CONCISE REPORT

Chlorambucil Therapy in Hairy Cell Leukemia: Effects on Lipid Composition and Lymphocyte Subpopulations


Two patients with progressive hairy cell leukemia following splenectomy were treated with low-dose daily chlorambucil. Both had an objective hematologic response as determined by a return to normal hematocrit and platelet count. This was also reflected in the mononuclear cell fraction by the normalization of cholesterol content, cholesterol/phospholipid ratio, and the lymphocyte subpopulations. This article confirms previous reports on the efficacy of chlorambucil in this setting and describes some morphological, immunologic, and biochemical concomitant events.

HAIRY CELL LEUKEMIA (HCL) is a disease characterized by the presence of circulating mononuclear cells with long processes that cover their surfaces. Clinically, patients present with splenomegaly and pancytopenia. The pancytopenia may reflect hypersplenism resulting from leukemic infiltration of the spleen by hairy cells (HC). While splenectomy results in improvement in about two-thirds of the cases, the remainder have progressive disease. Golomb and Mintz have reported that post splenectomy HCL patients with progressive disease usually benefit from treatment with chlorambucil.

In this article, we confirm the efficacy of chlorambucil therapy in two post splenectomy HCL patients with progressive disease with the concomitant return towards normal lymphocyte subpopulations.

MATERIALS AND METHODS

The clinical diagnosis of HCL was substantiated by morphological appearance and a positive tartrate-resistant acid phosphatase (TRAP) reaction of the characteristic cells. Bone marrow biopsy and spleen tissue morphology were confirmative in both cases. The methods of measuring cholesterol (C) and phospholipid (PL) have been published previously. The presence of the spleen had no effect on the C/PL content of HC or normal mononuclear cells. The percentage of T and B cells was determined by sheep erythrocyte-forming and erythrocyte-antibody-complement-forming rosettes (EAC). Although HC have been considered to be B cells as judged by the presence of Slg, they are not typical B cells since the EAC receptor is absent. Mononuclear cells were isolated by centrifugation on Ficoll-Hypaque gradients. Normal monocytes were removed by adherence to plastic as described previously. The purity of cellular preparations, which exceeded 90% for all experiments, was ascertained by cell sizing analyses on a Model B Coulter Counter equipped with a 100 μm aperture and calibrated with 10 μm latex particles. Mononuclear cells from patients with HCL have been shown to consist of two populations, a major one that is comparable to monocytes in volume and a minor one slightly larger than normal lymphocytes.

RESULTS AND DISCUSSION

Case 1 (See Fig. 1)

The patient is a 54-yr-old white male who was found to have HCL 4 yr ago on a routine complete blood count. At that time his white blood cell count (WBC) was $6.0 \times 10^3/\mu l$. Confirmatory bone marrow biopsy and TRAP were done. One year later, the hematocrit (Hct) decreased to 18% and the platelet count was $66\% \, 10^3/\mu l$. A splenectomy was performed with a subsequent rise in Hct to 27% and platelet count to $113 \times 10^3/\mu l$. However, within 1 yr, the Hct had decreased to 16%, platelet count had decreased to $88 \times 10^3/\mu l$, and the WBC had increased to $46 \times 10^3/\mu l$. The patient was treated with chlorambucil, 4 mg/day. The dosage was reduced to 2 mg/day within 1 mo. Three months after initiating treatment, the chlorambucil was discontinued. The Hct was 38%, WBC $2.0 \times 10^3/\mu l$, and platelet count $235 \times 10^3/\mu l$. Cholesterol and C/PL ratio returned to normal (Table 1). T-cell and B-cell lymphocyte percentages had also returned to normal (Table 1). Cell sizing confirmed the decrease in HC. In May 1981, the patient was hospitalized because of fever and a pulmonary infiltrate. Although no pathogen was cultured, he defervesced on clindamycin and gentamicin. During the hospitalization, the WBC increased to $5.0 \times 10^3/\mu l$ (77% granulocytes). Eighteen months after the discontinuation of chemotherapy, the hemogram was as follows: Hct 45%, WBC $3.5 \times 10^3/\mu l$, and platelet count $225 \times 10^3/\mu l$. Rare HC persist on the peripheral smear.

Case 2 (See Fig. 1)

The patient is a 65-yr-old white male who was found to have an elevated WBC 3.5 yr ago. The diagnosis of HCL was made upon referral to this institution 6 mo later when bone marrow biopsy and TRAP confirmed the diagnosis suggested on peripheral smear. At
that time, the Hct was 34%, WBC $29 \times 10^3/\mu l$, and platelet count $66 \times 10^3/\mu l$. A splenectomy was performed 1 yr later because of progressive splenomegaly, anemia, and thrombocytopenia. Following surgery, the Hct increased to 38% and the platelet count rose to $171 \times 10^3/\mu l$, but within 2 mo, the WBC had increased to $100 \times 10^3/\mu l$. The patient was treated with chlorambucil, 4 mg/day, which was decreased to 2 mg/day 6 mo later. Cholesterol, C/PL ratio, and T-cell percentages have returned to normal (Table 1) and EAC were 1%. Cell sizing shows that HC are now a very minor component when compared to the pretreatment values (Fig. 2). Four months later, with the patient still on treatment with chlorambucil, the Hct was 43%, WBC $5.7 \times 10^3/\mu l$ (28% granulocytes), and platelet count $308 \times 10^3/\mu l$.

Two patients with HCL and progressive disease following splenectomy have been treated with low-dose daily chlorambucil. Both cases showed an excellent response. This confirms the efficacy of this drug in the treatment of this disorder.5,6

Cell sizing accurately reflects the percentage of HC on peripheral smear.13 Chlorambucil appears to selec-

| Table 1. |
|-------------------------|--------------------------|--------------------------|--------------------------|
|                         | Cholesterol (μmol/10^9 Cells) | C/PL† | T Cell‡ | B Cell§ |
| HC                      | $4.7 \pm 1.5\ddagger$ | $0.60 \pm 0.09\S$ |
| Monocyte                | $5.6 \pm 2.1$            | $0.59 \pm 0.06\S$ |
| Lymphocyte              | $2.8 \pm 0.7$            | $0.50 \pm 0.07\S$ |
| Patient 1               |                         |      |          |        |
| Postsplenectomy          | $7.1 \pm 2.2$            | $0.60 \pm 0.09 (7)$ |
| Day 20 CLB rx*          | $2.7$                    | $0.42$ |
| Day 60 CLB rx           | $3.2$                    | $0.50$ |
| Patient 2               |                         |      |          |        |
| Presplenectomy           | $5.2 \pm 0.6$            | $0.60 \pm 0.11 (8)$ |
| Postsplenectomy          | $6.0$                    | $0.64$ |
| Day 80 CLB rx           | $4.1$                    | $0.46$ |
| Day 200 CLB rx          | $2.3$                    | $0.44$ |

*CLB rx, chlorambucil therapy.
†Cholesterol/phospholipid ratio.
‡Mean ± SD.
§Previously published data.7
Number in parenthesis is the number of samples.
\SPercent monocyte-depleted mononuclear cells.
tively decrease the larger of the two populations identified by cell sizing, i.e., HC (Fig. 1). Concomitantly, the cholesterol content and C/PL ratio of the mononuclear cell fraction returned to that of normal lymphocytes (Table 1). This demonstrates that the higher values of cholesterol and C/PL ratio seen in HCL are related to the presence of HC. Similarly, the decrease in the HC population leads to a relative increase in both B-cell and T-cell lymphocyte percentages (Table 1).

Chlorambucil treatment induces a return to normal Hct and platelet count (Fig. 2). Although the WBC remains somewhat low, granulocyte reserve may be adequate, as seen in patient 1 during an episode of pneumonia. Low-dose daily chlorambucil appeared effective in postsplenectomy HCL patients with progressive disease. Further studies are needed on the efficacy of this agent prior to splenectomy.

REFERENCES
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Chlorambucil therapy in hairy cell leukemia: effects on lipid composition and lymphocyte subpopulations

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