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.

The interleukin 2 receptor (IL2R), defined by its reactivity with CD25-related monoclonal antibodies, is not present on the surface of resting T or B lymphocytes but is rapidly expressed following activation. Malignant cells in certain B or T cell neoplasms, including Burkitt’s lymphoma, hairy cell leukemia, and adult T cell leukemia associated with the human T cell leukemia virus (HTLV-1), also express IL2R on their surface. Despite the rapid accumulation of information on cellular IL2R, its function in malignant cells is poorly understood.

IL2R in soluble form has been demonstrated both in vivo and in vitro. Rubin et al showed that activated normal lymphocytes and HTLV-1-positive T cell lines produced cell-associated as well as cell-free IL2R in vitro. The soluble IL2R is smaller than its cellular counterpart but retains the ability to bind IL2. Comparable levels of soluble IL2R have been detected in cord blood and in peripheral blood from normal adults. Increased serum levels of the receptor have been found in patients with HTLV-1-associated adult T cell leukemia, Sézary syndrome, Hodgkin’s disease, chronic lymphocytic leukemia, hairy cell leukemia and non-Hodgkin’s lymphoma.

In this study, we measured serum concentrations of soluble IL2R in a large group of children with acute lymphoblastic leukemia (ALL). The receptor was present in serum samples from all patients, and higher levels were associated with a poorer treatment outcome in children with non-T, non-B ALL. These results suggest that soluble IL2R may have an important immunoregulatory role in patients with lymphoid malignancies.

MATERIALS AND METHODS

Patients. IL2R levels were determined in serum samples taken before the start of chemotherapy from 344 children with newly diagnosed ALL who were admitted to St Jude Children’s Research Hospital from 1979 to 1983. The samples represented 80% of 431 patients enrolled in Total Therapy Study XI and having adequate follow-up. These 207 boys and 137 girls ranged in age from 0.2 to 19.5 years (median 4.7 years). The diagnosis of ALL was based on morphological criteria of the French-American-British (FAB) cooperative group and negative myeloid-associated cytochemical findings in bone marrow blast cells. The leukemia cells were classified as T, pre-B, common ALL antigen-positive (CALLA+) early pre-B (common), or CALLA− early pre-B, as previously described. In this study, common, pre-B, and CALLA− early pre-B ALL cases were collectively termed non-T, non-B ALL. Depending on their presenting features, the patients were treated with “standard” or more intensive chemotherapy. Virtually all T cell cases were treated with intensive therapy.

Determination of soluble IL2R. Soluble IL2R was measured with a coated-bead sandwich enzyme immunoassay kit (T Cell Sciences Inc, Cambridge, MA), as described previously. A reference preparation of 1,000 U/mL supernatant from phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes was used as a standard.

Statistical analysis. The Kruskal-Wallis test was used to compare soluble IL2R levels among different subgroups of patients. Time-to-failure curves were constructed by the Kaplan-Meier procedure, with differences analyzed by the log-rank test. Time to failure was defined as the interval between achievement of remission and relapse or death due to any cause. Patients who did not enter remission were assigned a failure time of zero in the analysis. The influence of potentially significant prognostic factors on time to failure was estimated with the Cox proportional-hazards model, which permits comparison of treatment outcome for two or more subsets of patients while simultaneously adjusting for the effect of other factors (covariates) in the model. The median IL2R level (2,000 U/mL) of the patients was used as the dividing point between high and low levels.

RESULTS

IL2R was detected in the sera of all 344 patients with ALL (267 to 80,000 U/mL, median 2,007 U/mL). Its concentra-
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 (including age, sex, race, and increases in its number 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. Such loss has been observed repeatedly for other factors in treatment programs featuring intensified chemotherapy.

Because soluble IL2R is capable of binding IL2, 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.

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. The use of effective intensive chemotherapy could have abolished any prognostic influence exerted by IL2R concentrations. Such loss has been observed repeatedly for other factors in treatment programs featuring intensified chemotherapy.

HTLV-positive T cell lines constitutively express cell surface IL2R and release large amounts of IL2R into supernatant. In patients with lymphoma, the demonstration of IL2R on tumor cells and in high levels in the malignant serous effusions 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+ (B4+) cases had a low percentage of blasts expressing cell surface IL2R. 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. Behn, 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.

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 and increased serum IL2R levels have been found in some benign clinical conditions. 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. Even so, the vast majority (95%) of children in those studies had receptor
concentrations <2,000 U/mL, the dividing point used in our analysis.

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