REVIEW

The Smoldering Myeloid Leukemic States: Clinical and Biologic Features

By Peter L. Greenberg

The clinical and biologic nature of these disorders will be examined with particular emphasis on determining whether the morphological features that have been used for diagnostic distinctions depict real differences regarding clinical outcome. Clinical characteristics distinguishing these patients from AML, CML, and benign cytopenias will be discussed. Biologic features of the SMLS, such as in vitro marrow cell myeloid growth and differentiation patterns and cytogenetics will be evaluated as adjunctive methods for assessing diagnosis, prognosis, evolution, and pathogenetic mechanisms underlying this spectrum of disorders. An issue of major controversy is whether the term preleukemia should only be used retrospectively (i.e., after the patients evolve into acute leukemia) or whether these patients are, in fact, already leukemic during their “preleukemic” phase. The critically reviewed data suggest that the patients considered to have SMLS already have a malignant clone established.

CLINICAL FEATURES

The clinical characteristics of the SMLS may be more comprehensively described using a biologic definition of leukemia. Leukemia has been defined as the proliferation of a clone of abnormal hemopoietic stem cells with variable degrees of abnormalities in cellular

From the Department of Medicine, Stanford University Medical Center and Veterans Administration Medical Center, Palo Alto, CA.

Supported in part by American Cancer Society Grant CH-219 and Veterans Administration Research Funds.

Submitted November 29, 1982; accepted January 11, 1983.

Address reprint requests to Peter Greenberg, M.D., Veterans Administration Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304.

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0006-4971/83/6106-0001$01.00/0

Blood, Vol. 61, No. 6 (June), 1983: pp. 1035–1044
Table 1. Clinical Characteristics of Patients With Smoldering Myeloid Leukemic States

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tbody>
<tr>
<td>1. Refractory cytopenias/cellular dysfunction</td>
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<tr>
<td>2. Marrow</td>
</tr>
<tr>
<td>Defective myeloid maturation, dysplasia</td>
</tr>
<tr>
<td>Moderate myeloid hypercellularity</td>
</tr>
<tr>
<td>3. Course</td>
</tr>
<tr>
<td>Indolent</td>
</tr>
<tr>
<td>Infection, hemorrhage major causes of death</td>
</tr>
<tr>
<td>Acute blastic transformation common</td>
</tr>
<tr>
<td>4. Elderly patients predominate, male &gt; female</td>
</tr>
<tr>
<td>5. Clonal abnormalities</td>
</tr>
<tr>
<td>In vitro marrow culture</td>
</tr>
<tr>
<td>Cytogenetics</td>
</tr>
</tbody>
</table>

The clinical features of these SMLS have been well described (Table 1). A high proportion of these patients are elderly (50% > 60 yr old), with a male predominance. The patients’ clinical courses are relatively indolent. However, eventually 20%-50% of patients progress to an acute blastic phase. Once such evolution occurs, the patients generally respond poorly to standard cytotoxic chemotherapy. In the chronic phase these patients exhibit qualitative and quantitative abnormalities of marrow hemopoietic cells and their peripheral blood progeny, evidenced by refractory cytopenias and hemopoietic cellular dysfunction (Table 2). Dyserythropoiesis is generally associated with a predominantly hypoprotective or ineffective refractory anemia. In addition, metabolically abnormal red cells have been well demonstrated in some of these patients, including altered RBC

Enzyme activities (decreased pyruvate kinase, 2,3-diphosphoglyceromutase [2,3-DPG mutase], and phosphokinase activities), hemoglobin F levels (increased), changes in the A, B, H, I red cell antigens, and paroxysmal nocturnal hemoglobinuria (PNH)-like lesions. In the neutrophils, decreased leukocyte alkaline phosphatase, myeloperoxidase, and chemotactic, phago- cystic and bactericidal activities have been reported. Abnormal platelet function has been demonstrated by tests of adhesivity, aggregation, and bleeding times.

Light microscopic and ultrastructural morphological lesions of peripheral blood cells have been prominent features in these patients. Macrocytosis, basophilic stippled erythrocytes, Pelger-Huet abnormalities, and hypogranularity of the neutrophils and hypogranular and abnormal-sized platelets are common. The morphological abnormalities seen by electron microscopy within erythroid precursors include multinuclearity, nuclear fragments, clefs and blebs, large irregular mitochondria with disorganization of the cristae encrusted with iron (ringed sideroblasts), and vacuolization of the cytoplasm. Ultrastructural platelet lesions coincident with abnormal platelet function include vacuolation, decreased glycoprotein content, absent microtubules, dilated canalicular systems, aggregates of platelets with few pseudopods, obliteration of the tight connections in the interplatelet space, and giant platelet granules.

Characteristic marrow morphology has been used to describe patients as having preleukemia, RAEM, or subacute myeloid leukemia. Morphological features generally distinguish patients with these disorders from those with AML and CML. In preleukemia (i.e., hemopoietic dysplasia), examination of the marrow indicates dysplastic maturation of at least two, and

Table 2. Cellular Dysplasia/Dysfunction in Smoldering Myeloid Leukemic States

<table>
<thead>
<tr>
<th>Neutrophils</th>
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<tbody>
<tr>
<td>Morphology</td>
</tr>
<tr>
<td>Hypogranularity, Pelger-Huet anomaly</td>
</tr>
<tr>
<td>Function</td>
</tr>
<tr>
<td>Enzyme defects (LAP, MPO)</td>
</tr>
<tr>
<td>↓ bactericidal, phagocytic, chemotactic activity</td>
</tr>
<tr>
<td>Red cells</td>
</tr>
<tr>
<td>Morphology</td>
</tr>
<tr>
<td>Inclusions</td>
</tr>
<tr>
<td>Functions</td>
</tr>
<tr>
<td>Enzyme defects (PK)</td>
</tr>
<tr>
<td>Cell surface antigen changes (A,B,H,I)</td>
</tr>
<tr>
<td>PNH-like lesions</td>
</tr>
<tr>
<td>↑ Hemoglobin F</td>
</tr>
<tr>
<td>Platelets</td>
</tr>
<tr>
<td>Morphology</td>
</tr>
<tr>
<td>Hypogranular, abnormal size/shape</td>
</tr>
<tr>
<td>Function</td>
</tr>
<tr>
<td>Abnormal adhesion, aggregation, bleeding time</td>
</tr>
</tbody>
</table>
generally all, of the granulocytic, erythroid, and megakaryocytic cell lines, including qualitative changes such as myeloid nucleocytoplasmic asynchrony, megakaryoblastic erythropoiesis, occasionally with ringed sideroblasts, and bilobed or micromegakaryocytes. The presence of abnormal myeloid mononuclear cells is particularly characteristic. These cells, comprising approximately 5%–10% of the myeloid cells, have granular bluish grey cytoplasm with a prominent nuclear hof (Golgi zone) and a reticulated nuclear chromatin pattern with pale staining nucleoli. The cells have been identified as abnormal promyelocytes by electron microscopic analysis. The cellularity of the marrow has been normal, decreased, or increased; when increased, this is due to erythroid hyperplasia, but generally not granulocytic hyperplasia. A quantitative increase in marrow myeloblasts is not present. These patients are distinguished from patients with RAEM or subacute myeloid leukemia who have a quantitative increase in marrow blasts and those with only single hemopoietic cell line defects (e.g., idiopathic sideroblastic ineffective erythropoiesis, idiopathic neutropenia, or idiopathic thrombocytopenia). Marrow morphology of the secondary forms of SMLS (i.e., those associated with prior exposure to chemotherapy) is similar to those whose diseases began de novo, except that marrow hypocellularity or fibrosis may be prominent.

Patients with subacute or “smoldering” myeloid leukemia have marrows with 10%–40% myeloblasts and varying amounts of persisting erythroid, megakaryocytic, and maturing myeloid cells, often with ringed sideroblasts. This compares to greater than 40% marrow myeloblasts in patients with AML. In subacute myeloid leukemia, maturation of the myeloid line generally progresses beyond the promyelocyte stage, in contrast to lack of such maturation in AML. In contrast to the absence of peripheral blasts in preleukemia, myeloblasts are often present in the peripheral blood in subacute ML patients. Morphological changes of red blood cells and bone marrow may be so prominent as to suggest a clinical diagnosis of DiGuglielmo’s disease or erythremic myelosis. Both groups of patients often present with refractory cytopenias and dysplastic marrow morphology.

RAEM, a disorder predominantly reported in the French literature, describes patients with a dysmyelopoietic syndrome and 10%–40% blasts and abnormal promyelocytes. Dysplastic precursors of the three hemopoietic cell lines are characteristic. This entity appears to include a mixture of patients with preleukemia, smoldering ML, and subacute ML. Recently, Auer rods have been demonstrated in the myeloblasts of a subset of patients with RAEM, and the clinical courses of these patients did not differ from individuals with RAEM lacking such cytoplasmic inclusions. This finding further is consistent with the thesis of establishment of a malignant clone during the “preleukemic” phase of this illness.

The clinical features of these groups of patients have been reviewed in order to determine whether the disparate nosologic terms, in fact, describe different disorders. In 20 studies encompassing some 744 patients, these subjects were characterized according to the criteria stated for the diagnoses preleukemia, RAEM, or subacute myeloid leukemia. As shown in Table 3, despite different marrow morphological criteria and the presence of peripheral blasts in SML, a striking degree of overlap of all clinical features was reported for these patients. Similarities among these patient groups appear to outweigh their differences. Cytopenias, singly or in combination, or monocytosis were present in all groups. Variable proportions (generally 20%–50%) of these patients underwent transformation to AML when viewed prospectively. With retrospective evaluation (i.e., assessing those patients who had evolved into AML), the clinical features demonstrated during the preleukemic phase were similar to the prospectively evaluated preleukemic patients. Splenomegaly was present in 10%–40% of preleukemic and subacute myeloid leukemia patients. However, in contrast to patients with AML and CML, leukemic infiltration was absent in spleens of SMLS patients who were examined at autopsy, by splenic puncture or after splenectomy. Although as a group, patients with subacute myeloid leukemia generally had somewhat shorter survivals, significant overlapping of most clinical features was present and differences in natural histories of patients with the SMLS were not predominantly determined by the morphological distinctions used to designate these entities. Rather, in some studies, certain clinical findings did define subsets within each group that correlated with prognosis. Poor risk features have included the initial presence of pancytopenia, age over 64 yr, absence of monocytosis, and hepatosplenomegaly. A recent effort by the FAB Collaborative Group has formulated somewhat new diagnostic criteria for the myelodysplastic syndromes. However, this proposed classification does not permit inclusion of many patients previously extensively described in the literature as having hemopoietic dysplasia, RAEB, or subacute/smoldering myeloid leukemia. In addition, prior studies do not support certain of the FAB report’s undocumented statements regarding similar natural histories of myelodysplastic patients with or without prior alkylator therapy or the poorer prognosis of patients having Auer rods.
Clinical responses of patients with SMLS to standard therapy were poor. Only 20%-30% of these patients have generally achieved complete remission using conventional chemotherapy, which is now associated with a 60%-70% remission rates for standard AML. Even lower response rates were found in patients developing SMLS after cytotoxic chemotherapy for other diseases. Although the follow-up period is short, one young patient with preleukemia has had a successful response to marrow transplantation from an identical twin. No amelioration of the anemia in RAEM or improvement in survival occurred after treatment with androgens. A small proportion of preleukemic patients have been reported to respond to corticosteroids, with in vitro marrow culture studies being predictive for defining which patients responded to such therapy.

**Biologic Alterations**

Several biologic parameters have provided useful insights for evaluating patients with SMLS and other myeloproliferative disorders. The methods used to assess these features have included patterns of marrow cell growth, maturation and regulation in culture, and cytogenetics.

**In Vitro Marrow Culture Studies**

In vitro marrow myeloid culture systems provide techniques for assessing the cellular and humoral factors involved in regulating hemopoiesis. Semisolid medium culture studies (using agar gel or methylcellulose as the support media) permit clonal growth of myeloid progenitor cells (CFU-GM), whereas liquid suspension cultures permit determination of cell proliferative and maturation parameters of the morphologically recognizable myeloid precursors. The glycoprotein substance, colony-stimulating factor (CSF or CSF-GM), is required for the in vitro growth of normal and leukemic myeloid precursors. Although evidence is accumulating, data have not rigorously established the physiologic relevance of CSF. Despite this limitation, numerous studies of in vitro parameters of myeloid cell growth have described biologic alterations of marrow cells in patients with SMLS and other myeloproliferative disorders (Table 4). The abnormal clonal proliferation of cells from marrows of patients with SMLS has included decreased frequency of CFU-GM, increased number of abortive clusters with defective maturation, and an increased proportion of abnormally light buoyant density CFU-GM. As the diseases evolve, progressive abnormalities in these parameters are frequently discerned and provide evidence for clonal evolution or progressive replacement of marrows with more abnormal granulopoietic cells. Patients with DiGuglielmo’s syndrome and those in blast crisis of CML generally have very low CFU-GM or excessive numbers of abortive clusters. The proportion of light density CFU-GM (<1.062g/ml) is increased in these patients. In contrast, patients with single line defects,
such as idiopathic sideroblastic ineffective erythropoiesis and idiopathic neutropenia with a low propensity to leukemic evolution, have normal marrow granulocytotoxic growth parameters. Patients who died without undergoing transformation generally did so as a result of infectious complications. The decreased marrow granulocytotoxicity in vitro (low frequency of normal CFU-GM) may reflect the patients’ marrows as being less capable of responding to demand for new cells. Factors other than in vitro growth patterns (possibly regulatory substances or host resistance) appear to contribute to transformation, as not all patients with abnormal clonal growth had poor prognoses.

Sequential investigations of in vitro clonal growth in patients with preleukemia and other myeloproliferative disorders have demonstrated that clonal evolution and alteration of regulatory factors occur as these diseases progress. Cytogenetic studies have shown nonrandom chromosomal changes concomitant with disease progression in some, though not all, patients. The findings of decreasing CFU-GM incidence, a higher proportion of light density CFU-GM, and increased cluster–colony ratios provide possible functional evidence of clonal evolution and prognostic information as these diseases progress toward acute transformation. In RAEM, study of 17 patients showed that macrocluster formation was associated with poor survival and increased transformation to AML. Abnormal proliferation and differentiation of hemopoietic precursors in preleukemia extends beyond the CFU-GM. Erythroid precursors also display aberrant growth patterns, as BFU-E and CFU-E are generally markedly decreased. However, the responsiveness of the CFU-E to erythropoietin appears normal. A recently developed assay permits clonal growth of blast cell progenitors from marrow and blood of patients with AML. Whereas these colonies are not present in normal individuals, the majority of patients in a recent study of preleukemia or RAEM had circulating blast cell progenitors, some of which were in active cycle. Further investigations correlating these findings with peripheral blasts, clinical status, and subsequent course will be important.

Proliferative and maturation characteristics of marrow cells of patients with SMLS have been studied in suspension culture. Considerable overlap was demonstrated in growth patterns of AML and subacute myeloid leukemia in liquid culture. Patients with classical AML and progressing subacute myeloid leukemia exhibited increased proliferative myeloid cell recovery associated with decreased maturation in liquid culture. Conversely, patients with slowly progressive AML and stable subacute myeloid leukemia had lower in vitro cell recovery and relatively greater maturation. The observed overlap in growth patterns in AML and subacute myeloid leukemia reflected a degree of in vitro cellular kinetic variation among patients that correlated with their clinical courses, seemingly independent of differences in myeloid maturation in vivo. In addition, cell kinetic analysis using autoradiographs has demonstrated ineffective erythropoiesis and decreased myelopoiesis during the preleukemic phase, whereas increased myeloblast proliferation occurred during the leukemic phase.

Leukemic cells are responsive to CSF in vitro. These cells are generally dependent on CSF for their proliferation. Increased responsiveness to the proliferative effects of CSF by aggressive myeloid leukemic cells has been shown in comparison to more indolent myeloproliferative diseases. Increased urinary and serum CSF levels have been reported in the SMLS and other chronic myeloproliferative disorders, and these levels may increase with disease evolution. Although cellular sources of CSF are needed for stimulation of human myeloid CFU-GM in vitro, in suspension culture recognizable human myeloid cells can be stimulated to proliferate by urinary and serum CSF sources. In various myeloproliferative disorders, a high incidence of acute transformation occurred within 10 mo when both decreased CFU-GM and increased urinary CSF developed.

Recent understanding of regulatory abnormalities in the myeloproliferative disorders has been extended by finding a variety of inhibitory substances active in vitro and, for some, in vivo. Lactoferrin, present in the secondary granules of neutrophils, decreases production of CSF by a specific subset of monocytes (HLA-DR-positive monocytes). Low levels of this neutrophil-associated lactoferrin have been found in CML. Prostagandin E, generated by monocytes and macrophages, inhibits growth of leukemic myeloid precursors to a much lesser degree than it does normal CFU-GM. A leukemic-associated inhibitory activity (LIA) has recently been identified as an acidic isoferritin, which also inhibits normal but not leukemic CFU-GM. Taken together, these data are consistent with the postulate that a growth advantage for leukemic over normal cells exists due to an abnormal balance of selective stimulatory and inhibitory signals. The role of the levels of these inhibitors in SMLS is currently under active investigation.

**Marrow Cytogenetic Abnormalities**

Abnormal clonal proliferation of hemopoietic cells has been documented using “banding” studies for...
karyotypic analysis. These investigations have demonstrated the presence of stable cytogenetic abnormalities in 50%-60% of patients with SMLS.\(^{58-60}\) Within the marrow of these patients, a mixture of normal and aneuploid clones is frequently initially present, suggesting the coexistence of competing clones of cells, possibly normal and leukemic (or potentially leukemic) clones. Using banding studies, these cytogenetic abnormalities are nonrandom, most frequently being specific deletions or translocations \([-5, 5q-, -7, +8, 20q-, +/−21, t(8;21)].\) Complex chromosomal changes (combinations of abnormalities) are also frequent in these patients. A patient with the Philadelphia chromosome has been reported.\(^{8}\) In patients developing SMLS following chemotherapy with potentially mutagenic drugs (generally alkylators) for other disorders, a particularly high incidence of nonrandom aneuploidy occurs (involving the same chromosomes as those found in AML or SMLS arising de novo: \(-5, -7\)). In 3 studies of such patients, 50 of 53 individuals (94%) had marrow cytogenetic abnormalities.\(^{11-13}\) In some cases, new cytogenetic lesions occurred at the time of acute transformation and were superimposed on those initially present in the preleukemic phase, suggesting clonal evolution or replacement of marrow by more abnormal cells at the time of AML. However, in other studies, no further cytogenetic changes occurred with clinical evolution to AML, suggesting that leukemia was established during the “preleukemic” phase.\(^{11,58,63}\)

### PROGNOSIS

As discussed above, a major limitation of the morphological categorization of patients with the SMLS is the difficulty of using these features to predict natural history. However, use of biologic features such as the proliferative/maturational indices of in vitro marrow culture or marrow cytogenetic abnormalities has provided some consensus regarding their clinical outcomes, permitting patients with these disorders to be placed in prognostic subgroups. These subgroups cut across morphological diagnostic categories, and as such, provide a framework for considering these SMLS patients to represent part of a spectrum of disease.

In vitro marrow clonal growth may be divided into “leukemic” and “nonleukemic” patterns. Leukemic-type growth includes micro- or macro-cluster formation with defective maturation or blasts within aggregates, single persisting blasts, or very low colony formation (<2 colonies/10⁵ marrow cells). Nonleukemic growth is marked by having persisting colony formation, even if moderately decreased in frequency. As shown in Table 5, 6 studies involving 179 SMLS patients correlated clinical outcome with in vitro marrow growth parameters.\(^{15-17,43,47,56}\) When patients were stratified according to in vitro growth patterns, subgroups of SMLS patients (encompassing those with subacute myeloid leukemia, RAEM, and preleukemia) with differing prognoses could be identified. The SMLS patients with nonleukemic in vitro growth patterns had a 21%-40% incidence of transformation and 9–50-mo median survivals. In contrast, SMLS patients with leukemic growth patterns had a 50%-80% incidence of transformation and 5–10-mo median survivals.

Clinical outcomes have also been correlated with marrow chromosome analysis in 6 studies that included 150 patients with SMLS.\(^{12,42,43,58,59,62}\) As shown in Table 6, those patients with normal karyotypes or a mixture of normal and abnormal marrow cell karyotypes had median survivals of approximately 10–30 mo, with 22%-40% undergoing acute transformation. This contrasted with the generally shorter median survivals (3–21 mo) reported for patients with dominant or complex chromosomal abnormalities, with 66%-77% undergoing acute transformation. Some of the poorer prognoses occurring in the cytogenetically abnormal patients were associated with prior

### Table 5. Prognosis of Smoldering Myeloid Leukemic States: Utility of In Vitro Myeloid Growth Patterns

<table>
<thead>
<tr>
<th>Growth Patterns</th>
<th>Incidence (%)</th>
<th>Transformation to AML (%)</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SML, oligoblastic leukemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>− 80 patients(^{57,54})</td>
<td></td>
<td>51 (45–56)*</td>
<td>9 (7–11)</td>
</tr>
<tr>
<td>Nonleukemic growth</td>
<td>33 (27–38)</td>
<td>31 (29–33)</td>
<td>20 (15–25)</td>
</tr>
<tr>
<td>Leukemic growth</td>
<td>68 (62–73)</td>
<td>60 (50–70)</td>
<td>7 (5–8)</td>
</tr>
<tr>
<td>RAEM − 17 patients(^{43})</td>
<td></td>
<td>41</td>
<td>14</td>
</tr>
<tr>
<td>Nonleukemic growth</td>
<td>70</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Leukemic growth</td>
<td>30</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>Preleukemia − 82 patients(^{16-17})</td>
<td></td>
<td>40 (35–44)</td>
<td>16 (9–20)</td>
</tr>
<tr>
<td>Nonleukemic growth</td>
<td>54 (30–74)</td>
<td>29 (21–40)</td>
<td>34 (9–50)</td>
</tr>
<tr>
<td>Leukemic growth</td>
<td>46 (26–70)</td>
<td>64 (50–80)</td>
<td>9 (4–10)</td>
</tr>
</tbody>
</table>

*Mean values and ranges of means for cited studies.
Table 6. Prognosis of Smoldering Myeloid Leukemic States: Utility of Marrow Cytogenetic Studies

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Incidence (%)</th>
<th>Transformation to AML (%)</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SML, RAEM — 15 patients</td>
<td>33 (0–55)*</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>43</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Abnormal karyotype</td>
<td>67 (40–100)</td>
<td>70</td>
<td>10 (8–21)</td>
</tr>
<tr>
<td>Preleukemia — 135 patients</td>
<td>66 (64–79)</td>
<td>31 (22–39)</td>
<td>12 (10–19)</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>42</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Abnormal karyotype</td>
<td>34 (21–36)</td>
<td>72 (66–77)</td>
<td>4 (3–5)</td>
</tr>
</tbody>
</table>

*Mean values and ranges of means for cited studies.

alkylator therapy. These patients also had extremely poor responses to chemotherapy. Thus, clinical outcomes of these SMLS patients more closely approximated the biologic parameters than the morphological descriptions of their marrow cells.

SUMMARY AND FUTURE DIRECTIONS

The studies reviewed in this article provide bases for certain conclusions for characterizing patients with SMLS.

(1) Spectrum of Clonal Hemopathies

These disorders represent a clinically relatively indolent spectrum of clonal hemopathies. The clonal nature of these disorders and the qualitative cellular and biologic abnormalities similar to those occurring in AML strongly suggest that the patients initially demonstrate critical neoplastic features, indicating that leukemia was likely established from onset of the disease. A major issue needing further study is the mechanism whereby this morphologically and functionally abnormal clone chronically retains its ability to differentiate with only limited capacity to expand. This group of disorders represents coexisting normal and leukemic clones within marrow in which the host copes effectively with the leukemic clone or is populated by a leukemic clone with greater in vivo differentiation. Factors related to abnormalities intrinsic to hemopoietic precursors and/or environmental control need to be determined.

(2) Biologic Parameters Aid Characterization of the SMLS

In vitro marrow culture studies are useful adjuncts in distinguishing patients with SMLS from those with benign refractory cytopenias. Altered production of and marrow cell response to growth regulatory factors appear to contribute to pathogenetic mechanisms in these disorders. Nonrandom cytogenetic abnormalities and their possible association with prior exposure to potentially mutagenic agents provide insight into initiating events in the pathogenesis of leukemia and preleukemic disorders. The relative specificity of the cytogenetic lesions suggests that critical genes involved in growth regulation/maturation may be affected in the transformation of the SMLS to AML.

(3) Prognostic Subsets of the SMLS Appear Better Defined by Certain Clinical and Biologic Features Rather Than by Marrow Morphology

Use of a biologic definition of leukemia, rather than morphological descriptions that require a quantitative increase in blasts, may diminish controversy related to which of these patients should be considered leukemic. The pace and clinical outcomes of these disorders correlate well with in vitro marrow culture and cytogenetic findings. Sequential analyses of blast regeneration and differentiation as clinical evolution occurs are needed to further clarify such associations.

(4) New Therapeutic Strategies Are Needed for These Patients

Standard chemotherapy for SMLS has been associated with relatively poor results. Physicians are understandably loath to use aggressive chemotherapy to treat patients who appear to have relatively indolent courses. Clinical trials may be aided by prospectively stratifying patients according to the biologic prognostic indicators reviewed above. Currently, some interest is being focused on agents that may act by enhancing cellular differentiation or decreasing self-replication of leukemic cells. In this regard, preliminary studies using the vitamin A metabolite 13-cis retinoic acid or low-dose cytosine arabinoside have demonstrated responses in some patients, suggesting that these agents warrant further evaluation. Although marrow transplantation could be considered in patients with SMLS, particularly those in the poor-risk category, a major consideration that precludes such an approach at present is the poor outcome of this mode of therapy in the elderly.

(5) Improvement in Management

Further improvement in the management of these patients will require knowledge of underlying pathogenetic mechanisms. Of particular importance will be assessment of the marrow microenvironment of these SMLS patients. This includes determination of pro-
duction and response of hematopoietic precursors to growth regulators and the immunologic responsiveness of these patients to leukemic hematopoietic precursors. In a lymphoid leukemia animal model for preleukemia, preleukemic cells were found to be immunogenic, inducing resistance to subsequent challenge with leukemic cells, whereas leukemic cells failed to induce such transplantation resistance. The proliferation of preleukemic cells was dependent on specific environmental requirements, in contrast to leukemic cells. These studies indicate the need to assess altered intrinsic cellular and host immune responses in human preleukemia compared to frank leukemia. During senescence, abnormalities of immune responses and hematopoietic stem cell replication have been found. As the SMLS occur predominantly in elderly patients, altered mechanisms of coping with leukemic cells in aged individuals need to be evaluated.

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