CONCISE REPORT

Serum Interleukin 2 Receptor Levels in Childhood Acute Lymphoblastic Leukemia


The clinical significance of interleukin 2 receptor (IL2R) concentrations in serum was determined for 344 children with newly diagnosed acute lymphoblastic leukemia (ALL). Serum levels of IL2R in patients (267 to 80,000 U/mL, median 2,007 U/mL) were significantly higher than normal control values (170 to 738 U/mL, median 347 U/mL) (P < .0001). Measurements in cases of T cell ALL were lower than in the non-T, non-B cases (P = .02). Among the 264 patients with non-T, non-B ALL, but not in those with T cell disease, higher serum IL2R levels (>2,000 U/mL) were associated with a poorer treatment outcome (P = .04). In a multivariate analysis, serum IL2R level contributed independent prognostic information beyond that conveyed by leukocyte count, race, and age (P = .04). One explanation for these results is that soluble IL2R competes with normal lymphocyte-integrated IL2R for the ligand and thus could suppress host antitumor immunity.

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tions were significantly higher in patients than in 215 healthy adult controls (170 to 738 U/mL, median 347 U/mL; \( P < .0001 \)). Among the 304 cases with complete blast cell immunophenotyping, serum IL2R levels differed significantly by major immunophenotypic subgroup. In the 40 patients with T cell ALL, values ranged from 355 to 10,345 U/mL (median 1,434 U/mL) as compared with 267 to 80,000 U/mL (median 1,918 U/mL) for the 264 non-T, non-B cases \( (P < .02) \). Lower serum IL2R levels were positively correlated with the presence of a mediastinal mass \( (P = .04) \), a higher platelet count \( (P = .007) \), and a higher hemoglobin level \( (P = .009) \), presenting features commonly seen in patients with T-cell ALL. Other well-recognized characteristics (including age, sex, race, leukocyte count, serum lactic dehydrogenase level, liver or spleen size, FAB classification, presence of central nervous system leukemia, and leukemic cell ploidy) lacked any statistical relationship to serum IL2R concentration (data not shown).

Higher serum levels of the receptor had no prognostic value in the 40 patients with T-cell ALL but connoted a poorer treatment outcome among the 264 patients with non-T, non-B ALL \( (P < .04) \). Stepwise Cox regression analysis was used to investigate the impact of serum IL2R level on time to failure among non-T, non-B cases after adjustment for the effects of other covariates. Leukocyte count, race, and age were identified as the three most important prognostic factors in the analysis. Serum IL2R level contributed independent prognostic information after adjustment was made for each of these factors \( (P < .04) \).

**DISCUSSION**

In this study, children with ALL had significantly higher serum IL2R levels than those of healthy adult controls. Moreover, increased levels of the receptor correlated with a poorer treatment outcome in patients with non-T, non-B ALL even after adjustment for leukocyte count, race, and age, the three most important prognostic factors in this disease.\(^{14}\) Although the function of soluble IL2R is unknown, and increases in its levels are by no means restricted to malignant disorders,\(^5\) measurements of the receptor have been demonstrated to have clinical utility. In hairy cell leukemia, for instance, serum levels of the receptor were correlated with disease-free remissions after therapy with recombinant \( \alpha \)-interferon.\(^{15} \) In Hodgkin's disease, high serum IL2R levels were associated with the presence of constitutional symptoms.\(^{16} \) In B-cell chronic lymphocytic leukemia, lower levels of serum IL2R were found in patients with less invasive disease, and cases with the lowest levels had T cells showing the best mitogenic response and helper capacity.\(^{17} \) We and other researchers\(^{8,10} \) have demonstrated independent prognostic significance for serum IL2R in patients with non-Hodgkin's lymphoma; that is, higher levels were associated with more advanced disease, greater tumor burden, and a poorer outcome.

Because soluble IL2R is capable of binding IL2,\(^6\) it might downregulate the host immune response by competing with normal lymphocyte cellular IL2R for the ligand. In this regard, increased serum levels of IL2R have been suggested to enhance neoplastic growth by suppressing host antitumor immunity in patients with lymphoid malignancies.\(^{6,7,9,10} \)

The lack of prognostic value of serum IL2R levels in our patients with T-cell ALL could be related to the small number of cases that were studied. Alternatively, the use of effective intensive chemotherapy could have abolished any prognostic influence exerted by IL2R concentrations.\(^{18} \) Such loss has been observed repeatedly for other factors in treatment programs featuring intensified chemotherapy.\(^{14} \)

HTLV-positive T cell lines constitutively express cell surface IL2R and release large amounts of IL2R into supernatant.\(^6\) In patients with lymphoma, the demonstration of IL2R on tumor cells\(^{10,19,20} \) and in high levels in the malignant serous effusions\(^{16} \) suggest that the serum IL2R in them was derived from tumor cells. The source of high serum IL2R in our patients is unclear. In one study of 38 cases of ALL, only two CD19\(^+\) (B\(^+\)) cases had a low percentage of blasts expressing cell surface IL2R.\(^{19} \) Using flow cytometry, we studied 74 consecutive cases of childhood ALL and found that only one of 11 T cell cases and one of 63 non-T, non-B cases expressed cellular IL2R detectable by binding to a CD25 monoclonal antibody (F.G. Behm, unpublished observations, 1987). Several studies, however, have shown that blast cells with a common ALL, pre-B or T-cell phenotype can be induced to express IL2R after in vitro activation.\(^{22,24} \) Leukemic cells outside the circulation may be more likely to express and release IL2R, especially in cases with a poor prognosis. On the other hand, IL2R-bearing lymphocytes were found in patients with a variety of benign reactive lymphoid processes\(^{20} \) and increased serum IL2R levels have been found in some benign clinical conditions.\(^{25} \) Thus, further studies are needed to define the source, the structure, and the immunoregulatory role of soluble IL2R in patients with ALL; such information would aid in understanding the lower serum IL2R levels we observed in patients with T-cell ALL. Finally, the value of sequential measurements of soluble IL2R in identifying cases in which relapse is apt to occur should be tested in a prospective manner.

**NOTE ADDED IN PROOF**

We recently learned that normal children less than 6 years of age have significantly higher serum IL2R levels than do adults.\(^{26,27} \) Even so, the vast majority (95\%) of children in those studies had receptor

**Fig 1.** Comparison of time-to-failure rates according to serum IL2R levels for 264 patients with non-T, non-B acute lymphoblastic leukemia. Higher levels of the receptor (>2,000 U/mL) were associated with a significantly poorer treatment outcome \( (P < .04) \). The origins of the curves reflect inclusion of induction failures in the Kaplan-Meier analysis. Tick marks represent patients still at risk of relapse.
concentrations <2,000 U/mL, the dividing point used in our analysis.

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