SAGE Open Medical Case Reports
Volume 11: 1–5

DOI: 10.1177/2050313X231200967
journals.sagepub.com/home/sco
Sage

A case of markedly impaired wound repair with angiostatic pazopanib in a patient who had Mohs surgery for a basal cell carcinoma

William J Nahm[1], Gail de Imus[2], Christopher A Mathe[3], Liliana Saap[4], Saiyan Joseph[5], Stanley Chen[6] and Vincent Falanga[7]

Abstract

This case report highlights the adverse effects of pazopanib, a vascular endothelial growth factor receptor inhibitor, on wound healing after Mohs surgery. A 79-year-old male with metastatic renal cell carcinoma of the lung, on 600 mg daily pazopanib, underwent Mohs surgery for a nodular basal cell carcinoma on his right leg. Despite multiple wound care strategies, his wound deteriorated over 4 months. Discontinuing pazopanib resulted in rapid wound closure within 2 months. However, metastatic lung nodules grew, prompting treatment with immune checkpoint inhibitors, nivolumab, and ipilimumab, which were discontinued due to complications. Near-complete wound healing was observed prior to reintroducing pazopanib (6 months after initial discontinuation), which again led to wound deterioration. Pazopanib negatively impacts wound repair by inhibiting cell proliferation and angiogenesis. Depending on the malignancy or tumor, cessation of pazopanib, or switching to a course of immune checkpoint inhibitors may be warranted perioperatively.

Keywords

Pazopanib, wound repair, basal cell carcinoma, VEGF, antiangiogenic

Date received: 8 June 2023; accepted: 21 August 2023

Introduction

Pazopanib is an antitumor therapy that selectively inhibits tyrosine kinase receptors—vascular endothelial growth factor receptor (VEGFR) -1, -2, and -3, platelet-derived growth factor receptors (PDGFRs), and c-Kit receptor (c-KitR). VEGFRs are significant contributors to angiogenesis and act by inducing intracellular signaling pathways that promote endothelial cell proliferation, differentiation, and migration.[1] PDGFRs also exhibit angiogenic properties. PDGFRs coordinate with VEGFRs by upregulating the production of vascular endothelial growth factors and inducing further endothelial cell proliferation, migration, and tube formation pathways.[2] C-kitR is another angiogenesis-promoting tyrosine kinase receptor that regulates mast cell growth and proliferation. Mast cells contain VEGF and PDGF, which are angiogenic cytokines and are thus a functional component of angiogenesis pathways.[3] These receptor targets suggest that pazopanib can disrupt angiogenesis through varied mechanisms of action.

Several studies also indicate that pazopanib's main antitumor properties stem from its ability to prevent angiogenesis in newly proliferating cells. One study revealed that angiogenesis and human tumor xenograft growth were inhibited in mice receiving pazopanib.[4] In a follow-up study, the tubule formation with human endothelial cells from bone marrow

[1]NYU Grossman School of Medicine, New York, NY, USA
[2]Dermatology and Skin Surgery, Providence Medical Group, Mukilteo, WA, USA
[3]California University of Science and Medicine School of Medicine, Colton, CA, USA
[4]Skin Unlimited, New Braunfels, TX, USA
[5]Boston University, Boston, MA, USA
[6]Massachusetts Institute of Technology, Cambridge, MA, USA
[7]Department of Dermatology, Dartmouth-Mary Hitchcock Medical Center, Lebanon, NH, USA

Corresponding Author:
William J Nahm, NYU Grossman School of Medicine, 550 1st Avenue, New York, NY 10016, USA.
Email: william.nahm@nyulangone.org

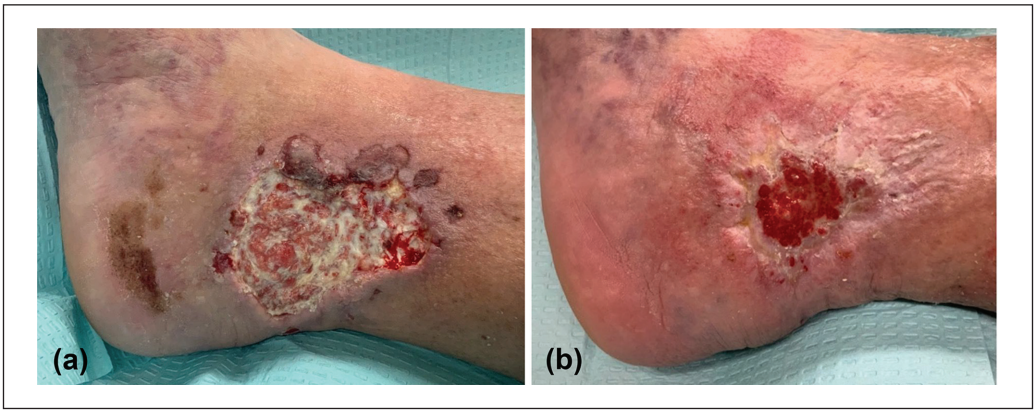

Figure 1. (a) Extensive ulceration 4 months after Mohs surgery on the medial aspect of the right ankle. The patient was currently taking pazopanib. The ulceration showed necrotic debris, exudate, steep edges, areas of undermining, and necrotic edges. (b) Healing ulceration with evidence of closure and good granulation tissue. Pazopanib had been discontinued for 2 months.

aspirates of multiple myeloma endothelial cells was also inhibited under the same treatment in a matrigel.[5] Pazopanib results in the inhibition of angiogenesis and cell growth, which is useful for preventing tumor growth and proliferation.[6] Appropriate targets for pazopanib include advanced renal cell carcinoma (RCC), non-small cell lung cancer, advanced soft tissue sarcoma, and epithelial ovarian cancer.[7]

Although the package insert recommends stopping pazopanib 7 days before surgery, at this time, there is no definite statement that the drug impairs healing. Yet, clinical studies with other antiangiogenics, like bevacizumab, demonstrate decreased wound repair. Moreover, nonclinical evidence indicates that TKIs, like pazopanib, prevent wound repair by inhibiting the VEGFR, PDGFR, and C-kitR pathways.[1–3,6,8] Angiogenesis is a fundamental component of the healing process,[9] and disruptions in these pathways could compromise wound healing. Here we report the first-ever clinical evidence for poor wound repair after Mohs surgery in a patient who was on a course of pazopanib, and we discuss wound repair management options.

Case presentation

A 79-year-old man with a history of RCC metastatic to the lungs presented with a large 3.2×3.5 cm biopsy-proven nodular basal cell carcinoma (BCC) on the medial aspect of the right lower extremity (LE). His medical history included arterial hypertension, obesity, extensive venous insufficiency, and recent deep vein thromboses in both LEs. He had been taking pazopanib 600 mg a day for his RCC for a year. He had the BCC successfully removed with three layers of Mohs surgery. Due to the large size of his surgical defect and the history of active pazopanib treatment, it was decided to implement a course of slow-release antiseptics (cadexomer iodine), wound debridement, human amnion/chorion membrane (HACM), human split-thickness skin allograft, and graduated leg compression. Despite all these modalities, over a 4-month period, his wound expressed progressive undermining, nonremovable necrotic debris, and necrotic edges (Figure 1a). After consulting with his oncologist, who determined dramatic size reductions in his metastatic nodules after recent lung scans, the patient was allowed to discontinue the pazopanib. Soon after the discontinuation, the patient experienced rapid and dramatic closing of his ulceration over 2 months (Figure 1b). The closure was facilitated by a similar course of slow-release antiseptics, gentle debridement, HACMs, human skin allografts, and compression of the LE. Two months after discontinuing pazopanib, the patient experienced difficulty in breathing, and the oncologist determined that metastatic lung nodules were dramatically increasing in size. It was decided that the patient would be started on a course of nivolumab/ipilimumab. After having three infusions of nivolumab/ipilimumab over 6 weeks, the patient was hospitalized for severe colitis and pneumonitis. After discharge from the hospital, the wound on the LE showed almost complete closure with buds of granulation tissue (Figure 2a). The patient was restarted on pazopanib due to tumor progression (6 months after discontinuation of initial pazopanib), and his wound site on the right LE began demonstrating increasing ulceration with some necrosis and extensive exudate over 2 months (Figure 2b and Table 1).

Discussion

Patients taking a course of VEGF inhibitors such as pazopanib can display markedly delayed wound healing. Treatment management must involve the patient's oncologist performing overall cancer monitoring, as knowing when to discontinue a TKI is vital. Although there are guidelines instructing cessation of pazopanib 7 days prior to surgery, based on half-life data in the prescribing information,[10] these protocols cannot be expected to provide direction in unique

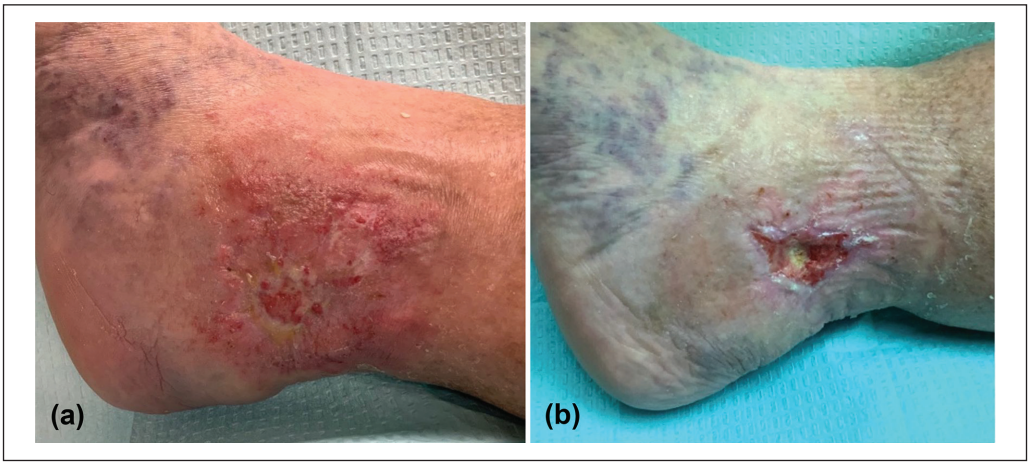

Figure 2. (a) Almost complete healing of the ulceration 3 months after discontinuation of pazopanib. (b) Recurrence of a deep ulceration 8 weeks after restarting pazopanib.

Table 1. Timeline of exposure treatments, including pazopanib and stages of ulceration and wound repair on patient treated with Mohs surgery.

Time point	Event
Baseline	Large nodular basal cell carcinoma (BCC) was identified on the right lower extremity (LE). The patient is being treated with pazopanib at 600 mg/day for metastatic renal cell carcinoma (RCC).
Post-Mohs surgery (Day 0)	Mohs surgery was performed to remove the BCC, creating a wound defect on the right LE.
Four months post-surgery	Wound enlargement with progressive undermining, edge necrosis, and nonremovable necrotic debris, despite treatment with slow-release antiseptics, debridement, amnion/chorion membranes, skin allografts, and compression. (Figure 1a)
Discontinuation of pazopanib	Consultation with an oncologist leads to discontinuation of pazopanib due to impaired wound healing
Two months post-initial discontinuation of pazopanib	Rapid closure of ulceration was observed after discontinuation of pazopanib. (Figure 1b)
Four months post-initial discontinuation	Metastatic lung nodules become more prominent; patient started on nivolumab/ipilimumab course (three infusions over 6 weeks).
5.5 months post-initial discontinuation	Hospitalization due to severe colitis and pneumonitis' nivolumab/ipilimumab course (three infusions over 6 weeks) discontinued. Almost complete closure of the wound with granulation tissue was observed (Figure 2a).
Six months post-initial discontinuation	Pazopanib restarted due to metastatic lung RCC progression.
Eight months post-initial discontinuation	While on 2 months course of pazopanib, the wound site on the right LE shows enlarging ulceration, necrosis, and exudate (Figure 2b).

circumstances such as an emergency where surgery is critical, and TKI treatment cannot be halted long enough for clearance. Although venous insufficiency in a distal extremity could be a factor for this patient's reduced wound healing, necrosis of surrounding unoperated tissue had not been observed in similar patients. After discontinuing pazopanib, surrounding necrotic tissue was gradually replaced with healthy tissue, and the healing rate increased. Moreover, after reinitiation of pazopanib, the wound on the LE began to expand with necrosis and exudate.

Pazopanib negatively impacts wound healing by inhibiting cell proliferation and angiogenesis, making it inappropriate for patients to receive flaps or grafts for wound closure post-Mohs surgery. Such a scenario warrants the cessation of the medication, reduction in dosage, or possible replacement of pazopanib with immune checkpoint inhibitors (ICIs) such as antibodies that target cytotoxic T lymphocyte antigen 4, programmed cell death 1 axis, and programmed cell death 1 ligand 1 axis. However, these ICIs come with their own toxic side effects, including encephalitis, colitis, pneumonitis, hepatitis, and myocarditis, that limit their prolonged usage.[11,12]

At the time of readministration of pazopanib, wound repair was not entirely complete, and subsequently, wound

progression was seen. If the wound had been completely closed with epithelial closure and remodeling allowed, the readministration of pazopanib may not have allowed the ulceration to form. Previous reports with bevacizumab, an anti-VEGF-A, demonstrated surgical site complications or poor surgical wound repair but no new ulcerations independent of surgery.[13] This kind of complication after surgery or previous ulcerations was also seen with other small molecule TKIs that target VEGFRs.[14]

Moreover, this patient also had extensive venous insufficiency. There is a correlation between elevated levels of VEGF in patients suffering from venous ulcers and the significant decline of these levels posttreatment. This decline was observed in conjunction with a corresponding reduction in the size of the ulcer.[15] But the role of VEGF in venous ulceration is currently unknown. Activity against VEGFR may play an unspecified role in worsening the venous insufficiency component of a wound.

Conclusion

This report provides the first direct clinical evidence that pazopanib leads to poor wound repair, as shown by ulceration changes after its discontinuation and re-administration. Amniotic membranes, human allograft tissue, and nontraumatic wound healing devices may be helpful for wound closure when TKI-impaired healing is present. Depending on the tumor, cessation of the pazopanib or switching to a course of ICIs may be the more prudent option for facilitating wound healing after removing cutaneous keratinocyte carcinomas. Readministration of TKIs, like pazopanib, to manage cancers may need to be instituted after complete wound repair has occurred. In the setting of pazopanib, management of wound repair will be based on oncologist input, tumor progression, and adverse events of the antitumor medications.

Acknowledgements

None.

Authors' contribution

W.J.N. G.D.I., C.A.M., L.S., S.J., and S.C. contributed to collection of information and writing of the article. V.F. contributed to the writing and final approval of the article. All authors read and approved the final version of the article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patients) for their anonymized information, including photographs, to be published in this article.

ORCID iDs

William J Nahm https://orcid.org/0000-0002-2335-8780
Stanley Chen https://orcid.org/0009-0006-6664-3158

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