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Survival Analysis of Scalp Angiosarcoma Patients for Treatment Modalities in our Hospital Over the Past 28 Years

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Abstract

Background: Angiosarcoma is a malignant neoplastic disease that often occurs in older people. The prognosis is poor and treatment effectiveness remains controversial.

Objective: We examined cases of scalp angiosarcoma treated in Nagoya City University Hospital from 1985 to 2013 and retrospectively analyzed treatment effectiveness.

Methods and materials: We identified 21 scalp angiosarcoma patients and followed up 18 patients among them. Disease-specific survival was calculated by the Kaplan and Meier method and compared between treatments.

Results: Median patient age was 75 years, and 14 patients (78%) were over 70 years of age. The 2- and 5-year disease-specific survival was 62.7% and 26.3%, respectively. Overall survival was significantly longer in those receiving radiotherapy or combination therapy with radiotherapy and chemotherapy. Thirteen patients (72%) received chemotherapy and 12 patients received taxane-based chemotherapy. Although toxicity occurred in 11 patients receiving taxane-based chemotherapy, most cases were grade 1 or 2.

Conclusions: Combination therapy with radiotherapy and taxane-based chemotherapy may be an effective medical treatment for scalp angiosarcoma, and can be performed safely even in older patients.

Keywords: Angiosarcoma; Treatment; Taxane; Radiotherapy

Introduction

Angiosarcoma is a malignant vascular tumor arising from both the vascular and lymphatic endothelium. The scalp and face are the most common anatomic sites of the disease, which occurs mainly in men and is almost always fatal [1,2]. Scalp angiosarcoma occurs with a predilection for older patients. In recent years, the number of scalp angiosarcoma patients visiting our hospital has increased with the aging of the population (Figure 1). Taxane-based chemotherapy was introduced into our hospital in 2005, and it is most commonly used as a combination therapy with surgery, radiotherapy, and chemotherapy. In the present study, we used Kaplan-Meier survival analysis to compare treatment effectiveness.

Materials and Methods

Patients

We identified 21 scalp angiosarcoma patients from the medical

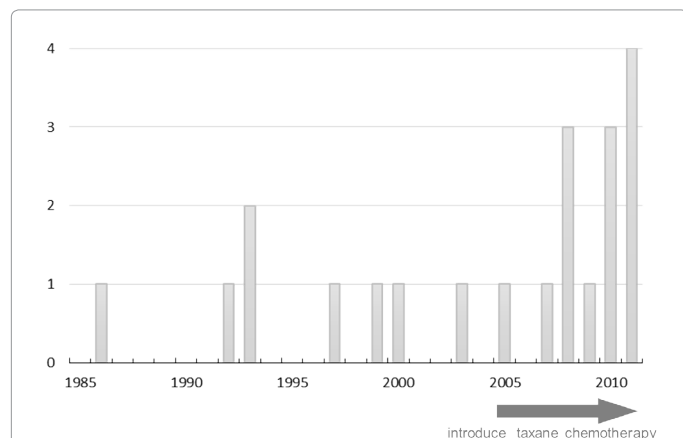


Figure 1: Number of scalp angiosarcoma patients who visited our hospital.

records at Nagoya City University Hospital from 1985 to 2013 by a retrospective review, and followed up 18 patients among them. All patients underwent pathologic examination. Patient age was defined as the age at the first visit. Toxicity was assessed using NCI-CTC version 3.0.

Treatment

For surgical treatment, we resected the primary tumor and implanted artificial dermis. Immunotherapy using recombinant interleukin-2 was administered intravenously or by injecting the area around the tumor. For radiotherapy, patients were irradiated with an electron beam (>60 Gy) or X-ray produced by a linear accelerator. Taxane-based chemotherapy has been used since 2005. Docetaxel or paclitaxel was infused intravenously over 1 hour at a dose of 30 or 80 mg/m² on days 1, 8, and 15 of a 4-week cycle.

Survival and statistical analysis

Disease-specific survival was calculated by the Kaplan and Meier method. Deaths caused by the disease were treated as an endpoint for disease-specific survival. Other deaths were treated as censored observations. The study was approved by the Ethics Committee of Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan. Excel Software (Microsoft Corporation, Redmond, WA) was

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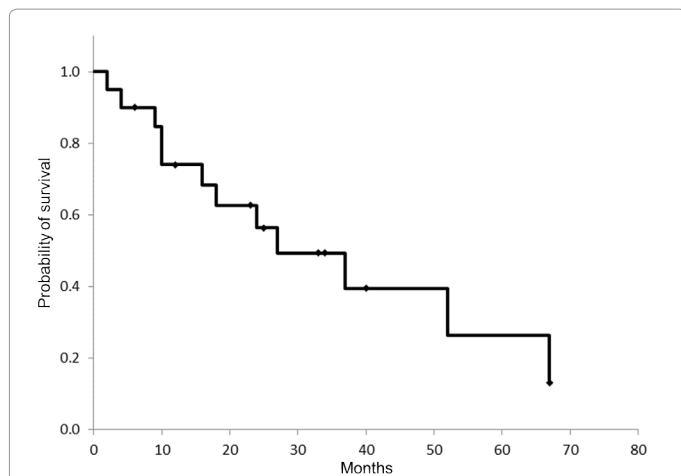


Figure 2: Overall-survival curves calculated by the Kaplan-Meier method in all scalp angiosarcoma patients treated in our hospital between 1985 and 2013.

Parameter	No. of patients	2-year overall-survival rate (%)	p-value
Surgery :SR			
Yes	7	71.4	0.6650
No	11	45.5	
Immunotherapy:IT			
Yes	9	55.6	0.2838
No	9	56.6	
Radiotherapy:RT			
Yes	16	62.5	0.0001
No	2	0	
Chemotherapy:CH			
Yes	13	61.5	0.0969
No	5	40.0	
SR+IT	3	66.7	0.6315
Both	15	53.3	
SR+RT	7	71.4	0.6398
Both	11	45.5	
SR+CH	5	80.0	0.4134
Both	13	46.2	
IT+RT	8	62.5	0.5893
Both	10	50.0	
IT+CH	4	75.0	0.7952
Both	14	50.0	
RT+CH	12	66.7	0.0275
Both	6	33.3	
Others			

Table 1: Treatment analysis of various prognostic factors for 2-year overall-survival rate in patients with scalp angiosarcoma. Significance between survival curves of populations was evaluated using log-rank testing and shown as p-value. SR: Surgery, IT: Immunotherapy, RT: Radiotherapy, CH: Chemotherapy.

used to determine the statistical significance. Significance between survival curves of populations was evaluated using the log-rank test for univariate influence and stepwise regression for multivariate influence. In all statistical analyses, $p < 0.05$ was considered significant.

Results

Patients

Of 21 scalp angiosarcoma patients identified, 18 (15 men and 3

women) were followed in the present study. Their ages ranged from 58 to 95 years with a median of 75 years, and 14 patients (78%) were over 70 years of age. We treated 7 patients (39%) with surgery, 9 patients (50%) with immunotherapy, 16 patients (89%) with radiotherapy, and 13 patients (72%) with chemotherapy. In our hospital, taxane-based chemotherapy was introduced in 2005, and 12 patients were treated with taxane-based chemotherapy (only docetaxel, $n=9$; both docetaxel and paclitaxel, $n=3$). Beginning in 1986, patients were treated with CYVADIC (cyclophosphamide, vincristine, adriamycin, dacarbazine).

Survival

The 2- and 5-year-disease-specific survival was 62.7% and 26.3%, respectively, with a median survival time of 27 months (range, 2-67 months; Figure 2). Univariate analysis revealed a significant impact of radiotherapy on overall-survival (Table 1). Bivariate analysis revealed that 12 patients (67%) treated with both radiotherapy and chemotherapy had significantly better prognoses than the 6 patients treated with either chemotherapy or radiotherapy alone, or neither (Table 2 and Figure 3).

Five patients (28%) survived for more than 3 years. Of these five patients, four were treated with both radiotherapy and taxane-based chemotherapy. There were two patients (11%) who survived for more than 5 years. Both two patients were administered with taxane-based chemotherapy and radiotherapy; one patient died (survival times:

Variable	Both RT and CH	Others	Total
N	12	6	18
Age			
Median (range)	75 (64-95)	74 (58-83)	75 (58-95)
< 75	7 (58.3)	3 (50.0)	10 (55.6)
≥ 75	5 (41.7)	3 (50.0)	8 (44.4)
Sex			
Men	9 (75.0)	6 (100.0)	15 (83.3)
Women	3 (25)	0 (0.0)	3 (16.6)

Table 2: Patient characteristics according to the treatment group. Values represent number of patients (%) unless otherwise indicated.

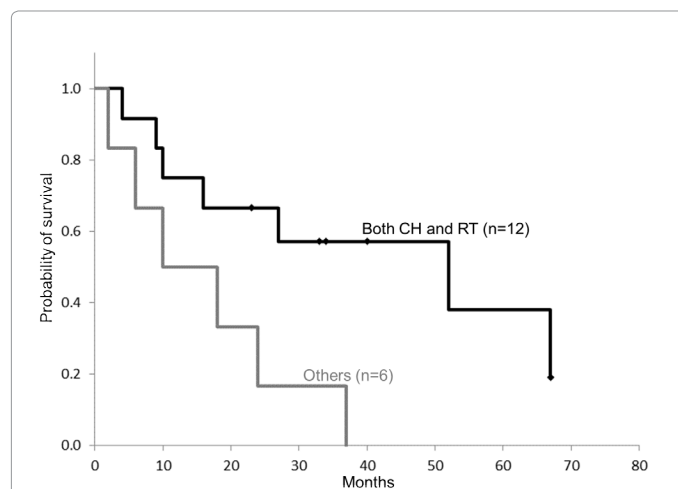


Figure 3: Overall-survival curves calculated by the Kaplan-Meier method according to the use of chemotherapy and radiotherapy in scalp angiosarcoma patients. Both chemotherapy (CH) and radiotherapy (RT; $n=12$) indicates patients treated with both CH and RT. Others ($n=6$) comprise patients treated with either CH or RT, and patients treated with neither CH nor RT ($p=0.0275$).

Adverse event	Total (n=12)	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	6 (50.0)	3 (25.0)	3 (25.0)	0	0
Edema	1 (8.3)	0	1 (8.3)	0	0
Nausea	2 (16.7)	0	2 (16.7)	0	0
Neutropenia	8 (66.7)	2 (16.7)	5 (41.7)	1 (8.3)	0
Palpitations	1 (8.3)	1 (8.3)	-	-	-
Pulmonary fibrosis	1 (8.3)	1 (8.3)	0	0	0
Thrombocytopenia	2 (16.7)	2 (16.7)	0	0	0

Table 3: Toxicity in taxane-based chemotherapy. Values represent the number of adverse events (%).

67 months) and one patients is alive with the treatment of paclitaxel (survival times: 67 months).

Toxicity

Toxicity was assessed in the patients treated with taxane-based chemotherapy (Table 3). Toxicity occurred in 11 patients (91.7%). Myelosuppression (75%) was the most frequent toxicity, but most cases were not severe (grade 1 or 2), and grade 3 neutropenia occurred in only one patient (8.3%). All patients with toxicity recovered quickly after a dose reduction or discontinuation of chemotherapy, and transfusion and granulocyte colony-stimulating factors were therefore not administered.

Discussion

The present analysis revealed that combination therapy with radiotherapy and taxane-based chemotherapy significantly prolonged overall-survival of scalp angiosarcoma patients.

In 2011, Yamazaki et al. reported the efficacy and safety of taxane regimens in patients with metastatic angiosarcoma [3]. Paclitaxel, the first taxane tested in clinical trials, is an antitumor drug with proven activity against solid cancers, such as ovarian, breast, and lung cancers. Paclitaxel was isolated from the bark of the Pacific yew tree, *Taxus brevifolia*, a scarce and slow-growing evergreen found in the old-growth forests of the Pacific Northwest. The extract was found in preclinical studies to have cytotoxic activity against many tumors. Paclitaxel was identified as the active constituent of this extract in 1971 [4]. Its main mechanism of action is stabilization of the microtubule polymer to protect from disassembly, mitotic arrest in the late G2/M phase, and inhibition of normal mitotic spindle assembly by tightly binding to tubulin. In addition, paclitaxel exhibits strong anti-angiogenic activity [5-7]. Several studies, including a Phase II study, have revealed that paclitaxel is effective against head angiosarcoma [8-10].

Docetaxel is a clinically well-established anti-mitotic chemotherapy medication. The mechanism of action of docetaxel is similar to paclitaxel, but docetaxel has greater cytotoxicity, possibly due to its more rapid intracellular uptake [11,12]. Nagano et al. reported that docetaxel is an effective and safe chemotherapy [13].

Taxanes block the G2/M phase, which is known from radiobiologic principles as the most radiosensitive phase of the cell cycle, and thus have a radiosensitizing effect [14-16]. Based on an analysis of 29 patients, Pawlik et al. and Ogawa et al. reported that postoperative radiation therapy is effective [17,18]. Combination therapy with radiotherapy and taxanes is considered more effective than each therapy alone.

Our study has some limitations. The sample size in each group was small, and nonuniform among groups. Further, the study was retrospective and the results of the statistical analyses were exploratory, not based on randomization. Therefore, the efficacy and safety of

taxane-based chemotherapy for scalp angiosarcoma should be analyzed further using a prospective study design.

In conclusion, these findings indicate that combination therapy with radiotherapy and taxane-based chemotherapy is effective, and can be performed safely even in older patients.

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