurrent sarcoma; however, most patients that demonstrated a response (n = 5/6) had angiosarcomas.[29] Another study conducted both kinase and

TABLE 5 Multivariate Cox regression analyses

Variable		KIT		PDGFR-α		PDGFR-β		VEGFR-1		VEGFR-2		VEGFR-3	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Group	0	1.00		0 1.00		0 1.00		0 1.00		0 1.00		1 or 2 1.00	
	1 or 2	11.84 (2.01–69.78)	0.006	1 or 2 4.35 (0.79–23.84)	0.091	1 1.13 (0.19–6.61)	0.894	1 3.59 (1.01–12.79)	0.049	1 0.09 (0.01–0.62)	0.015	3 0.23 (0.08–0.69)	0.009
						2 5.86 (1.06–32.43)	0.043	2 0.80 (0.12–5.53)	0.818	2 0.02 (0.00–0.24)	0.002		
						3 6.15 (0.98–38.58)	0.052	3 1.61 (0.32–7.99)	0.562	3 0.10 (0.02–0.62)	0.013		
Age (years)	<65	1.00		1.00		1.00		1.00		1.00		1.00	
	≥65	12.41 (2.99–51.60)	0.001	5.83 (1.78–19.07)	0.004	6.40 (2.17–18.91)	0.001	5.20 (1.70–15.90)	0.004	4.87 (1.49–15.92)	0.009	4.01 (1.50–10.71)	0.006
Gender	Female	1.00		1.00		1.00		1.00		1.00		1.00	
	Male	2.15 (0.83–5.56)	0.114	3.27 (1.20–8.94)	0.021	2.17 (0.76–6.18)	0.146	3.00 (1.11–8.07)	0.030	2.36 (0.92–6.06)	0.074	1.91 (0.74–4.93)	0.184
PS	0	1.00		1.00		1.00		1.00		1.00		1.00	
	1	0.14 (0.03–0.75)	0.022	0.64 (0.13–3.12)	0.580	0.57 (0.13–2.49)	0.451	0.18 (0.02–1.60)	0.122	0.66 (0.13–3.43)	0.625	0.63 (0.15–2.71)	0.536
Primary site	Skin	1.00		1.00		1.00		1.00		1.00		1.00	
	Other	0.45 (0.12–1.65)	0.227	0.91 (0.28–2.89)	0.866	1.46 (0.44–4.88)	0.543	0.74 (0.17–3.16)	0.679	0.75 (0.19–2.96)	0.684	1.51 (0.49–4.68)	0.472
Status at diagnosis	Primary	1.00		1.00		1.00		1.00		1.00		1.00	
	Metastatic	2.08 (0.74–5.82)	0.165	1.65 (0.62–44.40)	0.319	4.44 (1.22–16.13)	0.024	0.92 (0.36–2.36)	0.858	1.23 (0.40–3.77)	0.720	1.13 (0.46–2.79)	0.786
Radiation	No	1.00		1.00		1.00		1.00		1.00		1.00	
	Yes	0.60 (0.23–1.60)	0.310	1.13 (0.45–2.83)	0.793	0.33 (0.10–1.12)	0.076	0.70 (0.27–1.86)	0.475	0.81 (0.33–1.99)	0.643	1.07 (0.44–2.59)	0.887
History of lymphedema	No	1.00		1.00		1.00		1.00		1.00		1.00	
	Yes	0.86 (0.16–4.65)	0.862	3.14 (0.72–13.69)	0.128	0.84 (0.15–4.85)	0.847	3.34 (0.73–15.32)	0.121	2.47 (0.65–9.40)	0.186	3.06 (0.79–11.84)	0.105
Tumor size (cm)	<5	1.00		1.00		1.00		1.00		1.00		1.00	
	≥5	2.85 (1.09–7.51)	0.034	1.79 (0.65–4.91)	0.258	1.86 (0.70–4.96)	0.212	4.05 (1.25–13.16)	0.020	2.54 (0.96–6.73)	0.060	1.81 (0.68–4.78)	0.232

cellular assays for sorafenib, which potentially inhibited c-kit, PDGFR-β, and VEGFR-2.[30] In a preclinical study, angiosarcomas showed distinct up-regulation of VEGFR-2 and 10% of angiosarcomas exhibited activating mutations in VEGFR-2, encoding proteins whose autophosphorylation is blocked by VEGFR-2 antagonists.[31] On the basis of the high frequencies of expression of VEGFR and PDGFR-β kinases, we hypothesize that angiogenesis may play an important role in angiosarcomas, with corresponding prognostic implications. Thus, the previous study and our results support the potential efficacy demonstrated by the phase II trials described above. Further, our results suggest that PDGFR-β is a statistically significant prognostic factor that may aid in identifying high-risk patients who would benefit from molecularly targeted treatment. We therefore expect that antiangiogenic agents, particularly molecularly targeted drugs for PDGFR-β and VEGFR kinases, may be promising candidates for drug development either for use as single agents or in combination with paclitaxel for treatment of patients with angiosarcoma.

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シンポジウム 悪性骨・軟部腫瘍治療後の長期的問題点

悪性骨・軟部腫瘍治療後の晩期障害*

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はじめに

悪性骨・軟部腫瘍の治療成績は1980年代以後大幅に改善し，現在では原発性悪性骨・軟部腫瘍患者の約70%は5年以上の長期生存が期待できる時代となった．これは化学療法をはじめとする強力な集学的治療の達成した大きな成果であるが，反面，長期生存者が増加するにつれて，これら悪性骨・軟部腫瘍経験者の抱えるさまざまな問題も浮き彫りになってきた．これらはその原因によって，i)疾患自体によって生じるもの，ii)疾患治療に関連して生じるもの，iii)治療終了後の成長や加齢によって顕在化するものに，また，その種類によって，a)患肢に関する問題，b)全身的な問題，c)社会生活上の問題などに大別することが可能である[1,2]．本稿ではこれら多岐にわたる問題の中から，全身的・肉体的な長期的問題(晩期障害：late effects)について述べる．

晩期障害

悪性骨・軟部腫瘍治療後の晩期障害として大きな問題となるのは，臓器機能障害，生殖機能障害，成長・発達障害，二次がんなどである．これらの晩期障害を来す最も大きな原因は抗がん剤による化学療法と当該臓器への放射線照射である．臓器機能障害のなかで，シスプラチン，イホスファミドによる腎機能障害，アドリアマイシンによる心機能障害はときに患者の生命予後を脅かす重大な障害となりうる．またシスプラチンによる聴力障害，ビンクリスチンによる末梢神経障害は患者のQOLを大きく損なう．生殖機能障害，いわゆる妊孕力に関してはイホスファミドによる男性患者の無精子症，女性患者の骨盤照射や手術が問題となるが，妊娠合併症や出生児催奇形率の有意な増加はないとされている[3]．成長・発達障害として，小児悪性骨・軟部腫瘍において成長終了後の低身長，骨密度の低下が報告されている．二次がんに関しては，骨肉腫・Ewing肉腫などの小児悪性骨腫瘍のみでなく成人悪性軟部腫瘍においても，骨・軟部腫瘍経験者は高頻度に他の悪性腫瘍を合併することが報告されている．またtopoisomerase II阻害薬などの抗がん剤による二次性白血病の発生も報告されている(表1)[4]．

北米CCSS(Childhood Cancer Survivor Study)によると，小児がん経験者の長期生命予後はコントロール群に比較して有意に悪く，30年後の生存率は約80%まで低下することが報告されている．死亡原因としては，原病の再発が58%と最も多いが，再発は約15年後からはプラトーになるのに対し，15年以後に死亡原因として問題になってくるのは，心合併症(標準化死亡比5.7)，呼吸器合併症(同7.6)，二次がん(同12.8)などのいわゆる晩期障害である[5]．Aksnesらは，Scandinavian Sarcoma Group Studyにおける四肢の原発性悪性骨腫瘍の長期生存者133名(骨肉腫106，Ewing肉腫27；フォローアップ中央値12年)の健康状態を調査し，長期生存者の33%がシスプラチンによると考えられる聴力障害，13%が腎機能障害を有し，42%の長期生存者が1つあるいはそれ以上の臓器機能障害を有していること，コントロール群に対する疾患罹患のオッズ比は心疾患7.9(p=0.001)，高血圧

Key words: Bone and soft tissue tumor, Late effects, Renal impairment, Cardiac toxicity, Second malignancy

*Late effects in patients treated for malignant bone and soft tissue tumors

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表1 抗がん剤治療に伴う急性毒性と晩期障害

骨肉腫抗がん剤治療に伴う急性毒性		抗がん剤治療後の晩期障害
Toxicity	Patients (%)	
Leucopenia (G4)	52%	• **Renal impairment**
Thrombocytopenia (G4)	31%	• **Cardiac toxicity**
Hemoglobin (G4)	13%	• Ototoxicity
Transaminases (G4)	30%	• Neurotoxicity
Renal impairment	10%	• Respiratory failure
Neurotoxicity	5%	• Thyroid dysfunction
Ototoxicity	40%	• Pregnancy problems
Cardiac toxicity	0.4%	• Height and weight problems
(Ferrari S et. J Clin Oncol 2005; 23: 8845-52)[4]		• Psychological problems
		• **Second malignancy**

3.4 ($p=0.03$)，甲状腺疾患 3.0 ($p=0.04$) であることを報告している[6]．

以下，生命に直結する重大な晩期障害として，腎機能障害，心機能障害，二次がんについて，悪性骨・軟部腫瘍における頻度，リスク因子などについて述べる．

腎機能障害

悪性骨・軟部腫瘍の治療に用いられる抗がん剤のうち，腎毒性が大きな問題となるのはシスプラチンとイホスファミドの2剤である．ともに近位尿細管障害と急性腎不全を生じる危険性を有し，投与に際しては十分な輸液と尿量の確保，厳密な電解質のチェックと補正が必要である．両薬剤とも，用量依存性に腎毒性が増加するため，骨肉腫や転移性腫瘍など薬剤の累積投与量の多くなる症例では，晩期障害として重篤な腎障害を惹起する危険性が高い．

Skinner らは，イホスファミドによる治療を受けた若年性骨・軟部腫瘍患者 148 例(投与量中央値 62.0 g/m²) の腎機能について検討し，50%が軽度，20%が中等度，8%が重度の腎機能障害を有していたと報告している[7]．また，国立がん研究センターでイホスファミドを含む多剤併用化学療法を受けた四肢骨肉腫 97 例では，最終観察時 32 例(33%)でなんらかの腎機能障害(尿糖/尿蛋白陽性あるいは血清 Cr 上昇)が認められた．中にはシスプラチンおよびイホスファミドによる骨肉腫治療後，10 年後に腎不全を生じ人工透析となった症例も存在する(図1)．イホスファミドによる腎機能障害は，イホスファミド治療終了後も，軽快することなくむしろ悪化する傾向を示すことが知られており，輸液による尿量の確保や累積投与量の制限により腎機能障害の発生を予防することが最も重要である[8]．イホスファミドの累積投与量が 119 g/m² を超えると重篤な腎機能障害を生じる危険性がきわめて高く，腎機能障害の危険性を下げるためには，イホスファミドの累積投与量は 84 g/m² 未満に抑えることが望ましいとされている[7]．また，シスプラチンとイホスファミドを併用した症例では，遅発性の腎機能障害を生じる危険性がより高くなることも報告されている[9]．

骨肉腫に対する代表的プロトコールにおける各抗がん剤の累積投与量を表2に示す[10)-12)]．NECO-95J, NCCH2003, JCOG0905 等では，術前化学療法による原発巣の組織学的壊死率が 90%未満の症例に対しては，イホスファミドの累積投与量が 84 g/m² を超えるよう計画されており，腎機能障害の発生の危険性に関して注意深い長期の経過観察が必要と考えられる．

心機能障害

抗がん剤による心毒性は心電図上の軽度の変化から，不整脈，心筋障害に至るまで多岐にわたるが，心筋細胞にはいわゆる再生能がないため，一度生じた心毒性が不可逆的な心機能障害を残す可能性があり，致死的になりうる点とあわせて厳重な注意が必要である．

骨・軟部腫瘍の治療に用いられる抗がん剤のうち，心毒性が大きな問題となるのはアドリアマイシンを代表とするアントラサイクリン系抗がん剤である[13]．アドリアマイシンによる心筋障害は，組織学的には心筋細胞の空胞変性や壊死(Adria cells)，線維化として認められ，臨床的にはうっ血性心不全を引き起こす．心不全の発症リスクはアドリアマイシンの累積投与量に

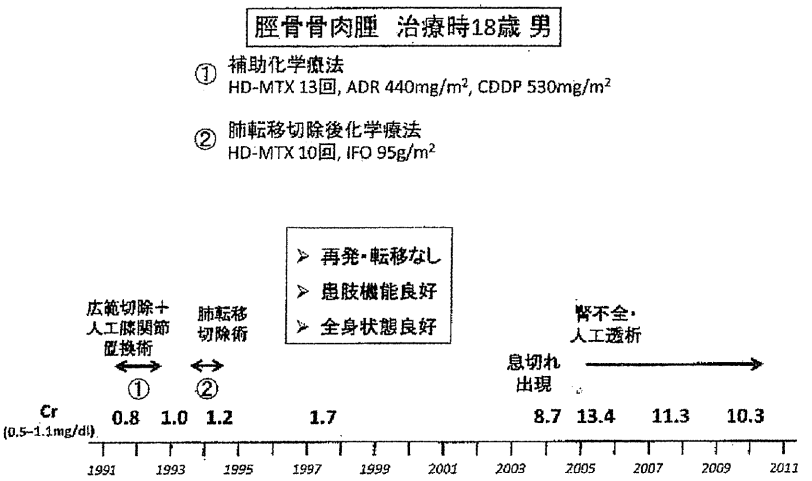

図1　骨肉腫治療長期経過後に腎不全を発症した症例．脛骨骨肉腫およびその肺転移に対する手術・化学療法の後，再発転移を認めず全身・局所状態ともに経過良好であったが，10年目に誘因なく息切れが出現，血清クレアチニンの上昇，高度の腎機能低下を認め，人工透析を余儀なくされた．

表2　各種骨肉腫治療プロトコールにおける抗がん剤予定累積投与量

Study	Group	MTX (回)	ADR (mg/m²)	CDDP (mg/m²)	IFO (g/m²)
NECO-95J[10]	Good	12	420	480	–
	Medium	10	240	480	84
	Poor	10	300	600	140
IOR/OS-N5[11]	Good	4	330	480	60
	Poor	5	420	600	75
SWOG 9139[12]			500	480	32
NCCH 2003	Good		300	600	70
	Poor		360	720	84
JCOG 0905	Good	10	420	480	
	Standard	8	240	480	90

比例し，550 mg/m² で約7%，1000 mg/m² では約50%の危険率とされており[14]，アドリアマイシンの総投与量は，通常の症例で550 mg/m²，ハイリスク症例では450 mg/m² を上限とすることが望ましい(表2)．

わが国における多施設共同研究 NECO-93(95)J では，骨肉腫113例中3例(2.7%)がアドリアマイシンによると考えられる心不全のため死亡している[10]．また，われわれの施設で過去30年間にアドリアマイシンを含む化学療法を受けた骨肉腫127例中2例(1.6%)が心不全のために亡くなっている．いったん発症したうっ血性心不全に対しては，強心剤，利尿剤の投与以外に積極的な治療法がないため，アドリアマイシンによる心機能障害に関しては，総投与量上限の順守，ハイリスク患者への投与の回避・投与量の減量などによる発症の予防が最も重要である．

アドリアマイシンによる心機能障害の危険因子としては，総投与量のほかに，他の心毒性を有する薬剤(アルキル化剤等)の併用，縦隔への放射線照射，投与

表3 アドリアマイシンによる心機能障害の危険因子

アドリアマイシンによる心機能障害の危険因子		心機能障害予防のために
High total cumulative dose of ADR		• Limiting the cumulative dose of ADR less than 450 mg/m²
High peak serum level of ADR		
Combination with other cardiotoxic drugs	⇨	• Anthracycline analogues (EPI, pirarubicin)
Mediastinal radiation therapy		• Continuous slow infusion
Age at time of exposure		• Antioxidants and chelating agents
History of cardiac diseases		• Hematopoietic cytokines

表4 悪性骨・軟部腫瘍における二次がん発生の報告

Primary	Institute	Period	N	SMNs	Interval	
Bone						
OS	St. Jude	1962-1996	334	9 (2.7%)	median 6.3 y	Cancer 1997[18]
OS	MSKCC	1973-2000	509	14 (2.8%)	median 5.5 y	Cancer 2002[19]
OS	Rizzoli	1972-2001	1205	26 (2.1%)	median 7.6 y	JPH Oncol 2006[20]
ES	CESS	1981-1991	674	8 (1.2%)	NA	IJR Oncol 1998[21]
ES	Rizzoli	1972-1999	597	14 (2.3%)	mean 8.1 y	JPH Oncol 2005[22]
ES	St. Jude	1979-2004	237	12 (5.1%)	NA	Eur J Cancer 2008[23]
OS+ES	COG	1976-2005	2842	17*(0.6%)	median 7 y	Cancer 2008[24]
						*solid SMN (exclude hematologic malignancies)
Soft tissue						
STS	Tel-Aviv	1995-1999	375	28 (7.5%)	before 14, after 14	Cancer 2001[26]
STS	NCCH	1962-2003	406	35 (8.6%)	before 15, after 20	JJCO 2005[27]
Child STS	SEER	1973-2000	1499	27 (1.8%)	NA	Cancer 2005[28]
STS	Lund*	1958-2004	818	164 (20%)	before 90, after 113	Br J Cancer 2006[29]
						*National Swedish Cancer Registry

SMN: second malignant neoplasm, OS: osteosarcoma, ES: Ewing's sarcoma, STS: soft tissue sarcoma

時年齢，心疾患の既往などが報告されている(表3)[13]．特にこれらの患者に対するアドリアマイシンの投与前には，心エコーで心機能の評価を行い，心駆出率(ejection fraction)が50%以上であることを確認し，低下が認められた場合には投与中止なども考慮する必要がある．また，アドリアマイシンによる心毒性は投与時の血中ピーク濃度が高いほど生じやすいことが知られており，Casperらは悪性軟部腫瘍に対するアドリアマイシン投与時，ワンショット静注した患者(投与量中央値420 mg/m²；心機能障害61%)は，72時間点滴投与した患者(投与量中央値540 mg/m²；心機能障害42%)に比べて心機能障害を生じる危険性が高いことを報告している[15]．

二次がん

悪性腫瘍の治癒後，原疾患とは異なる悪性腫瘍(二次がん)が発生する現象は，急性リンパ性白血病，Hodgkin病などにおいては比較的古くから知られていたが，悪性骨・軟部腫瘍においても，その治療成績の向上に伴い二次がんの発生が報告されるようになってきた[16,17]．骨肉腫，Ewing肉腫など青少年発生の高悪性度骨腫瘍における二次がんの発生頻度は2-5%，発生までのintervalは5-8年とされている(表4)[18-24]．二次がんの内訳は固形腫瘍と血液疾患がほぼ半数ずつで，固形腫瘍としては，原疾患治療時の放射線照射野内から発生する肉腫・骨肉腫が多くを占める(表5)[21-23,25]．また，化学療法の強度が強くなるほど，二次がん，特に白血病の発生頻度が高くなることが報告されている[25]．一方，成人に好発する悪性軟部腫瘍においては，悪性軟部腫瘍患者の7-20%が当該疾患罹患の前あるいは後に他の悪性腫瘍にも罹患することが明らかになっている(表4)[26-29]．国立がん研究センタ

表5 Ewing肉腫における二次がん発生の検討

Primary	Institute	Period	N	SMNs	Leukaemia	Solid tumor
ES	CESS[21]	1981-1991	674	8	5	3(Sa* 3)
ES	Rizzoli[22]	1972-1999	597	14	3	11(OS* 8, Ca 3)
ES	St. Jude[23]	1979-2004	237	12	8	4(OS* 2, Ca 2)
ES	CCG/POG[23]	1988-1992				
	Regimen A (VDCA)		262	5	3	2
	Regimen B (VDC-IE)		256	4	2	2
	Regimen C (higher dose)		256	6	6	0

*Sarcoma (Sa) or osteosarcoma (OS) which developed in previous radiation field, Ca: cancer

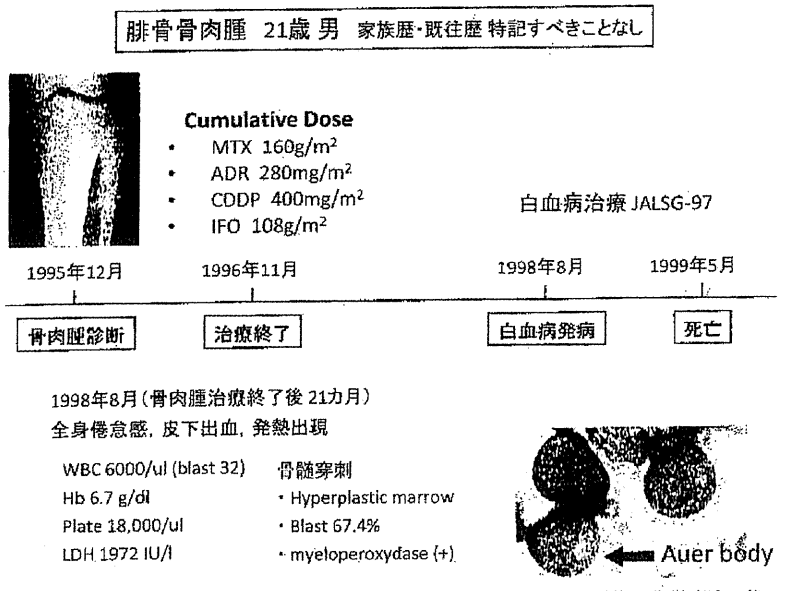

図2 骨肉腫治療後に白血病を発症した症例[20]. 腓骨骨肉腫に対する手術・化学療法の後, 再発転移を認めず経過良好であったが, 骨肉腫治療終了後21カ月で急性骨髄性白血病を発症した.

一における悪性軟部腫瘍406例の検討では, 35例(8.6%)が約5年のintervalで他の原発性悪性腫瘍を発症しており, 累積発生頻度は5年7.6%, 10年12.3%であった. また, そのリスクは組織型によって異なり, myxofibrosarcomaでハザード比2.38と最も高い値を示した[27].

図2は, NECO-95Jに準じて骨肉腫治療を行った後, 急性骨髄性白血病を発症した症例の臨床経過を示す[20]. 術前化学療法による組織学的壊死率が90%以下であったため, 術後はイホスファミドを含むレジメンにて化学療法を施行した. 骨肉腫治療終了時の各薬剤の累積投与量はメトトレキサート160 g/m², アドリアマイシン280 mg/m², シスプラチン400 mg/m², イホスファミド108 g/m²であった. 術後経過良好であったが, 骨肉腫治療終了後21カ月で全身倦怠感および皮下出血が出現, 血液検査にて高度の貧血および芽球の出現, 骨髄穿刺でAuer bodyを伴う骨髄の過形成を認め, 急性骨髄性白血病(M2)と診断された. 染色体分析にてt(8;21)(q22;q22), AML1遺伝子の転座が認められた. JALSG97プロトコールによる治療を行うも, 白血病発症後9カ月で死亡した. 二次性白血病を生じるリスクの高い抗がん剤としてはトポイソ

メラーゼII阻害剤のエトポシドが有名であるが，骨肉腫においては，同様の作用機序を示すアドリアマイシンに，シスプラチンやアルキル化剤によるDNA障害が加わることにより白血病発症に至ることが推察された．

ま と め

近年，多くの原発性悪性骨・軟部腫瘍では，患肢を温存しつつ5年以上の長期生存を期待することが可能となった．これは，手術・化学療法をはじめとする強力な集学的治療の達成した大きな成果であるが，一方では長期生存者の増加とともに，これら悪性骨・軟部腫瘍経験者の抱えるさまざまな晩期障害も大きな問題となりつつある．本稿では，生命に直結する重大な晩期障害として，腎機能障害，心機能障害，二次がんについて，悪性骨・軟部腫瘍における頻度，危険因子などについて述べた．悪性骨・軟部腫瘍の治療においては，今後，原疾患に対して最良の治療成績獲得を目指すとともに，これら晩期障害発生のリスク，その予防と治療についても十分な配慮を行うことが必要と考えられる．

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Current Organ Topics

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Musculoskeletal Tumor
骨・軟部腫瘍
骨盤に発生した悪性骨腫瘍の治療

〔*Jpn J Cancer Chemother* 38(3): 370-371, *March*, 2011〕

総括

骨盤周辺の悪性骨・軟部腫瘍

骨盤，骨盤周辺発生の悪性骨軟部腫瘍は，発症，診断の遅れから巨大腫瘍塊を形成し，特に高悪性度腫瘍では局所進行，遠隔転移を併発した初診時進行例が3割を超え，未だ予後不良である。進行例の多くでは，骨盤内の静脈叢への腫瘍浸潤，腫瘍塞栓形成，神経を含めた軟部，骨組織への浸潤をしており，局所根治性の大きな障害である。

近年の目覚ましい診断装置の進歩で，鮮明な多断層面の画像情報や3D画像処理情報として提供され，複雑な解剖学的構造の骨盤腫瘍の浸潤，広がり状況を直感的に理解することが容易になった。精密な画像情報を基に，切除縁，照射治療計画を立て，計画的な切除手術や放射線治療の実践が重要となった。

四肢発生の巨大腫瘍では，薬物療法が奏効せず，腫瘍周辺の浸潤状況が鎮静化していない無効例でも，切離断で救済可能である。一方，薬物抵抗性の骨盤腫瘍の多くは，小骨盤腔の切除縁，仙骨，神経叢，静脈叢への浸潤確保が不十分となりやすく，切離断でも安全な救済治療となり得ず，生命予後も不良である。有効な全身，局所治療方法の開発が打開策となるはずである。

一方，初期導入治療が奏効し腫瘍周辺の浸潤や反応性変化が鎮静化した骨肉腫やユーイング肉腫では，四肢と同様な治療戦略で治療可能であり，条件がそろえば40%程度の根治も期待できる。腫瘍周辺に広範な浸潤や浮腫，反応層を有し，静脈叢も発達していることも多い高悪性度の巨大腫瘍も，術前治療が奏効すると，腫瘍周辺の反応性変化は鎮静化し，腫瘍辺縁をより判断しやすくなる。導入治療が奏効後，より精密な局所治療を計画し，根治性の高い局所療法を実施すべきである。3D画像情報に基づき治療計画や手術計画を立てることが可能な技術環境が整いつつある昨今，精密照射放射線，粒子線治療装置を駆使し，数mm単位レベルの切除手術手技を実践することも可能であり，局所再発も少ない。

低悪性度の通常型軟骨肉腫，高分化脂肪肉腫は，外科治療が基本であり，広範切除を目標に一塊切除手技の実践が重要となる。仮に一部辺縁切除となっても，追加切除を行って完全な切除縁確保することで救済されるとの報告もある。この分野の安全性，成績向上は，術中の迅速切除縁評価，殺細胞処理を併用した手術手技の開発が大きなテーマである。小骨盤腔内直腸，膀胱，尿管，重要神経，仙骨，関節部分で安全に外科処理を実践するために，多方向からの展開や血管や腸管処理，術中大量出血対策や術後感染対策も含めた周術期の管理が不可欠であり，Tumor Boardを整備するなど骨盤外科，血管外科との連携チーム医療が不可欠である。さらに，通常放射線治療が無効な低悪性度骨・軟部腫瘍に対する重粒子線，陽子線，高線量精密照射応用は実験的治療の段階であるものの，切除困難な局所進行症例や再発例を対象に試行錯誤の結果が集積されつつあり，放射線治療医との連携を密にした計画的な術前，術後への応用も今後の重要な問題である。

術後の創傷治癒遷延や感染の合併率は30～50%と高く，骨盤周辺の外科治療の重篤な障害因子である。軟部組織の処理法，複合組織移植を併用した再建方法などの技術進歩もみられるが未だ未成熟であり，より体系的な再建手順，方法の確立で，人工物，巨大同種骨組織移植，再生医学の応用への道が開かれるはずである。再手術の非常に困難な体幹，骨盤部治療での晩期機能低下が少なく，治療関連骨壊死，二次がん発生に対する配慮した治療体系の

整備を押し進める時代を迎えつつある。

全国レベルでの強力な医療連携の確立が実感される現在の状況を鑑みて，今井先生には，放射線治療や粒子線治療，下地先生には，外科治療の成績，晩期機能障害，治療関連有害事象を考慮した治療体系の確立について荒木先生に論述して頂く骨盤腫瘍の特集で，多くの腫瘍内科や骨盤外科の先生方にも多くの関心を持って頂けると幸いである。