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Editorial

Possible Effect of Histamine-2 Receptor Blockade on the Antitumour Response to Interleukin-2

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TREATMENT OF metastatic melanoma or renal cell carcinoma using human, recombinant interleukin-2 (rIL-2) alone or in combination with other biological treatment modalities has attracted considerable interest during recent years [1, 2]. Response rates of up to 50% have been achieved in studies comprising few patients, while the rates in larger trials range from 10 to 20% [1–3]. Because rIL-2 does not have a direct effect on cancer cells, but rather mediates its antitumour activity by altering host immune reactions, these data represent the best available evidence that immunological therapy for cancer can be effective, particularly in treatment of immunogenic tumours. Despite these promising results obtained without additional chemotherapy, the long-term survival is, however, not significantly improved. Moreover, due to the severe toxic side-effects observed in patients treated with rIL-2 based regimens, the treatment is currently restricted to selected patients [1, 2].

Consequently, major concern for prevention of the severe toxicity induced by rIL-2 [2, 3] has prompted the use of concomitant, supportive medication. Among others, the histamine-2 receptor antagonists (H-2RA), ranitidine [2] and cimetidine [4], have been administrated in the majority of published studies [5]. Considerable evidence has emerged suggesting that both ranitidine and cimetidine have immunomodulatory effects in immunocompromised patients [5, 6]. Of particular interest is the beneficial effect of these drugs in patients with cancer. Thus, cimetidine improved long-term survival in patients operated for gastric carcinoma [5], ranitidine improved trauma-, blood transfusion- and sepsis-induced immunosuppression in patients with colorectal cancer [6], improved antibody synthesis to protein and coupled protein-polysaccharide antigen challenge in patients with chronic lymphocytic leukaemia [5], improved overall immune reaction and survival, and induced tumour response in patients with liver metastasis from colorectal cancer [5]. Several mechanisms have been suggested to explain the beneficial effect of H-2RA. Currently, the immunomodulatory effect is well established and most conceivable [5, 6], and similar to the immunomodulatory effect achieved by low-dose rIL-2 [3, 5, 6]. Another possible mechanism could be blockage of H-2 receptors expressed by tumour cells [7, 8], subsequently preventing tumour cell proliferation induced by the increased histamine concentrations often detected in cancer patients [5, 8]. Finally, a third effect of ranitidine and cimetidine could be their action as powerful oxygen free radical scavengers [6], possibly preventing free radicals to participate in the process of changing normal, healthy tissue to growth medium for tumour cells [5, 6].

Toxic side-effects induced by rIL-2, such as fever, hypotension, pruritus, microedema, arthralgia, arrhythmia etc., appear to be related to release of monocyte-derived pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), prostaglandin E_2 (PGE_2) and granulocyte-macrophage colony stimulating factor (GM-CSF) [3]. However, toxicity could also be related in part to basophil-derived pro-inflammatory substances and cytokines, including histamine, serotonin, elastase, prostaglandins, leukotrienes, platelet activating factor (PAF), superoxide anions, TNF-α and chemotactic factors for lymphocytes, neutrophils and eosinophils [9]. Consequently, leucocytes may be recruited from the bone marrow, and subsequently, histamine released by basophils may stimulate release of the hypertoxic mediator, eosinophil cation protein, by action on H-2 receptors expressed by eosinophils [9]. This assumption seems to be supported by the well known eosinopholia and lymphocytosis observed in patients receiving rIL-2 based immunotherapy [3]. In fact, we have shown rIL-2 to induce *in vitro* histamine release by leucocytes taken from healthy volunteers and patients with untreated colorectal cancer in a dose-dependent manner (Nielsen *et al.*, unpublished). Furthermore, the histamine release was twice as high in leucocytes from colorectal cancer patients compared to healthy volunteers after incubation with equal amounts of rIL-2. This may suggest leucocytes to be more vulnerable in cancer patients than in healthy persons [5, 8]. Moreover, it has recently been shown that exogeneous IL-2 increases H-2 receptor expression on CD8+ T-lymphocytes and that these cells subsequently inhibit *in vitro* antibody synthesis [10]. Incubation with cimetidine was shown to antagonise the IL-2-induced inhibited antibody synthesis [10]. These results indicate that rIL-2 may stimulate both monocyte, basophil and eosinophil synthesis and release of pro-inflammatory cytokines, and the action of some of these molecules may be antagonised by H-2RA [5, 6, 8]. Finally, several experimental studies have shown a synergistical effect of H-2RA and rIL-2 on both immune modulation and antitumour activity [5, 6].

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Human rIL-2 apparently induces objective tumour response, particularly in immunogenic tumours, via its immunomodulatory effects [2, 3]. This indicates a possible basis for immune response to tumours, and through this, its exploitation for prevention and treatment. However, based on the emerging knowledge of the immunomodulatory and antitumour activity of H-2RA [5, 6, 8], results from some previous rIL-2 based studies may be difficult to translate, because ranitidine and cimetidine, given as supportive medication for the purpose of attenuating toxic side-effects of rIL-2 may also have induced immunomodulation as well as antitumour response. As treatment of some malignant diseases with biological response modifiers may be advantageous, future studies should be stimulated to consider the eventual synergistical, beneficial effect of low-dose IL-2 [3] in combination with H-2RA [5, 6, 8].

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