Glucocorticoid Receptors in Subpopulations of Childhood Acute Lymphocytic Leukemia

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SUMMARY

In view of the known differences in sensitivity to glucocorticoids among functional subcategories of lymphocytes in the mouse and the awareness that different subcategories of acute lymphocytic leukemia may represent proliferation of different clones of lymphoblasts, we examined lymphoblast populations with known surface markers for differences in specific cytoplasmic glucocorticoid receptor activity. Lymphoblasts were divided into those that formed sheep erythrocyte rosettes (T-lymphoblasts) and those that lacked all surface markers (null lymphoblasts). The latter were further subdivided by their ability to stimulate allogeneic donors in mixed lymphocyte culture (MLC). Lack of stimulation in MLC is a characteristic of mature T-cells. Eighteen patients had null lymphoblasts that did stimulate in MLC, and glucocorticoid binding sites in these ranged from 4.096 to 21,869 sites/cell (median, 7,571). Eighteen patients with T-lymphoblasts had binding sites ranging from 0 to 5,887 sites/cell (median, 2,173). This difference in specific glucocorticoid receptor levels is highly significant (p < 0.001). Nine patients whose lymphoblasts lacked identifiable surface markers but failed to stimulate in MLC had intermediate values for receptor sites. Thus it appears that null lymphoblasts are more likely to have higher numbers of specific glucocorticoid receptor than T-lymphoblasts. The differential capacity of lymphoblasts to bind steroid may prove useful in designing therapeutic regimens for the different subcategories of acute lymphocytic leukemia.

INTRODUCTION

Acute lymphocytic leukemia is a heterogeneous form of cancer. Approximately one-fifth of patients have lymphoblasts that form spontaneous rosettes with E-rosettes* and these patients, in general, have a more aggressive form of disease (2, 28, 29). Most patients have lymphoblasts that lack identifiable surface markers. Thus, the subcategories of acute lymphocytic leukemia in humans probably represent proliferation of different clones of lymphoblasts. There are known differences in glucocorticoid susceptibility among functional subcategories of lymphocytes in mice (24, 27, 31, 32). We therefore assayed lymphoblasts for a variety of surface markers and then examined lymphoblast populations with known characteristics for differences in specific cytoplasmic GR activity and responsiveness as a function of these various surface markers.

MATERIALS AND METHODS

Patients. Forty-five patients with acute lymphocytic leukemia were studied. Diagnoses were established in all cases by standard morphological diagnostic criteria (20). The age range was from 1 to 20 years. There were 16 females and 29 males. Four of the males were black. Lymphoblasts were obtained from the peripheral blood of 40 patients prior to initial therapy and from 5 patients in relapse and stored frozen in a viable state, as described below. No treated patients had received any glucocorticoid therapy within 2 weeks prior to their inclusion in this study.

Storage of Malignant Cells. Leukemia blast cells were collected from the peripheral blood of patients by conventional leukopheresis (22), by use of the IBM-NCI continuous cell separator (7) or by phlebotomy, at the time of diagnosis or relapse before chemotherapy was given. Peripheral blood specimens were collected in 5 units of heparin per ml (Upjohn Co., Kalamazoo, Mich.). The cells were frozen in a viable state at a concentration of 1 to 2 x 10^9 cells/ml with 10% dimethyl sulfoxide and stored in the vapor phase of liquid nitrogen by a method previously described (8). At the time of the study, the cells were thawed rapidly and then placed on a Ficoll-Hypaque density gradient (Ficoll-Paque; Pharmacia Fine Chemicals, Piscatawy, N. J.). The resulting interface cell suspension was >95% mononuclear cells and >95% viable as measured by trypan blue dye exclusion.

Lymphocyte Surface Markers. Lymphocytes were examined for their ability to form E-rosettes by a previously described (19) modification of the method of Weiner et al. (30), using neuraminidase-pretreated sheep RBC. At the end of the procedure, the cells were spun in a cytocentrifuge (Cytospin; Shandon Elliott Co., Surrey, England), and smears were made and stained with Giemsa stain so that differential counts could be performed; the cells at the
center of the rosettes were confirmed to be blasts. EAC-rosettes were measured with the use of a commercially available reagent (EAC; Cordis Labs, Miami, Fla.) by a previously reported method (3).

Receptors for the Fc portion of the immunoglobulin molecule were measured by a previously described method (21). Cells were incubated initially with an antigen-antibody complex consisting of keyhole limpet hemocyanin and an affinity column-purified rabbit anti-keyhole limpet hemocyanin IgG antibody. They were then washed and incubated with fluorescein-labeled goat anti-human immunoglobulin to see whether intact immunoglobulin molecules were coating their surface.

**MLC.** Heparinized whole blood (Heparin; Upjohn Co.; 5 to 10 units/ml of blood) was spun at 225 x g, and cell-rich plasma aspirate was placed on a Ficoll-Hypaque gradient and spun for 15 min at 20°C at 2000 x g. Cells at the interface, which were 95 to 100% lymphocytes, were used as responding cells. Leukemic lymphoblasts and normal lymphocytes from both patients and unrelated donors were used as stimulating cells. Stimulating cells were irradiated with 5000 R in a 137Ce source (Gamma M; Kewaunee Scientific Engineering, Adrian, Mich.). Triplicate cultures were set up with 10⁶ responding lymphocytes and 10⁵ stimulating leukemic blasts or normal lymphocytes in a 0.2-ml volume in TC 199 (Flow Labs, Rockville, Md.). Details of the culture method have been described previously (25). Cultures were incubated for 6 and 7 days in 5% CO₂. Eighteen hr prior to harvest, 0.8 µCi of tritiated thymidine, specific activity, 6.7 mCi/mmol (New England Nuclear, Boston, Mass.), were added to each well in a 20-µl volume. Cultures were harvested and dpm/culture were calculated. SR are expressed as the dpm in the sample containing the responding lymphocytes plus the X-irradiated blast preparation divided by the dpm in the sample containing the responding lymphocytes plus X-irradiated lymphocytes. A technically satisfactory study was one in which the normal allogeneic donor responded to the remission lymphocytes of the patient, or to the cells of another individual. Stored blast cells were considered stimulatory if there was a vigorous response (SR > 5) to them on 1 occasion. They were considered nonstimulatory if they had failed to stimulate at least 3 different allogeneic normal donors on 3 separate occasions, or if the median ratio of multiple determinations was less than 2 even though 1 or 2 ratios might be above that.

**Cytoplasmic Glucocorticoid Receptor Determination.** Cell populations obtained as noted above were suspended at a density varying between 0.5 and 10 x 10⁶ cells/ml in Eagle's minimal essential medium supplemented with 25 mM N-tris(hydroxymethyl)methylglycine and 0.6 g glutamine per liter. Most measurements of binding were made at cell concentrations between 1 and 3 x 10⁶ cells/ml. Aliquots of 0.8 ml of the cell suspension were delivered into 12- x 75-mm glass tubes. [3H]Dexamethasone (28 Ci/mmol; Amersham/Searle Corp., Evanston, Ill.) in ethanol was diluted in Eagle's minimal essential medium, supplemented as described above, to yield a concentration 5 times the final concentration desired. Final ethanol concentration was always less than 0.1%, a concentration that has no effect on binding. Dexamethasone was used rather than cortisol, since the former will not bind to transcortin (corticosteroid-binding globulin) (18), and small amounts of serum proteins might conceivably have remained adherent to cells throughout the purification procedure. To one-half of this steroid solution, a 100-fold excess of unlabeled competing dexamethasone was added. Aliquots of 0.2 ml of this 5-fold concentration were added to the 0.8-ml cell suspensions, and the tubes were gently mixed. In some experiments, complete binding curves were constructed by using multiple concentrations (3 to 7) of radioactive dexamethasone, with and without unlabeled dexamethasone, run in triplicate. In other experiments, because of limited cell numbers, triplicate or quadruplicate determinations of binding at a single steroid concentration (2 x 10⁻⁸ M) or 2 steroid concentrations (2 and 1 x 10⁻⁸ M) estimated to be about 5 and 2.5 times the dissociation constant, respectively, were used. Every 15 min, the cells were gently resuspended by brief mixing or were incubated continuously using a rocker platform (Belco Glass, Inc., Vineland, N. J.). Incubations were performed at 21°C. At the end of 2 hr, 2 ml of cold PBS, pH 7.4, were rapidly added to each tube. This time interval exceeds that required for maximal binding, as determined by kinetic studies described below. Viability, as determined by trypan blue exclusion, invariably exceeds 90% under these assay conditions (15). Cell pellets were collected by centrifugation at 1100 to 1200 rpm for 5 min in a Model PR-6 centrifuge (International Equipment Co., Needham Heights, Mass.) and then resuspended and washed twice more in ice-cold PBS. The cell pellets were then suspended in 0.2 ml PBS and 1 ml of ethanol to assist in extraction of protein-bound steroid. This suspension was transferred to liquid scintillation vials and counted in 12 ml of Aquasol (New England Nuclear, Boston, Mass.) at an efficiency of 40%. Simultaneously, 0.2-ml samples of the 5-fold concentrations of radioactive steroid solutions, with 1 ml of ethanol added, were counted in 12 ml of Aquasol. Cytoplasmic binding sites per cell and equilibrium dissociation constants were obtained from Scatchard analyses (26) prepared by computer-assisted analysis of the binding data (1). Binding sites per cell reported are, in all cases, those obtained at the highest steroid concentrations and are, therefore, 15 to 20% below the total receptor capacity.

**RESULTS**

After the surface marker studies were analyzed, all the lymphoblasts could be classified (Table 1) as either those that did make E-rosettes and were called T blasts, or those that had no markers and were called null blasts. No lymphoblasts that formed EAC-rosettes or had Fc receptors were seen in this group of patients. We have previously shown (13) that lymphoblasts that make E-rosettes usually share with normal human E-rosette-forming cells the inability to stimulate allogeneic responders in the MLC. We have postulated that the inability or loss of ability to stimulate in MLC may represent maturation along the pathway of T-cell differentiation. We therefore subdivided the null lymphoblasts into 2 categories by whether or not they stimulated in MLC for the purposes of analysis in this paper. The 3 groups...
of patients are described in Table 2. Group I (18 patients) had lymphoblasts that lacked identifiable surface markers but did stimulate in MLC. These were called N+ blasts. These patients ranged in age from 3 to 18 with a median of 7.3 years at diagnosis. There were 9 males and 9 females. The WBC ranged from 2,800 to 200,000/cu mm with a median of 15,000. Group II (9 patients) had lymphoblasts that also lacked identifiable surface markers, but these cells failed to stimulate in MLC and were called N– blasts. These patients ranged from 1 to 18.5 years of age with a median of 4.5 at diagnosis. There were 6 males and 3 females, and the WBC ranged from 2,400 to 1,000,000/cu mm with a median of 17,200. Group III (18 patients) had E-rosette-forming or T-lymphoblasts. Sixteen of these failed to stimulate allogeneic donors in MLC and 2 did stimulate. These patients ranged in age from 3 to 20 years with a median of 12.7 years at the time of diagnosis. There were 14 males and 4 females. Median WBC was 22,000 with a range from 1,900 to 415,000/cu mm. There were differences in the age and sex pattern within the patient groups, with Group III patients tending to be older and more often male, as has been reported for E-rosette-forming leukemia (29). These patients were selected for study because they had a high percentage of circulating blasts at the time the cells were collected.

**Effect of Cell Concentration on Glucocorticoid Binding.** In order to determine the effect of cell concentration in this assay, tests were performed at varying cell concentrations, ranging from 0.5 to 10 x 10^6 cells/ml. In Chart 1, it can be seen that this assay is linear within a broad range of cell concentrations. Results are identical at concentrations of 1 x 10^6 cells/ml and higher, for both null and T-lymphoblasts, and all determinations were done well within this range, most at 3 x 10^6 cells/ml.

At concentrations less than 1 x 10^6 cells/ml, results were variable, presumably due to loss of cells in washing at these low concentrations.

**Affinity of Glucocorticoid Binding to Cytoplasmic Receptor.** In order to characterize the affinity of the binding, uptake of glucocorticoid was measured at varying concentrations of tritiated dexamethasone, ranging from 3 x 10^-10 to 2 x 10^-8 M. The binding curves obtained for representative null and T-lymphoblasts are shown in Chart 2. The lower curve represents T-lymphoblasts, while the upper curve represents null lymphoblasts. As can be seen, although the total number of sites per cell differs markedly, the shape of the curves is the same, with both approximately 70% saturated at a concentration of 0.8 x 10^-8 M dexamethasone. The inset shows the data replotted for each of the curves by the Scatchard technique (26). Parallel straight lines are obtained, indicating an identical dissociation constant of 3.9 x 10^-8 M for both null and T-blasts. The linear relationship obtained, for each cell type, is consistent with radioactive dexamethasone binding to a single class of
Glucocorticoid Receptors in Childhood Leukemia

2.632 $\times 10^{-8}$ M can be calculated for the binding reaction, which is in good agreement with $3.89 \times 10^{-8}$ M which was obtained from the equilibrium data for dexamethasone shown in Chart 2.

Specificity of Glucocorticoid Binding to Cytoplasmic Receptor. Evidence that dexamethasone is binding to a specific glucocorticoid receptor is shown in studies graphically illustrated in Charts 5 and 6. The ability of various unlabeled steroids, present in molar excess, to compete with $10^{-8}$ M tritiated dexamethasone is shown for both null and T-lym-

receptor sites of uniform affinity. Similar results were obtained in all 14 cases where sufficient cells were available to obtain complete binding curves.

Kinetics of the Specific Glucocorticoid Binding Reaction. The rates of association and dissociation between dexamethasone and specific glucocorticoid binding sites were studied. Chart 3 shows the time course of specific binding of dexamethasone to GR at 21°. It can be seen that, at a concentration of steroid sufficient to saturate the GR, the reaction has approached equilibrium after about 1 hr. Although not shown in this chart, there was no difference in binding at 2, 4, 6, or 8 hr. In the binding reaction

Dexamethasone + GR $\xrightarrow{k_1} \text{ (dexamethasone-}$

specific GR complex) $\xrightarrow{k_2}$

2nd-order kinetics may apply. If this is the case, a plot of time versus log$_e$ (unbound dexamethasone concentration/ unbound specific GR concentration) should give a straight line. Results are seen in Chart 3, inset, and are consistent with 2nd-order kinetics in the binding reaction (23). From the slope of the line ($r = 0.94$) the association rate constant ($k_1$) may be calculated to be $2.025 \times 10^6$ M$^{-1}$.

The dissociation reaction of the dexamethasone-GR complex was also studied. After the GR was allowed to become saturated with radiolabeled dexamethasone, a 100-fold excess of nonradioactive dexamethasone was added as a chase, and specifically bound counts, at 21° (Chart 4), demonstrate the reversibility of the cytoplasmic GR-binding reaction. If it is assumed that the dissociation reaction follows 1st-order kinetics, than a plot of log$_e$ (bound steroid concentration) versus time should be linear (20), as shown in the inset of Chart 4. From the slope of this line ($r = 0.91$), the dissociation rate constant ($k_2$) of $5.33 \times 10^{-3}$ t$^{-1}$ is obtained. From the dissociation and association rate constants, an overall equilibrium (dissociation) constant ($k_o$) of
phoblasts. Biologically active glucocorticoids, such as dexamethasone and 11β-hydroxycortisol, compete with labeled dexamethasone. Biologically inactive steroids, such as 11α-hydroxycortisol, or the reduced metabolite, tetrahydrocortisol, and the sex steroids, compete little, if at all.

In these experiments, the various unlabeled steroids were added to the incubation mixture before the tritiated dexamethasone was added. While this exaggerates the competition of biologically active glucocorticoids at the various molar ratios, it also emphasizes the failure of biologically inactive steroids to compete for these binding sites. Thus, binding appears specific for known biologically active glucocorticoids. The curves shown here for null and T-lymphoblasts are virtually identical.

Correlation between Surface Markers and Specific Cytoplasmic GR Binding Sites. Chart 7 compares GR activity in the lymphoblasts from the patients, as described in Table 1.

In the 18 patients in Group 1 with N+ lymphoblasts, GR sites ranged from 4,096 to 21,869 sites/cell, with a mean of 10,117 and a median of 7,571 sites/cell. In the 9 Group 2 patients with N− lymphoblasts, GR sites ranged from 2,936 to 16,469, with a mean of 6,729 and a median of 4,484 sites/cell. In the 18 Group 3 patients with T-lymphoblasts, GR sites ranged from 0 to 5,887 with a mean of 2,538 and a median of 2,173 sites/cell.

While there is overlap of the intermediate Group 2 with Groups 1 and 3, there is very little overlap between Groups 1 and 3. Fourteen of the 18 patients with T-lymphoblasts had less than 4000 sites/cell, while none of the 18 patients with N+ blasts and only 3 of 9 patients with N− blasts had less than 4000 sites/cell.

Using the 2-tailed Wilcoxon rank sum test, each of the groups is different from the others. Group 1 is different from Group 2 at \( p < 0.1 \). Group 2 is different from Group 3 at \( p < 0.01 \), and Group 1 is different from Group 3 at \( p < 0.001 \).

These results were quite reproducible from day to day at various cell concentrations within the optimal range, as shown in Table 3 for 4 of the patients in whom tests were performed on more than one occasion.

There was, within the different groups, some variation in GR levels with age and with sex. However, these variations were not consistent and, in most instances, not statistically significant. In Table 4 it can be seen that, in the N+ group, patients over 10 years of age had higher levels of receptor (median, 12,480 sites/cell) than those under 10 years (median, 7,571 sites/cell), although not significantly different (\( p = 0.8 \)). In the N− group, just the opposite is seen. Those under 10 years had higher receptor levels (median, 6,783 sites/cell) than those over 10 years (median, 3,265 sites/
Reproducibility of results

GR sites per cell values obtained for the same patient’s lymphoblasts when tested on different days and using different cell concentrations between 1 and $3 \times 10^6$ cells/ml were quite reproducible, as shown here.

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. of tests</th>
<th>GR sites/cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. P.</td>
<td>3</td>
<td>1.706, 2.095, 1.834</td>
</tr>
<tr>
<td>M. A.</td>
<td>2</td>
<td>1.796, 2.181</td>
</tr>
<tr>
<td>J. B.</td>
<td>2</td>
<td>2.746, 2.676</td>
</tr>
<tr>
<td>C. M.</td>
<td>5</td>
<td>20.933, 22.816, 21.666, 22.242, 21.555</td>
</tr>
</tbody>
</table>

Table 3
Reproducibility of results

Table 4
Glucocorticoid receptor levels and age

Lymphoblasts were isolated and assayed for specific cytoplasmic glucocorticoid receptor levels. Variation of GR levels with age, within each group, is shown.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cell type</th>
<th>Total no. of patients</th>
<th>No. of patients</th>
<th>GR sites/cell</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>N+</td>
<td>&lt;10</td>
<td>12</td>
<td>7.571, 12.480, 4.096-16.236</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;10</td>
<td>6</td>
<td>4.748-21.869</td>
</tr>
<tr>
<td>2</td>
<td>N−</td>
<td>&lt;10</td>
<td>6</td>
<td>6.783, 3.265, 3.582-16.459</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;10</td>
<td>3</td>
<td>2.936-4.463, p = 0.048</td>
</tr>
<tr>
<td>3</td>
<td>T</td>
<td>&lt;10</td>
<td>4</td>
<td>2.601, 1.995, 160-4.420</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;10</td>
<td>14</td>
<td>0-5.887, NS</td>
</tr>
</tbody>
</table>

Table 5
Glucocorticoid receptor levels and sex

Lymphoblasts were isolated and assayed for specific cytoplasmic glucocorticoid receptor levels. Variation of GR levels with sex, within each group, is shown.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cell type</th>
<th>Total no. of patients</th>
<th>No. of patients</th>
<th>GR sites/cell</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sex</td>
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</tr>
<tr>
<td>1</td>
<td>N+</td>
<td>M</td>
<td>9</td>
<td>5.721, 8.836, 4.906-21.869</td>
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<tr>
<td></td>
<td></td>
<td>F</td>
<td>9</td>
<td>6.365-21.548</td>
</tr>
<tr>
<td>2</td>
<td>N−</td>
<td>M</td>
<td>6</td>
<td>4.033, 5.570, 2.936-16.459</td>
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<tr>
<td></td>
<td></td>
<td>F</td>
<td>3</td>
<td>4.463-7.995, NS (p = 0.714)</td>
</tr>
<tr>
<td>3</td>
<td>T</td>
<td>M</td>
<td>14</td>
<td>2.174, 2.869, 160-5.672</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>4</td>
<td>0-5.887, NS (p &gt; 0.56)</td>
</tr>
</tbody>
</table>

DISCUSSION

From Scatchard analysis of our concentration curves (Chart 2) we conclude that the cytoplasmic receptors we are studying are of high affinity, and from the competition studies (Charts 5 and 6) we conclude that they are specific for glucocorticoids. While binding capacity differed, there appeared to be no difference in binding affinity or specificity between receptors in T- and null lymphoblasts. Thus, specific cytoplasmic glucocorticoid receptors are present in larger quantities in null than in T-lymphoblasts, and lymphoblasts with intermediate characteristics have intermediate values.

Animal models might lead us to predict whether this determination will be clinically useful for predicting in vivo tumor response to steroid. Lampkin and Potter (12) and Baxter et al. (2) have studied steroid-sensitive and steroid-resistant lymphoma cell lines from identical parent tumors. In such pairs, the resistant sublines bound quantitatively less steroid than the sensitive sublines; in 1 pair of such tumors, studied by Baxter (2), the sensitive and the resistant sublines from the same parent tumor had the same number of steroid receptors. A "transitory sensitive" cell line was also described (2) in which the cells were transiently inhibited but not killed in the presence of glucocorticoid.
G. S. K. Yarbro et al.

Gehring et al. (6) described glucocorticoid action on hybrid clones derived from cultured mouse myeloma and lymphoma cell lines. Cells of a mouse myeloma line contained specific cytoplasmic glucocorticoid receptors and were killed by dexamethasone. Cells from a mouse lymphoma line also containing specific glucocorticoid receptors were resistant to glucocorticoids. Two different hybrid clones derived by fusion of the resistant lymphoma and the sensitive myeloma contained specific receptors, and both hybrids were killed by dexamethasone.

Thus we might predict that a critical number of cytoplasmic receptors may be required by a tumor line for a steroid response to occur. However, since many steps distal to the initial binding of steroid to receptor may well be defective in resistant cells, it is certainly possible that cells may contain apparently adequate, or even increased, amounts of cytoplasmic receptor activity and yet fail to respond to glucocorticoids. We have previously reported this result in both rodent and human leukemic cells in culture (17).

We have also previously shown that glucocorticoid inhibition of DNA synthesis in leukemic cells in vitro correlates with quantitative differences in receptor activity (16). In lymphoblasts sensitive to glucocorticoid, glucocorticoid receptor binding increases with increasing dexamethasone concentration, and then plateaus. Dexamethasone inhibits thymidine incorporation at concentrations that closely correspond to those that saturate receptor sites. A very different pattern of binding and biological effect was seen in lymphoblasts that lacked significant glucocorticoid receptor activity. No concentration of glucocorticoid tested was inhibitory of thymidine incorporation. All of 28 samples containing significant glucocorticoid receptor were inhibited by dexamethasone, and none of 6 lacking significant receptor activity were so inhibited. Thus, lack of receptor activity and lack of biological response were correlated.

Cline and Rosenbaum (4, 5) studied uridine incorporation in acute lymphocytic leukemia cells incubated for 24 hr in the presence or absence of glucocorticoids. They concluded that in vitro cytotoxicity was partially successful in predicting in vivo steroid effect, defined as 50% reduction in circulating or bone marrow blasts or organomegaly during a 14-day treatment period, but was not successful in predicting remission induction.

In general, patients with T-cell leukemia have a poorer prognosis than those with null cell disease (9, 28, 29), and perhaps the inability of their lymphoblasts to bind steroid to the same extent as null lymphoblasts is one factor in this poorer prognosis. However, while poor steroid binding within a general class of lymphoblasts may be partially related to the poor prognosis of the group as a whole, a high level of cytoplasmic glucocorticoid receptors probably does not guarantee a good response for any individual patient, since steps distal to the initial binding of steroid to receptor may be defective (14).

It seems clear, however, that specific cytoplasmic glucocorticoid receptors can be conveniently detected on small numbers of leukemic lymphoblasts. It appears, from these studies, that null lymphoblasts are more likely to have larger numbers of these receptors than T-lymphoblasts. If one bears in mind that the presence of these cytoplasmic receptors may be required, although not sufficient alone, for steroid effect, the differential capacity of lymphoblasts to bind glucocorticoid may prove useful in designing therapeutic regimens for the different subcategories of acute lymphocytic leukemia, particularly if it is possible to show, in studies currently underway, that these quantitative differences in receptor activity are correlated with differences in glucocorticoid effect in vivo.

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