Effectiveness of combined low-dose radiotherapy and pazopanib for controlling the local manifestations of taxane-resistant recurrent angiosarcoma of the head

Hiroshi Kato, MD, PhD, Motoki Nakamura, MD, PhD, Takao Oda, MD, and Akimichi Morita, MD, PhD
Nagoya, Japan

Key words: angiosarcoma; immune checkpoint inhibitor; low-dose radiation therapy; low-dose radiotherapy; pazopanib; soft tissue sarcoma.

INTRODUCTION

Angiosarcomas are soft tissue sarcomas arising in the blood or lymphatic vessels. The scalp and face are the most commonly affected sites. The prognosis of angiosarcoma is poor, with 5-year survival observed in less than 51% of cases.[1] Local recurrence after radiotherapy decreases the quality of life. Bleeding from a locally recurrent lesion and pneumohemothorax caused by lung metastasis are the main causes of death in patients with angiosarcoma. Surgical treatment (resection with a wide margin) is usually recommended for local and small lesions, whereas radiotherapy is recommended for large lesions. In contrast to other soft-tissue sarcomas, angiosarcomas are responsive to taxane-based chemotherapy.[2] Here we report a locally recurrent case 3 years after combined treatment with low-dose radiotherapy and pazopanib.

CASE REPORT

A 72-year-old man was referred to our clinic with skin ulcers and purpura on his head. Based on the results of a skin biopsy obtained from the purpura on his head, angiosarcoma (T1a, N0, M0; stage II) was diagnosed.

The tumor appeared to be circumscribed; therefore, extended resection was performed and weekly docetaxel chemotherapy initiated. Recurrence was observed around the surgical site 2 months after starting the therapy. For the recurring lesion, radiation therapy (66 Gy) and biweekly paclitaxel were administered. The response to chemoradiation therapy was complete remission 2 months later (as the first evaluation). An exponential increase in the size of the tumor and frequent bleeding, however, were observed 29 weeks later (Fig 1). Due to repeated bleeding, he frequently visited the emergency department. Combination therapy with low-dose radiation (daily dose of 1.8 Gy [electrons], fraction number of 25, total 45 Gy per fraction, bolus of 5-mm tissue thickness, 2-cm clinical target volume, 1-cm planning target volume) and pazopanib (400 mg) was applied to the cheek and head lesions where repeated bleeding was observed. The safety of pazopanib and radiation has been reported in breast cancer patients but not in angiosarcoma patients.[3] We selected a 400-mg dose in anticipation of a drug-radiation interaction. The irradiance level of the radiation therapy was decreased because the lesion size decreased with the previous 66 Gy of irradiation. Therefore, 45 Gy of irradiation (early ending or boost was considered) was prescribed because the intention of the irradiation was to stop the bleeding. The lesion disappeared 3 weeks after starting the radiation therapy. Furthermore, bleeding from the head and face lesions did not recur. At 4 months, however, thrombocytopenia was detected. Frequent platelet transfusions were not effective for treating the

From the Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences.

Funding sources: None.
Conflicts of interest: None disclosed.

Correspondence to: Hiroshi Kato, MD, PhD, Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, 1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. E-mail: h-kato@med.nagoya-cu.ac.jp.

JAAD Case Reports 2020;6:713-5.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.06.006

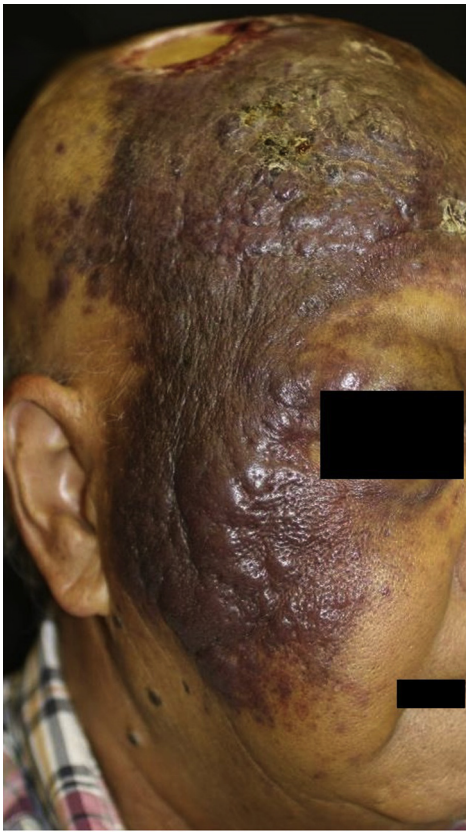

Fig 1. Before combination therapy with radiation and pazopanib. Frequent bleeding was observed from the cheek lesion.

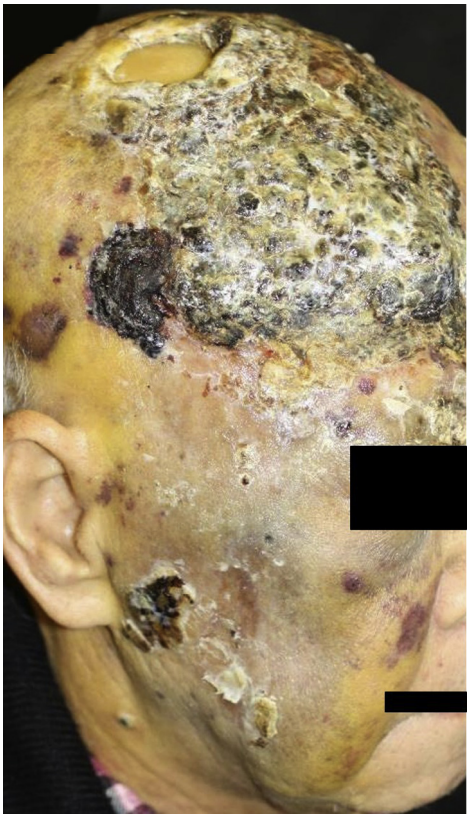

Fig 2. One month after discontinuing the pazopanib. There was no recurrence of the radiated cheek lesion.

thrombocytopenia due to disseminated intravascular coagulation caused by the sarcoma, and the pazopanib was discontinued. After cessation of the pazopanib, no bleeding from the lesions occurred. Spinal and lung metastases were detected 1 month after discontinuing the pazopanib. Shortly thereafter, the patient died of respiratory failure.

DISCUSSION

Pazopanib is a multitargeted receptor tyrosine kinase inhibitor that blocks tumor growth and inhibits angiogenesis. It is used for the treatment of soft tissue sarcoma and renal cell carcinoma.[4] Some case reports present radiation (especially in low doses) combined with pazopanib as an adjuvant and neoadjuvant therapy for osteosarcoma and breast cancer.[3,5] This combination therapy, however, has not been reported for angiosarcoma. Radiation recall dermatitis induced by pazopanib is observed in some cases.[6] Other side effects of pazopanib include blood pressure increase, thrombocytopenia, and hepatopathy. In this case, the taxane therapy gradually became less effective, and bleeding from the tumor increased.

The efficacy of eribulin mesylate[7] and immune checkpoint inhibitors[8] on angiosarcoma was recently reported. Few studies have reported the effects of these drugs for controlling recurrent and bleeding local lesions such as those observed in our patient. Martin-Broto et al[9] reported the safety and efficacy of combined low-dose radiotherapy and trabectedin for patients with metastatic soft tissue sarcomas. In their study, combined radiotherapy at a dose of 30 Gy and trabectedin was effective for patients with metastatic soft-tissue sarcomas. The overall response was 72% and 60% for local and central assessments, respectively. Meredith et al[10] reported an interaction between pazopanib and radiation therapy in an in vivo model. In our study, combination therapy with low-dose radiation (daily dose of 1.8 Gy and fraction number of 25, total 45 Gy) and pazopanib was found to be effective for repeated bleeding and tumor growth with fewer side effects. No bleeding was observed from the irradiated lesions after discontinuing pazopanib until the patient's death (Fig 2). Considering the results of our case, combined low-dose radiation and pazopanib was effective for treating bleeding lesions of angiosarcoma. The findings from this case indicate that this

combined treatment may reduce tumor size and prolong overall survival, but further studies in multiple cases are required to confirm the safety and efficacy.

We thank Editage (www.editage.com) for English-language editing.

REFERENCES

1. Albores-Saavedra J, Schwartz AM, Henson DE, et al. Cutaneous angiosarcoma. Analysis of 434 cases from the surveillance, epidemiology, and end results program, 1973-2007. *Ann Diagn Pathol*. 2011;15:93-97.
2. Fujisawa Y, Yoshino K, Kadono T, Miyagawa T, Nakamura Y, Fujimoto M. Chemoradiotherapy with taxane is superior to conventional surgery and radiotherapy in the management of cutaneous angiosarcoma: a multicentre, retrospective study. *Br J Dermatol*. 2014;171:1493-1500.
3. Goyal S, Shah S, Khan AJ, Danish H, Haffty BG. Evaluation of acute locoregional toxicity in patients with breast cancer treated with adjuvant radiotherapy in combination with pazopanib. *ISRN Oncol*. 2012;2012:896202.
4. Van Der Graaf WTA, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012; 379:1879-1886.
5. Haas RLM, Gelderblom H, Sleijfer S, et al. A phase I study on the combination of neoadjuvant radiotherapy plus pazopanib in patients with locally advanced soft tissue sarcoma of the extremities. *Acta Oncol*. 2015;54:1195-1201.
6. Azad A, Maddison C, Stewart J. Radiation recall dermatitis induced by pazopanib. *Onkologie*. 2013;36:674-676.
7. Fujisawa Y, Fujimura T, Matsushita S, et al. The efficacy of eribulin mesylate for patients with cutaneous angiosarcoma previously treated with taxane: a multi-center, prospective, observational study [e-pub ahead of print]. *Br J Dermatol*. 2020. https://doi.org/10.1111/bjd.19042.
8. Florou V, Rosenberg AE, Wieder E, et al. Angiosarcoma patients treated with immune checkpoint inhibitors: a case series of seven patients from a single institution. *J Immunother Cancer*. 2019;7:213.
9. Martin-Broto J, Hindi N, Lopez-Pousa A, et al. Assessment of safety and efficacy of combined trabectedin and low-dose radiotherapy for patients with metastatic soft-tissue sarcomas: a nonrandomized phase 1/2 clinical trial. *JAMA Oncol*. 2020;6: 535-541.
10. Meredith RF, Raisch KP, Bonner JA, et al. Pazopanib combined with radiation: In vivo model of interaction. *Cancer Biother Radiopharm*. 2014;29:247-250.