Locoregional Interaction of Ixabepilone (Ixempra) After Breast Cancer Radiation

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Key Words. Ixabepilone • Radiation recall • Breast cancer • Microtubule stabilizer

Learning Objectives

Describe the significant locoregional clinical interaction that may result from ixabepilone chemotherapy following radiation.

Explain the importance of awareness, detection, and management of radiation recall by both the medical and the radiation oncologist.

Describe the spectrum of toxicity represented by radiation recall that can range from erythema to chest wall necrosis requiring reconstructive surgery.

ABSTRACT

Background. Radiation recall is an acute inflammatory reaction within a previously irradiated field triggered by chemotherapy administration. We observed a series of patients with unexpectedly severe reactions that included radiation recall and delayed healing when patients received the microtubule stabilizer ixabepilone (Ixempra; Bristol-Myers Squibb, Princeton, NJ) after radiation. We therefore decided to evaluate our experience in patients receiving ixabepilone following radiotherapy.

Methods. We performed a retrospective chart review of all patients treated with curative intent in the Department of Radiation Oncology at the MD Anderson Cancer Center from 2008–2011 who received any ixabepilone after completion of external-beam radiation therapy. These patients received adjuvant ixabepilone on one of two protocols, either for locally advanced breast cancer or for metastatic breast cancer. In to-

tal, 19 patients were identified and their charts were subsequently reviewed for evidence of ixabepilone-related toxicity.

Results. Of the 19 patients identified who received ixabepilone following radiation therapy, three (15.8%) had unexpectedly serious reactions in the months following radiation therapy. Complications included delayed wound closure and drain placement into the seroma, intense erythema, and delayed wound closure and grade 4 chest wall necrosis requiring latissimus flap and skin grafting. The average number of days between the end of radiation therapy and documentation of reaction was 99.

Conclusions. Ixabepilone chemotherapy may induce radiation recall and delayed wound healing when used shortly after the completion of external-beam radiotherapy. Significant clinical interactions have not been previously reported and merit further evaluation. *The Oncologist* 2013;18:265–270

Implications for Practice: Chemotherapy-radiotherapy interactions are uncommon but potentially serious adverse events. We identified 3 of 19 patients with clinically significant interactions when ixabepilone was given shortly after radiotherapy. We concluded that all acute radiation effects should be resolved prior to administration of ixabepilone. Concurrent treatment should be approached with caution.

INTRODUCTION

Radiation recall, also referred to as radiation recall dermatitis (RRD), is a poorly understood inflammatory skin reaction that occurs within a previously irradiated area [1]. The reaction can occur within days to years after exposure to radiation, but by definition must occur after resolution of any skin changes resulting from the radiation treatment itself [2]. The shortest reported onset is 2 days after radiation treatment and the longest is 5 years [3, 4]. It is often precipitated by the use of systemic therapy after radiation, although nonchemotherapeutics have also been implicated.

Initially described in 1959 by D'Angio et al. [5] and separately by Tan et al. [6] with the use of actinomycin D, a number of chemotherapeutic agents have been associated with the development of radiation recall, including docetaxel [7–9], 5-fluorouracil [10], hydroxyurea [11], vinblastine [12], methotrexate [13], doxorubicin [14–16], etoposide [17], paclitaxel [2, 18–20], gemcitabine [21, 22], pemetrexed [23], and capecitabine [24]. Interferon alfa-2b [25], tamoxifen [26, 27], statins [4, 28], and the antibiotics

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cefotetan [29] and azithromycin [30] have also been implicated.

The incidence of radiation recall is estimated as 1%–10% in patients receiving chemotherapy, although it is generally considered to be rare [31, 32]. Dermatologic manifestations are most common, although recall can manifest in other organ systems with mucositis, vaginitis, gastritis, pneumonitis, and colitis [2]. The degree of recall can vary, with mild cases associated with mild to moderate erythema within the treatment field and more severe cases manifesting with edema, ulceration, and skin or chest wall necrosis [31]. The cutaneous effects do not appear to be correlated with dose, with reports detailing recall after delivery with doses in the range of 10–81 Gy [8].

The pathogenesis of RRD is not known. One hypothesis is that the implicated cytotoxic drugs inhibit cell proliferation and division, thereby affecting those cells that have previously undergone sublethal repair by radiation treatment. Other groups have postulated that the effect is a result of depletion of tissue stem cells, vascular damage, and epithelial cell damage [2, 33, 34]. Drug hypersensitivity reactions have been put forth to explain the reactions after noncytotoxic drug administration [2]. This is perhaps why corticosteroids have been found to have a protective effect and are often used to treat symptoms [35].

The severity of the radiation recall reaction is quantitated based on the Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE 4.0) [36], by which RRD is defined as “a finding of acute skin inflammatory reaction caused by drugs, especially chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent.” The spectrum of toxicity ranges from grade 1 toxicity, denoting faint erythema or dry desquamation, to grade 4 toxicity, which denotes life-threatening consequences with skin necrosis or ulceration, and grade 5 toxicity, which is death. Grade 2 toxicity is described as moderate to brisk erythema with patchy moist desquamation, largely confined to skin folds and creases, or moderate edema, whereas grade 3 describes progression of moist desquamation to areas other than skin folds and creases along with friable skin that bleeds with minor trauma or abrasion.

A number of microtubule-stabilizing chemotherapeutic agents are known to interact with radiotherapy, and some have been associated with radiation recall. Paclitaxel-related radiation recall has only been reported in case reports [7, 19, 20]. Mizumoto et al. [37] described a radiation recall incidence of 1.8% in a relatively large study of 461 patients receiving docetaxel, 171 of whom received radiation. There have also been case reports of patients experiencing RRD with vinblastine and vinorelbine [38, 39]. There have been no reported cases of RRD with vincristine. Collectively, these data suggest that RRD in the context of microtubule-stabilizing chemotherapeutics is exceedingly rare, on the order of $\leq 1\%$.

Ixabepilone (Ixempra; Bristol-Myers Squibb, Princeton, NJ) is a relatively new semisynthetic analog of epothilone B, a natural product synthesized by the myxobacterium *Sorangium cellulosum*. Ixabepilone binds to β -tubulin, stabilizes tubulin, disrupts microtubule homeostasis, and induces G₂/M cell cycle arrest and apoptosis [40–42]. Ixabepilone was approved by the U.S. Food and Drug Administration in 2007 for use in patients with locally advanced or metastatic breast cancer in

whom anthracyclines, taxanes, and capecitabine have been proven to be ineffective, because ixabepilone is largely insensitive to mechanisms of drug resistance [43]. A spectrum of phase I trials demonstrated responses in patients with melanoma, lymphoma, non-small cell lung cancer, ovarian cancer, and breast cancer [44–46]. However, dose-limiting toxicities, including neuropathy, grade 4 neutropenia, fatigue, and gastrointestinal discomfort led to the recommended 40-mg/m² dose that has been used in most phase II studies. Multiple phase II studies with ixabepilone monotherapy for metastatic breast cancer have demonstrated objective response rates in the range of 0%–57% [47–52]. A randomized phase III trial of ixabepilone (40 mg/m² i.v. over a 3-hour infusion every 3 weeks) and capecitabine also demonstrated a better progression-free survival outcome, suggesting that ixabepilone could potentially replace taxane-based initial therapy in the metastatic setting [53, 54]. Interestingly, no grade 3 or grade 4 cutaneous toxicities were noted in that trial [55]. A review by Cobham and Donovan (2009) noted grade 3 skin rash and skin hyperpigmentation in 17% and 11% of patients, respectively, with no grade 4 cutaneous toxicity [56].

At our institution, we observed a series of patients with unexpectedly severe reactions following radiation therapy on protocols involving treatment with ixabepilone. We therefore decided to evaluate our experience in patients receiving ixabepilone following radiotherapy.

MATERIALS AND METHODS

Patients

This retrospective analysis was approved by the institutional review board (IRB) at The University of Texas MD Anderson Cancer Center. We reviewed the records of all patients treated with curative intent in the Department of Radiation Oncology at the MD Anderson Cancer Center from 2008–2011 who received ixabepilone on protocol as a component of their treatment for breast cancer. These patients received adjuvant ixabepilone on one of two IRB-approved protocols, either for locally advanced breast cancer or for metastatic breast cancer. All of these patients had significant residual disease following neoadjuvant chemotherapy. We initially identified a total of 34 patients who had received any amount of ixabepilone at any time during their care. We subsequently identified a subset of 19 patients who received ixabepilone following administration of external-beam radiation therapy; these patients were the subjects of the current study. The medical records of these patients were extensively reviewed for any evidence of toxicity related to ixabepilone, particularly related to the integumentary system. If a severe reaction that could be attributed to radiation was identified, this information was reaffirmed with the attending clinicians involved in the patient's care. Per protocol, ixabepilone was administered at recommended doses of 40 mg/m² i.v. over 3 hours every 3 weeks.

RESULTS

All 19 patients had either locally advanced disease or metastatic disease at the time of ixabepilone administration. Pathologies included invasive ductal carcinoma (12 of 19 patients, 63%) and inflammatory breast cancer (seven of 19 patients, 37%). Side effects related to ixabepilone chemotherapy were common, with 16 of 19 patients (84%) experiencing treatment-related alopecia, 15 patients (79%) experiencing

Figure 1. Prevalence of side effects attributed to ixabepilone in our patient population ($n = 19$). Numbers represent percentages of patients who experienced the documented side effect.

Figure 2. Representative images of a patient who experienced a severe reaction with ixabepilone. (A): Five weeks after radiation, there is treatment-related erythema. (B): After three cycles of ixabepilone, there is delayed wound healing. (C, D): After four cycles, progressive chest wall necrosis necessitates flap reconstruction. (E): Nine months after radiation, 4 months after surgery, the graft appears healthy.

fatigue, 15 patients (79%) experiencing myalgias or arthralgias, 13 patients (68%) experiencing constipation, 13 patients (68%) experiencing paresthesias, 12 patients (63%) experiencing nausea, 10 patients (53%) experiencing anorexia, 10 patients (53%) experiencing diarrhea, 6 patients (32%) experiencing vomiting, 6 patients (32%) experiencing sore or painful extremities, 5 patients (26%) experiencing mucositis, 4 patients (21%) experiencing fever, neutropenia, or infection, and 4 patients (21%) demonstrating a rash. Two patients (10%) experienced a cough and one patient (5%) was noted to have either chronic, tearing, pelvic pain or back pain (Fig. 1). Notably, 3 of the 19 patients (16%) had unanticipated and serious events that were consistent with radiation recall and/or with delayed wound healing.

Seven patients discontinued ixabepilone therapy prior to completion of the six cycles designated on protocol. Six dis-

continued because of nondermatologic toxicities (neuropathy, myalgias, nausea, fatigue). One patient discontinued therapy because of skin toxicity within the radiation treatment field and an additional patient completed all six cycles of therapy without documented skin toxicity but experienced delayed wound closure requiring drain placement.

Of the three patients who experienced a severe interaction between radiation and ixabepilone chemotherapy, two had inflammatory breast cancer and one had invasive ductal carcinoma. By the CTCAE 4.0, as previously described, one patient with inflammatory breast cancer (cT4dN3M0) experienced grade 2 erythema after just one cycle of ixabepilone and was able to tolerate three of the six cycles on protocol but discontinued secondary to severe fatigue and myalgias and arthralgias. Her symptoms resolved after being discontinued on the protocol with no further in-

intervention required. A second patient with invasive ductal carcinoma (cT3N1M0) was able to tolerate the entire six cycles of ixabepilone; however, she continued to have an open wound during her radiation treatment and ultimately required drain placement for a 14-cm seroma after completion of her systemic therapy. A third patient with inflammatory breast cancer (cT4dN2M0) experienced grade 4 chest wall necrosis requiring a latissimus flap and skin grafts (Fig. 2).

Four weeks prior to commencing ixabepilone therapy, ~5 weeks after completing radiation therapy, the third patient's physical examination demonstrated mild erythema consistent with her prior radiation treatment; however, there was no evidence of skin breakdown (Fig. 2A). Treatment with ixabepilone was started prior to complete resolution of her radiotherapy-induced skin changes. After three cycles of ixabepilone therapy, abnormal skin architecture became apparent (Fig. 2B), which subsequently progressed to chest wall necrosis after four cycles of ixabepilone therapy (Fig. 2C, 2D). The patient's systemic therapy was subsequently discontinued and she was seen by plastic surgery, undergoing latissimus flap and skin grafting. The patient was successfully managed with this intervention, with her chest necrosis no longer apparent on follow-up 4 months after her surgery (Fig. 2E). For the three patients with severe interaction, the number of days between the end of radiation therapy and documentation of the reaction was 62, 124, and 110, respectively, with an average onset 99 days after completion of radiation therapy. The number of days between the end of radiation therapy and commencement of ixabepilone therapy was 41, 19, and 35, respectively, with an average of 32 days.

DISCUSSION

Breast cancer is the most commonly diagnosed cancer among women [57]. In 2011, an estimated 230,000 women in the U.S. were diagnosed with breast cancer, with nearly 40,000 expected to die as a result of their disease. At diagnosis, presumably because of mammographic screening, the majority (52%–61%) of women have localized disease, whereas relatively few have distant metastases (6%–9%) [58]. The 5-year survival rate for patients with localized breast cancer at diagnosis is relatively high (98.6%); however, the 5-year survival rate for patients with metastatic disease at diagnosis is much lower, at ~23.4% [57].

For women who present with hormone receptor–negative, metastatic disease, chemotherapy is indicated as primary treatment, with options including anthracyclines, taxanes, capecitabine, vinorelbine, gemcitabine, ixabepilone, and eribulin [59, 60]. In patients who become resistant to anthracyclines or one of the other more traditionally used agents, ixabepilone may be a viable treatment option. In most trials, ixabepilone has been reported to cause neurologic, hematologic, and gastrointestinal toxicities, among others [48, 53, 61]. These findings are corroborated by our study. However, 3 of our 19 patients also experienced radiation recall and/or delayed wound healing, an endpoint commonly not described in studies of systemic therapy. This highlights the necessity of continued follow-up in this patient population. Moreover, this finding and the degree of toxicity witnessed in our study, including one patient requiring reconstructive surgery for chest wall necrosis, suggests that radiation recall is a

phenomenon that requires the attention of the radiation oncologist as well as the medical oncologist.

The radiation recall incidence and pathogenesis are poorly understood. Although some studies suggest an incidence as high as 49% [62], most studies quote closer to 20% [63]. The duration ranges from weeks to months to years following the completion of radiation therapy. It is likely to differ based on the inciting agent; however, our incidence of 16% is consistent with what has been widely described. The phenomenon has been reported not only for systemic chemotherapies but also for certain antibiotics [29, 30]. It is unclear what causes it; it has been described for high doses and relatively low doses of radiation, shorter and longer treatment intervals, i.v. and oral therapy administration, and after first exposure to a drug as well as repeated exposure [2, 3, 35]. Management usually entails discontinuation of the impending agent, supportive care, and sometimes corticosteroids. However, in two of our patients, surgical wound healing presented a significant issue requiring active intervention, including drain placement and reconstruction. Previous to this analysis, our practice was to introduce ixabepilone chemotherapy as soon as 3 weeks after completing radiation therapy; we have now modified our practice to commence ixabepilone only after any acute dermatitis related to radiation therapy has resolved.

CONCLUSION

Radiation recall, although relatively uncommon and generally mild in nature, can present with more pronounced toxicity. We report three patients (16% of our study population) in whom ixabepilone chemotherapy likely induced radiation recall and/or delayed wound healing shortly after the completion of external-beam radiotherapy. This degree of interaction has not been previously reported and requires further evaluation and prompt clinical attention to minimize patient morbidity.

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