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

In Response: We thank our colleagues for their letter and discussion. Sandberg and Moll note that interleukin-2 (IL-2) combined with highly active antiretroviral therapy (HAART) administered over 1 year for human immunodeficiency virus infection results in increased iNKT cells (1) and suggest that a similar effect might occur with high-dose IL-2 for cancer. They propose that although chronic infection with human immunodeficiency virus and IL-2 dosage may contribute to the different effects on iNKT levels, their later follow-up is “the most likely explanation…” There are several difficulties in comparing the two studies. We suspect the first two differences they cite as contributing are key. Chronic infection with human immunodeficiency virus is known through their work as well as ours and others to rapidly deplete iNKT (2–4), partly although not completely explained by direct infection of CD4+ iNKT (3–5) and lower IL-2 dosage over a longer period for human immunodeficiency virus (>10-fold higher dose for cancer, also known to produce much more severe side effects). Furthermore, in their human immunodeficiency virus study, the patients receiving IL-2 also received HAART and we have shown that antiretroviral therapy increases iNKT levels (6). This was also seen in the Moll study (1), but the addition of IL-2 resulted in higher iNKT levels. Examination of the effects of long-term use of low-dose IL-2 alone in this setting would be informative. Interruptions in HAART have been tried in the context of other trials. Therefore, although we agree that follow-up time may contribute to different observations, differences in disease, other medications, and dosage are major factors.

As they point out, one could speculate that the transient change in circulating iNKT levels may have deleterious consequences. We noted a relative increase in DN iNKT after the 1st week of HD IL-2, which would not be expected to be detrimental for cancer patients. Additionally, we observed an increase in the total number of iNKT before the second HD IL-2 administration and actually a nonsignificant decrease after the first administration. The latter might reflect a higher responsiveness of conventional T cells to IL-2 (compared with iNKT) that would be reflected as a decrease in the iNKT percentage of total lymphocytes.

We agree that data from longer-term follow-up may be informative. However, in this patient population, a significant number of patients have progressed by even 6 to 8 weeks and are receiving other treatment modalities that may affect their lymphocyte subsets. Long-term follow-up is unfortunately not practical for most patients given high-dose IL-2. We did look at 2 months posttreatment in limited numbers of evaluable patients and did not observe an increase in iNKT percentage compared with baseline.

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References

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