A CASE OF RADIATION RECALL MUCOSITIS ASSOCIATED WITH DOCETAXEL

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Abstract: Background. Radiation recall reactions, in particular dermatitis, are well documented in the literature. However, radiation recall mucositis is a rare clinical phenomenon.

Methods. We report a case of a 45-year-old man diagnosed with squamous cell carcinoma of the base of tongue. He was treated with surgery followed by chemotherapy and radiation therapy. Several months after completing treatment, he had a recurrence develop outside of the previously irradiated field. He was offered radiation therapy concurrent with docetaxel as salvage therapy.

Results. During salvage therapy, acute recall mucositis developed corresponding to his previously irradiated fields. His chemotherapy with docetaxel was withheld, and his symptoms rapidly improved.

Conclusions. This case describes radiation recall mucositis associated with docetaxel, a rare but potentially serious clinical situation. Given the potential severity of the reaction and increasing use of docetaxel as second-line treatment of recurrent head and neck cancers, it is important to be aware of this phenomenon. © 2004 Wiley Periodicals, Inc. Head Neck 26: 197–200, 2004

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Radiation recall phenomenon is well documented in the literature but rarely clinically seen. It is manifested as an inflammatory reaction within a previously irradiated field after the administration of a chemotherapeutic agent. It can occur weeks to years after radiation therapy.1 Dermatitis is the most frequently described inflammatory reaction. Although generally mild, in a review of 37 cases by Camidge and Price,1 25% of patients had severe skin reactions develop.

Docetaxel has been implicated in radiation recall dermatitis in several case reports.2–4 The severity of the dermatitis described with docetaxel ranged from grade 1–3, with two of three cases reporting a rapid recovery over several days. Other recall reactions, including mucositis and pneumonitis, have rarely been reported.5,6 To our knowledge, this is only the second reported case of docetaxel-associated radiation recall mucositis.7

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Although recall mucositis seems to be a rare phenomenon, it is not insignificant for two reasons. First, because the incorporation of docetaxel within palliative chemotherapy regimens for relapsed head and neck squamous cell carcinoma after primary radiotherapy is becoming more popular, more cases might be seen in the future. Second, it can potentially be a serious or even lethal condition, depending on the magnitude of the previously irradiated volume. Its early recognition and proper management can be crucial for outcome.

CASE REPORT

A 45-year-old man was seen at The University of Texas Medical Branch with a 7-month history of dysphagia, painful swelling of the tongue, and otalgia. On physical examination, he was found to have a firm mass involving the left base of tongue, which crossed midline and extended anteriorly to involve the posterior lateral oral tongue. A mass was palpated in level II of the neck. A CT of the neck confirmed a 5.2- × 3.2-cm left tongue mass crossing midline and involving the anterior tonsillar pillar. A biopsy specimen revealed squamous cell carcinoma. He underwent a total glossectomy with laryngeal preservation, left modified radical neck dissection, right selective neck dissection, and tracheotomy. He was reconstructed with a left pectoralis major myocutaneous flap. He was staged as pT3N2c squamous cell carcinoma of the base of tongue. No extracapsular extension was noted. Histopathologic examination revealed a close margin (1 mm) at the left lateral aspect of the specimen, although additional tissue was taken from that area intraoperatively. He was enrolled in a phase II trial using early postoperative paclitaxel followed by paclitaxel and cisplatin concurrent with radiation therapy for resected, high-risk squamous carcinoma of the head and neck. After surgery, he received three cycles of weekly paclitaxel, 80 mg/m², with the first cycle administered approximately 14 days postoperatively. This was followed by concurrent weekly chemotherapy (paclitaxel, 30 mg/m², and cisplatin, 20 mg/m²) and radiation therapy (66 Gy at 2 Gy per fraction). The concurrent paclitaxel and cisplatin were started during the fourth week of radiation therapy and given weekly for three cycles. His radiation therapy was delivered using opposed lateral fields with 6-mV photons to the upper neck for the initial 44 Gy. An additional 6 Gy was delivered off-cord using opposed laterals. An additional boost was delivered, with the highest areas at risk receiving a total of 66 Gy. Sixteen Gy were delivered to his right and left posterior cervical strip, using 9-MeV electrons to bring the total dose to this area to 60 Gy. Three-dimensional CT planning was used to optimize dosimetry. The radiation fields can be seen in Figure 1.

Approximately 2 months after completing radiation therapy, the patient reported the onset of diplopia and intermittent headaches. A CT of the head showed an ill-defined enhancing lesion at the right skull base. An MRI confirmed replacement of the right petrous bone by abnormal tissue, which also encompassed the right petrous carotid artery. The area of failure was located cranial to the superior edge of the prior radiation field. A CT scan of the chest was negative. Given the patient’s good performance status and the presence of only one site of disease, he was offered salvage radiotherapy and chemotherapy for treatment of the recurrence. Sixty-five Gy in 50 fractions at 1.3 Gy per fraction were prescribed for the gross tumor volume as seen on the CT scan and MRI. At the same time, 55 Gy were prescribed for a larger volume extending inferiorly to the upper edge of the treatment field. Radiation therapy was planned using an intensity modulated radiation therapy technique. He was started on concurrent chemotherapy with weekly docetaxel (25 mg/m²). Four days after the second cycle, he had severe pain in his mouth limiting his oral intake. On examination, confluent mucositis

FIGURE 1. Lateral radiation fields used after surgical resection for the base of tongue carcinoma. The red, green, yellow, and blue lines correspond to a dose of 44, 50, 60, and 66 Gy, respectively. Posterior cervical electron fields are not shown.
(grade 3) was present in the oral cavity and oropharynx, matching the areas previously treated with radiation therapy. Consequently, he lost 17 pounds over a 3-week period. Placement of a gastrostomy tube was advised; however, he initially refused. He had regained swallowing function after the glossectomy and was able to maintain a liquid diet.

Further review of his current radiation plan confirmed that no dose was delivered to the oral cavity and oropharyngeal mucosal regions. The docetaxel was discontinued, and he noticed rapid improvement in his symptoms over the next week. Further challenge with docetaxel was not attempted, and he completed his planned course of radiation therapy.

Approximately 3 weeks after being diagnosed with recall mucositis and 4 days after completing radiation therapy to the recurrence, he reported liquids draining from his mouth to the anterior neck. Examination revealed dehiscence of the pectoralis flap from its anterolateral insertion onto the mandible. An orocutaneous fistula was present from the anterior floor of mouth to the anterior neck. Biopsy specimens of the area showed necrosis, granulation tissue, and changes consistent with radiation therapy without evidence of recurrence. A gastrostomy feeding tube was placed after the diagnosis of the fistula. The fistula eventually healed after clindamycin rinses and instructions to take nothing in by mouth.

**DISCUSSION**

Radiation recall is associated with a variety of chemotherapeutic agents and primarily manifests itself as dermatitis. To our knowledge, only two cases have been reported in the literature, with mucositis as the primary expression of the recall phenomenon. Taxanes are often associated with the recall phenomenon and are used frequently in the treatment of head and neck cancers. Specifically, docetaxel has been shown to be effective in the treatment of recurrent squamous cell carcinomas of the head and neck after primary radiotherapy. When treating recurrent disease in head and neck patients with docetaxel, radiation recall reactions could be extensive and severe, mainly depending on the prior irradiated volume.

Although the mechanism for the recall phenomenon is unknown, several potential etiologies have been proposed. Abadir and Leibmann proposed that radiation induces epithelial stem cell depletion. The stem cells remaining maintain a functional role; however, they must cycle at a faster rate to account for the depleted numbers. Thus, the stem cells are more susceptible to drugs active against rapidly dividing cells. It has also been proposed that lethal mutations among the progeny of a surviving cell might be the basis for radiation recall. An enhanced response to chemotherapy could be due to the inability of the stem cells to proliferate. However, an experiment by Kitani et al was unable to confirm this hypothesis. Moreover, stem cell inadequacy does not explain the rapid onset seen in some cases or why the reaction does not worsen after rechallenge with the same drug. A third possibility proposed is an idiosyncratic drug hypersensitivity reaction activating inflammatory pathways. This mechanism of action can explain the rarity, onset time, and extreme drug specificity.

In our case, an idiosyncratic drug hypersensitivity reaction seems the most likely explanation. Our patient’s rapid improvement in symptoms with discontinuation of docetaxel concurs with this explanation. Also, it is unlikely that a rapid recovery within days could occur with inadequate stem cells. It is interesting to note that in our patient, the reaction was limited to the mucosa and did not involve the skin. On review of the original plan, the oral cavity and pharyngeal wall received the full dose of 66 Gy. The skin dose was estimated at 41 Gy. The skin dose was estimated at 41 Gy. However, it is difficult to accurately predict the skin dose with the treatment planning system. The skin lies within the buildup region, which may provide some degree of uncertainty, as well as uncertainty caused by the mask. A radiation threshold was described by Yeo et al around 18 Gy at 3 Gy per fraction for dermatitis associated with docetaxel. Although a radiation threshold could explain why our patient experienced mucositis and not dermatitis, our findings do not concur with the case described by Yeo et al. Also, in our patient, the severe mucositis did not seem to correlate with myelosuppression. His leukocyte count throughout his initial treatment and salvage therapy has remained within normal limits. It is likely that the recall mucositis contributed to the dehiscence of the pectoralis flap, resulting in the orocutaneous fistula. The disrupted mucosal barrier could have allowed an infection to establish itself in the region of the flap, resulting in the dehiscence. A recurrence of the tumor, although still possible, is unlikely, given the negative biopsy specimens obtained from this region.
In conclusion, radiation recall mucositis is a rare event, and the actual incidence is unknown, although the increasing use of docetaxel as first-line palliative chemotherapy may lead to an increased number. In these patients, mucositis can be a potentially severe problem and predispose to late complications. It is therefore important to be aware of this possibility and to recognize this phenomenon in clinical practice.

REFERENCES