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Radiation-recall Dermatitis with Docetaxel: Establishment of a Requisite Radiation Threshold

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DOCETAXEL IS a member of the taxane group of chemotherapeutic agents that cause disruption of cell division by enhancing microtubule assembly and inhibiting tubulin depolymerisation. It has been reported to show promising results in the treatment of metastatic breast cancer [1]. We report a particularly striking case of radiation-recall dermatitis, the first to be associated with docetaxel, and the first in which a threshold for the radiation dose could be clearly established.

A 51 year-old woman was initially diagnosed to have carcinoma of the right breast in 1992. She underwent modified radical mastectomy and axillary dissection followed by adjuvant tamoxifen therapy. She remained well until December 1995 when she was found to have liver metastases for which she received weekly intravenous 5-fluorouracil whilst continuing with tamoxifen. In January 1996 she was referred to our institute for further management. Bone scintigraphy showed metastases in the skull, at multiple levels of the spine, in multiple ribs, the bony pelvis and both scapulae and femori.

As her main symptom was severe bone pain, mainly involving the lower spinal and pelvic areas, she was given palliative radiotherapy to the spine and pelvis. Over a 10-day period from January 23 (day 1), she received 30 Gy in 10 fractions to the T10-L4 spine and pelvis. Photons (6 MeV) from a linear accelerator was given to the patient in a prone position (Figure 1a). The spine was treated by a single posterior field. The skin dose at the back and front were 8.7 Gy and 18.7 Gy, respectively. The pelvis was treated by a pair of anterior–posterior opposing fields and the skin dose at the back and front were 16.8 Gy and 21.5 Gy, respectively. The difference in dose was due to the presence of a thin perspex support apposing the skin at the front. During this time, she suffered mild nausea and vomiting, and developed severe diarrhoea from day 13 to day 24, which required hospitalisation for rehydration; there was no sign of radiation skin toxicity at this stage.

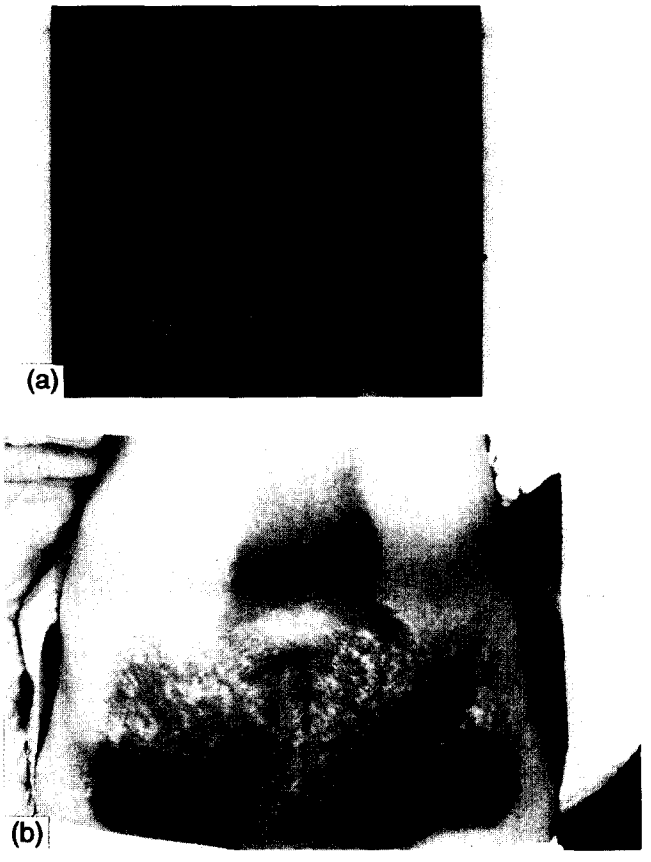

Figure 1. (a) Radiotherapy fields for T10 to L4 spine and pelvis. (b) The appearance of radiation-recall dermatitis over anterior abdominal wall and groin areas

After the diarrhoea had settled, she was started on docetaxel at a dose of 100 mg/m^2 on a three-weekly basis, with dexamethasone cover for 5 days from the day prior to each cycle of docetaxel. The first and second doses were given on days 38 and 59, respectively, and she developed neutropenic fever after each dose. On the second admission with neutropenic fever (day 63), she developed a well-defined erythematous skin lesion over the anterior abdominal wall and groin areas which corresponded closely to her previous radiotherapy fields (Figure 1b). This was accompanied by the recurrence of diarrhoea. An infective screen, including stool microbiology, was negative and the fever responded to imepanem. The diarrhoea and skin rash gradually subsided over the following week. With documented partial response of the liver metastases, she gave her consent to continue with further docetaxel therapy. At the time of writing, she had undergone two further cycles of docetaxel. Although she was admitted again with neutropenic fever after the third dose, despite dose reduction, she had no further signs of radiation-recall reactions.

Radiation-recall is the occurrence, with subsequent chemotherapy administration, of an acute toxicity in a previous radiation field and has been observed weeks to years after the completion of radiotherapy. The development of such reactions has been well documented with certain chemotherapeutic agents, particularly doxorubicin and actinomycin D [2–4]. Other drugs implicated include idarubicin, bleomycin, cyclophosphamide and methotrexate [1]. More

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recently, 5 cases of paclitaxel-associated radiation-recall reactions [5–7] and a single case of radiation-recall mucositis associated with docetaxel have been reported [8]. The precise mechanism is unknown. One hypothesis suggests that cytotoxic treatment after radiotherapy causes a 'remembered' reaction in the remaining surviving cells within the previously irradiated field. An alternative proposition suggests that radiation induces heritable mutations within surviving cells which then produce a subgroup of defective stem cells that are unable to tolerate the second insult of chemotherapy [9]. Paclitaxel [10] has been found to be a radiosensitiser, but it is unclear how this might correlate with an ability to reactivate latent radiation effects in normal tissues.

It is interesting to note that the skin reaction occurred in only two of the four regions of irradiated skin, i.e. anteriorly where the skin doses were 18.7 Gy and 21.5 Gy over the spine and pelvic areas, respectively, but not posteriorly where the corresponding skin doses were 8.7 Gy and 16.8 Gy, respectively. The existence of four levels of skin doses suggests a 'threshold' radiation dose for the recall reaction of between 16.8 and 18.7 Gy in this case. It would be interesting to look for a similar 'threshold' dose from the data in other cases, but unfortunately, in most cases, only the tumour dose, rather than the skin dose, are reported.

To our knowledge, our patient represents the first case of radiation-recall dermatitis with docetaxel. In the few reported cases of recall reactions associated with taxanes, one case of radiation-recall dermatitis has been reported to be recurring with repeated administration of paclitaxel [6]; however, our patient treated with docetaxel and 2 patients reported by Shenkier and associates [7] who were treated with paclitaxel did not have signs of recurrent reactions with repeated therapy using the same drugs. This suggests that there may be a specific time period during which patients are susceptible to recall dermatitis. Alternatively, in our case, there may be a drug dose threshold since the two cycles in which the dermatitis did not occur were associated with a dose reduction.

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Cathepsin D Content in Malignant Tumours of Corpus Uteri

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DUE TO degradation of the basement membrane and digestion of the extracellular matrix, lysosomal proteases may participate in invasion and metastasis of cancer. Of particular interest is cathepsin D, elevated levels of which have been correlated with poor prognosis of breast cancer [1, 2]. The enhanced expression of cathepsin D has also been reported for tumours of different origin [1]. The aim of the present study was to determine the concentration of cathepsin D in normal and malignant tissues of corpus uteri (30 matched pairs) and to assess the relationship between cathepsin D content and some clinical and pathohistological parameters.

Characteristics of the tumours and patients studied are given in Table 1. The classification of tumours and histo-

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