Clinical case

Radiation myositis: The possible role of gemcitabine

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Key words: chemotherapy, gemcitabine, radiotherapy, radiation myositis

Introduction
In the October 1999 issue of this journal, Welsh et al. [1] reported an intriguing case of radiation myositis. In our center, we observed a similar case, in which a potential role of gemcitabine is suggested.

Case presentation
A 58-year-old woman underwent surgical treatment of a squamous-cell carcinoma of the inferior lobe of the right lung in January 1996. The disease stage was T3N2. The patient received post-operative radiotherapy (RT). A cumulative dose of 45 Gy (5 x 2 Gy per week) was delivered from 22 March 1996 to 24 April 1996. A boost of 10 Gy was also delivered to the right hilar region. In January 1997, the patient developed bone metastases. The bone scan showed abnormal fixation in the right pubo-ischiatic and cotyloid region and metastasis was confirmed by magnetic resonance imaging. Radiotherapy was delivered to opposed anterior and posterior fields (Figure la) as a total dose of 33 Gy in 11 fractions over 15 days. At the end of February 1997, pain had been well controlled and the patient began a chemotherapeutic regimen combining gemcitabine (GEM) and cisplatin (CDDP). On February 17, 1997: GEM was administered at a dose of 1000 mg/m² on days 1, 8 and 15 and CDDP at a dose of 100 mg/m² on day 15. The patient had received three courses by April 1997, but the CDDP dose was reduced because of poor gastrointestinal tolerance. At the end of May 1997, the patient developed very painful 'cellulomyositis' of the right buttock. The bone scan showed abnormal fixation in the right gluteal muscles that coincided with the radiation fields, together with significant regression of the pathologic bone fixation (Figure lb). The CT scan of the region was considered normal. Magnetic resonance imaging showed a diffuse hypersignal and edema on the T2-weighted images of gluteal soft tissue, coinciding with the radiation fields and compatible with the diagnosis of radiation myositis. Symptomatic treatment, consisting in oral opiates, antibiotics and steroids, was prescribed. The pain was very difficult to control but was progressively alleviated over three months. The patient's course was characterized by progression of the bone metastases and the patient died in January 1998.

Comments
Radiation-induced muscle injury is infrequently reported in the literature, as Welsh et al. point out in their article [1]. A possible determinant of radiation-related muscle injury is a 'high' dose per fraction [2], but lesions usually (but very infrequently) occur at a total dose of over 50 Gy.

Although there was no histological confirmation of subacute radiation induced myositis, the case history appeared very similar to that reported by Welsh et al. [1]. A potential role of gemcitabine was considered in view of the similarity in the chronology of the present case and that previously reported. Moreover, since those two cases, at least two other reports of radiation recall have recently been published [3, 4].

The time sequence of the clinical case reported herein is not consistent with a classic radiation recall phenomenon, because symptom onset occurred after the third chemotherapeutic cycle and because radiation therapy was delivered less than six months previously, while six months is considered the lag time for subacute radiation reactions [5]. Phase I–II studies evaluating combined GEM and radiotherapy showed that GEM dose must be considerably reduced, in comparison to combination chemotherapy without radiation therapy, because of severe side effects, probably related to major potentiation of the cytotoxic effects of combined GEM and radiation therapy [6, 7].

The mechanisms by which GEM enhances subacute reactions to radiation therapy have yet to be elucidated. Gemcitabine is a pyrimidine analogue like cytosine-arabinoside. After crossing the cell membrane, GEM is activated by deoxycytidine kinase, forming mono-, di- and triphosphate metabolites. A deficit in that enzyme is
the principal mode of resistance [8]. X-ray radiation may induce increased thymide phosphorylase (dThdPase) levels in some tumors. The later is the essential enzyme in activation [9] of capecitabine, which is also a nucleoside analogue with radiosensitizing properties [10]. Those observations are consistent with an indirect effect mediated by TNF-α and induced by X-ray irradiation in tumors and possibly host stromal normal cells. These processes may take six days and peak nine days post-irradiation, but have not been studied at later time points. The mechanism has been identified as one of the potential radiosensitization factors observed with capecitabine. To our knowledge, there is no data on the influence of X-ray irradiation on intracellular deoxycytidine deaminase levels in tumors, or on those in normal tissues, and particularly the muscles.

The very intriguing points in these two clinical cases are: 1) the time sequence; 2) the use of GEM about two months after radiotherapy; 3) the sites of the radiation myositis (i.e., the gluteal region) and 4) the favorable course after about two months.

References


Received 10 April 2000; accepted 11 May 2000.

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