Variations in Serum Alkaline DNase Activity: A New Means to Assess Early Detection of Relapse in Patients Treated for Acute Nonlymphoblastic Leukemia

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Our previously published clinical results on various malignancies indicated that the variations in serum alkaline DNase activity (SADA) could be a sensitive test for therapeutic monitoring of human malignancies. In the present study, the clinical efficacy of SADA detecting relapse in 32 acute nonlymphoblastic leukemia (ANLL) patients in remission was tested. The observation period ranged from 3 to 17 months. A simple and rapid biochemical technique based on spectrophotometric measurements was used to assay SADA. Of the 32 patients, 17 remained in remission and had less than a 15% variation in SADA levels. They had no clinical symptoms of recurrence at any time. In the remaining 15 patients, after a period of stability, a progressive decrease in SADA, with variations of more than 15%, was observed without any treatment. At that time, no abnormalities of clinical parameters were detected in these patients. A recurrence of disease as evidenced by routine examinations was found relatively late after the first decrease in SADA in all 15 patients (range 1.5 to 5.5 months). These results suggest that periodic measurements of SADA during the posttherapeutic course can be used as a means to assess early detection of an eventual recurrence.

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Supported by a grant from Sopar S.A. and Ministère des Technologies Nouvelles de la Région Wallone, Belgium.

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A TEST THAT rapidly predicts the sensitivity of a tumor to therapy as well as maintenance of remission or an eventual occult disease might permit a better monitoring of cancer patients and a rapid selection of more effective therapeutic means.1 Alkaline DNase is present in the serum of all mammals.2,3 Love and Hewitt4 observed that at least five isoenzymes exist in human serum and that the major isoenzymatic form of human alkaline DNase may originate from the pancreas. However, no definite physiologic role has yet been assigned to alkaline DNase.5

Our clinical studies during the follow-up of patients with different kinds of malignancies indicated that the variations in SADA level in an individual patient correlate closely with response to therapy. SADA also appeared to be useful in estimating prognosis in the long-term follow-up of cancer patients.6

We investigated whether the variations in SADA could have a prognostic value in early detection of recurrence of cancer. SADA was systematically examined as a possible marker for eventual recurrence in patients who have achieved complete remission after ANLL treatment.

MATERIALS AND METHODS

The patients were examined and followed in the Hospital of the University of Louvain in Brussels. Thirty-two adults aged 17 to 75 years in first remission after induction and consolidation therapy were followed during their posttherapeutic course. Regular SADA measurements were made and compared with clinical and biologic criteria. The observation period ranged from 3 to 17 months.

Five to 10 milliliters of blood were collected in tubes without anticoagulants. After coagulation, the blood was centrifuged and the serum was stored at -20°C. Under these conditions, the SADA is stable for more than 6 months.

For biochemical detection of SADA, the generally known spectrophotometrical technique originally described by Loiselle and Carrier6 was adapted.6 The amount of oligonucleotides liberated during incubation was measured at 260 nm. A control specimen to which EDTA was added (to block enzyme activity) was used as a blank. The results are expressed in international kilo units per liter (kU/L) of serum. The intraassay and interassay coefficients of variation were 3.6% and 8.5%, respectively.

Clinical information concerning peripheral blood (PB) counts, smears, and bone marrow (BM) examination for leukemic cells (blast cells), were collected, analyzed, and used to evaluate the remission status. Complete remission was defined as normocellular BM (less than 5% blasts). Disease was considered to have recurred when leukemic cells were observed in PB or BM aspirates or both. Data were analyzed statistically by variance analysis with subsequent t test and by Pearson correlation test.

RESULTS

Of the 32 patients, 17 had a stable SADA level for months after discontinuation of chemotherapy (Fig 1). The 17 patients had no clinical symptoms of recurrence. Periodic blood smears and BM examinations showed no leukemic cells at any time.

After a period of stability of SADA level, however, the remaining 15 patients showed a progressive decrease of enzyme activity at each examination (Fig 2). During the period of stability of enzymatic activity, no leukemic cells were detected in these patients. In addition, for several months after the decrease in SADA began, clinical parameters such as white blood cell (WBC) counts, score of blasts in PB, and percentage of blasts in the BM showed no abnormalities in these 15 patients. Relatively late after the first decrease in SADA ranging from 1.5 to 5.5 months, a recurrence of disease as evidenced by PM smears or BM examinations or both was detected in the 15 patients.
DISCUSSION

This study shows that ANLL patients who remain in remission have less than a 15% variation in SADA levels, whereas patients who relapse show a progressive decrease in SADA of more than 15% during the period without any treatment. This decrease in SADA precedes clinical detection of recurrence evidenced by the presence of leukemic cells in PB or BM aspirates or both. The interval between initial SADA decrease and clinical relapse ranged from 1.5 to 5.5 months.

Factors that determine the alterations that occur in SADA levels in malignancy are unknown.4,5 The early decrease in SADA levels before any detectable signs of relapse may suggest a direct correlation between SADA depression and cancer growth. Indeed, our recent experimental results indicate that SADA decreases rapidly after transplantation of tumor cells to rats, and this decrease precedes detection of tumor mass.11

Observations of different investigators12-14 suggest a complex mechanism of regulation of alkaline DNase activity in tissues and body fluids in which several factors may be
involved. Viable\textsuperscript{15-17} and necrotic\textsuperscript{18} cells of malignant tumors have characteristic changes of alkaline DNase activity that depend on natural inhibitor(s) (eg, actin). Such changes in malignant tumors may in a direct way or by some intermediate mechanisms influence SADA variations.

The variations in SADA level may be linked to qualitative or quantitative variations of the inhibitor(s) or other factor(s). A greater amount of the inhibitor may be released into the circulation, preferably when cells are in proliferation, thus decreasing the enzymatic activity, or an “uptake” process of the serum enzyme may occur through increased content of inhibitor in the tumor cells.

Our results confirm our hypothesis that the variations in SADA level in an individual patient could be a useful predictor of length of remission and of relapse. The possibility of therapeutic intervention on the ground of SADA results alone should be considered as a possible future development. In the meantime, SADA could be used as an early warning sign of recurrence and thus could accelerate the clinician’s decision to make clinical tests sooner. The present findings should be confirmed in more leukemia patients involved in multicenter trials; SADA variations would be measured in local laboratories. Measurements of SADA in patients who have had BM transplantation as well as fundamental aspects of SADA variations in cancer-bearing humans and animals are under investigation.

ACKNOWLEDGMENT

We thank Dr A. Ferrant, Département de Médecine Interne, and Dr M. Opsomer for providing all clinical facilities for the study, V. Allacys and C. Heusdains for excellent technical assistance, and S. Suciu for valuable comments.

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