Purine Degradative Enzymes and Terminal Transferase in Acute Myelogenous Leukemia: Clinical Relevance*

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ABSTRACT

Intracellular adenosine deaminase (ADA), purine nucleoside phosphorylase (PNP) and terminal deoxynucleotidyl transferase (TdT) activities were investigated in adult patients with acute myelogenous leukemia (AML) in order to relate these enzymatic activities to the stage of differentiation and maturation and to the clinical outcome of AML. Both ADA and PNP were measured spectrophotometrically using the method of Hopkinson et al.,25 and TdT was investigated using liquid scintillation technique15,16 with slight modification. The level of ADA was above normal in patients with AML whereas the level of PNP and the PNP/ADA ratio were below normal. Short survival was observed in the majority of the patients with markedly increased levels of ADA and decreased levels of PNP and PNP/ADA. Normal patients and patients with AML had no significant differences in TdT activity. Significant differences in ADA, PNP and TdT among AML subtypes were not observed. The levels of ADA and PNP seemed to reflect the clinical severity of this disease.

Introduction

Malignant cells have been found to differ from normal cells in quantitative enzyme level.24,27 The biochemical abnormalities can be used diagnostically or may be relevant to the treatment of particular types of acute leukemia with enzyme inhibitors.

Decreased levels of some purine pathway enzymes such as adenosine deaminase (ADA), 5′ nucleotidase (5′N), and purine nucleoside phosphorylase (PNP) have been reported in patients with
immunodeficiency diseases. In normal individuals, the highest levels of ADA in the body occur in cortical thymocytes. This enzyme catalyzes the conversion of deoxyadenosine and adenosine to deoxyinosine and inosine, respectively. Among leukemia, activity of ADA varies between different types of leukemias. It tends to be higher in T-acute lymphoblastic leukemia (T-ALL) than acute myelogenous leukemia (AML). Also, activity of ADA is higher in lymphoid as compared with myeloid blast transformation of chronic myelogenous leukemia (CML). Both normal and raised activity of ADA have been found in patients with AML. Raised levels were associated with short survival of the patients in at least one study. The activity of ADA in AML and ALL blast cells has been found to return to the normal range during remission induced by conventional chemotherapy. Another purine degradative enzyme, purine nucleoside phosphorylase (PNP), acts sequentially with ADA. It degrades guanosine and inosine and their deoxy derivatives to the corresponding bases. Activity of PNP was significantly more reduced in T-ALL and B-ALL than in AML or C-ALL.

Terminal deoxynucleotidyl transferase (TdT) is one of the best studied and most often used enzyme marker. It catalyses the polymerization of deoxynucleoside monophosphate onto the 3' end of single stranded DNA primer without the need for template instruction. Among normal tissues, TdT has been found in more than 90 percent of cortical thymocytes, two percent of marrow lymphocytes, and less than 0.1 percent of cells in peripheral blood. Terminal deoxynucleotidyl transferase is almost always positive in acute lymphoblastic leukemia (ALL) but usually negative in acute and chronic myelogenous leukemia (AML and CML). Among the immunologically defined subgroups of ALL, over 90 percent of cases of C-ALL, T-ALL, and pre B-ALL are TdT-positive, while B-ALL is generally negative for TdT. High levels of TdT have been found in up to 20 percent of patients with AML who appear to have had particularly bad prognosis. In addition, cases of AML not expressing TdT at presentation have shown a marked increase in the level of TdT at relapse. Other enzymes that have been intensively studied as potential enzyme markers in acute leukemia have been reviewed elsewhere.

Intracellular activity of ADA, PNP, and TdT were investigated in untreated patients with AML and normal individuals in order to relate these enzymes' activities to stage of differentiation and maturation of leukemic cells, and to the clinical outcome of patients with AML. The results might provide an appropriate diagnostic category for each patient and a new method of prognostication.

Materials and Methods

A total of 66 adult patients with newly diagnosed AML, registered at the Division of Hematology, Department of Medicine, Siriraj Hospital, were studied. The patients were classified according to the French-American-British (FAB) morphologic classification. The enzymes ADA, PNP, and TdT were analysed. Control patients consisted of normal donors from the Blood Bank Department of Siriraj Hospital. Verbal consent was obtained from all patients and normal donors prior to the investigation.

Ten ml specimens of venous blood were collected into heparinized (1,000 U per ml) syringes prior to mononuclear cell preparation. Morphological diagnosis and subclassification of AML were based on Wright's and cytochemical stains of bone marrow and peripheral blood smears as described previously. Mononuclear cells (MNC) were obtained
by separation of peripheral blood cells on ficoll-hypaque (d = 1.077) as described by Boyum.  

**Determination of Protein**

Protein analysis was performed by the modified Lowry method as described previously. Protein samples were diluted to one ml with water and treated with 0.9 ml of solution A containing 0.2 percent (w/v) potassium sodium tartrate and 10 percent (w/v) Na₂CO₃ in 1:2 N NaOH solution. A blank and a standard were set up in the same way. The tubes were placed in a water bath at 50°C for 10 minutes, cooled to room temperature (21 to 25°C), and treated with 0.1 ml of solution B containing two percent (w/v) potassium sodium tartrate and one percent (w/v) CuSO₄ · 5H₂O in 1:10 N NaOH. The solutions were left at room temperature for at least 10 minutes, then three ml of 0.15 N Folin-Ciocalteu solution (solution C) was forced in rapidly to ensure mixing within one second. The tubes were again heated at 50°C for 10 minutes and cooled to room temperature. Absorbancies were read in one cm cuvets at 650 nm.

**Assays of ADA and PNP**

The levels of ADA and PNP were investigated in 66 adult patients with AML. The MNC were resuspended with stabilizing solution containing 2.7 mM of ethylenediamine tetraacetic acid (EDTA) and 1 mM of 2-mercaptoethanol in 50 mM of potassium phosphate buffer, pH 7.5. The suspended volume was adjusted to yield a density of 1 × 10⁷ cells per ml and homogenized with 50 strokes of a motor-driven teflon pestle homogenizer. The homogenate was centrifuged at 7000 g for 10 minutes. The supernatant fraction was used for assays of ADA and PNP. Intracellular activities of ADA and PNP were investigated by the method of Hopkinson et al using a Gilford-250 spectrophotometer. Briefly, 50 µl of enzyme extract were added to a reaction mixture which contained: 3 ml of 0.05 M phosphate buffer, pH 7.5, 0.3 µmole of adenosine (for ADA assay), or 0.06 µmole of inosine (for PNP assay), and 0.04 unit of xanthine oxidase. The blank cuvette was identical to the test one except that adenosine or inosine was omitted. The activities of ADA and PNP were measured by recording the increase in optical density at 293 µm for 15 minutes. The optimum temperature for the reaction was 37°C. The increase in optical density results from the conversion of adenosine (for ADA) or inosine (for PNP) to uric acid. One unit of ADA activity is defined as the activity of enzyme that catalyzes the deamination of one nmole per ml of adenosine per minute (AmM = 8.65). One unit of PNP is the activity of the enzyme that catalyzes the deamination of one nmole per ml of inosine per minute. Specific activity is defined as unit per mg protein.

**Assay of TdT**

Quantitative analysis of the enzyme TdT was investigated in 52 adult AML patients with AML, six adult patients with ALL, and 10 normal donors, using the methods, with modification, described by Coleman et al and by Chang and Bollum. Briefly, the mononuclear cell pellet was resuspended in 0.25 M of potassium phosphate buffer, pH 7.5, which contained one mM of 2-mercaptoethanol. The final concentration of cell suspension was adjusted to 1 × 10⁸ cells per ml. The suspension was sonicated at 30 watt output for 20 seconds at 4°C and then centrifuged at 100,000 g for one hour. The supernatant enzyme extract was used for assay of TdT. Thirty µl of the enzyme extract was added into the reaction mixture which contained 0.2 M of
potassium cacodylate buffer, pH 7.5, one mM of deoxyguanosine triphosphate (dGTP) and \(^3\)H-dGTP, specific activity of 7230 cpm per nmole, 50 \(\mu\)g per ml of oligodeoxypolyadenylic acid [p(dA)], one mM of 2-mercaptoethanol, 0.5 mM of MnCl\(_2\), and 125 \(\mu\)g per ml of bovine serum albumin, to be a final volume of 125 \(\mu\)l. The reaction mixture was incubated at 37°C for three hours. The reaction was terminated by application of 30 \(\mu\)l aliquots onto a 0.45 micron Millipore filter disc which had been wetted with ice-cold five percent trichloroacetic acid (TCA) containing one percent of sodium pyrophosphate (Na\(_4\)P\(_2\)O\(_7\) • 10H\(_2\)O). The filter was then washed three times with five percent trichloroacetic acid (TCA) under vacuum aspiration and left to air dry at room temperature. The dried filters were placed in plastic liquid scintillation vials filled with 10 ml of scintillation fluid. The radioactivity was determined by 10 minutes counting in Beckman model 7000 liquid scintillation counter. Activities were expressed in units per mg protein, where one unit equals one pmole of dGTP polymerized onto oligo-d(pA) per hour.

**Results**

Median age of the patients (33 males and 33 females) at presentation was 36.3 years (range 15 to 66 years). The median survival from diagnosis was 11.8 weeks. Shorter survival was observed in subtype M1 and M3 than in M2 and M4. The levels of intracellular purine degradative enzymes in normal control patients and patients with AML are shown in Table I and figure 1. Activity of ADA was higher in patients with AML than in normal patients (\(P < 0.001\), t-statistic), whereas the activity of PNP as well as the ratio of PNP/ADA were lower in patients with AML (both \(P \text{ values} < 0.001\), t-statistic). The influence of each of these enzyme parameters on patient survival was not significant as analysed by univariate regression analysis (r' = 0.032, 0.137, and 0.126 for ADA, PNP, and PNP/ADA ratio) and t-statistics (\(P = 0.224\) for ADA and 0.124 for PNP). Nevertheless, some associations of enzyme activity with short survival were observed: cases with a prominently increased level of ADA (>9.4 U per mg; based on \(X(ADA) + 1\ S.D.\)), markedly decreased level of PNP (<9.3 U per mg; based on \(X(PNP) - 1 \ S.D.\)) and markedly decreased PNP/ADA ratio (<1.8; based on \(X(PNP/ADA) - 1 \ S.D.\)). As seen in table II, seven of nine patients with very high levels of ADA, nine of eleven patients with very low levels of PNP, and 10 of 11 patients with very low PNP/ADA had short survival and did not survive more than three months after their first presentation. No differences in the enzymatic activities among various subtypes of AML were detected (table III).

The level of the enzyme TdT in normal donors, patients with ALL, and patients with AML are compared in table IV. There was a significant difference in activity of TdT only between normal donors and patients with ALL (\(P = 0.001\)) but not patients with AML. The
FIGURE 1. Adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) activities and PNP/ADA ratio in control and patients with acute myelogenous leukemia. △ = normal and • = acute myelogenous leukemia.

effect of this enzyme on survival of patients with AML was not significant. No significant differences in activity of TdT among subtypes of AML, and no correlations between activity of TdT and survival of patients with AML in each subtype were observed (table V).

Discussion

The biochemical study of intracellular enzymes is of value in classifying as well as in prognostic ALL. Conflicting results have been published in the case of AML. High levels of TdT have been reported to be both good and poor prognostic signs.\(^{28,33}\) In our study, intracellular activity of TdT in patients with AML was not different from that in normal individuals, whereas the activity of TdT in patients with ALL was significantly higher than in normal as reported by Skoog et al.\(^{32}\) There were considerable variations in activity of TdT among FAB subtypes of AML. Relatively high activities were observed in M1, M2 and M3, and low activities in M4 and M5. This is in accordance with other reports that monocytes in general have low levels of TdT.\(^{22,30,32}\) Thus, analysis of TdT might be of some value in the classifying AML; increase in enzyme activity is most likely to be found in AML blasts of granulopoietic origin.
TABLE II
Association Between High Adenosine Deaminase, Low Purine Nucleoside Phosphorylase, Low Purine Nucleoside Phosphorylase/Adenosine Deaminase and Short Survival of Patients with Acute Myelogenous Leukemia

<table>
<thead>
<tr>
<th>Categories</th>
<th>Number of Patients</th>
<th>Number of Cases</th>
<th>Cases More Than 3 Months</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>High ADA (&gt; 9.4 U/mg)</td>
<td>9</td>
<td>7</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Low PNP (&lt; 9.3 U/mg)</td>
<td>11</td>
<td>9</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Low PNP/ADA Ratio (&lt; 1.8)</td>
<td>11</td>
<td>10</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

ADA = adenosine deaminase. PNP = purine nucleoside phosphorylase.

Correlations between detectable levels of TdT and patient survival have been previously described, with both positive and negative correlations reported. Our study found no correlation between survival and activity of this enzyme.

Differences were found by us in the cellular level of ADA, PNP, and their ratio (PNP/ADA) between normal individuals and patients with AML. However, levels of these enzymatic parameters are not correlated with patient survival. Our recent data (unpublished) has revealed that survival of patients with AML is affected by other multiple parameters and in a different degree. These parameters are proliferative capacity of AML cells (P < 0.001), age (P = 0.005), WBC count (P = 0.007), cytogenetics of AML cells (P = 0.04), differentiative capacity of AML cells (P = 0.001), and peripheral blood neutrophil count (P = 0.04). Using multivariate regression analysis to determine the influences of multiple independent parameters on survival, the first four parameters showed meaningful affects on survival with the multiple 'r' value of 0.691 (P < 0.001) (data are not shown).

The lack of relationship between ADA and survival rate of patients with AML has been reported by Skoog et al. In contrast, Bertazzoni et al found that increased level of ADA was associated with short survival and also with M4 and M5 FAB subtype. The increased level of ADA in AML was described as a result of

TABLE III
Purine Degradative Enzyme Level and Survival of Patients with Acute Myelogenous Leukemia as Categorized by the French-American-British Morphologic Classification

<table>
<thead>
<tr>
<th></th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
<th>M6</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Cases</td>
<td>14</td>
<td>22</td>
<td>21</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ADAa (U/mg)</td>
<td>6.0 ± 1.0</td>
<td>6.0 ± 0.8</td>
<td>6.1 ± 0.6</td>
<td>6.1 ± 0.9</td>
<td>4.3 ± 1.3</td>
<td>8.1 ± 0.6</td>
</tr>
<tr>
<td>PNPb (U/mg)</td>
<td>13.2 ± 1.4</td>
<td>16.0 ± 1.5</td>
<td>16.2 ± 1.3</td>
<td>15.8 ± 2.3</td>
<td>14.1 ± 0.4</td>
<td>17.7 ± 0.7</td>
</tr>
<tr>
<td>PNP/ADA ratio</td>
<td>2.6 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>2.9 ± 0.2</td>
<td>2.7 ± 0.4</td>
<td>2.3 ± 1.3</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td>Survivalc (week)</td>
<td>13.9 ± 3.9</td>
<td>32.1 ± 8.4</td>
<td>13.9 ± 4.3</td>
<td>23.5 ± 9.5</td>
<td>86.0 ± 27.6</td>
<td>5.8 ± 2.7</td>
</tr>
</tbody>
</table>

a Adenosine deaminase, Mean ± SEM.
b Purine nucleoside phosphorylase, Mean ± SEM.
c Survival, Mean ± SEM.
the synthesis of structurally normal enzyme. The expression of the ADA gene in acute leukemia is controlled at a post-transcriptional level. Differences in expression of ADA are the result of differences in processing and/or stability of ADA pre-mRNA within the nucleus. In our study, total activities of ADA among subtypes M1, M2, M3, and M4 were not statistically different. Although one of the two patients with M5 showed relatively low activity of ADA (2.49 U per mg) and both patients with M6 showed a relatively high level of this enzyme (8.98 and 7.20 U per mg), the number of patients in these two subtypes was inadequate, and a conclusion could not be drawn. Nevertheless, Berkvens et al reported a decrease in the expression of total ADA in the course of differentiation of human promyelocytic leukemic cell line. Differentiation to monocytes leads to a more pronounced reduction of enzyme activity than does a differentiation to myelocytes. In an analysis by Ratech et al for expression of various isozymes of ADA, including ADA1 (40 kd) and ADA2 (110 kd) in acute and chronic leukemia, revealed that ADA2 was expressed exclusively in nonlymphoid cells whereas ADA1 was found in both lymphoid and nonlymphoid cell types. In addition, AML with a monocyctic component tended to have a greater percentage of ADA2 than AML without a monocyctic component.

Our result concerning the level of PNP in AML was in accordance with Morisaki et al, who found a low level of activity of PNP in mononuclear cells from patients with acute myelogenous and lymphoblastic leukemia (ALL) and with chronic lymphocytic leukemia (CLL). The decrease in activity of PNP in leukemia cells was suggested to be due to alteration of the regulatory mechanism of

<table>
<thead>
<tr>
<th>Group of Patients</th>
<th>TdT Activitya (U/mg)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n = 10)</td>
<td>33.7 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>ALL (n = 6)</td>
<td>190.6 ± 30.2</td>
<td>0.001 b</td>
</tr>
<tr>
<td>AML (n = 52)</td>
<td>82.8 ± 15.8</td>
<td>NS c</td>
</tr>
</tbody>
</table>

TdT = terminal deoxynucleotidyl transferase. ALL = acute lymphoblastic leukemia. AML = acute myelogenous leukemia.

a Mean ± SEM.
b Normal vs. ALL, Mann Whitney U test.
c Normal vs. AML, Mann Whitney U test.

<table>
<thead>
<tr>
<th>M1 (n = 13)</th>
<th>M2 (n = 19)</th>
<th>M3 (n = 14)</th>
<th>M4 (n = 4)</th>
<th>M5 (n = 2)</th>
<th>Total (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TdT activitya (U/mg)</td>
<td>126.0 ± 52.2</td>
<td>69.2 ± 15.6</td>
<td>82.4 ± 20.3</td>
<td>34.7 ± 26.0</td>
<td>19.4 ± 8.9</td>
</tr>
<tr>
<td>Survivala (week)</td>
<td>10.0 ± 2.9</td>
<td>21.7 ± 6.5</td>
<td>10.8 ± 2.9</td>
<td>13.7 ± 6.3</td>
<td>73.5 ± 36.5</td>
</tr>
<tr>
<td>Correlation coefficient (r)</td>
<td>0.24</td>
<td>0.20</td>
<td>0.19</td>
<td>0.61</td>
<td>—</td>
</tr>
</tbody>
</table>

TdT = terminal deoxynucleotidyl transferase. a Mean ± SEM.
enzyme synthesis in purine metabolism in the leukemic clone, which might lead to a decreased rate of enzyme synthesis. Sylwestrowicz et al. on the other hand, found little difference in levels of PNP between normal individuals and patients with AML.

About 91 percent of our patients with AML whose PNP/ADA ratios were less than 1.8 had short survival; these patients survived no more than three months from their first presentation. The high ADA, low PNP enzyme pattern was also reported in T-ALL and CD10 positive T-ALL (mix C + T-ALL phenotype). The T-ALL marker is important in the determination of the clinical course and prognostic significance of ALL in children; children with T and CD10 positive T-ALL phenotype, in contrast to C-ALL, experience more frequent relapses and shorter survival. Our findings on AML imply, to a certain extent, that the association between low PNP/ADA (either as the result of increase in ADA or decrease in PNP) and short survival may reflect the clinical severity of the diseases rather than specific characteristics of subpopulations of AML, because no significant differences in these enzymes were found among AML subtypes. As PNP deficiency results in a selective lack of T cell development, the decreased level of PNP in intramonomonuclear cells in patients with AML might lead, at least partially, to a reduction in host immune surveillance against cancer which, in turn, could reduce chances of survival. There is still no concrete evidence supporting this hypothesis.

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