

## Low-dose prednisone and increased risk of development of bone metastases

Marini et al. report that low-dose continuous prednisone (7.5 mg/day) added to adjuvant CMF chemotherapy is associated with an increased risk of development of bone metastases [1]. As suggested by the authors, this puzzling observation could be due to the effects of corticosteroids on bone metabolism. This is even more disturbing that corticosteroids are more and more used in oncology, notably for the control of emesis [2]. The authors suggest that inhibition of cytokines in bone by steroids could impair the organ specific natural anti-neoplastic activity.

More specifically, there are data to suggest that this possible relationship could be due to increased bone resorption induced by the corticosteroids. It has been demonstrated that the administration of comparable doses of corticosteroids enhances bone resorption and induces a significant bone loss [3, 4] and a stimulation of bone resorption could well be important for the development of bone metastases and the pathophysiology of tumor-induced osteolysis [5].

The propensity of breast cancer cells to metastasize and proliferate in bone could be due to the rich supply of relevant growth factors present in the skeletal microenvironment. This 'seed and soil' concept has been recently reviewed [6]. Breast cancer cells (the 'seed') appear to secrete factors such as parathyroid hormone-related protein (PTHrP) potentiating the development of metastases in the skeleton which constitutes a fertile 'soil' rich in cytokines and growth factors that can stimulate breast cancer cell growth. Local production of PTHrP and of other osteolytic factors such as transforming growth factors (TGFs) by cancer cells in bone would stimulate osteoclastic bone resorption by inducing osteoclast differentiation from hematopoietic stem cells and/or by activating mature osteoclasts already present in bone. Increased osteoclast activity would then cause local foci of osteolysis, which could further stimulate cancer cells proliferation since products of bone resorption can enhance tumor cell growth [5–7]. This reasoning actually forms the basis for the use of bisphosphonates in cancer patients to target bone-resorbing cells for the treatment and the prevention of tumor-induced osteolysis [8].

The data of Marini et al. indicate that it is appropriate to investigate the deleterious effects of the use of corticosteroids on bone metabolism in cancer patients, especially concerning a possible increase in the incidence of bone metastases. If these data are confirmed, they would have obvious important clinical implications, especially since the introduction of potent bisphosphonates in our therapeutic armamentarium that can prevent glucocorticoid-induced osteolysis [9–10].

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## Ifosfamide encephalopathy and methylene-blue: A case report

Ifosfamide is one of the most widely used alkylating agents. Before mesna was introduced, its dose-limiting toxicity was haemorrhagic cystitis, but at present, neurotoxicity is one of its most worrisome side effects. Ifosfamide-induced encephalopathy (IIE) is a dose-dependent condition reported to have been fatal in a number of patients [1, 2]. IIE is more frequently seen in patients with renal and liver dysfunction, low levels of serum albumin, pelvic disease, poor performance status, prior central nervous system alterations (metastases, radiotherapy) and previous treatment with cisplatin. It also seems to be more common in female and elderly patients. Küpfer et al. have suggested the use of methylene-blue (MB) for both the treatment and prophylaxis of this toxicity. They found excessive urinary excretion of glutaric acid and sarcosine in a patient with IIE [3]. These can be detected in type II glutaricaciduria, an intrinsic flaw probably due to a deficiency in electron-transferring flavoprotein or in its dehydrogenase. Acyl-CoA dehydrogenases cannot transfer their electrons to the respiratory chain and become ineffective, leading to the accumulation of toxic metabolites. MB might oxidize the reduced dehydrogenases and allow further oxidation of the enzyme substrates [4]. We report a case of ifosfamide-induced encephalopathy successfully treated with methylene-blue.

The patient was a 46-year-old woman with stage IV ovarian carcinoma (pleural effusion with malignant cytology), and bulky pelvic and peritoneal disease. She had previously received four cycles of a carboplatin-cyclophosphamide regimen, with disease progression, followed by four cycles of