Effects of Interleukin-2 Treatment on CD1d-Restricted Natural Killer T Cells

To the Editor: Interleukins (IL) are potent biomolecules used for immunotherapy in cancer and infectious diseases. The clinical benefit of cytokines is linked to their strong effects on immune cells, and these effects are important to study in patients undergoing treatment because the cellular responses in vivo may differ from those seen in vitro. We therefore read with interest the study by van der Vliet et al. (1) concerning the effect of high-dose IL-2 on immunoregulatory cell subsets in patients with advanced melanoma and renal cell cancer. The main conclusion presented by the authors is that CD25+ regulatory T cells, which have an inhibitory effect on adaptive T-cell responses, increased during therapy. Conversely, the CD1d-restricted natural killer T (NKT) cells, which have mainly activating effects on other immune cells, decreased in numbers during therapy. One might speculate that such effects of IL-2 could suppress some cellular immune responses against the tumor and thus be detrimental to the patient.

The negative effects on NKT cells reported in this study are, however, in apparent contrast to the expansion of these cells we have observed recently in patients with primary human immunodeficiency virus-1 infection undergoing IL-2 treatment in conjunction with effective antiretroviral therapy (2). We observed a significant increase in absolute NKT cell counts over the course of 12 months without detectable changes in the CD4+/CD4- NKT cell ratio. There are several possible explanations to the contrasting results in the two studies. First, there may be disease-specific factors that affect the response to IL-2, which differ between these conditions, although both human immunodeficiency virus-1 infection and cancer are associated with NKT cell loss (3, 4). Second, treatment protocols probably differ with lower doses given to human immunodeficiency virus-1 patients.

However, the third and most likely explanation to the contrasting results is the timing of samples taken for study. van der Vliet et al. analyze samples drawn from patients immediately before and after two cycles of IL-2 given just 1 week apart (1, 5). The decrease in NKT cells directly after 5 days of high-dose IL-2 may reflect an acute response to massive IL-2 exposure, and assessment of what happens to the cells over time may be more immunologically relevant. Indeed, the data indicate that already at the "pre 2" time point, the absolute counts of NKT cells have actually increased. Data from additional time points may shed light on this, if such samples are available. It would certainly be important to determine if there is a consistent NKT cell response to IL-2 in vivo or if human immunodeficiency virus–infected subjects and cancer patients respond differently to this treatment.

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References
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