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Letters

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Mixed Response to Chemotherapy, a New Entity in Soft Tissue Sarcomas

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SOFT TISSUE sarcomas only account for 1% of all malignancies. They tend to spread haematogenously [1]. Numerous studies on systemic chemotherapy to control these distant metastases have been performed [2–4], all using common WHO criteria for reporting responses. Mixed response to systemic therapy is a well known entity in other malignancies, but was previously never reported for soft tissue sarcomas. However, between 1991 and 1994, we observed mixed responses to chemotherapy in 4 patients with advanced soft tissue sarcomas.

Patient 1 was a 46-year-old woman with a resected gastric epitheloid leiomyosarcoma. She was found to have a tumour in the right upper lobe of the lung, histologically proven to be a metastasis of a leiomyosarcoma. The patient was treated with doxorubicin (DX) 75 mg/m^2 intravenous (i.v.) and 24-h continuous infusion ifosfamide (Ifos) 5 g/m^2 on day 1, with GM-CSF (granulocyte-macrophage colony stimulating factor) 250 μg/m^2/day on days 3–17, cycles given every 3 weeks. After two cycles, a minor regression of the lung metastasis was observed. After two additional courses, there was further regression of this lesion, but with coinciding occurrence of a new (histologically confirmed) lesion in the left lung, thus qualifying for mixed response.

Patient 2, a 52-year-old woman with a uterine leiomyosarcoma grade III, developed lung metastases observed on a chest X-ray and cytologically proven to originate from the sarcoma. She was treated with the same chemotherapy as patient 1. Disease initially stabilised, but progressed after seven courses. Because of this, chemotherapy was changed to cisplatin (CDDP) 100 mg/m^2 plus docetaxel 75 mg/m^2 given once every 3 weeks. After the third cycle, there was a mixed response with the chest X-ray showing that several lesions in the right lung were regressing, while at the same time other pulmonary metastases were progressing (Figure 1).

Patient 3 was a 35-year-old man who was diagnosed as having a malignant fibrous histiocytoma of the left thigh with pulmonary metastases. For local control the patient was treated by limb perfusion with tumour necrosis factor-α (TNFα), interferon-α and melphalan, but he refused systemic chemotherapy. After 5 months, there was progression of the lung lesions, and the patient requested to be treated with chemotherapy. He received DX 50 mg/m^2 i.v. plus 24-h continuous infusion Ifos 5 g/m^2 on day 1, cycles given every 3 weeks. After four cycles, there was a minor regression of lung metastases noted on the CT-scan, with coinciding occurrence of a mass in the left groin, proven to be a metastasis with the same histology. Despite this mixed response, treatment was continued. After a further five cycles, all lesions progressed and new lung lesions developed. Chemotherapy was switched to docetaxel 100 mg/m^2 given every 3 weeks. The evaluation after the third cycle of docetaxel showed a partial remission of all lesions except one, confirmed by independent external review. The non-responding, left pericardial lung lesion was progressing, and thus this patient again had a mixed response.

Patient 4, a 31-year-old man, was diagnosed as having an epitheloid sarcoma grade III of his left buttock. Staging revealed multiple lung metastasis on both sides. The patient was given chemotherapy with the same regimen as patients 1 and 2. The first evaluation after the second cycle showed stable disease. After four cycles, the mass of the left buttock was stable, and the chest CT-scan showed lung metastasis in regression, except for one lesion, adjacent to the proximal part of the aorta thoracalis, which was progressing.

Soft tissue sarcomas are rare diseases. Because of this, chemotherapy is usually restricted to clinical trial programmes, always using standard WHO criteria for reporting responses [5]. Although response rates in soft tissue sarcomas at best range to 45% [4], they are high enough to enable the observation of unusual responses. Nevertheless, mixed responses to chemotherapy (well known entities in other diseases) have never previously been reported for soft tissue sarcomas. In our hospital, where all patients with soft tissue sarcoma are treated within clinical trials, we did not observe any mixed response in 151 patients receiving chemotherapy between 1980 and 1990, but

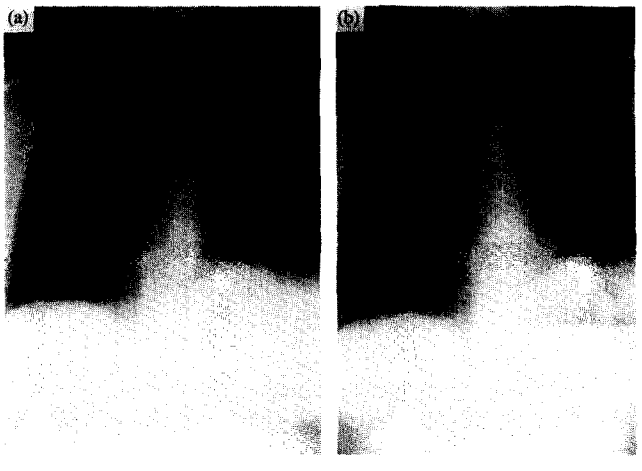

Figure 1. Chest X-ray before treatment (a) and after three cycles (b) showing regressing peripheral lung metastases in the right lung, while the right hilar mass and the lesion in the left lung progress.

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the 4 cases (4.6%) of mixed response reported here were seen among the 87 ptients treated between 1991 and 1994. The mechanism underlying the occurrence of mixed response can only be speculated on. Whether different clones of tumour cells have a different sensitivity to chemotherapy, which in turn may be related to proven differences between tumour cells in overexpression of P-glycoprotein [6], remains to be elucidated. However, other, yet unknown factors may be as important. Although mixed response to chemotherapy for soft tissue sarcomas remains a rare experience, physicians should be aware of the possibility of this type of response.

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Mitoxantrone, 5-Fluorouracil and Leucovorin in Metastatic Breast Cancer

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THE DRUG regimen containing mitoxantrone, 5-fluorouracil and leucovorin (MFL), first described by Hainsworth and associates [1] has been widely applied in metastatic breast cancer [2–10]. We report our results with this regimen since the responses in our study in anthracycline-pretreated patients differ from other published data [1–3, 7–10].

We treated 33 patients with metastatic breast cancer with the MFL regimen as first- to fourth-line chemotherapy, consisting of mitoxantrone (12 mg/m^2 intravenous (i.v.) bolus on day 1), 5-fluorouracil (350 mg/m^2 i.v. bolus on days 1–3) and leucovorin (300 mg over 1 h before 5-FU, i.v. on days 1–3), repeated every 3 weeks. In the case of leucopenia $< 3000/\mu l$ or thrombocytopenia $< 100\,000/\mu l$, chemotherapy was delayed for 1 week. If there was no recovery, the dose of mitoxantrone was reduced to 75%. If further toxicity occurred in subsequent courses, stepwise reduction by 25% of the initial mitoxantrone dose was performed. Because of age (> 70 years), toxicity from previous chemotherapy or extensive radiotherapy in 9 patients, the initial mitoxantrone dose was set at 9 mg/m^2 and reductions as above were applied. Response was evaluated after two or three cycles and again after five or six cycles if no progression occurred. 31 patients were evaluable: treatment was first-line in 11, second-line in 12, third-line in 7 and fourth-line in 1 patient. There were 9 patients who had previously received anthracycline treatment, and MFL was third-line therapy for most of those (7/9). 2 patients, not evaluable for response due to protocol violation, are included in the report on toxicity. Evaluable patients' characteristics and their response to MFL are shown in Table 1.

32% (10/31) of patients (95% confidence interval: 15–48%) showed an objective response, all partial. 42% (13/31) had stable disease and 26% (8/31), all heavily pretreated patients, had progression. Of the evaluable patients receiving 9 mg/m^2 mitoxantrone from the start, two were partial responders, three had stable disease and 3 had progressive disease. When MFL was used as first-line therapy, the response rate was 72%. In the subgroup of patients receiving MFL as second-line therapy only, without previous anthracyclines, the response was reduced to 18%. No response was seen after an anthracycline-based chemotherapy for metastatic disease. The mean duration of response was 7 months (range 4–10) from the start of treatment. Toxicity (WHO criteria), being assessed in 164 chemotherapy cycles, was generally mild, with myelosuppression causing a dose reduction in 24% of cycles. Alopecia grade 3 was never recorded. Nausea and/or vomiting appeared in 13% of patients.

This report on MFL reveals the benefits and major limitations of the regimen. Toxicity is limited. The overall respone rate of 32% is lower than the 65% reported by Hainsworth and associates [1], due to differences in patients' selection. Indeed, Hainsworth's group preferred MFL as second-line therapy. Only 6% of those patients had previous anthracycline treatment for metastatic disease, never within 6 months from MFL, whereas in our evaluable population, 29% had previous anthracyclines of which one-third had received this within 6 months.

Compared with studies of only anthracycline-pretreated patients, with responses from 38 to 59% [2, 3, 7–10], our 0% response in this subgroup is strikingly low. It remains to be proven that bolus instead of infusional 5-fluorouracil administration accounts for this poor response, as suggested by Jolivet and associates [4]. We conclude that MFL is a well tolerated and active regimen as first-line therapy for metastatic breast cancer. Previous treatment with anthracyclines compromises the response rate of the regimen and should, therefore, be avoided.

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