Response to a Novel Multitargeted Tyrosine Kinase Inhibitor Pazopanib in Metastatic Merkel Cell Carcinoma

A 69-year-old woman presented with a 2-year history of gradually increasing scalp swelling in December 2001. The patient was in good general condition, but physical examination revealed a 5-cm fleshy tumor on the right scalp, with pathology consistent with Merkel cell carcinoma on excisional biopsy. A metastatic work-up, including computed tomography (CT) of the thorax and abdomen, mammography, and gastroscopy, was negative, and the patient underwent a subsequent wide excision with superficial skin graft. No adjuvant radiotherapy was administered at this time. In August 2002, the patient had a local recurrence of a bulky 12-cm mass fixed to the skull, and biopsies of the right upper deep cervical and supraclavicular lymph nodes were inconclusive for involvement. The tumor was inoperable, and the patient underwent radical radiotherapy for a total of 70 Gy, with excellent response at all tumor sites. In March 2003, two small nodules developed in the field, which were believed to represent either soft tissue radionecrosis or possibly a second local recurrence. In October 2003, the patient underwent repeat wide excision with right level II to V neck dissection for nodal and scalp tumor recurrence. Histopathologic examination of the tissue revealed Merkel cell carcinoma with eight of 19 positive lymph nodes and negative margins. The tissue was strongly positive for neuron-specific enolase, with cytoplasmic and perinuclear dot positive for AE1/3, CAM5.2, and epithelial membrane antigen (Fig 1A). Synaptophysin was focally positive, whereas S-100 protein was weakly staining, and chromogranin was negative. CT of the thorax/abdomen revealed multiple pulmonary lesions consistent with metastatic disease. The patient was given six cycles of carboplatin with etoposide, and achieved a partial response. In July 2004, a 1.6 × 1.2 cm right neck mass developed just deep to the flap with a necrotic center at C2-C3, and the pulmonary metastases also showed progression on follow-up CT. The patient underwent repeat wide excision of the neck mass, and postoperative chemotherapy was begun with weekly paclitaxel. Stable disease was maintained until December 2004, when pulmonary metastases progressed, and a 2.3-cm subcarinal lymph node was noted on CT. The patient enrolled onto a clinical trial of tegafur, 5-chloro-2,4-dihydroxypyridine, and oxonic acid (S1) at 30 mg/m² twice daily. A partial response of the pulmonary metastases was achieved, and the patient continued to receive S1 for 35 cycles until relapse occurred in December 2006, with a 1.5-cm nodule above the right ear. Fine-needle aspiration of the nodule was consistent with Merkel cell carcinoma. The patient was observed closely until April 2007, when the right ear mass had grown to 3.5 cm, and pulmonary metastases had progressed on CT imaging. The patient was enrolled onto a clinical trial of a novel multitargeted tyrosine kinase inhibitor pazopanib at 800 mg daily after written informed consent was provided according to institutional guidelines. Consent to use her data for this report was obtained and...
studies in this report were done with the approval of the institutional review board. Two months later, repeat CT scans showed a complete response in the scalp lesion (Fig 2A, before treatment; Fig 2B, after treatment) and a partial response in the pulmonary metastases (Figs 2C, before treatment; and 2D, 2 days after treatment). The sum of the longest diameters of these target lesions in the lungs showed a reduction of 57%, according to RECIST (Response Evaluation Criteria in Solid Tumors). The patient tolerated pazopanib well, with minimal adverse effects. Because of an episode of gallstone pancreatitis 3 months into the trial, the dose of pazopanib was reduced to 400 mg daily. Despite this dose reduction, the patient maintained a partial response for a total of 6 months while receiving pazopanib, until a CT scan in October 2007 revealed progression of disease in the scalp and lungs. Pazopanib was discontinued at this time and palliative doxorubicin was administered. The patient ultimately died as a result of progressive disease of the lungs and liver in August 2008.

Merkel cell carcinoma is a rare, highly aggressive cutaneous neoplasm, typically arising as a flesh-colored, nontender nodule in the head, neck, or extremities of elderly patients. There have been no prospective studies to guide therapeutics, and most data are from retrospective analyses in single institutions. The tumor arises as a nested arrangement in the dermis and typically stains positive for cytokeratin 20 and negative for cytokeratin 7, distinguishing it from other neuroendocrine tumors, and stains negative for S-100 protein, distinguishing it from melanoma. Despite reports of 5-year disease-specific survival rates for early-stage disease of slightly more than 60%, local recurrence and metastasis are common and the mortality rate is high. Wide surgical excision is the treatment of choice for nonmetastatic disease, with some institutions performing sentinel lymph node biopsy. Although adjuvant radiotherapy to the primary site and involved lymph nodes may reduce the rate of local recurrence, the value of adjuvant chemotherapy is less clear. Locally advanced...
and metastatic disease is often responsive to first-line chemotherapy; cyclophosphamide in combination with platinum or anthracycline-based regimens are used most commonly. In a retrospective study of 107 patients, there was overall objective response rate of 61% to first-line chemotherapy. However, chemotherapy-related toxicity in this elderly population was high, and the median overall survival for patients with metastatic disease was only 9 months from the initiation of chemotherapy, with a 3-year overall survival of 17%. Therefore, alternative treatment approaches are needed. We report impressive tumor regression in a patient with metastatic Merkel cell carcinoma during treatment with the novel small-molecule multitargeted tyrosine kinase inhibitor pazopanib, and explore possible mechanisms of response to this agent through immunohistochemical analyses of targets relevant to receptor tyrosine kinase inhibition. Pazopanib is a second-generation multitargeted tyrosine kinase inhibitor against vascular endothelial growth factor receptor (VEGFR) -1, -2, and -3; platelet-derived growth factor receptor (PDGFR) -α and -β; and c-kit. Preclinical studies demonstrated potent antitumor and antiangiogenic activity, with good oral bioavailability. Phase I clinical trials revealed favorable pharmacokinetics and a benign adverse effect profile, with activity in renal cancer and other tumors. To correlate the favorable clinical response in the context of tyrosine kinase targets of pazopanib, we studied the expression of c-kit, VEGF, flt-1/kdr, flt 4, PDGFR-α, and PDGFR-β in this patient and two other patients with Merkel cell carcinoma. We also sequenced known mutations in exon 9 and 11 of c-kit, and a recently described 1432T>C mutation in PDGFR-α. Immunohistochemistry showed similar characteristics for all three patient samples: c-kit negative (DAKO Polyclonal, Carpinteria, CA); VEGF (Clone C-1, sc-7269; Santa Cruz Biotechnology, Santa Cruz, CA) positive (Fig 1B); VEGFR-1 (sc-74007; Santa Cruz Biotechnology), VEGFR-2 (A-3; Santa Cruz Biotechnology), and VEGFR-3 (Clone C1.1, DM3512P; Acris Antibodies, Herford, Germany) all negative; PDGFR-A negative (sc-9974; Santa Cruz Biotechnology); and PDGFR-β (sc-339; Santa Cruz Biotechnology) weakly positive (Fig 1C). No activating mutations were found in exon 9 and 11 for c-kit, however, a 1432T>C mutation in PDGFR-α (ser478pro) gene was found in all three patient tumor samples, as well as in their germline DNA (Fig 3, tumor mutation analysis of patient and two other historical control patients with Merkel cell carcinoma). We found the allelic frequencies of this mutation to be 13.4% in Chinese (n = 75), 17.9% in Malays (n = 14), and 25% in Indian (n = 8) healthy individuals. Previous expression studies have revealed frequent expression of VEGF-A, VEGF-C, VEGFR-2, and PDGFR-A in Merkel cell carcinoma, and suggested a possible role of multitargeted receptor tyrosine kinase inhibitors in the management of this cancer. Initial investigations of the classic mitogen-activated protein kinase pathway in Merkel cell carcinoma failed to detect activating mutations in the BRAF gene, suggesting that drugs in the sorafenib family might be less effective. In vitro studies have shown a decrease in proliferation of Merkel cell carcinoma with the tyrosine kinase inhibitor imatinib. In addition, Merkel cell carcinoma has been shown to overexpress several of the targets of receptor tyrosine kinase inhibitors. Tissue microarray data have suggested that VEGF is upregulated, particularly in aggressive tumors. VEGFR-2 is also overexpressed in Merkel cell carcinoma by immunohistochemistry. The data for the involvement of c-kit in Merkel cell carcinoma is less clear, with some studies showing positive c-kit expression, and others, as in our patients, showing a lack of c-kit staining or activating mutations.


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The September 10, 2009, Diagnosis in Oncology article by Davids et al, entitled “Response to a Novel Multitargeted Tyrosine Kinase Inhibitor Pazopanib in Metastatic Merkel Cell Carcinoma” (J Clin Oncol 27:e97-e100, 2009), contained an error in the spelling of the first author’s name. It was originally given as Matthew Davids and should have been Matthew S. Davids. The authors apologize to the readers for the mistake.

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The February 1, 2010, article by Shen et al, entitled “DNA Methylation Predicts Survival and Response to Therapy in Patients With Myelodysplastic Syndromes” (J Clin Oncol 28:605-613, 2010), contained an error. In Figure 3, some of the data depicted in the bar graph were incorrect for decitabine (DAC), complete remission and partial remission (CR/PR), hematologic improvement (HI), stable disease (SD), and progressive disease (PD). The corrected figure is reprinted below in its entirety.

The online version has been corrected in departure from the print. The authors apologize to the readers for the mistake.

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The May 1, 2010, article by Sekeres et al, entitled “Phase I Combination Trial of Lenalidomide and Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes” (J Clin Oncol 28:2253-2258, 2010), contained an error in the spelling of the fifth author’s name. It was originally given as Rebecca Ganetsky and should have been Rebecca Ganetzky. Journal of Clinical Oncology apologizes to the authors and readers for the mistake.

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