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Palliative Effect of Gemcitabine in Osteosarcoma Resistant to Standard Chemotherapy

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GEMCITABINE HYDROCHLORIDE, 2′,2′-difluorodeoxycytidine hydrochloride (Gemzar), a chemotherapeutic antimetabolite, is a pyrimidine nucleoside analogue. Although gemcitabine is similar in structure to cytosine arabinoside, it exhibits different characteristics and pharmacology which enhance its usefulness in the treatment of patients with solid tumours. A mild toxicity profile has been observed with gemcitabine. It inhibits DNA replication by inhibiting DNA synthesis and by blocking repair mechanisms through masked chain termination. Additionally, gemcitabine exerts several other actions that self-potentiate its cytotoxic activity. Gemcitabine is usually well tolerated by patients and its common associated side-effects are not severe, and include low grade myelotoxicity, 'flu-like syndrome, fever and rash, and nausea and vomiting (Lilly Research Laboratories, Indianapolis, U.S.A. and [1–3]). Gemcitabine has demonstrated significant clinical activity and clinical responses have been noted in a variety of tumours, including pancreatic, ovarian, breast, bladder, non-small cell lung (NSCLC) and small cell lung cancer (Lilly Research Laboratories and [3]). Herewith we report an unusual effect of gemcitabine on recurrent osteosarcoma of the pubis following standard chemotherapy.

A 26 year old female with a history of papillary carcinoma of the thyroid, treated by total thyroidectomy (1991), a total dose of 130 mCi ^{131}I (end of 1991) and eltroxin (on-going), conceived for the first time. On a routine ultrasonographic fetal organ screening, performed in October 1995, a 9 cm tumour was detected in the lower part of the pelvis, attached to the pubic bone. After giving birth to a normal baby, a computed tomography (CT) scan of the pelvis demonstrated a 15 cm necrotic tumour destroying the right pubic bone, compressing the bladder and the small bowel, but not invading the pelvic structures. A magnetic resonance imaging (MRI) study revealed involvement of the abdominal wall by the tumour. A ^{131}I whole body scan revealed no pathological uptake. Staging studies, including a bone scan, a whole body MIBI scan, chest plain film, and a CT of the abdomen and chest were negative for metastases. A biopsy, performed in January 1996, demonstrated a high grade fibroblastic osteosarcoma. Pre-operative chemotherapy, consisting of two courses of cyclophosphamide, vincristine, doxorubicin and dacarbazine (CyVADIC) followed by one course of cisplatin plus doxorubicin were administered. Marginal resection of the tumour, pelvic and retroperitoneal lymphadenectomy, resection of the right pubis, partial resection of the right acetabulum and femoral head, partial resection of the bladder and the abdominal wall were carried out in March 1996. Pathologically, only 25% of the 24×17.5×10 cm resected osteosarcoma was necrotic. Two courses of postoperative chemotherapy, including doxorubicin (70 mg/m^2/2 days), cisplatin (100 mg/m^2/day), methotrexate (10 gm/m^2/day), and ifosfamide plus mesna (each 8 gm/m^2/5 days) were administered until October 1996, when the patient complained of increasing pain in the right hip joint and lower pelvis. Her narcotic consumption was at that time morphine-controlled release tablets (MCR) 360 mg/day and morphine-immediate release (MIR), given PRN, 180 mg/day, together with nimesulide 200 mg/day. Her Karnofsky's performance status was 50%, spending most of the time in a wheel-chair. CT studies demonstrated a recurrent lower pelvic mass involving the lower abdominal wall and the right labia majora. A bone scan showed pathological uptake in the pubis and the right acetabulum. No metastases were evident in either study. Weekly gemcitabine 1000 mg/m^2 for 7 consecutive weeks every 8 weeks was started in December 1996, after being approved for this case by the ethical committee of the hospital. Towards the end of the second cycle, a marked reduction in the narcotic consumption, taken for the previous 3.5 months, was reported (MCR 260 mg/day with no MIR and no nimesulide) together with improvement in the quality of life, i.e. improved performance status (70%), using crutches for walking instead of a wheel-chair, hair re-growth, improved appetite and a feeling of well-being. A CT scan of the pelvis demonstrated stabilisation of the pelvic tumour. The third course was characterised by weakness, mild papular rash, swelling of the lower limbs (deep vein thrombosis was excluded), afebrile neutropenia (900/mm^3), asymptomatic thrombocytopenia (70 000/mm^3) lasting for more than 10 days, and anaemia (Hb 7.5 g/dl) requiring blood transfusion. No alopecia or vomiting were reported. The gemcitabine dose was reduced by 20%. Towards the end of the fourth cycle, in September 1997, a bone scan showed no pathological uptake in the pubis nor in any new site. A CT scan of the pelvis, performed in November 1997, showed tumour stabilisation.The treatment is to be continued until disease progression or drug intolerance.

Osteosarcoma is a relatively drug-resistant neoplasm. The results of studies of the activity of single agents and of combinations of drugs against macroscopic osteosarcoma have been disappointing. Few drugs, i.e. cyclophosphamide, melphalan, mitomycin C, dacarbazine and actinomycin-D, have produced responses in 15% of patients, and most responses were partial. Notable exceptions are the responses rates of 30–40% observed in trials with doxorubicin, cisplatin high-dose methotrexate (HDMTX) with leucovorin rescue, and more recently, ifosfamide in a standard to high doses [4]. Although no data regarding the use of gemcitabine in osteosarcoma are available in the literature, we use this agent in our patients for several reasons. Gemcitabine has been found to be active on

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xenograft of soft tissue sarcoma growing in nude mice [5]. It has a documented activity in relatively chemoresistant diseases, such as cancer of the pancreas [1, 2], and a palliative role in other malignancies [6]. Finally, it was the hopeless prognosis of our young patient with relapsing osteosarcoma while under chemotherapy that led us to the enthusiastic application of one of the available new and unexplored agents [4]. Our experience in this unique case of osteosarcoma points to several facts. Gemcitabine was found to be effective in achieving stabilisation and even a minimal response of an osteosarcoma refractory to standard chemotherapy consisting of doxorubicin, high-dose methotrexate, cisplatin and ifosfamide. Although disease stabilisation is generally accepted as failure of chemotherapy, in this rare case it should be regarded as success in view of the failure of other drugs, Gemcitabine administration also resulted in a clear clinical benefit response, manifested by improvement of quality of life, reduction of narcotic consumption, restoration of mobility, improvement of the Karnofsky performance status, and recovery from previous alopecia. The toxicity profile was low and included mild myelotoxicity, limb oedema and rash. It is clear that no treatment recommendations can be made on the basis of a single case report. However, it may be warranted to investigate the activity of gemcitabine in other patients with refractory osteosarcoma.

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Severe Anaphylactic Reactions to Oxaliplatin

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OXALIPLATIN (L-OHP, *trans*-L-1,2-diaminocyclohexane oxaliplatinum), is a new platinum compound which has shown *in vitro* and *in vivo* antitumoral activity in colorectal cancer. Oxaliplatin has been largely studied in patients with metastatic colorectal cancer. Administered as a single agent, the response rate according to WHO criteria is 10% in patients resistant to 5-fluorouracil (5-FU) and 27% in previously untreated patients [1]. A synergy with 5-FU has also been demonstrated, with constant-rate or chronomodulated infusions [2, 3]. The toxicity profile of oxaliplatin is different from cisplatin: there is no renal or auditory toxicity and the main dose-limiting toxic effect is a cumulative sensitive peripheral neuropathy. Other toxic effects include mild myelosuppression [1, 2].

We report that anaphylactic reactions to oxaliplatin can occur and be life threatening. The first case occurred in a 59 year old man treated for metastatic colon adenocarcinoma. After failure of a 5-FU–leucovorin combination after five cycles, he was included in a phase II study with high-dose leucovorin and 5-FU in continuous infusion combined with oxaliplatin (100 mg/m^2) every 2 weeks. Six cycles passed uneventfully. Immediately after the beginning of the seventh cycle 2-h infusion of oxaliplatin, the patient complained of a burning sensation of the neck and the face with a flush, shortness of breath, sweating and dizziness. Oxaliplatin was immediately discontinued. Clinical examination revealed a reduced systolic blood pressure (SBP < 50 mm Hg) and urine loss. He was consequently treated with intravenous dexamethasone, epinephrine, macromolecules and nasal oxygen. He fully recovered 9 h after the accident. Two weeks later, the same regimen was reintroduced with a longer perfusion time of oxaliplatin. As soon as the drug was delivered, the patient developed the same symptoms. The drug was definitively withdrawn.

Currently, we have observed four additional cases with the same severe anaphylactic reaction (see Table 1). The estimated frequency is 2%.

Anaphylactic reactions to cisplatin have already been described. The reactions consist of facial oedema, wheezing, tachycardia and hypotension within a few minutes of intravenous administration [4]. Carboplatin has also been shown to be responsible for allergic reactions. Based on skin test reactivity, it has been shown that there is a cross-reactivity

Table 1. *Five cases of anaphylactic reactions to oxaliplatin*

Age	Sex	Cycle	Oxaliplatin dose (mg/m^2)	Symptoms
59	M	7	100	Reduced SBP, flushing, sweating, dizziness, burning sensation
77	M	8	100	Reduced SBP, flushing, sweating, mouth pricking sensations. Same symptoms at reintroduction
64	F	5	85	Reduced SBP, flushing, sweating
75	F	8	85	Reduced SBP, tachycardy, sweating
70	M	12	100	Reduced SBP, flushing, headache, tachycardy, respiratory distress

SBP, systolic blood pressure.