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Short Communication

Acute Effects of Pamidronate Administration on Serum Levels of Interleukin-6 in Advanced Solid Tumour Patients with Bone Metastases and their Possible Implications in the Immunotherapy of Cancer with Interleukin-2

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Bisphosphonates are potent inhibitors of bone resorption and are commonly used in the treatment of bone metastases. In addition, they seem to influence cytokine secretion. Since the efficacy of IL-2 cancer immunotherapy, in part, depends on endogenous cytokine secretion, bisphosphonates could be effective in modulating IL-2 activity. High pretreatment levels of IL-6 seem to correlate with resistance to IL-2. On this basis, a pilot study was performed to evaluate the *in vivo* effects of the bisphosphonate, pamidronate, on blood levels of IL-6. The study included 7 patients with bone metastases due to solid tumours. Pamidronate was injected intravenously at 60 mg over 3 h. Venous blood samples were drawn before, at 1-h intervals during pamidronate infusion, then after 1 and 3 days. Mean serum levels of IL-6 significantly decreased during pamidronate infusion. After 1 and 3 days, IL-6 mean levels still remained lower than control level, but differences were not significant. This preliminary study shows that pamidronate infusion induces a rapid but transient decline in IL-6 blood concentrations, and suggests a possible use of bisphosphonates to modulate the efficacy of IL-2 cancer immunotherapy. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: bisphosphonates, immunotherapy, interleukin-6, pamidronate

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INTRODUCTION

SEVERAL CLINICAL investigations have demonstrated that the antitumour effect of interleukin-2 (IL-2) depends on host immune status, particularly cytokine secretions [1–4]. In particular, it has been shown that high pretreatment blood levels of interleukin-6 (IL-6) correlate with resistance to IL-2 antitumour therapeutic activity [5, 6]. Therefore, therapeutic strategies capable of reducing IL-6 levels could enhance the efficacy of IL-2. Currently, both chemotherapeutic and biological strategies have been shown to inhibit IL-6 secretion. Several cytokines appear to have an inhibitory effect on IL-6 production, including IL-4 [7], IL-10 [8] and IL-13 [9], as does cisplatin, which my be one of the mechanisms responsible for cisplatin-induced enhancement of IL-2 efficacy in the immunotherapy of human neoplasms [11]. In addition, recent data suggest that modulation of cytokine secretion may also be achieved through the administration of bisphosphonate agents [12], which are commonly used in the palliative therapy of bone metastases. However, they could also be used to modulate the biological response to IL-2 cancer immunotherapy, because of their potential inhibitory effect on IL-6 release.

This pilot study was carried out to investigate the effects of an acute infusion of bisphosphonates on IL-6 blood concentrations in patients with advanced solid tumours with bone metastases.

PATIENTS AND METHODS

The study was performed in 7 patients with advanced solid tumours with multiple bone metastases. The characteristics of patients are reported in Table 1. Patients were

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Table 1. Characteristics of bone metastasis patients treated by pamidronate infusion

Characteristic	
n	7
M/F	4/3
Median age (years)	68 (46–73)
Median Karnofsky score	70 (40–80)
Tumour histotype	
Non-small cell lung cancer	4
Breast cancer	1
Colon cancer	1
Cervix carcinoma	1
Metastases other than bone locations	
No other location	3
Lung metastases	1
Liver metastases	3
Previous chemotherapy	7

studied during the first administration of the bisphosphonate agent, disodium pamidronate, as palliative therapy for bone metastases. No patient was under therapy with cytotoxic or hormonal agents during the study. Disodium pamidronate was given at a dose of 60 mg in 250 ml of 5% glucose over a 3-h intravenous infusion starting at 8.00 a.m. To evaluate IL-6 levels, venous blood samples were collected before the onset of the infusion, and at 1-h intervals until the end of the infusion. Moreover, venous blood samples were drawn in the morning after 1 and 3 days. On a separate occasion, venous blood samples were collected during a saline infusion as a control. Serum levels of IL-6 were measured in duplicate by an immunoradiometric method and commercial kits. Normal values of IL-6 (95% confidence limits) obtained in our laboratory were less than 35 pg/ml. Data were reported as mean ±SE, and statistically analysed by the Student's *t*-test and the analysis of variance, as appropriate.

RESULTS

Mean serum levels of IL-6 observed in patients before and during the pamidronate infusion are illustrated in Figure 1. Abnormally high pretreatment serum levels of IL-6 were observed in 5/7 patients, while they were within the normal range in the other 2 patients (lung cancer: 1; colon cancer: 1). A decrease greater than 30% in IL-6 concentrations occurred during pamidronate infusion in 6/7 patients, including both patients with normal pretreatment values of IL-6. Moreover, mean serum levels of IL-6 observed during pamidronate infusion were significantly lower with respect either to the pretreatment values or to the values found with saline infusion alone ($P < 0.05$). The minimum mean levels were seen after 2 h of infusion. After completion of the pamidronate infusion, a rapid increase in IL-6 levels occurred in the 2 patients who had had normal pretreatment values of IL-6. Moreover, as illustrated in Figure 1, mean concentrations of IL-6 observed at days 1 and 3 of the post-treatment period were not significantly different from those seen before pamidronate infusion, although they remained lower than the control saline values and the mean pretreatment values. No pamidronate-related toxicity was observed.

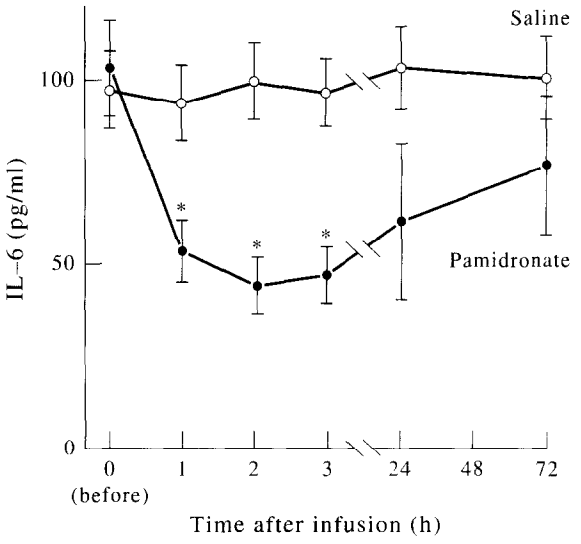

Figure 1. Mean serum levels (±SE) of IL-6 during pamidronate infusion or saline alone in 7 cancer patients with bone metastases. *P value <0.05, pamidronate treated verses 0 h; pamidronate treated versus saline.

DISCUSSION

This pilot study shows that pamidronate infusion can induce a rapid but transient decline in IL-6 mean blood concentrations in patients with bone metastases due to solid tumours. The results of this study, which have to be confirmed in a greater number of patients, disagree with those previously reported by other authors [13], where bisphosphonates were shown to stimulate IL-6 secretion. These controversial data could depend on the different schedule of treatment and/or on the different timing of blood sampling. Moreover, since a rapid increase in IL-6 levels occurred in our study in the 2 patients with normal pretreatment values of IL-6, it is possible that the effects of bisphosphonates on IL-6 secretion may depend, at least in part, on host IL-6 production itself.

Bisphosphonates have been shown to have some benefit for patients suffering from multiple myeloma [12]. Our results indicate that, since IL-6 has been proven to be a growth factor for myeloma cell proliferation [14], the therapeutic effect of bisphosphonates in myeloma patients could depend, at least in part, on their inhibitory effect on IL-6 production. Moreover, the inhibitory effect of bisphosphonates on IL-6 secretion is also suggested by their inhibitory action on monocyte proliferation in experimental conditions [12], since monocyte proliferation is stimulated by IL-6 [14].

The influence of bisphosphonates on IL-6 secretion could have particular importance in the immunotherapy of cancer with IL-2. In fact, since high pretreatment levels of IL-6 appear to correlate with resistance to IL-2 immunotherapy [5, 6], bisphosphonates could be combined with IL-2 in an attempt to enhance its efficacy by reducing IL-6 blood concentrations and/or by counteracting IL-2-induced stimulation of IL-6 secretions [1–4]. However, further studies are needed to confirm bisphosphonates inhibition of IL-6. Because of their transient inhibitory effect on IL-6 levels, as shown by the present study, other schedules, different from those commonly used for the treatment of bone metastases, would have to be determined for pamidronate, as well as

with other bisphosphonates, in an attempt to achieve a chronic block of IL-6 secretion.

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