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Soluble Intercellular Adhesion Molecule-1 in Melanoma Patients Treated with Liposomes Containing Muramyl Tripeptide

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A SOLUBLE form of intercellular adhesion molecule-1 (sICAM-1) has been recently identified in patients with malignant melanoma [1]. It has been demonstrated that inflammatory cytokines can modulate the cellular expression of ICAM-1 [2] and the shedding of this molecule by cells [3–5]. To our knowledge, few data exist on serum sICAM-1 levels in cancer patients treated with immunomodulators [6]. Liposomes containing muramyl tripeptide (MLV MTP-PE) can activate monocytes from cancer patients *in vitro* and *in vivo*, making them cytotoxic for tumour cells, and increasing the serum levels of inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [7–10]. The purpose of the present study was to evaluate the levels of sICAM-1 and their possible correlation with serum inflammatory cytokine levels in melanoma patients treated with MLV MTP-PE. The sera from 9 patients with metastatic melanoma, treated with MLV MTP-PE 4 mg intravenously (i.v.) twice a week for 12 weeks, were tested using an ELISA system to detect sICAM-1, TNF-α, IL-6, IL-1β and interferon-γ (IFN-γ) before, 2 and 24 h after the first, 12th and 24th infusion of MLV MTP-PE. Baseline sICAM-1 levels were elevated in all 9 patients (median 540 ng/ml; range 400–1030). Two hours after the first infusion, serum sICAM levels were similar to baseline values; the median value was 565 ng/ml (range 250–940). Twenty-four hours after the first infusion of MLV MTP-PE, we observed an increase in sICAM-1 levels in 6 patients, a decrease in 1 and stable values in 2, and the median value at this point was 720 ng/ml (range 410–1820; $P=0.060$).

At the 12th infusion, all of the 7 evaluable patients had elevated baseline sICAM-1 levels (median 500 ng/ml: range 415–1080), and 2 h later the median value was 450 ng/ml (range 330–1440). Twenty-four hours after the 12th infusion, sICAM-1 increased in 3 patients and did not change in 4 patients; the median value was 790 ng/ml (range 495–1650; $P=0.069$).

At the 24th infusion, baseline and 2-h median values of sICAM-1 were similar (650 and 630 ng/ml, respectively) in the 6 evaluable patients. At 24 h, sICAM-1 increased in 4 of the 6 evaluable patients and remained stable in 2; the median value, which at this time point was significantly higher than baseline levels, was 802 ng/ml (range 510–1450; $P=0.045$). In order to analyse the variations in sICAM-1, the patients were arbitrarily divided into two groups according to the clinical behaviour of their tumours: 4 patients had stable disease (all lesions, 2 patients; some lesions, 2 patients; group A); and 5 patients had progressive disease (group B). In group A, sICAM-1 levels remained stable or showed a modest increase during treatment (except in 1 patient, who exhibited a substantial variation after the 12th infusion) (Figure 1a). In contrast, very high levels of sICAM-1 were observed in group B, at the beginning of the study therapy in 1 patient and after the first infusion in 3 other patients; these values remained high until the 24th infusion (Figure 1b).

In the majority of patients, TNF-α and IL-6 increased in 2 h after the first infusion, but not therafter. IFN-γ was never detected; IL-β was detectable in a few cases, but only before the infusions.

In conclusion, baseline levels of sICAM-1 were elevated in all patients, and increased further during treatment in patients with more aggressive disease. In our experience, no correlation was found between sICAM-1 and inflammatory cytokines. There were no differences in the cytolytic activity of monocytes or in the number and intensity of inflammatory episodes (fever or an increase in acute phase reactants) between the two groups of patients and, moreover, their cytokine production was also similar. Consequently, we may speculate that the higher levels of sICAM-1 observed in patients with progressive disease could

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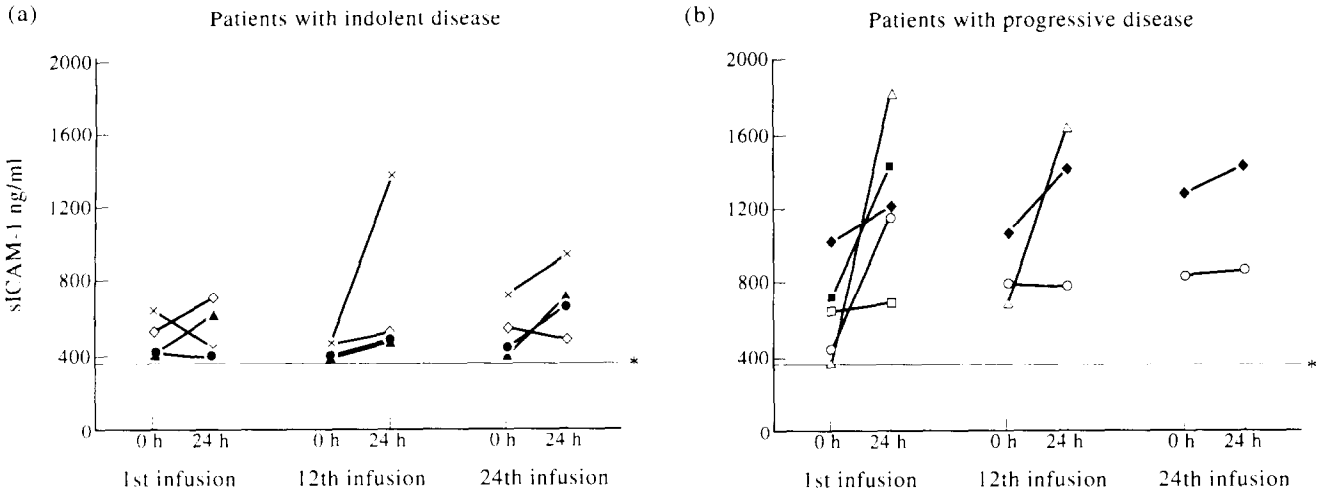

Figure 1. Serum soluble intercellular adhesion molecule-1 (sICAM-1) levels before and 24 h after the first, 12th and 24th infusion of muramyl tripeptide (MLV MTP-PE) in patients arbitrarily divided into two groups according to the clinical behaviour of the tumours. *383 ng/ml: this value represents the mean value of normal healthy donors plus 2 S.D. Values higher than this were considered elevated.

possibly be due to melanoma cells, and could represent a mechanism by which tumour cells escape from the immunological response. It would, therefore, seem that in patients with advanced disease higher levels or progressive increases in sICAM-1 may be unfavourable prognostic factors. This should be verified in a larger patient population.

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Nuclear DNA Content of Persistent Tumour Lacks Prognostic Relevance for Length of Survival in Patients Undergoing Second-look Laparotomy for Ovarian Cancer

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ACCORDING TO several studies, flow cytometric analysis of DNA content, either expressed as DNA ploidy or DNA index (DI: the ratio between the aneuploid and the diploid peak), provides additional independent prognostic information in early [1] and advanced [2, 3] ovarian carcinomas. In addition, it has been reported that there is a longer survival for patients with recurrent ovarian carcinomas that are DNA diploid than in those with DNA aneuploid carcinomas [4]. If confirmed on patients with persistent disease after cisplatin-based first-line chemotherapy, this observation could lead to better stratification of patients receiving second-line chemotherapy. Aiming at evaluating whether DNA content could provide additional information on the length of survival for patients with persistent disease after

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