Cancer Cell International

BioMed Central

Poster presentation

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Addition of histamine to IL-2 treatment augments T1 cell-function in melanoma patients *in vivo*: results from a randomized clinical trial of IL-2 with or without histamine (MP 104)

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from Association for Immunotherapy of Cancer: Cancer Immunotherapy – 2nd Annual Meeting
Mainz, Germany, 6–7 May 2004

Published: 1 July 2004

Received: 28 April 2004

Cancer Cell International 2004, **4**(Suppl 1):S47

This article is available from: http://www.cancerci.com/content/4/S1/S47

Histamine is used as an adjunct to interleukin-2 (IL-2) in tumor immunotherapy due to its protective effect on NK and T cell inhibition by monocyte-derived reactive oxygen metabolites *in vitro*. Results from a first randomized phase III trial showed an increase in survival in stage IV melanoma patients with liver involvement (Agarwala SS, *J Clin Oncol* 2002, **20**). Here we have analyzed the effect of histamine on T cell cytokine production in patients treated with IL-2 without or with histamine within a second randomized multicenter phase III trial. A significant increase (mean 2.2-fold) in frequencies of CD3+ T cells producing IFN-γ (T1 cells) in response to mitogen stimulation was detected in patients treated with histamine plus IL-2 (n = 7 patients) while IL-2 alone (n = 10 patients) had no effect on the frequency of IFNγ-producing CD3+ T cells. In contrast, frequencies of CD3+ T cells producing IL-13 (T2 cells) significantly increased in patients receiving IL-2 (mean 2.7-fold) and this effect was not modulated by histamine (mean increase 2.9-fold). These effects were observed for both CD3+CD8+ as well as CD3+CD4+ T cells. *In vitro* experiments using separated T cells and monocytes from healthy subjects show that while histamine does not induce IFN-γ production in T cells it protects T cells from monocyte-induced down-regulation of IFN-γ. Melanoma-specific T cell responses were analyzed in the 9 HLA-A2+ patients (IL2 + histamine, n = 4; IL-2, n = 5) against HLA-A2+ melanoma cell lines using intra-cellular cytokine staining. Induction or augmentation of melanoma-reactive IFN-γ and IL-13-producing T cells could be shown in 2 HLA-A2-positive melanoma patients treated with histamine and IL-2, but in none of the patients in the IL-2 arm. Both patients had received previous vaccination with HLA-A*0201 binding tyrosinase peptide and also tyrosinase-specific T cell responses were detected after IL-2 plus histamine treatment. In summary, treatment with histamine in combination with IL-2 increases T1 responses and stimulates melanoma-specific T cells.