Radiation recall dermatitis triggered by multi-targeted tyrosine kinase inhibitors: sunitinib and sorafenib

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Small molecule tyrosine kinase inhibitors are rapidly being integrated into the management of cancer. This is the first report of sorafenib and sunitinib, both small molecule tyrosine kinase inhibitors of vascular endothelial growth factor and platelet-derived growth factor receptors, triggering radiation recall dermatitis. The pathophysiology of radiation recall is poorly understood, and several possible mechanisms have been proposed. The clinical presentations of these two cases were consistent with one hypothesized mechanism of radiation recall, an idiosyncratic drug hypersensitivity reaction. ***Anti-Cancer***

Drugs **21:206–209 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2010, **21:**206–209

Keywords: dermatitis, radiation recall, sorafenib, sunitinib, tyrosine kinase inhibitor

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Received 3 August 2009 **Revised form accepted** 5 October 2009

Introduction

Small molecule tyrosine kinase inhibitors are rapidly being integrated into the management of many types and stages of cancer. Often this occurs in the setting of multi-agent systemic therapy or multimodality treatment concurrently or sequentially with radiation. Side effect profiles of these targeted agents as monotherapy have been defined, but interactions of these drugs with other cancer therapies, including chemotherapy agents and radiotherapy, are not well established. This is the first report of sorafenib and sunitinib, both small molecule tyrosine kinase inhibitors of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors, triggering radiation recall dermatitis.

Case history 1

A 62-year-old man with a history of epilepsy managed with valproic acid and carbamazepine presented with a 2-week history of unrelenting low thoracic back pain unassociated with any neurological compromise. Investigations including a computed tomography scan and magnetic resonance imaging showed lytic lesions in the left iliac bone, as well as in the C5, T9, and T10 vertebrae. Surgical resection of the lesions at T9 and T10 vertebrae and a soft tissue component abutting the spinal cord established the diagnosis of stage IV clear cell renal cell carcinoma. Abdominal imaging revealed the primary tumor *in situ* and only the limited bony disease described above.

After surgery, the patient received palliative radiotherapy with a dose of 3000 cGy in 10 fractions to two regions, T8–T12 vertebrae and C4–C6 vertebral levels. The latter treatment caused grade 2 (CTCAE v3.0)-radiation dermatitis on the caudal aspect of the bilateral shoulders (left > right) with patchy bright red erythema. This was a result of the radiation dose being delivered tangential to the skin in this area, thus reducing the skin-sparing effect of high-energy photons, as shown in the coronal view of the dose distribution of the area of treatment. (Fig. 1) The maximum dose to the skin from this field was 2600 cGy, located in the left shoulder. Despite a lateral beam arrangement intended to reduce the volume of oral and esophageal mucosa receiving full radiotherapy dose, the patient developed grade 2 acute mucositis in the lower posterior oropharynx and esophagus. Both the dermatitis and the mucositis resolved completely within 3 weeks after completion of radiotherapy without any specific medical intervention.

Ten weeks after completion of radiotherapy, after complete recovery of the acute radiation side effects, systemic therapy for metastatic renal cell cancer was initiated with sunitinib on a standard schedule of 50 mg orally once daily for 4 weeks on and 2 weeks off treatment. Two weeks after starting sunitinib, the patient was re-assessed for a nonpruritic, nontender rash on his left shoulder. This area of skin had patchy erythema and dry desquamation in the distribution of the patient's earlier radiation fields, consistent with radiation recall dermatitis. (Fig. 2) The remainder of his earlier irradiated skin in the C-spine and T-spine fields remained asymptomatic. The patient had no recurrent symptoms of mucositis.

Sunitinib was continued at the same dose of 50 mg once daily 4 weeks on and 2 weeks off despite the recall reaction. The skin reaction subsided over the next 2 weeks without any medical intervention and was not visible at the patient's next reassessment 6 weeks later. After two further cycles of sunitinib, the dose was reduced to 37.5 mg daily, on account of neutropenia. The patient completed this third cycle of sunitinib at a dose of 37.5 mg daily for 4 weeks, at which time he inadvertently

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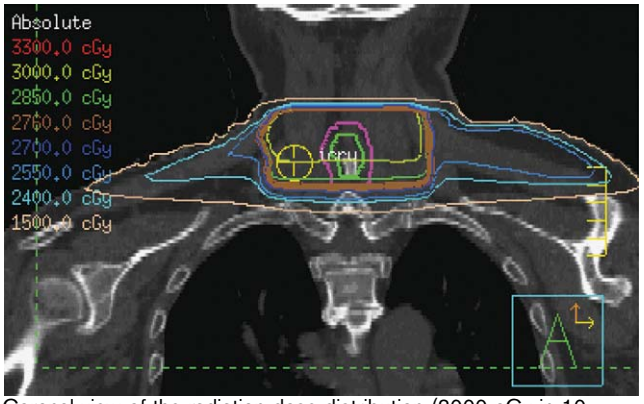
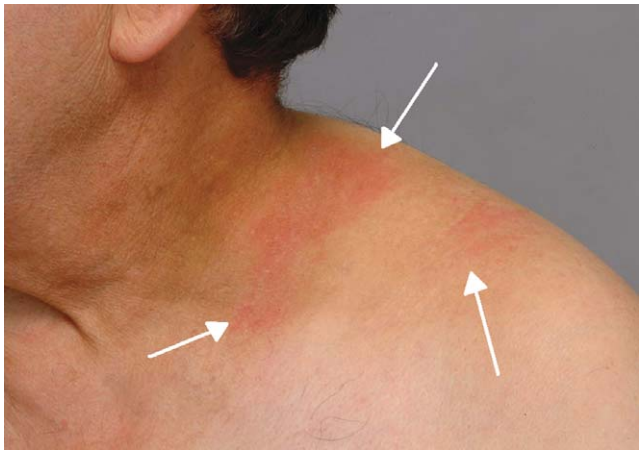
Fig. 1



Coronal view of the radiation dose distribution (3000 cGy in 10 fractions) of the C-spine field showing significant dose to bilateral shoulders (Case history 1).

Fig. 2



Anterior image of radiation recall reaction in the left shoulder, triggered by sunitinib (Case history 1).

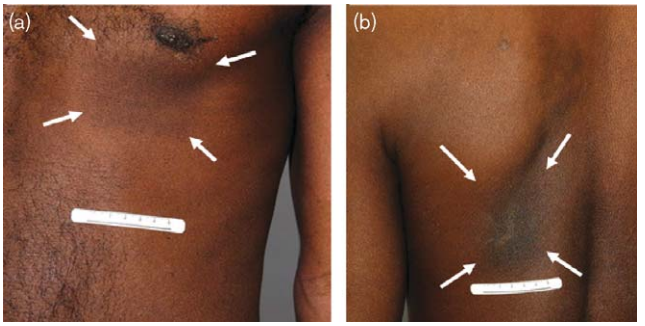
stopped sunitinib for 6 weeks. He presented 6 weeks after stopping sunitinib with a painful right hip and leg and left shoulder and arm. Bone scan confirmed multiple bony metastases, with activity in the right ischium and femur, and the left humerus. The patient received palliative single fraction treatments of 8 Gy to the right hip and femur and left humerus. Sunitinib was continued during these treatments. Good pain relief was achieved. No further skin toxicity or subsequent radiation recall reaction was observed despite the continuation of sunitinib concurrently with radiotherapy.

Case history 2

This 38-year-old man from Haiti with chronic hepatitis B and a viral load of 6-log IU/ml presented with a 1-month history of decreased appetite associated with a 10-lb weight loss, fatigue, and dull right upper quadrant pain. During his work-up, an upper and lower endoscopy had shown *Helicobacter pylori* gastritis, and he was found to have non-syphilitic treponemal disease, and both of these were considered possible causes for his symptoms. An abdominal ultrasound at this time showed abnormal liver echotexture but no definite liver masses. However, a subsequent abdominal magnetic resonance imaging showed a cirrhotic liver with multiple liver lesions: a 7×9.6 cm lesion in segment 6; a 3.5×5 cm lesion in segment 5; 1.7×2.2 cm and 1.1×0.8 cm lesions in segment 2; and a 3×1.8 cm lesion in segment 4. The α-feto protein was elevated to 261 710. Transarterial chemoembolization was initially planned but because of progressive right upper quadrant pain, palliative radiation was started. The patient received palliative hypofractionated radiotherapy directed to the three larger lesions; 30 Gy were delivered in six fractions over 2 weeks. This was well tolerated, with no nausea, vomiting, diarrhea, or gastrointestinal bleeding. There was only grade 1 acute radiation dermatitis noted with these treatments.

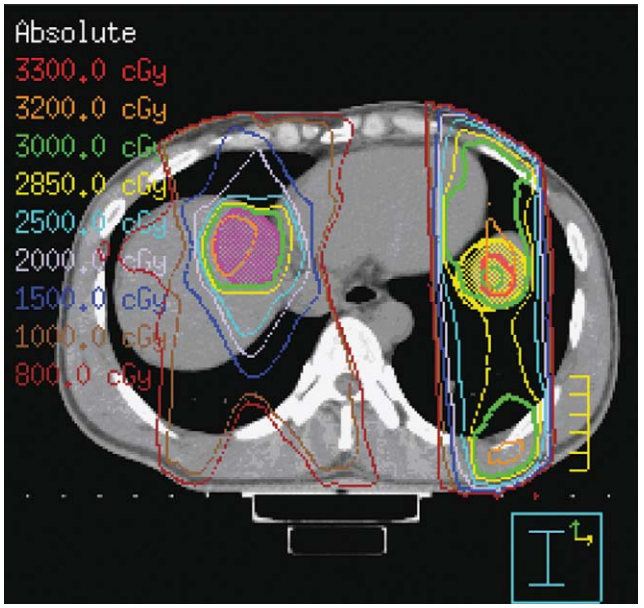
Three weeks after completing radiotherapy to the liver metastases, sorafenib was started at a dose of 200 mg orally twice daily. This systemic therapy was started in order to improve local control of the three large lesions that were irradiated and to address the multifocal metastatic lesions that were not irradiated. Several days after starting sorafenib, the patient noticed progressive pruritus of the skin on the left posterior flank and mild increase in fatigue. When assessed by radiation oncology 12 days after starting sorafenib, there was patchy hyperpigmentation and dry desquamation in the areas, consistent with the patient's recent radiation treatment fields for the left-sided hepatocellular carcinoma, consistent with radiation recall dermatitis. (Fig. 3a and b) The left posterior liver metastasis was treated with a beam arrangement that resulted in a higher dose of radiation to the skin compared

Fig. 3



(a) Anterior image of radiation recall in the left lower chest wall after radiotherapy for left-sided hepatocellular carcinoma, triggered by sorafenib. (b) Posterior image of radiation recall in the left back after radiotherapy for left-sided hepatocellular carcinoma, triggered by sorafenib (Case history 2).

Fig. 4



Axial view of the radiation dose distribution (3000 cGy in 6 fractions over 2 weeks) showing a higher dose of radiation to the skin on the left side owing to the opposed beam arrangement (Case history 2).

with the other areas of treatment. The dose delivered to this area is shown in Fig. 4: mean dose to the skin was 2000 cGy with a maximum dose to skin was 2800 cGy in this area. Topical steroid cream was prescribed to address the pruritus, and sorafenib was continued at 200 mg twice daily. The pruritus and skin changes resolved over 2 to 3 weeks, and the patient eventually went on to tolerate a dose escalation of sorafenib to 400 mg twice daily with no further exacerbations of radiation recall dermatitis. When last evaluated, he had completed 1 month of sorafenib at 200 mg twice daily and 2 months at 400 mg twice daily, with a plan to continue at this dose as long as it was tolerated.

Discussion

Radiation recall dermatitis is an acute and localized inflammatory reaction in previously irradiated skin after exposure to a recall-triggering drug [1]. A wide range of drugs has been associated with radiation recall dermatitis [2,3]. More recently, reports of radiation recall reactions after targeted therapies have emerged. These include a case report of radiation recall dermatitis triggered by chemotherapy agents, carboplatin/gemcitabine, following concurrent therapy with radiation and cetuximab, a monoclonal antibody that binds to the extracellular domain of epidermal growth factor receptor [4] as well as two recent cases of radiation recall dermatitis triggered by a noncytotoxic agent, trastuzumab (monoclonal antibody to the HER2 protein), after radiotherapy [5,6]. However, this is the first report of sunitinib or sorafenib triggering radiation recall dermatitis. Sunitinib is a tyrosine kinase inhibitor of VEGF receptors 1 and 2, PDGF receptor, and other receptor tyrosine kinases including rearranged during transfection, colony stimulating factor 1 receptor and fms-related tyrosine kinase 3 [7]. Sorafenib is a tyrosine kinase inhibitor of VEGF receptors 2 and 3, PDGF receptor, stem cell factor, and raf kinase receptor [8].

Multi-targeted tyrosine kinase inhibitor drugs such as sorafenib and sunitinib, which have anti-angiogenic properties through inhibition of VEGF and PDGF receptors, have been associated with distinct skin reactions including hand–foot syndrome, seborrheic dermatitis, maculopapular rash, and folliculitis. There is one case report of increased acute radiation dermatitis with sorafenib and intensity-modulated radiotherapy for hepatocellular carcinoma. This patient had developed acute, grade 3 hand–foot syndrome, and dermatitis of the scrotum and alopecia on sorafenib monotherapy. When he was treated with concurrent sorafenib and radiotherapy to an area of progressive disease, he developed acute, grade 3 dermatitis within the treatment portals and on the hands and feet, a presumed repeat exacerbation of hand–foot syndrome [9]. This is consistent with our own observations from an ongoing phase I study combining sorafenib treatment with palliative radiotherapy (manuscript in preparation).

The pathological findings of skin biopsies from small molecule tyrosine kinase inhibitor-related skin reactions show varying degrees of keratinocyte damage, parakeratosis with faulty but accelerated keratin production, and necrosis with intracytoplasmic eosinophilic bodies [8]. In contrast, acute radiation dermatitis is primarily an inflammatory wound-healing process mediated by various cytokines and growth factors [2]. Interestingly, radiation recall dermatitis can have both pathological features observed in skin reactions from the targeted therapies with dyskeratotic keratinocytes and an inflammatory component with mononuclear cells and neutrophils, as observed in acute radiation dermatitis [10].

Radiation recall dermatitis is generally thought to be a rare condition, the mechanism and etiology of which is poorly understood. However, the available information is largely limited to case reports. Tan *et al.* presented the only data on the incidence, in which 47% of pediatric patients developed radiation recall dermatitis triggered by actinomycin D [11]. On the basis of its rapid onset and unpredictable effect with drug re-challenge, one proposed mechanism is an idiosyncratic drug hypersensitivity reaction [1,12]. Topical or oral steroids and antihistamines have been commonly used, but they have not shown any effect on the time to resolution of symptoms [1,3]. The two cases presented here support these findings, as one patient used topical steroids and the other did not, but the time to resolution of their recall dermatitis was similar. Furthermore, in our two cases, continuation of the inciting drug and even dose escalation

of the inciting drug did not affect the onset or resolution of the recall reaction. Earlier cases of radiation recall with chemotherapy agents, such as paclitaxel, have also shown that the inciting drug could be continued without further recall reactions [13]. This self-limited reaction to a drug is typical of an idiosyncratic drug hypersensitivity reaction. Nonetheless, in more severe cases, the inciting drug is typically stopped, as there are no other effective therapeutic interventions for radiation recall dermatitis [12]. This case report highlights the clinical presentation and time course of radiation recall dermatitis in two patients receiving tyrosine kinase inhibitors, sorafenib, and sunitinib, shortly after radiotherapy, and alerts clinicians to this potential reaction with these drugs in patients who have received radiotherapy in the past.

Acknowledgement

Conflicts of interest: Research funding from Bayer (L.A.D., A.M.B.). Research funding from Pfizer (A.M.B.). Funding sources: Bayer, Pfizer.

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