A case report of angiosarcoma of the scalp successfully treated with pazopanib

Hajime Tomita[1], Yuta Koike[1], Misachi Asai[1], Fumihide Ogawa[1], Kuniko Abe[2], Miki Tanioka[3], Atsushi Utani[1]

[1]Department of Dermatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki; [2]Department of Pathology, Nagasaki University Hospital, Nagasaki; [3]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto

Address correspondence and reprint requests to Dr. Atsushi Utani, Department of Dermatology, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan.
Phone: +81-95-819-7333
Fax: +81-95-849-7335
E-mail: utani@nagasaki-u.ac.jp

Manuscript word count: 472

Figure count: 2

References count: 4

The authors declare that they have no conflict of interest.

To the Editor: Angiosarcoma of the scalp has one of the worst prognoses among malignant skin tumors [1]. Standard treatment guidelines for angiosarcoma do not currently exist [1]. To the best of our knowledge, this is the first case of angiosarcoma of the scalp that responded significantly to oral pazopanib administration.

A 63-year-old man presented with scalp tumors that had developed two months before. Histopathologic examination revealed atypical, hyperchromatic endothelial cells, which were positive for CD31, CD34, D2-40, and VEGFR2, and formed vascular channels. The two tumors, 60 and 20 mm in diameter, were excised with negative surgical margins; however, four additional surgical operations were required to remove multiple recurrences. Subsequently, weekly docetaxel (25 mg/m^2, on days 1, 8, and 15, and every 4 weeks thereafter) was administered at 8 months after initial onset, but failed to suppress the development of further cutaneous tumors. Therefore, intravenous recombinant interleukin-2 (7×10^5 U/day) combined with a 100-Gy electron beam irradiation was administered for 11-18 months after onset. However, new tumors grew outside the area of irradiation. At 18 months after onset, multiple ulcers were visible on the patient's scalp, a 30 × 20 mm indurated plaque on

40 the left cheek, marked edema of the face (Fig. 1A), and the involvement of multiple
41 cervical, mandibular, and intraparotid lymph nodes (Fig. 2A).

42 Owing to the refractory tumors, pazopanib treatment was initiated at a dose of
43 800 mg once daily. At day 3 of pazopanib treatment, edema of the face began to subside,
44 and the patient began to open both eyes; the edema finally disappeared by day 14. The
45 left cheek indurated plaque completely disappeared (Fig. 1B). In addition, a computed
46 tomography scan at day 19 showed shrinking of the multiple cervical, mandibular, and
47 intraparotid lymph nodes (Fig. 2B). Toxic side effects of grade 3 thrombocytopenia and
48 grade 2 neutropenia were apparent. Pazopanib therapy was discontinued two weeks and
49 restarted at a reduced dose of 600 mg once daily. Thereafter, grade 3 proteinuria
50 required dose reduction of 400 mg once daily. However, partial tumor reduction was
51 maintained for 24 weeks and the patient is now undergoing a pazopanib treatment
52 without toxic side effects.

53 Pazopanib is a multi-targeted receptor tyrosine kinase inhibitor of VEGFR-1,
54 VEGFR-2, VEGFR-3, PDGFR-a/β, and c-kit [2]. VEGFR-2 have been found to be
55 up-regulated in angiosarcoma [3]. Angiosarcoma cells in the present case were also

positive for VEGFR-2, suggesting that the signal through VEGFR-2 stimulates tumor. Accordingly, it is possible that pazopanib leads to clinical improvement by inhibition of VEGFR-2 tyrosine kinase activity.

The present case showed the rare toxic effects [4]. It is possible that taxane chemotherapy contributed to these toxic effects.

Other VEGFR inhibitors (bevacizumab, sorafenib, and sunitinib) have also been reported to be effective treatments for angiosarcoma [1]. Thus, VEGFR inhibitor, including pazopanib, may be an additional optional for treating angiosarcoma.

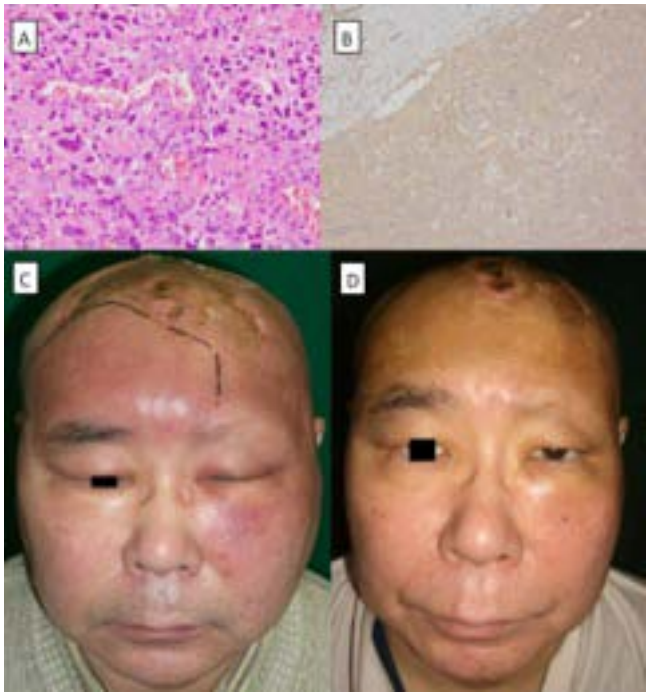
64 References

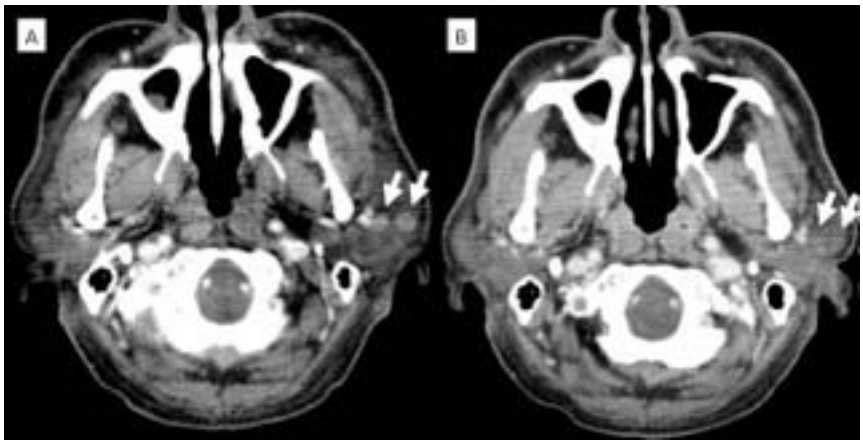
65 1. Young RJ, Brown NJ, Reed MW, Hughes D , Woll PJ. Angiosarcoma. The
66 lancet oncology 2010;11:983-91.
67 2. Heudel P, Cassier P, Derbel O, Dufresne A, Meeus P, Thiesse P et al.
68 Pazopanib for the treatment of soft-tissue sarcoma. Clinical pharmacology :
69 advances and applications 2012;4:65-70.
70 3. Miettinen M, Rikala MS, Rys J, Lasota J , Wang ZF. Vascular endothelial
71 growth factor receptor 2 as a marker for malignant vascular tumors and
72 mesothelioma: an immunohistochemical study of 262 vascular endothelial
73 and 1640 nonvascular tumors. The American journal of surgical pathology
74 2012;36:629-39.
75 4. Sternberg CN, Hawkins RE, Wagstaff J, Salman P, Mardiak J, Barrios CH
76 et al. A randomised, double-blind phase III study of pazopanib in patients
77 with advanced and/or metastatic renal cell carcinoma: Final overall survival
78 results and safety update. Eur J Cancer 2013.
79

Figure legends

Figure 1: Improvements in edema and erythema and reduction in the left cheek indurated plaque are seen following pazopanib therapy. (A) Before pazopanib therapy. (B) 14 days after commencement of pazopanib therapy.

Figure 2: Serial computed tomography scans. Scans show varying responses in multiple intraparotid lymph nodes (arrows). (A) Before pazopanib therapy. (B) 19 days after commencement of pazopanib therapy.




A
B