CD39 as a Novel Marker of In Vivo Immune Activation

To the Editor:

We read with interest the review on lowest-dose interleukin-2 (IL-2) immunotherapy by Smith. Various IL-2-mediated effects provide evidence for a nonlinear dose-response curve with biologic and therapeutic activity far below maximum cytokine levels tolerated in humans. The key aspect of therapeutically administered IL-2 is an appropriate in vivo activation of IL-2-responsive cell populations, ie

B cells, T cells, and natural killer (NK) cells. CD39 represents a novel lymphocyte activation antigen on both T and NK cells, with potential relevance for the monitoring of in vivo immune activation. Delayed induction and prolonged expression of CD39 presents a unique feature when compared with established leukocyte activation antigens such as CD25 and CD7. However, the in vivo relevance of CD39 on spontaneously and therapeutically activated T and NK cells has not been studied in detail.

We analyzed CD39 expression in 103 patients with advanced malignancies (77 renal cell carcinomas, 13 melanomas, 8 colorectal carcinomas, 2 mesotheliomas, 1 B-cell lymphoma, 1 malignant fibrous histiocytoma, and 1 malignant schwannoma) receiving an immunomodulatory therapy consisting of low-dose recombinant IL-2 (rIL-2) at doses between 4.8 and 18.0 Mio IU/m²/day administered subcutaneously. Because CD39 is constitutively expressed on B lymphocytes, only the number of CD39⁺ peripheral blood lymphocytes exceeding CD20⁺ B cells was evaluated. Absolute cell counts were enumerated before, during (week 3), and after one treatment course (week 7) using flow cytometry. Effective therapeutic immune activation was monitored by measuring the clinical response of the lymphocytes with maximum levels in patients who achieved complete response groups. Patient subgroups exhibited no statistically significant differences as to sex and age.

We observed a generalized expansion of circulating CD39⁺ lymphocytes with maximum levels in patients who achieved complete or partial tumor remission on therapy. This increase relates to de novo expression on both T and NK cells. However, in this study, no further subdivision was made between those two cell types. Therefore, in vivo relevance of CD39 for the immunomonitoring of other diseases, including chronic immune disorders and infections.

**Fig 1.** rIL-2 induction of circulating CD39⁺ T or NK cells in vivo. Circulating CD39⁺ T or NK cells were enumerated as CD39⁺ lymphocytes exceeding the total number of B cells as measured by CD20. Absolute cell counts in correlation to treatment response before (day 0, □), during (week 3, ■), and after (week 7, □) rIL-2-based immunomodulating therapy in a total of 103 advanced tumor patients were analyzed. Mean values (+ standard errors) are given for all patients (CR/PR, n = 26; SD, n = 51; PD, n = 26). The treatment-related increase of circulating CD39⁺ cells was found to be significant in all response groups. Patient subgroups exhibited no statistically significant differences as to sex and age.

**REFERENCES**

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