Characteristics of Blast Crisis in Chronic Granulocytic Leukemia

By Susan Rosenthal, George P. Canellos, Vincent T. DeVita, Jr., and Harvey R. Gralnick

The terminal phase of most patients with Ph' -positive chronic granulocytic leukemia (i.e., blast crisis) resembles acute leukemia. The clinical and hematologic features of blast crisis in 73 patients with chronic granulocytic leukemia have been reviewed. Two major morphological subgroups, lymphoblastic and myeloblastic, were identified. The lymphoblastic group in general had more profound thrombocytopenia and a greater number of blasts, while the myeloblastic group had more severe anemia. Extramedullary leukemia was documented in 27 patients. In 12 patients extramedullary leukemia preceded or occurred simultaneously with blast crisis in the bone marrow and peripheral blood. On the basis of this study we present hematologic criteria for the diagnosis of blast crisis and emphasize the importance of extramedullary leukemia in heralding the onset of blast crisis.

Blast crisis is the major cause of death in chronic granulocytic leukemia (CGL); recent series have indicated that between 56% and 86% of patients with CGL expire in blast crisis.1-3 The reasons for this abrupt transformation of a readily controlled, well-differentiated proliferation of cells (termed premalignant by some4) into an acute leukemia are entirely unknown. No one set of criteria for the diagnosis of blast crisis is universally accepted, and morphologic, immunologic, and biochemical heterogeneity of the acute leukemic phase have been described.5 12

In this study we analyze the blastic phase of CGL in 73 patients followed at the National Cancer Institute (NCI); we compare the findings in a group of patients with a lymphoblastic transformation, previously reported to have an improved prognosis,5 13 with those in a larger group with myeloblastic morphology. In this way we attempt to define blast crisis of CGL more accurately and to identify additional clinical and hematologic parameters associated with an improved response rate and survival in blast crisis.

MATERIALS AND METHODS

The records of all patients with Philadelphia chromosome (Ph') -positive CGL admitted to NCI between January 1968 and June 1975 were reviewed. A diagnosis of blast crisis was made in 73 patients who were subsequently treated with combination chemotherapy. Sixty-seven had bone marrow biopsies or aspirations done at the time of blast crisis which were available for review.

Bone marrows, either by aspiration alone or with posterior iliac crest biopsy, were obtained within 2 wk prior to the initiation of blast crisis chemotherapy in all 67 cases. Biopsies, clot sections, and aspirate smears were reviewed by two hematologists who were unaware of the clinical course and response to therapy of the patients. Bone marrows were evaluated for cellularity, presence and degree of fibrosis, megakaryocyte content, extent of infiltration with blasts,
and other features of hematopoiesis. The blasts were categorized morphologically as myeloblastic, erythroblastic, or lymphoblastic according to previously reported criteria. Where mixed populations occurred, the predominant blast cell type in a 300 blast cell differential count determined the classification. One hundred cell differentials on the bone marrow aspirate smear, touch preparation, and peripheral blood smear were done in all cases where the material was available. Peripheral smears, bone marrow aspirates, and biopsy touch preparations were stained with a modified Romanowsky stain, and aspirate and biopsy sections were prepared as previously described.

All white blood cell counts and hemoglobin determinations were made on the Coulter Model S automated cell counter. Platelet counts were performed on the Coulter Model B from 1968 to 1974 and on the Technicon Autocounter subsequently. Low platelet counts or platelet counts in the presence of high white counts were confirmed by phase microscopy or evaluation of the peripheral blood smear.

The patient records in all 73 cases and autopsy protocols in 65 cases were reviewed to determine signs and symptoms at onset of blast crisis, chemotherapeutic response, occurrence of extramedullary manifestations of blast crisis, cause of death, and postmortem findings. All sites of extramedullary blast crisis were documented either by biopsy or cytology or were suspected clinically and subsequently confirmed at autopsy.

There were 44 males and 29 females. The mean age at onset of blast crisis was 43. The majority were treated primarily with busulfan or dibromomannitol during the chronic phase. Three patients required no chronic phase chemotherapy. Two other patients presented in blast crisis.

Treatment for blast crisis was according to protocols then current at the NCI. Most of these patients have been previously reported. Thirty-two patients were randomly assigned to vincristine-prednisone or cytosine arabinoside-6-thioguanine chemotherapy. Prior to this assignment, 38 consecutive patients received vincristine-prednisone and 3 received cytosine arabinoside-BCNU. No patient treated with a single agent for blast crisis was included. The definition of the blastic phase of the disease and the criteria for its response to therapy used in these patients have been published previously.

RESULTS

At the onset of blast crisis 21 patients had blast cells in the bone marrow indistinguishable from the lymphoblasts seen in patients with acute lymphocytic leukemia (ALL). The cells had a high nuclear-to-cytoplasmic ratio (≥0.8), absent nucleoli or occasionally one nucleolus per cell, "smudged" nuclear chromatin pattern, scant basophilic cytoplasm without granulation, and prominent nuclear clefting and folding.

The blasts in 38 patients were indistinguishable from myeloblasts seen in acute myelocytic leukemia (AML). These cells were characterized by a low nuclear-to-cytoplasmic ratio, multiple prominent nucleoli, a vesicular nuclear chromatin pattern, a moderate amount of blue-gray cytoplasm with a variable degree of azurophilic granulation, and smooth round nuclear contours without clefting or folding. No Auer rods were seen.

Seven patients underwent an erythroblastic transformation. Their blasts were morphologically indistinguishable from proerythroblasts and basophilic erythroblasts having a low nuclear-to-cytoplasmic ratio, multiple poorly defined, blue-hued nucleoli, a finely stranded nuclear chromatin pattern, deeply basophilic cytoplasm, and round nuclear contours with a sharply defined nuclear membrane.

One patient had a unique blast type at the onset of blast crisis. This cell was extremely large with a low nuclear-to-cytoplasmic ratio and abundant basophilic cytoplasm. The nucleus was large and vesicular with one or more large, irregularly shaped eosinophilic nucleoli. There was no cytoplasmic granulation...
Table 1. Clinical Presentation at Blast Crisis

<table>
<thead>
<tr>
<th></th>
<th>Lymphoblastic (n = 21)</th>
<th>Myeloblastic (n = 46)</th>
<th>Total* (n = 73)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Fever</td>
<td>14 (67)</td>
<td>26 (57)</td>
<td>44 (60)</td>
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<tr>
<td>Musculoskeletal pain</td>
<td>9 (43)</td>
<td>26 (57)</td>
<td>39 (53)</td>
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<tr>
<td>Abdominal enlargement/pain</td>
<td>7 (33)</td>
<td>18 (39)</td>
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<td>Malaise</td>
<td>10 (48)</td>
<td>34 (74)</td>
<td>48 (66)</td>
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<tr>
<td>Dyspnea, cough</td>
<td>10 (48)</td>
<td>15 (33)</td>
<td>28 (38)</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>10 (48)</td>
<td>23 (50)</td>
<td>34 (47)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>4 (19)</td>
<td>15 (33)</td>
<td>21 (29)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>3 (14)</td>
<td>9 (20)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (5)</td>
<td>5 (11)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Ankle edema</td>
<td>1 (5)</td>
<td>5 (11)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>7 (33)</td>
<td>29 (63)</td>
<td>36 (49)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>14 (93)†</td>
<td>30 (88)†</td>
<td>44 (59)†</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>1 (5)</td>
<td>2 (4)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Accelerated phase †</td>
<td>8 (38)</td>
<td>22 (48)</td>
<td>32 (44)</td>
</tr>
</tbody>
</table>

*Includes six patients for whom blast crisis bone marrow specimens were unavailable.
†Per cent of those who had not been previously splenectomized.
†A minimum of a 1-mo period prior to blast crisis characterized by rising WBC, anemia, thrombocytopenia, refractoriness to previous therapy, or significant hypermetabolic symptoms.

or nuclear cleaving or folding. The morphology was most consistent with a histiocytic cell line.

For the purposes of comparison with those patients having bone marrows clearly lymphoblastic in character, the 38 myeloblastic, 7 erythroblastic, and 1 histiocytic marrows were classified together as myeloblastic (total 46).

Table 1 shows the incidence of signs and symptoms at the onset of blast crisis for both the lymphoblastic and myeloblastic groups. There were no marked differences between the groups. Most patients presented with a combination of hypermetabolic symptoms and splenomegaly; 44% had a gradual myeloproliferative acceleration of their disease, lasting between 1 and 18 mo, prior to the development of frank blast crisis. These patients were treated with hydroxyurea in an attempt to control their rising white blood count and correct their anemia and thrombocytopenia. The remainder of the patients underwent an abrupt clinical and hematologic transition from the chronic phase to blast crisis. These patients tended to have fewer symptoms and several were asymptomatic when the onset of blast crisis was detected by a sudden change in routine blood counts.

Splenomegaly was an almost universal finding among patients not previously splenectomized. In many cases its proportions were massive. No patient, however, presented with a splenic infarct or splenic rupture at the onset of blast crisis. In one case splenic rupture, necessitating emergency splenectomy, occurred during the course of blast crisis chemotherapy.

The hemoglobin, white blood cell count, and platelet count values at the onset of blast crisis in the lymphoblastic and myeloblastic patients are shown in Table 2. Of the lymphoblastic patients, 71%, and only 37% of myeloblastic patients had hemoglobin levels greater than 10 g/100 ml. Of the myeloblastic group, 46%, and only 24% of the lymphoblastic group had platelet counts

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Table 2. Hematologic Values at the Onset of Blast Crisis

<table>
<thead>
<tr>
<th></th>
<th>Lymphoblastic (n = 21)</th>
<th>Myeloblastic (n = 46)</th>
<th>Total* (n = 73)</th>
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<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Hemoglobin (g/100 ml)</td>
<td></td>
<td></td>
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<tr>
<td>4-5.9</td>
<td>0 (0)</td>
<td>3 (7)</td>
<td>3 (4)</td>
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<tr>
<td>6-9.9</td>
<td>6 (29)</td>
<td>26 (57)</td>
<td>36 (49)</td>
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<td>10-11.9</td>
<td>8 (38)</td>
<td>15 (33)</td>
<td>23 (32)</td>
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<tr>
<td>≥ 12</td>
<td>7 (33)</td>
<td>2 (4)</td>
<td>11 (15)</td>
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<tr>
<td>White blood count (× 1000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>2 (10)</td>
<td>4 (9)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>5-10</td>
<td>0 (0)</td>
<td>3 (7)</td>
<td>3 (4)</td>
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<tr>
<td>11-50</td>
<td>11 (52)</td>
<td>14 (30)</td>
<td>28 (38)</td>
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<td>51-100</td>
<td>5 (24)</td>
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<td>21 (29)</td>
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<tr>
<td>&gt; 100</td>
<td>3 (14)</td>
<td>10 (22)</td>
<td>15 (21)</td>
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<tr>
<td>Platelet count (× 1000)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt; 20</td>
<td>2 (10)</td>
<td>7 (15)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>20-100</td>
<td>14 (67)</td>
<td>18 (39)</td>
<td>35 (48)</td>
</tr>
<tr>
<td>101-300</td>
<td>5 (24)</td>
<td>12 (26)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>&gt; 300</td>
<td>0 (0)</td>
<td>9 (20)</td>
<td>9 (12)</td>
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*Includes six patients whose blast crisis bone marrows were unavailable for review.

greater than 100,000/cu mm. Of the myeloblastic patients, 20% had platelet counts in excess of 300,000/cu mm at the time of blast crisis. The distribution of white blood counts in the two groups was roughly equivalent.

The percentages of blasts in both bone marrow and peripheral blood at the onset of blast crisis are shown in Table 3. In about two-thirds of the cases the percentage of blasts in the bone marrow equaled or exceeded that in the peripheral blood. In only 10 cases were there fewer than 10% blasts in the peripheral blood. There were no cases in which the bone marrow blast count was under 10%. The lymphoblastic patients tended to have higher blast counts than the myeloblastic patients; 43% of lymphoblastic patients and only 10% of my-
eloblastic patients had more than 80% blasts in the marrow. A greater incidence of high peripheral blood blast counts in the lymphoblastic patients was also noted. All patients had at least 30% blasts in bone marrow or peripheral blood at the time the diagnosis of blast crisis was made.

Other peripheral blood findings at the time of blast crisis are given in Table 4. A higher proportion of myeloblastic patients than lymphoblastic patients had the following peripheral blood abnormalities: pseudo-Pelger-Huet cells and uninuclear Pelger-Huet cells, abnormal red blood cell morphology (aniso- and poikilocytosis, target cells, schistocytes, and teardrop forms) and nucleated red blood cells. Eosinophilia was not marked in either the lymphoblastic or myeloblastic group, but basophilia was prominent in both.

Table 5 shows the qualitative bone marrow features at the time of blast crisis. Hypercellularity was the rule, except in the patients with extensive bone marrow fibrosis, the incidence of which was roughly equal in the lymphoblastic and myeloblastic groups. There was a striking difference in megakaryocyte content between the groups; the lymphoblastic patients almost invariably had...
decreased or absent megakaryocytes, while 42% of the myeloblastic patients had normal or increased megakaryocytes. Gaucher-like cells were not common in either group in blast crisis.

Twenty-seven patients (37%) developed extramedullary leukemia. Twelve patients (16%) presented with extramedullary leukemia either shortly before or simultaneously with the onset of bone marrow or peripheral blood blast crisis. Two patients had leukemic skin infiltrations (one had vaginal mucosal infiltrations as well) documented by biopsy 2 and 3 mo prior to bone marrow transformation. Two patients had biopsy-proven extramedullary blast crisis in lymph nodes 2 mo before marrow blast crisis. Both were treated with local radiotherapy. The karyotype of the lymph node blasts in one was 48,2Ph', while the bone marrow remained 46Ph0 through the blast crisis. Two additional patients had nodal involvement at the time that bone marrow blast crisis developed. Three patients had lytic bone lesions which developed at the time of blast crisis, and in one patient a lytic lesion of the femur preceded blast crisis by 1 mo. Finally, two patients presented in blast crisis with neurologic findings due to leukemic infiltration. One patient had an extradural mass with spinal cord compression and another had severe peripheral neuropathies secondary to nerve infiltration with myeloblasts.

Extramedullary leukemia occurred after the onset of bone marrow blast crisis in the remaining 15 patients. Nine patients developed meningeal leukemia after the onset of blast crisis. Four of these patients had lymphoblastic morphology, three had myeloblastic and two erythroblastic. Five of these nine were chemotherapy responders. The median blast crisis survival in this group was 9 mo (mean 9.8 mo), compared to 4 mo for the entire series. The remaining six patients who developed extramedullary leukemia after the onset of blast crisis had involvement of mucous membranes, retina, skin, lymph nodes, orbit, and synovial and pleural fluids.

Postmortem findings in the 65 autopsied cases were reviewed. Six patients (11%) had no evidence of residual leukemia and died of complications of blast crisis chemotherapy. Central nervous system leukemia, including both meningeal involvement and intracerebral leukostasis, occurred in 12%. Significant hemorrhage, most commonly gastrointestinal and genitourinary, was seen in 34%. Renal failure and congestive heart failure were relatively uncommon terminal events, but pneumonia secondary to infection, aspiration, or leukemic pulmonary involvement was present in 60% at the time of death. Infection as a significant cause of death was seen in 82%. Bacterial infection, especially that due to gram-negative rods, predominated, but 31% had fungal infection, often superimposed on bacterial sepsis. Pneumocystis, cytomegalovirus, and toxoplasmosis infections occurred in approximately 10% of the autopsied cases.

Second malignancies occurred in only two patients in this series. One woman had a radical mastectomy and postoperative radiotherapy for an infiltrating ductal carcinoma of the breast 2 yr prior to the diagnosis of CGL. She was also treated with 32P, radiation oophorectomy, and androgens before CGL occurred. Cyclophosphamide and melphalan were used successfully in the chronic phase of CGL to control both the leukemia and the metastatic breast cancer. She underwent a myeloblastic transformation and died without response to vincristine–prednisone chemotherapy.
A second patient with a history of possible radiation exposure in Hiroshima in 1945 developed CGL in 1963, underwent a lymphoblastic transformation 4 yr later, and had a complete remission with vincristine-prednisone chemotherapy. At autopsy 13 mo later a large invasive hepatocellular carcinoma was found.

**DISCUSSION**

Lymphoblasts were the predominant blast cell in 21 of 67 blast crisis bone marrows in this series. Previous reports, both ours and those of others, have demonstrated an increased response rate and survival among patients with a lymphoblastic morphology at blast crisis as compared with those with a myeloblastic morphology. Others have found immunologic and biochemical lymphoblast markers in some cases of blast crisis of CGL, although an improved response rate or survival for these patients is yet to be reported. The present study was undertaken to provide an updated description of the clinical and hematologic features of the terminal phase of CGL and to attempt to identify any clinical and hematologic correlates of the lymphoblastic morphologic picture.

Fever, malaise, and splenomegaly were the most common signs and symptoms noted at presentation in blast crisis in both the lymphoblastic and myeloblastic patients, as well as in previous reports in the literature. Documented infection, however, was uncommon and was seen in only 8% of patients in this series. The source of the fever so frequently encountered at the onset of blast crisis has not been determined. That it was related to the activity of the underlying disease was demonstrated by its almost invariable defervescence following successful chemotherapy for blast crisis and the failure of the fever to respond to antibiotic chemotherapy in the absence of an antileukemic response.

Extramedullary blast crisis complicated the course of the disease in 37% of this series. Although numerous case reports have documented the occurrence of extramedullary leukemia in CGL, this high incidence in an unselected series of patients has not previously been recognized. Of the cases of extramedullary blast crisis in this series, 44% (12/27) represented patients in whom the extramedullary lesion appeared prior to or simultaneously with the development of bone marrow transformation. Soft tissue and nodal involvement preceded marrow transformation by up to 3 mo. In one case chromosome analysis of the involved lymph node revealed a karyotype of 48, 2Ph1, at a time when the bone marrow remained 46 Ph1. Extramedullary clonal development of a new aneuploid cell line has been reported previously in spleen and lymph node, and has in each instance been quickly followed by the development of marrow transformation.

Of the cases of extramedullary blast crisis, 56% (15/27) occurred after the onset of marrow transformation. All nine cases of meningeal leukemia were in this group. The median blast crisis survival of the patients with meningeal leukemia (9 mo) was more than twice that of the entire series (4 mo). It seems likely that CGL blasts, like those in ALL, were able to seed the meninges and persist there despite adequate systemic chemotherapy. Those patients who survived longer were then at greater risk of developing meningeal leukemia. Recent improvements in the treatment regimens for de novo AML and diffuse
histiocytic lymphoma have also been associated with the development of meningeal involvement.\textsuperscript{30,31} almost certainly because the longer survivals now allowed expression of this complication. This problem has rarely been reported previously in CGL,\textsuperscript{49} probably because the response rate and median blast crisis survival have in the past been so low. In the future, prophylactic central nervous system treatment may have to be considered in the overall plan of therapy for CGL blast crisis.

Substantial differences in hematologic values at onset of blast crisis were encountered between the lymphoblastic and myeloblastic groups. Less than one-third of the lymphoblastic patients had hemoglobin values below 10 g/100 ml, while two-thirds of the myeloblastic patients did. By contrast, Karanas and Silver\textsuperscript{2} reported that 87\% of their patients had hemoglobin values less than 10.5 g/100 ml at the onset of the terminal phase. Despite their relative freedom from marked anemia, most of the lymphoblastic patients had significant thrombocytopenia, while the myeloblastic patients tended to have much higher platelet counts. Sixty per cent of the entire series had platelet counts under 100,000/cu mm, which was similar to the findings in previous reports.\textsuperscript{2,5}

The white blood counts at the onset of blast crisis were distributed similarly in the myeloblastic and lymphoblastic groups. Almost all patients had white blood counts greater than 10,000/cu mm, and about one-half had counts greater than 50,000/cu mm. Peterson et al.\textsuperscript{5} also found that 50\% of their patients had white blood counts above 50,000/cu mm, and Karanas and Silver\textsuperscript{2} found that 72\% in their series had white counts above 30,000/cu mm.

Some of the reasons for the differing hematologic values between the lymphoblastic and myeloblastic groups lie with differences in their bone marrow features. Although hypercellularity was extremely frequent in both groups, megakaryocytes were almost invariably absent or decreased only in the lymphoblastic group, while 40\% of the myeloblastic group had either normal or increased megakaryocytes at the onset of blast crisis. The platelet counts in the two groups reflect this discrepancy; 77\% of lymphoblastic patients had platelet counts below 100,000/cu mm. The reasons for this difference may include the generally higher percentage of blasts and the marked tendency for the blast infiltration to be extensive and diffuse in the lymphoblastic patients, while the infiltration was focal in more than one-third of myeloblastic patients. In the extensively infiltrated bone marrows, normal myeloid activity was much more severely restricted than in the focally infiltrated marrows, and the platelet counts in the former group were necessarily lower. The lack of marked anemia in the lymphoblastic group remains unexplained.

Myelofibrosis occurring late in the course of CGL has been associated with a poor prognosis. The survival after development of myelofibrosis was short, and in most cases myelofibrosis heralded or accompanied the onset of blast transformation.\textsuperscript{14} In the present series 40\% of patients had myelofibrosis at the onset of blast crisis. The median survival of these patients was 2 mo, while that of the entire series was 4 mo. The response rate of these patients was 24\%, while that of the entire series was 27\%. Neither difference was significant. Myelofibrosis itself appeared not to worsen the prognosis of a patient already in blast crisis.

The autopsy findings in this series indicate that death in blast crisis is pri-
Both in this series and in that reported by Peterson et al., one-third of the patients have had higher blast percentages in peripheral blood than in bone marrow. Criteria for blast crisis that ignore peripheral blood blast counts might omit some of these patients from inclusion. We propose that blast crisis in a patient with previously diagnosed CGL be defined as 30% or more blast forms in either the peripheral blood or bone marrow. Furthermore, we suggest that patients who develop either an extramedullary myeloblastic tumor or a major new aneuploid cell line in the bone marrow are at extremely high risk for imminent blastic transformation. Many patients with marked leukocytosis and progressive granulocytic immaturity accompanied by transfusion-dependent anemia and thrombocytopenia have fewer than 30% blasts and yet require intensive treatment. These patients may be considered to be in an accelerated phase of CGL, but this should not be considered as evidence of blast crisis. There is sufficient heterogeneity of blast crisis itself, however, so that only those patients meeting strict objective criteria should be admitted to future trials of blast crisis therapy.

ACKNOWLEDGMENT

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Characteristics of blast crisis in chronic granulocytic leukemia

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