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Has Radiation Therapy Any Role in Signet-ring Cell Breast Adenocarcinoma?

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SIGNET-RING CELL carcinoma of the breast is a rare entity (2–4%), containing intracytoplasmatic PAS-positive mucin. "Pure" signet-ring cell carcinoma variant is exceptional with local and lymph node invasion, serosal avidity with unusual metastatic pattern. Mean age of presentation is 50 years old, the breast mass has a median tumour size of 5 cm (range 3–15 cm), with pain being the most frequent symptom due to the tumour's infiltrative pattern. Although surgery is the treatment of choice, when feasible, other therapeutic alternatives must be considered since the clinical initial presentation may not always allow a therapeutic approach with curative intent [1, 2]. The role of radiotherapy as a palliative treatment has not been clearly defined in this entity. We present a case of a 64-year-old woman with a local, painful, breast mass, with ulcerative and necrotic macroscopic elements. A biopsy was performed and a "pure" signet-ring cell adenocarcinoma was diagnosed. Staging examination was negative. Her tumour progressed even with chemo-hormonal therapy treatment, when the patient was referred to our hospital. Physical examination revealed a bulky (24 × 24 cm), locally extensive, presternal mass, with involved bilateral axillary lymph nodes, and infiltration of both breast and pericardium, soft tissues, sternum and first and second ribs was confirmed by computed tomography (CT scan) and magnetic resonance imaging (MRI); surgical treatment was rejected. A palliative irradiation treatment was administered through a linear accelerator with 6 MV photon beam energy, giving a total dose of 39.6 Gy, 1.8 Gy/fraction, five fractions per week. A boost with a 20 MeV electron beam up to a total dose of 28 Gy, 2 Gy per fraction was later performed. Complete resolution of the pain was obtained and all the external components of the tumoral mass disappeared (Figure 1a,b).

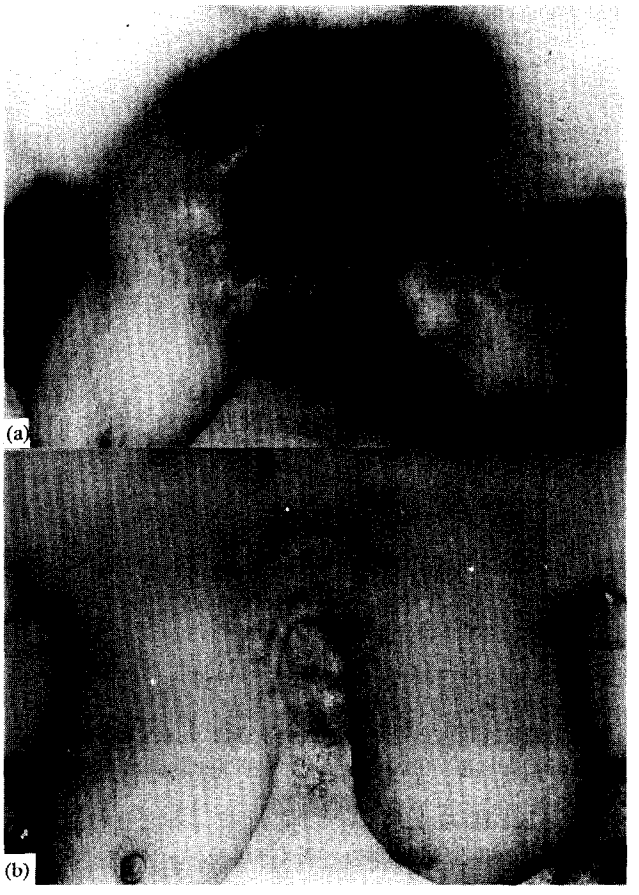

Figure 1. Signet-ring cell breast adenocarcinoma (a) before and (b) after radiotherapy treatment.

For 10 months, the patient remained asymptomatic and free of disease progression with a good quality of life. Subsequently, the patient had uncontrolled distant metastases and died, aged 68 years. In spite of the well-known clinico-pathological pattern and treatment of ductal infiltrating carcinoma, a pure signet-ring cell adenocarcinoma in breast requires special attention due to its local invasion and axillary positive nodes (73% of cases). Mortality is high (53% of cases), despite standard surgical treatment [3]. Surgery is not recommended in bulky disease at presentation, so that both chemotherapy and hormonal treatment are the most frequent alternative treatments employed, in spite of the poor response observed in positive receptor tumours treated with tamoxifen [4].

The role of radiotherapy as a palliative treatment is a well-known and effective modality in solid tumours [5], but in signet-ring cell adenocarcinoma, it has not been clearly described as shown in the literature reviewed. The only intention of treatment in this patient was to improve symptoms and to diminish the tumour mass.

In conclusion, radiotherapy should be considered as an effective, alternative, palliative treatment in signet-ring cell breast adenocarcinoma, even in a bulky infiltrate tumour mass which has progressed following chemo-hormonal treatment.

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Considerable Plasma Levels of a Cytotoxic Etoposide Metabolite in Patients Undergoing High-dose Chemotherapy

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ETOPOSIDE (VP16) has been used in the treatment of various tumours for many years, but its elimination from the body, particularly its metabolism, is still not completely understood. *In vitro* studies in human liver microsomes revealed mono-*O*-demethylation, catalysed by cytochrome P450 3A4, as a metabolic pathway of etoposide in man [1]. The formed catechol metabolite has been shown to be highly cytotoxic in cellular cultures [2]. It directly interacts with DNA leading to DNA damage and inactivation [3]. Its binding to calf thymus DNA is 10 times more extensive compared to parent etoposide [2]. However, the clinical significance of the catechol is still unclear since, so far, it has never been detected and quantified in the plasma of cancer patients.

We investigated 12 patients with germ cell cancer treated with 2400 mg/m^2/4 days etoposide given as four short infusions over 1 h, 1500 mg/m^2/3 days carboplatin given as three short infusions over 1 h and 10 g/m^2/4 days ifosfamide as constant rate infusion. All patients received stem cell support 7 days after the beginning of chemotherapy. Twenty-three serial plasma samples were drawn and analysed for etoposide and etoposide catechol by two different reversed-phase HPLC assays using UV detection for the parent drug and electrochemical detection for the metabolite. Etoposide catechol was synthesised by mono-*O*-demethylation of etoposide [4]. The identity of the metabolite was verified by NMR and mass spectroscopy. Pharmacokinetic parameters were calculated using non-compartmental methods.

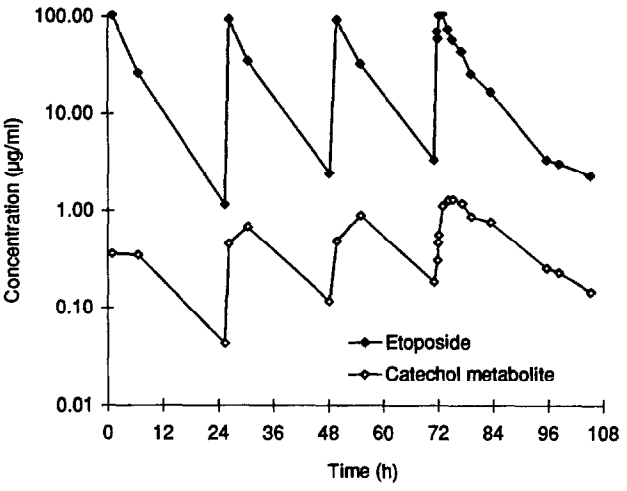

Figure 1. Plasma levels of etoposide and etoposide catechol in a representative patient receiving high-dose chemotherapy.

Etoposide catechol could be quantified in all patients up to 36 h following the last infusion of etoposide exhibiting characteristic metabolite kinetics (Figure 1). Plasma concentrations increased during therapy reaching peak values of 1.3 ± 0.5 µg/ml on the fourth day of treatment 3.4 ± 1.2 h after the start of etoposide infusion. The apparent metabolite half-life of 8.4 ± 3.0 h was only slightly longer than the corresponding half-life of the parent drug. The area under the concentration–time curve (AUC) of the metabolite reflecting its systemic exposure was calculated for the fourth day of treatment when most plasma samples were drawn. It was found to be $2.5 \pm 0.9\%$ of the AUC of etoposide.

To our knowledge, this is the first report that demonstrates that cancer patients receiving high-dose etoposide are exposed to considerable plasma levels of the cytotoxic catechol metabolite. Interindividual variability in its formation may, therefore, have clinical implications. Other anticancer agents might induce or inhibit this metabolic pathway leading to different kinetic profiles of the catechol depending on the regimen used. Future pharmacokinetic investigation should include measurements of this metabolite to reveal its contribution to tumour response as well as to treatment-induced toxicity.

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