INDUCTION OF LFA-1/CD11a AND ICAM-1/CD54 ADHESION MOLECULES ON NEOPLASTIC B CELLS DURING IN VIVO TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA WITH INTERFERON-α2

To the Editor:

Lymphoproliferative disorders of B cells including chronic lymphocytic leukemia (B-CLL), hairy cell leukemia (HCL), and subsets of low grade non-Hodgkin’s lymphomas have been reported to lack expression of leukocyte function antigen-1 (LFA-1/CD11a)6 and/or of intercellular adhesion molecule-1 (ICAM-1/CD54).1,5 CD11a and its specific ligand CD54 are cell adhesion molecules that play an important role in mediating cell to cell interactions during immune processes3 and lymphohematopoietic differentiation.8 It has been suggested that the low amounts of CD11a and CD54 on B-CLL and HCL cells might account at least in part for the tendency to hematogenous dissemination and tissue distribution of these disorders.1,2,4,6

Jansen et al9 have recently reported a very interesting study demonstrating that interferon-α2 (IFN-α) induced CD11a and CD54 on HCL cells both in vitro and in vivo. Induction of these adhesion molecules was accompanied by enhanced susceptibility of tumor cells to lysis by cloned cytotoxic T lymphocytes.9 The investigators also suggest that induction of CD11a and CD54 adhesion molecules may be relevant to the therapeutic effect of IFN-α in HCL patients. Because IFN-α has shown clinical activity in early stage B-CLL,10,11 with a still unclear mechanism of action, we wished to determine whether, also in this disorder, in vivo treatment with IFN-α resulted in the regulation of cell adhesion molecules on neoplastic B cells.

Three immunologically defined B-CLL patients, with stage A (Binet) or 0-I (Rai) disease, were treated with IFN-α2 (3 × 10^6 U; Schering-Plough, Milan, Italy; subcutaneously, three times a week). Serial peripheral blood samples were collected after 24 hours and then once a week during IFN-α therapy and mononuclear cells, recovered by Ficoll-Hypaque centrifugation and monocyte-depleted by plastic adherence, were studied for the simultaneous expression of CD19, CD20, and CD11a or CD54 antigens by two-color flow cytometry. Neoplastic B cells from all of the patients before therapy were CD11a- and CD54-negative (fluorescence histograms superimposable to isotypic controls; <10% of positive cells) while coexpressed CD19, CD20, and CD5 antigens and displayed clonal surface Igs with a weak intensity. After in vivo treatment with IFN-α a significant increase in CD11a-specific fluorescence on neoplastic B cells, identified by anti-CD19 and anti-CD20 antibodies, was clearly detected by flow cytometry (Fig 1, right upper panels). In two of three subjects IFN-α therapy resulted also in the induction of CD54 molecules on leukemia B lymphocytes (Fig 1, right lower panels). CD11a induction was observed within 2 weeks after the start of IFN-α therapy while induction of CD54 was already detectable after 1 week of IFN-α treatment. In one patient immunologic studies showed increased expression of CD54 already at 24 hours from the first injection of IFN-α (data not shown). The up-regulation of CD11a and CD54 molecules appeared stable (ie, detectable up to 22 months of continuous IFN-α treatment) in one patient and transient in the other two (reduction of specific fluorescence starting from 1 to 2 months after the start of IFN-α). In one of these latter subjects CD11a and CD54 density on neoplastic cells, although weaker than at the peak time (28 days), remained stronger with respect to pretherapy treatment levels up to 12 months of continuous IFN-α administration so far.

Continuous treatment with IFN-α resulted in a significant reduction of absolute lymphocyte counts by greater than 50% of pretreatment levels and of CD20+ B cells with an average count of 63,839 ± 52,681 (range 10,533 to 169,200) and 26,828 ± 22,728 (range 1,950 to 72,215) × 10^6/L on day 0 and 8 weeks, respectively, in all of the patients. This was paralleled by an increase in neutrophils and in CD3+ T lymphocytes, and reduction of lymph nodes size in one patient. It is of note that in the subject displaying a stable upregulation of CD11a and CD54 antigens continuous treatment with IFN-α resulted in a stable clinical response up to 24 months so far.

Our data demonstrate that in vivo treatment with IFN-α is able to induce CD11a and CD54 expression on B-CLL lymphocytes in analogy to what was reported by Jansen et al9 for HCL. Whether the regulation of cell adhesion molecules plays a role in mediating the clinical response to IFN-α in B-CLL patients remains to be established. B-CLL is characterized by abnormal recirculation and homing of neoplastic B cells and it is conceivable that modifications in adhesion surface repertoire as induced by IFN-α might alter the patterns of growth and trafficking of neoplastic lymphocytes. In addition to a direct effect on tumor cells as shown by Jansen et al9 in HCL and by us in B-CLL, IFN-α might also regulate the expression of adhesion molecules on accessory cells (fibroblasts, dendritic reticulum cells, endothelial cells) within lymphoid and bone marrow microenvironment. The upregulation of CD11a on neoplastic B cells from one side and of its specific ligand CD54 on accessory cells during IFN-α therapy might, in fact, modify heterotypic interactions of tumor cells with microenvironmental components regulating growth, differentiation, and trafficking of B lymphocytes. In any instance if the reported lack of CD11a and of CD54 molecules in B-CLL...
lymphocytes is somewhat responsible for tumor overgrowth and spread, the therapeutic activity of IFN-α in this disorders might be caused, at least in part, by the restoration of the adhesive machinery regulating the trafficking of neoplastic cells.

Our results suggest that the observed reduction of absolute lymphocyte counts and of circulating neoplastic (CD19⁺, CD20⁺) B cells in different series of B-CLL patients treated with IFN-α, may be caused by both a direct activity of the drug on tumor cell proliferation and to IFN-α-induced modifications of surface molecules involved in recirculation and homing of tumor cells. Further studies are warranted to clarify whether the regulation of CD11a and CD54 molecules exerted in vivo by IFN-α in B-CLL patients results also in an enhanced susceptibility of neoplastic cells to immune effectors, as shown by Jansen et al in HCL cells.

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REFERENCES


RESPONSE

The data presented by Marotta et al interestingly show that in vivo induction of LFA-1 and ICAM-1 after IFN-α treatment is not restricted to hairy cell leukemia (HCL), but can also be observed in chronic B-lymphocytic leukemia (B-CLL). Because B-CLL is a more frequent disease than HCL, and the numbers of circulating B cells are generally higher than in HCL, this disease may be preferred to further study the effect of IFN-α-induced expression of LFA-1/ICAM-1 on homing, homotypic and heterotypic cellular interactions, etc. However, because the therapeutic effect of IFN-α seems to be more consistent in HCL than in B-CLL, and because B-CLL probably represents a more heterogeneous group than the very uniform group of HCL patients, it will be interesting to study both B-cell malignancies at the same time. Considering the heterogeneity in B-CLL, it will be interesting to see if there is a correlation between the clinical response and the induction of LFA-1 and ICAM-1 in larger groups of patients. Hopefully, these kinds of studies will yield information about the role of LFA-1 and ICAM-1 expression on normal and malignant cells and they may give more insight in the mechanism behind the therapeutic effect of IFN-α in these diseases.

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Induction of LFA-1/CD11a and ICAM-1/CD54 adhesion molecules on neoplastic B cells during in vivo treatment of chronic lymphocytic leukemia with interferon-alpha 2 [letter; comment]

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