Cyclic Leukocytosis in Chronic Myelogenous Leukemia: New Perspectives on Pathogenesis and Therapy

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Studies were performed on a teen-age female identical twin with cyclic leukocytosis and Ph'-positive chronic myelogenous leukemia (CML), in an attempt to analyze the relationship of these cycles to her disease and to utilize the cycles as reference points for kinetic studies and as landmarks in the progression of her disease. She remained untreated for 21/2 yr. Colony-stimulating factor levels showed an inverse relationship to the peripheral leukocyte count. Two distinct phases in cyclic patterns of peripheral leukocyte counts prior to treatment could be appreciated in retrospect: phase 1, a stable 15-mo period during which leukocyte counts peaked every 10 wk and then returned to baseline levels, and phase 2, an 18-mo period of insidious deterioration during which the low points of successive cycles became progressively higher and leukocytes were accumulating in the peripheral blood at a rate of $400 \times 10^6$/day. We propose that the increased marrow production of myeloid cells in this disease does not represent a life-threatening situation until cell accumulation begins. We attempted, therefore, to halt or to reverse this accumulation by cell separator leukapheresis.

Over the past 5 yr, we have had the unique opportunity to observe the natural history of chronic myelogenous leukemia (CML) in a now 17-yr-old girl, an identical twin. Because the patient was asymptomatic when first seen, treatment was withheld. Shortly thereafter, it was realized that her peripheral leukocyte count was cycling between 4000 and 130,000 cells/cu mm approximately every 72 days. At that point, studies were designed to analyze...
the course and progression of her disease by utilizing the peaks and troughs of her cycles as landmarks or reference points. A comparative analysis of the following parameters was undertaken: differential leukocyte counts, leukocyte alkaline phosphatase (LAP) scores, lysozyme and glycosphingolipid levels, the numbers of Philadelphia chromosome (Ph') positive cells in peripheral blood and bone marrow, colony-stimulating factor (CSF) activity, bone marrow kinetics, and neutrophil function, survival, and turnover.

By far, the most striking changes observed before treatment was initiated were in the peripheral leukocyte count (Fig. 1), which, in retrospect, can be divided into two phases: phase 1—a stable period of 15 mo from time of diagnosis, and phase 2—a period characterized by progressive accumulation of myeloid cells in the peripheral blood over the next 18 mo. On the basis of conclusions reached from these studies, therapy was aimed specifically at assisting host mechanisms in the removal of myeloid cells with the aid of a cell separator (Aminco Celltrifuge). The purpose of this communication is to emphasize the association of cyclic leukocyte counts in a patient with CML, to report the changes observed in the parameters listed above at high and low points of these cycles during the two pretreatment phases of her disease, and to describe briefly the effects of leukapheresis therapy.

CASE REPORT

The patient, a 12-yr-old white female, began complaining of vague aches and pains during the spring of 1968. Her leukocyte count and a subsequent bone marrow examination were interpreted as showing myelocytic leukemia. She was referred to the University of Minnesota Hospitals in October 1968.

At birth, she was one of identical twins and weighed 2 lb 3 oz. A maternal uncle had died with aplastic anemia and leukemia. Another maternal uncle has two children with cancer of the colon.

On initial physical examination, the patient's liver and spleen were both palpable 2 cm below the costal margin. The remainder of the exam was normal. Initial hemoglobin was 14.3 g/100 ml; white blood count was 19,500 cells/cu mm containing 72% neutrophils, 11% lymphocytes, 7.4% monocytes, 2.2% eosinophils, 3.2% basophils, 3.0% myelocytes, and 0.4% promyelocytes, and the platelet count was 450,000/cu mm. Initial LAP score was 63 (normal 64–176), and serum B12 level was 1470 (normal range 150–600). The vitamin B12 disappearance time was normal, and the fetal hemoglobin was 1%. Philadelphia chromosomes were identified in 28 of 35 metaphases counted among bone marrow cells cultured without addition of phytohemagglutinin. The patient was discharged without treatment with a diagnosis of CML.

Over the next several months, periodic blood tests revealed the cyclic nature of her peripheral leukocyte counts (Fig. 1). It was also noted that when the leukocyte count was at its peak, the patient suffered from headaches, fatigue, and mild malaise, and her spleen was enlarged. Biannual studies of the identical twin, including physical examination, complete blood counts, and bone marrow karotyping, have all been normal to the present. (Identity of the twins is supported by blood typing, dermatoglyphics, and appearance.)

KINETIC STUDIES OF CYCLIC LEUKOCYTOSIS

The cycles observed in this patient have been of uniform periodicity for a period of over 48 mo with an average duration of 72 days. The amplitude of individual cycles has ranged from 30,000 (cycle 10) to 124,000 (cycle 6) cells/cu mm. The pattern of early cycles suggested a stable period of uniform oscillations, with leukocyte counts returning to normal or near normal after each rise; we have called this phase 1.
CYCLIC LEUKOCYTOSIS

Fig. 1. Cyclic pattern of patient's peripheral leukocyte counts is demonstrated over 3-yr period. Levels of colony-stimulating factor activity in urine and serum are also shown in relation to peripheral leukocyte counts. Note inverse relationship of these two parameters.

Beginning in January 1970, the low points of successive cycles showed a progressive increase (dashed line, Fig. 1), a trend that continued over the next 18 mo; we have called this phase 2. Calculations based on the slope of this trend line indicated an increase of approximately $29 \times 10^9$ leukocytes in the patient’s peripheral blood after each new cycle, an average increase of $400 \times 10^6$ leukocytes/day during this phase. During the latter months of phase 2, the patient’s spleen remained palpable throughout all phases of the peripheral leukocyte cycles. She also experienced more frequent headaches, occasional dizziness, and increased fatigue and malaise. In June 1971, cell separator leukapheresis therapy was initiated, thus ending phase 2.

In addition to the cyclic pattern observed prior to treatment in the total leukocyte count, cycling was noted in the peripheral lymphocyte, monocyte, and platelet counts. These cycles were in exact phase with the total leukocyte count cycles during phase 1 and phase 2. During cycle troughs in phase 2, absolute numbers of both lymphocytes and monocytes failed to return to normal ranges, similar to the total leukocyte count pattern during this phase. However, the percentages of lymphocytes and monocytes in the peripheral blood were never greater than normal. Erythrocyte counts did not appear to be cycling.

**Differential Counts**

Prior to treatment, differential counts of peripheral blood smears were obtained weekly over two periods, one of 8-mo duration covering cycles 2-5 of phase 1 (Fig. 2A and B) and one of 10-mo duration covering cycles 10-14 of phase 2 (Fig. 3). In phase 1, the order of appearance and disappearance of myeloid cells in the peripheral blood followed the order of their maturity (Fig. 2A and B). The 72-day cycles of the total leukocyte count persisted during these periods. Furthermore, a trend toward increasing numbers of all immature myeloid forms, including bands, can be appreciated in Fig. 3 by comparing absolute numbers in each cell compartment at successive high or low points. This trend may represent the very early origins of a blastic crisis. Differential counts of bone marrow specimens were obtained on 11 different occasions and are recorded in Table 1.

**Marrow Cellularity**

Marrow cellularity was assessed both by histologic inspection of slides and by measurement of the ME layer (Fig. 4). (The myeloid-erythroid layer is the percentage of nucleated cells in a 1 ml aspirate of bone marrow, as assessed by measuring the buffy coat in a
Fig. 2. (A and B) Changes in absolute numbers of mature and immature myeloid cells in peripheral blood during three cycles early in phase 1 (see Fig. 1). Note that order of appearance of less mature cells follows their degree of maturity, with the least mature cells appearing last and disappearing first.

Wintrobe tube after centrifugation at 3000 rpm for 30 min. This layer includes myeloid and lymphoid cells, normoblasts, monocytes, and megakaryocytes.) All values in phases 1 and 2 were elevated (normal 4%-9%). Fluctuation of these measurements during cycles 6 and 9 suggested a cyclic pattern of marrow cellularity that was in phase with peripheral leukocyte counts. Of great interest was the ME layer of 1% immediately following 12 leukaphereses by cell separator over an 8-wk period. Two months later, at the peak of the next cycle, marrow cellularity was again markedly increased (38%). Following a second course of 18 leukapheresis treatments 1 yr later, the ME layer similarly fell to 2%.

Marrow specimens obtained during high and low points of cycle 6 were pulsed for 1 hr with tritiated thymidine and were processed for radioautographic analysis in order to measure the labeling index of the various cell compartments. (This index represents the proportion of cells labeled in each compartment, i.e., myeloblast-promyelocyte, myelocyte, or metamyelocyte.) A labeling index of 80% in the myeloblast-promyelocyte compartment (vs. 32% in normals) indicated that active proliferation exists in this compartment just prior to the cycle peak. At the low points, when the ME layer was 10%, a labeling index of 47% indicated only slightly increased proliferative activity in this compartment at this time. Labeling indices in the myelocyte compartment were normal on both occasions. These observations indicate increased marrow production of early myeloid elements and suggest cyclical changes of proliferative activity in the patient's marrow during early cycles.

Fig. 3. Changes in absolute numbers of mature and immature myeloid cells in peripheral blood during four cycles in phase 2 (see Fig. 1). Compare with Fig. 2A and B and note failure of immature forms to disappear from peripheral blood during cycle troughs in phase 2. Note, also, gradual increase in absolute numbers of immature cells, especially bands and metamyelocytes.
<table>
<thead>
<tr>
<th>Date</th>
<th>Promyelocyte</th>
<th>Myelocyte</th>
<th>Metamyelocyte</th>
<th>Bands</th>
<th>PMN</th>
<th>Erythrocyte Precursors</th>
<th>Neutrophilic Monocyte</th>
<th>Other</th>
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<td>4</td>
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<td>10</td>
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<td>22</td>
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<td>15</td>
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<td>14</td>
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<td>14</td>
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<td>10</td>
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Similar pulse-labeling studies performed late in phase 2, just prior to treatment, again showed an elevated labeling index (69%) in the myeloblast-promyelocyte compartment and a normal labeling index in the myelocyte compartment. On this occasion, 7% of the metamyelocytes were labeled.

**LAP Scores**

When first studied, the patient's LAP score was just below normal levels. It was not appreciated at the time that her leukocyte count was at a cycle low point. Later measurements of LAP ranged from 3 to 48; the former value occurred when the leukocyte count was 106,250 cells/cu mm (just prior to peak of cycle 6). Figure 5 demonstrates an inverse relationship between the peripheral leukocyte count and the LAP score.

**Lysozyme (Muramidase)**

Serum lysozyme levels were measured on 26 occasions during the 3-yr study period. All but two values were elevated. No correlation was noted with leukocyte cycles or with absolute leukocyte counts.

**Philadelphia Chromosome**

Cytogenetic studies of peripheral blood (unstimulated cultures) and bone marrow (direct squash preparations) cells at high and low points of leukocyte cycles during phase 1 consistently revealed cells containing a Philadelphia chromosome.

**Colony-stimulating Factor (CSF) Activity**

Beginning with cycle 6, urine and/or serum specimens were collected periodically for measurement of CSF activity. As seen in Fig. 1, peak levels were observed when the peripheral leukocyte count was at its lowest point between cycles 6 and 7. CSF activity
again reached a peak 73 days later at the time of the next leukocyte low point. The next CSF peak, however, did not correspond with a peripheral leukocyte low point. The pattern of subsequent CSF levels was erratic for the remainder of phase 2 and may reflect the fact that during this period the leukocyte count was never below 28,000 cells/cu mm. Following leukapheresis in 1971, a striking peak of CSF activity in both urine and serum specimens followed the fall of the leukocyte count from 128,000 to 19,000 cells/cu mm and again corresponded with the lowest point of the peripheral leukocyte counts recorded during that period (Fig. 1). A similar rapid rise in CSF levels was observed during leukopheresis treatment given 1 yr later.

It is of further interest that it was not necessary for the leukocyte count to fall to truly neutropenic levels in order for the CSF levels to peak: cycle 6–7 peak, WBC 16,000; cycle 7–8 peak, WBC 21,000; in 1971, WBC 19,000; peak after second treatment, WBC 75,000.

**Glycosphingolipid Levels**

Serum glycosphingolipid levels were measured at the low point of cycle 7–8 and at the high point of cycle 9 early in phase 2 (courtesy of Dr. W. Krivit and Dr. R. Desnick). On both occasions, fraction 2 (GI-2) was elevated: 1.50 <sup>2</sup>S <sub>M/100 ml</sub> and 4.42 <sup>2</sup>S <sub>M/100 ml</sub>, respectively (normal 0.3–0.5 <sup>2</sup>S <sub>M/100 ml</sub>). Lipid-laden “Gaucher-type” macrophages have been observed in the bone marrow of this patient.

**Inflammatory Response**

Rebuck skin window studies were normal at high and low points in the peripheral leukocyte cycle, suggesting a normal response of the peripheral leukotactic factors.

**Neutrophil Studies**

We attempted to evaluate the degree to which the marrow reserves of neutrophils could be delivered to the peripheral circulation at opposite phases of the patient’s cycles. When endotoxin (20 × 10<sup>8</sup> killed typhoid-paratyphoid organisms) was infused intravenously over 1 hr at the high point of cycle 6 late in phase 1, a 37% increase in the absolute neutrophil count was noted with a peak at 6 hr. When this study was repeated at the next low point 7 wk later, an 83% increase was observed with a peak at 4 hr. Similar studies were performed during cycle 6 using 100 mg hydrocortisone, intravenously, as the stimulant for leukocytosis. Comparable results were obtained: at the high point, a 16% increase by the sixth hour; at the low point, a 75% increase by the third hour, suggesting intact mechanisms of marrow release at both phases of this cycle.

To evaluate the marginal pool release of peripheral neutrophils, epinephrine (0.4 cc/sq m) was given subcutaneously, and increases of 28% and 102% were observed at respective high and low points of cycle 6. Peak responses were noted at 30 and 45 min after injection, respectively.

Intravascular granulocyte survival was measured on four occasions by reinfusion of autologous granulocytes after in vitro labeling of 10% of blood volume with radioactive diisopropylfluorophosphate (DFP<sup>32</sup>), according to the method of Deinard and Page. The results are summarized in Table 2. Prolonged intravascular granulocyte survival times (t½) have been previously described in CML. The technique employed for measuring granulocyte survival depends on unidirectional trafficking of granulocytes from marrow into the peripheral circulation and then into tissues. Because there is some evidence that granulocytes in CML patients may recycle through the marrow compartment and reenter the circulation, we find it difficult to interpret these measurements.

**DISCUSSION**

Although not commonly appreciated, cyclic leukocytosis has been previously described in patients with CML. In the four patients described by Morley et al., the periods of oscillation were 30, 40, 50–55, and 110–120
Table 2. Granulocyte Kinetics

<table>
<thead>
<tr>
<th>Date</th>
<th>Weight (kg)</th>
<th>Point in Cycle</th>
<th>TBGP* (× 10⁹/kg)</th>
<th>t½ t (hr)</th>
<th>GTR* (× 10⁹/kg/day)</th>
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<tr>
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<td>48</td>
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<td>22</td>
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<tr>
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<td>—</td>
<td>0.65</td>
<td>4–9</td>
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*Total blood granulocyte pool.
†Intravascular granulocyte survival half-time.
‡Granulocyte turnover rate.

days. These figures are based on 80–200-day observation periods in patients receiving therapy for their disease. Vodopik et al. described a patient with chronic myelogenous leukemia whose leukocyte and platelet counts cycled every 66 days even after 2 yr of radiation therapy to her spleen and liver. Kennedy observed cycling of this nature in several CML patients who were receiving hydroxyurea therapy.

Morley et al. have suggested that in patients with cyclic leukocytosis and CML the bone marrow is either unduly sensitive to a feedback stimulus or is acted on intermittently by an abnormally strong stimulus originating at a site other than the bone marrow. In 1970, we suggested that this intermittent stimulus might be CSF on the basis of preliminary observations of a cyclic pattern of urinary CSF activity in this patient. Robinson and Pike also showed that CSF activity was elevated in each of five CML patients studied; cycling, however, was not observed in these patients. Since CSF is clearly responsible for differentiation of marrow precursor cells in vitro, it is entirely possible that this factor may act in vivo as a stimulus for leukopoiesis in the bone marrow.

We noted an inverse relationship between our patient's CSF levels and her peripheral leukocyte counts. This relationship has since been documented in rats and dogs as well. These observations suggest a causal relationship between CSF levels and peripheral leukocyte counts. Indeed, it has been proposed that CSF may originate primarily from the destruction of peripheral neutrophils. Our studies in this patient do not support this proposal, since we observed a marked rise in CSF following mechanical removal of neutrophils with a cell separator. It would appear, therefore, that CSF is released from another site(s) in response to a falling leukocyte count.

The inverse relationship of our patient's LAP score to peripheral leukocyte counts strongly suggests that a normal LAP-positive neutrophil population predominated during phase 1 cycle troughs and that an abnormal "leukemic," LAP-negative neutrophil population predominated during phase 1 cycle peaks and throughout the cycles during phase 2. Since only segmented neutrophils are scored in a leukocyte alkaline phosphatase determination, the large numbers of immature myeloid cells present during cycle peaks in phase 1 and at all times during late phase 2 would not alter the LAP score. Chervenick et al. have recently demonstrated two populations of myeloid...
precursor cells in the bone marrow of CML patients by inducing such cells
to differentiate in a methylcellulose medium followed by karyotyping. They found both Ph'-positive and Ph'-negative cells in different colonies
(i.e., clones) within the same culture plate.

Discordance for this disease among identical twins provides strong
support for the hypothesis that CML is an acquired disorder. The normal
twin siblings have remained well; the longest documented follow-ups are
8 yr. In only one family, out of ten reported, were identical twins concordant for CML. In that family, an older brother was also diagnosed
as having Ph' CML. All three diagnoses were established within several
weeks of one another. The absence of the Ph' chromosome in lymphocytes
and fibroblasts of most CML patients also argues against a hereditary basis
for this chromosomal abnormality, an abnormality that has remained a
pathognomonic finding of CML since its original description by Nowell and
Hungerford in 1960.

An approach to the treatment of our patient was suggested by these
studies. It appeared, in retrospect, that the natural course of her disease
could be divided into two distinct phases: one was stable and apparently
benign; the other was progressive and life threatening if left untreated. Quite
apart from primary pathogenetic mechanisms that appear to result in massive
overproduction of myeloid cells in the bone marrow, her peripheral leukocyte
cycles during the first 15 mo described a pattern indicating that the excessive
numbers of myeloid cells could nevertheless be cleared from the peripheral
blood before the beginning of the next cycle. Thus, her leukocyte counts
returned to base-line levels during phase 1 cycles. In contrast, during phase 2,
those largely unknown mechanisms that are responsible for clearing myeloid
cells from the peripheral circulation appeared to be gradually falling behind
the rate of production of these cells. It cannot be determined from our studies
whether this accumulation of myeloid cells in the peripheral blood during
phase 2 reflects primarily an increase in cell production or a progressive loss
of cell-clearing capacity with little or no change in rates of production. It is
also not clear whether a reduction of cell-clearing capacity might be the
result of a defective membrane marker that perturbs cellular egress from the
peripheral circulation or of faulty cell catabolism mechanisms. It is obvious,
however, from the slope of the dashed line of Fig. 1 that leukocytes were
accumulating in the peripheral blood of this patient at a rate of \(400 \times 10^6\) \text{/day}
during the 18-mo period preceding therapy. We interpreted this fact as a
warning that any form of treatment that would destroy large numbers of
cells in vivo, such as conventional chemotherapy, might further compromise
cell catabolism mechanisms and possibly be detrimental to the patient. In
addition, we reasoned that if cell clearance mechanisms were primarily
responsible for the progressive rise in the leukocyte counts during phase 2,
then periodic leukapheresis might heal or even reverse the rising leukocyte
levels and provide sufficient therapy to maintain such a patient in relatively
good health for years.

Following leukapheresis, the first cycle observed was of low amplitude
and the leukocyte count returned to near the baseline level established at
the beginning of that cycle (Fig. 6). The observed ME layer of 1% in the bone marrow, immediately following 8 wk of intensive leukapheresis, provides a preliminary indication of the potential efficiency of this form of treatment in reducing the abnormally increased marrow cellularity in this disease and of its effectiveness in removing mature and immature cells from the marrow, as well as from peripheral blood. The patient was clinically improved following leukapheresis and remained well without any additional treatment for 1 yr. However, subsequent cycles indicated reaccumulation of myeloid cells in the peripheral blood. Peripheral leukocyte cycles continued to last 72 days (Fig. 6). The patient has recently undergone another course of leukapheresis treatment that brought her peripheral leukocyte count to below 10,000/cu mm. This is followed by a low amplitude cycle, similar to that seen following previous treatment, and a resumption of the cyclic leukocytosis.

The relevance of our studies to other patients with CML will depend on several factors: (1) Is cyclic leukocytosis in CML a rule or an exception? It seems likely that if a valid attempt is made to document cycling before therapy is initiated, it will be found in other patients with CML. (2) Is this 16-yr-old girl's CML basically the same disease as CML in adults? The presence of the Philadelphia chromosome and the absence of elevated fetal hemoglobin levels differentiate her disease from the usual childhood form of CML. (3) Will the apparent "phases" observed in this patient be appreciated in other CML patients? This will depend whether cycling is present to permit us to see these phases unassisted by more sophisticated analyses and whether the diagnosis is made early enough, since there may be little reason for a patient to seek medical attention during the "benign" phase. The duration of these cycles may also have prognostic significance. (4) Does leukapheresis constitute an effective means of therapy for CML? It is too early to evaluate this form of treatment either in our patient or in others who have been similarly treated. When compared to present therapeutic alternatives,
however, cell separator leukapheresis appears promising in the management and further study of this disease.

ACKNOWLEDGMENT

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