Ann. Cancer Res. Therap. Vol. 15, No. 2, pp. 61-64, 2007

Clinical Experience regarding Paclitaxel Treatment for Scalp Angiosarcomas : A Preliminary Report

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Abstract

Background: Scalp angiosarcoma is an aggressive tumor characterized by a rapid and fatal course. The overall prognosis of scalp angiosarcomas is poor. Recently, paclitaxel was found to be useful for scalp and facial angiosarcomas.

Methods: We conducted a retrospective review of paclitaxel in the treatment of scalp angiosarcoma patients who were admitted to the Veterans General Hospital, Taipei from 1996 to 2005 (10 years). Of these patients, 4 initially received paclitaxel and radiotherapy (1 patient underwent surgery in addition to this treatment), and 6 patients underwent either surgery alone or surgery combined with radiotherapy. Disease-free interval and overall survival duration were calculated. Statistic analyses were carried out using Student's t-test.

Results: The disease-free interval was significantly prolonged in patients who received paclitaxel in the initial treatment protocol (17.8 vs. 5.7 months, p = 0.016). The overall survival duration was also prolonged in these patients; however, the difference was not significant (26.5 vs. 11.1 months, p = 0.075). The prognosis was poor in the case of disease recurrence or metastases.

Conclusions: Although it was difficult to completely eliminate selection bias in this retrospective review due to the limited number of cases, paclitaxel as an initial treatment regimen for primary scalp angiosarcoma after surgery or radiotherapy appeared to prolong the disease-free interval and improve patients' quality of life.

Keywords: Scalp, Angiosarcoma, Paclitaxel, Radiotherapy

(Received September 10, 2007; Accepted December 11, 2007)

Introduction

Scalp angiosarcoma is a rare cancer characterized by an aggressive course with multifocality and early metastasis[1)]. Current treatment modalities, including surgical excision, radiotherapy, polychemotherapy, and immunotherapy, are not satisfactory. The overall prognosis is poor, with a 5-year survival rate of 10–22% and mean survival duration of 24 months[2)]. In 1998, complete recovery was observed in a patient with scalp angiosarcoma who was treated with paclitaxel in a Phase II trial[25)]. Subsequently, a cohort study of 9 patients with scalp or face angiosarcomas revealed that paclitaxel as a single agent has substantial activity against angiosarcoma, even in patients previously treated with chemotherapy or radiation therapy[3)]. To ascertain the effect of paclitaxel for the treatment of scalp angiosarcoma, we retrospectively reviewed 10 patients who had received primary treatment at our hospital in the past 10 years. The disease-free interval and overall survival duration in patients who received paclitaxel and those who did not were compared and are presented as a preliminary report.

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Materials and Methods

This study included 12 consecutive patients with primary scalp angiosarcoma who were treated at Taipei Veterans General Hospital (VGH-TPE) between 1996 and 2005. Information regarding their clinical manifestations, pathology, treatment, and survival were obtained by retrospective medical record review. All patients underwent primary treatment; 4 patients received paclitaxel and radiotherapy as the initial treatment, while 8 patients underwent surgical excision initially in the plastic surgery department due to tumor bleeding. Of these, 2 patients (without paclitaxel treatment) were lost to follow up. Patients were staged according to the TNM system of the American Joint Committee on Cancer for soft tissue sarcoma. The Committee on Clinical Investigation at VGH-TPE approved this study and waived individual informed consent for reviewing the patients' medical re-

cords. Mean values were compared using Student's t-test. Results were considered significant when the P value was less than 0.05. Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) 15 software (SPSS Inc., Chicago, USA.).

Results

The patient age, gender, location, lesion size, initial treatment course, salvage therapy of recurrent or metastatic disease, disease-free interval, overall survival duration, and causes of death are summarized in Table 1. This study included 9 male patients and 1 female patient; the mean age at presentation was 78.6 years (61–90 years).

The most common presenting symptoms were an enlarging bruise, single or multiple blue-black nodules, or an ulcer that bled easily on contact. The most common location of the primary tumor was the parietal scalp region. Multifocal presentation was noted in 2 patients. The diagnosis of angiosarcoma was established histologically by the presence of anastomosing channels lined by spindle or plump, anaplastic atypical endothelial cells. Focal necrosis and hemorrhage were noted. The cells displayed prominent mitotic activity.

Of 10 patients, 9 had stage II or III disease at the time of diagnosis. Metastasis to neck lymph nodes was present in 1 patient at the time of diagnosis (stage IV). The treatment modalities used included surgical excision, radiotherapy, and paclitaxel administration. The safe margin of wide excision ranged from 3 to 5 cm. Persistent tumor bleeding was present in the patient with stage IV disease, for which palliative surgical management was performed. The dosage of radiotherapy ranged from 4000–7000 cGy in 20–35 fractions. The median duration of paclitaxel regimen was 10 weeks (3–20 weeks; 80 mg/m^2/wk).

For the initial treatment, 3 patients received paclitaxel and radiotherapy; 1 received combined surgery, radiotherapy, and paclitaxel; 3 underwent surgery alone; and the remaining 3 patients underwent both surgery and radiotherapy. The mean disease-free interval was 10.5 months (range, 2–26 months), and the intervals according to different treatment protocols were as follows: 15 months (range, 13–18 months) in patients who received paclitaxel + radiotherapy, 8 months (range, 3–15 months) in patients who underwent surgery alone, and 3.3 months (range, 2–6 months) in patients who underwent surgery + radiotherapy.

In addition, the disease-free interval was 17.8 months in patients who received paclitaxel (in addition to radiotherapy or surgery + radiotherapy) in the initial treatment protocol and 5.7 months in patients who underwent surgery alone or surgery + radiotherapy ($p = 0.016$). In patients who received paclitaxel + radiotherapy or paclitaxel + surgery + radiotherapy, only 1 case of local recurrence occurred. On the other hand, recurrence was seen in all the patients who underwent surgery alone or surgery + radiotherapy.

Metastases were present in 8 of 10 patients (80%), including 5 patients with metastases to the lung, 2 patients with metastases to the neck lymph nodes, and 1 patient with cervical spine (C-spine) metastases. In 5 patients who received paclitaxel as a salvage protocol due to recurrence or disease progression, the mean interval from recurrence/metastasis to death was 8.8 months, compared to 8.7 months in patients who received radiotherapy ($p = 0.746$).

The mean overall survival duration was 17.2 months (3–41 months), with a median follow up of 17 months. In patients who received paclitaxel in the initial treatment protocol, the mean overall survival duration was 26.5 months, compared to 11.1 months in patients who underwent surgery alone or surgery + radiotherapy ($p = 0.075$). The major cause of death was lung metastasis (62.5%).

Discussion

Angiosarcoma is extremely rare, constituting less than 1% of all sarcomas[4]. In approximately 50% cases, the head and neck region are involved[5,6]. These tumors usually occur on the scalp in elderly men[5,7,8]. Male predominance is noted, with a male/female ratio of 4:1[4]. Most lesions present as an enlarging bruise, a blue-black nodule, or a nonhealing ulceration[5]. The clinical pattern of the lesions may be nodular, superficial diffuse, or ulcerated. Initially, the lesions can be confused with cellulitis, edema, bruising, or infection, leading to a delay in diagnosis. The etiology of angiosarcoma is unknown, but environmental exposure (thorium dioxide, vinyl chloride, etc.), chronic lymphedema, and previous trauma have been reported as associated conditions[9,10].

Angiosarcoma of the scalp is a highly aggressive tumor with the capacity to spread locally as well as distally[11]. The only statistically significant prognostic factor was tumor size. Tumors less than 10 cm have a more favorable prognosis[5]. The 5-year survival rate with combined modality therapy is 5–10%[6]. Local recurrence and metastasis usually occur within 2 years. The average mean survival time reported in the literature ranges from 10.5 to 20 months. Death usually results from cardiopulmonary metastases or local tissue invasion[10,13].

The treatment of scalp angiosarcoma represents a therapeutic challenge. The modalities of treatment include surgery, chemotherapy, radiotherapy, and immunotherapy[14]. Radiotherapy with Co^{60} and megavoltage electron beam therapy for the treatment of scalp angiosarcomas has been reported[15,16,17]. The reported 5-year control rate and 5-year survival rate were 24–40% and 13–50% respectively. Chemotherapy has had poor re-

Table 1 Patient data

Pt	1	2	3	4	5	6	7	8	9	10
Age (y)	80	90	85	61	80	88	83	72	72	75
Sex	M	M	M	M	M	M	F	M	M	M
Tumor location (scalp)	O	T	F	Pa	Pa	Pa	Pa	Pa	O	Pa
Tumor size (cm × cm)	6 × 5	3 × 2	6 × 5, 2 × 2	19 × 17	6 × 4, 4 × 1	5 × 5	5 × 4	6 × 5	8 × 7	3 × 3
Stage	II	II	III	III	III	III	III	III	IV	II
Initial treatment	P + RT	P + RT	P + RT	S + P + RT	S	S	S	S + RT	S + RT	S + RT
Recurrence	–	–	+	–	+	+	+	+	+	+
Metastasis	Neck	Lung	–	Neck	–	Lung	Lung	Lung	Lung	Cervical spine
DFI (mo)	14	13	18	26	6	15	3	6	2	2
Salvage therapy	P + RT	P*	S + P + RT	S + P + RT	S + P + RT	–	–	RT	RT	RT
Survival time (mo)	20	14	31	41	9	16	5	7	3	26
Cause of death	Pn	LM	Pn	Su	Su	LM	LM	LM	LM	SCC

*, Intrapleural injection.
DFI, disease-free interval; O, occipital; T, temporal; F, frontal; Pa, parietal; P, paclitaxel; S, surgery; RT, radiotherapy; Pn, pneumonia; LM, lung metastasis; Su, survived; and SCC, spinal cord compression.

sults in the treatment of angiosarcoma[13,18-22]. Multidrug systemic or intra-arterial chemotherapy (adriamycin or vincristine) followed by radiotherapy is reserved for unresectable lesions[23]. Immunotherapy with interferon alpha exerts antiproliferative activity on endothelial cells but is not useful for the treatment of angiosarcomas of the scalp or face[24].

Paclitaxel has antiangiogenic and apoptotic effects[3]. Its antitumor activity has been reported in Kaposi sarcoma. Since angiosarcoma cells originate from endothelial cells, it is conceivable that the antiangiogenic activity of paclitaxel is a mechanism that contributes to its efficacy in angiosarcoma. In 1998, Fata et al. described promising results in a phase II trial after systemic paclitaxel therapy in patients with angiosarcoma of the scalp and face[25]. In 1999, Fata et al. reported regarding 9 patients with angiosarcoma of the scalp and face who were treated with paclitaxel between 1992 and 1998. Of these 9 patients, 8 showed major responses (4 partial responses and 4 clinical complete responses) and 1 patient showed a minor response, yielding a major response rate of 89%. The median duration of response was 5 months (range, 2–13 months). Neutropenia and peripheral neuropathy were the most frequent dose-limiting toxicities. They concluded that paclitaxel as a single agent has substantial activity against angiosarcoma of the scalp or face, even in patients previously treated with chemotherapy or radiotherapy[3].

In this retrospective review, we showed that paclitaxel in the treatment of scalp angiosarcoma provided longer disease-free intervals, and that the difference was significant. From the viewpoint of local control of soft tissue sarcomas, radiotherapy remains the first choice. Mark et al[6]. reported that of patients treated initially with surgery alone, 8% remained disease-free, as compared to 67% of those who received postoperative radiotherapy, with or without chemotherapy. Of patients treated primarily with radiotherapy, with or without chemotherapy, 14% remained disease-free at follow up after 5 years. In our experience regarding local recurrence control, paclitaxel combined with surgery or radiotherapy was better than surgery alone or surgery + radiotherapy; however, we could not precisely compare the effects of paclitaxel with those of radiotherapy alone.

The overall survival duration in the paclitaxel-treatment group was better but not significantly different from the survival duration in other groups. However, once the disease progressed (recurrence or metastasis), the prognosis was poor regardless of the type of salvage therapy administered, and the mean survival duration was only approximately 8.7 months. Early diagnosis is very important in order to avoid metastasis and local relapse, which are caused by tumor multifocality and the aggressive behavior of the tumor. The most common sites of metastasis are, in order, the cervical lymph nodes, lungs, and liver[12]. In our series, the major cause of death was lung metastasis.

Because of the rarity of angiosarcoma and its undefined management protocol, a prospectively randomized trial examining paclitaxel treatment for angiosarcoma is unlikely. Furthermore, bias exists in our study, and we need a better study design to clarify the effect of paclitaxel in angiosarcoma. First, the size of the study group was very small. Second, there was no unified protocol. Third, the treatment course and compliance of paclitaxel differed. Because of the older age, it was not unusual for the patient or family to refuse aggressive treatment. Overall, wide surgical excision or chemoradiation remains the initial choice of treatment modality in angiosarcoma. At present, paclitaxel appears to effectively

prolong the disease-free interval when administered in addition to surgery or radiation; however, no significant difference was noted in the overall survival duration.

Conclusion

Scalp angiosarcoma is difficult to treat due to its multifocality, easy recurrence, and early metastasis. Surgery and radiotherapy are the mainstay of treatment. The anti-angiogenic effect of paclitaxel is beneficial theoretically, but the rarity of the disease and the lack of a unified protocol limit the study result. In our preliminary report, the mean disease-free interval was significantly prolonged in patients who received paclitaxel in the initial treatment protocol and better local control was obtained. Paclitaxel is beneficial in improving the quality of life in these patients. Overall, the survival duration was prolonged, but the difference was not significant. Once the disease progressed, the prognosis was poor. In the future, a prospective randomized study or a multi-center controlled study is required to definitively clarify the role of paclitaxel in the treatment of scalp angiosarcoma.

References

1) Wollina, U., Graefe, T. and Füller, J. (2001) Angiosarcoma of the scalp: new treatment modalities. J. Eur. Acad. Dermatol. Venereol. 15: 370-371.
2) Caldwell, J.B., Ryan, M.T., Benson, P.M. and James, W.D. (1995) Cutaneous angiosarcoma arising in the radiation site of a congenital hemangioma. J. Am. Acad. Dermatol. 33: 865-870.
3) Fata, F., O'Reilly, E., Ilson, D., Pfister, D., Leffel, D., Kelsen, D.P., Schwartz, G.K. and Casper, E.S. (1999) Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer 86: 2034-2037.
4) Batsakis, J.G. and Rice, D.H. (1981) The pathology of head and neck tumors: vasoformative tumors, part 9B. Head Neck Surg. 3: 326-339.
5) Holden, C.A., Spittle, M.F. and Jones, E.W. (1987) Angiosarcoma of the face and scalp, prognosis and treatment. Cancer 59: 1046-1057.
6) Mark, R.J., Tran, L.M., Sercarz, J., Fu, Y.S., Calcaterra, T.C. and Juillard, J.F. (1993) Angiosarcoma of the head and neck: the UCLA experience 1955 through 1990. Arch. Otolaryngol. Head Neck Surg. 119: 973-978.
7) Morales, P.H., Lindberg, R.D. and Barkley, H.T. Jr. (1981) Soft tissue angiosarcomas. Int. J. Radiat. Oncol. Biol. Phys. 7: 1655-1659.
8) Hodgkinson, D.J., Soule, E.H. and Woods, J.E. (1979) Cutaneous angiosarcoma of the head and neck. Cancer 44: 1106-1113.
9) Lopes, M., Duffau, H. and Fleuridas, G. (1999) Primary sphenoorbital angiosarcoma: case report and review of the literature. Neurosurgery 44: 405-407; discussion 407-408.
10) Maddox, J.C. and Evans, H.L. (1981) Angiosarcoma of skin and soft tissue: a study of forty-four cases. Cancer 48: 1907-1921.
11) Fakih, M.G., Defrances, M.C., Ohori, N.P. and Ramanathan, R.K. (2001) Unusual tumors involving the head and neck region. J. Clin. Oncol. 19: 4173-4179.
12) Liu, A.C., Kapp, D.S., Egbert, B., Waters, L. and Rosen, J.M. (1990) Angiosarcoma of the face and scalp. Ann. Plast. Surg. 24: 68-74.
13) Knight, T., Robinson, H. and Sina, B. (1980) Angiosarcoma of the scalp. Arch. Dermatol.
14) Tran, L.M., Mark, R., Meier, R., Calcaterra, T.C. and Parker, R.G. (1992) Sarcomas of the head and neck: prognostic factors and treatment strategies. Cancer 70: 169-177.
15) Brand, C.U., Yawalkar, N., von Briel, C. and Hunziker, T. (1996) Combined surgical and X-ray treatment for angiosarcoma of the scalp: report of a case with a favorable outcome. Br. J. Dermatol. 134: 763-765.
16) Morrison, W.H., Byers, R.M., Garden, A.S., Evans, H.L., Ang, K.K. and Peters, L. (1995) Cutaneous angiosarcoma of the head and neck. A therapeutic dilemma. Cancer 76: 319-327.
17) Sagar, S.M. and Pujara, C.M. (1992) Radical treatment of angiosarcoma of the scalp using megavoltage electron beam therapy. Br. J. Radiol. 65: 421-424.
18) Girard, C., Johnson, W.C. and Graham, J.H. (1970) Cutaneous angiosarcoma. Cancer 26: 868-883.
19) Jones, E.W. (1976) Malignant vascular tumors. Clin. Exp. Dermatol. 1: 287-312.
20) Millstein, D.I., Tang, C.K. and Campbell, E.W. Jr. (1981) Angiosarcoma developing in a patient with neurofibromatosis (von Recklinghausen's disease). Cancer 47: 950-954.
21) Newton, J.A., Spaull, J., McGibbon, D.H. and Wilson Jones, E. (1985) Malignant angiosarcoma of the scalp: a case report with immunohistochemical studies. Br. J. Dermatol. 112: 97-105.
22) Rosai, J., Sumner, H.W., Major, M.C., Kostianovsky, M. and Perez-Mesa, C. (1976) Angiosarcoma of the skin. Hum. Pathol. 7: 83-109.
23) Kacker, A., Antonescu, C.R. and Shaha, A.R. (1999) Multifocal angiosarcoma of the scalp: a case report and review of the literature. Ear Nose Throat J. 78: 302-305.
24) Guillot, B., Raison-Peyron, N., Acevedo, M., Meunier, L., Dandurand, M., Meynadier, J. (2000) Angiosarcoma of the scalp and face: failure of an interferon alpha treatment. Eur. J. Dermatol. 10: 300-302.
25) Casper, E.S., Waltzman, R.J., Schwartz, G.K., Sugarman, A., Pfister, D., Ilson, D., Woodruff, J., Leung, D. and Bertino, J.R. (1998) Phase II trial of paclitaxel in patients with soft-tissue sarcoma. Cancer Invest. 16: 442-446.