Thrombocytosis in Chronic Granulocytic Leukemia: Incidence and Clinical Significance

By Joe E. Mason, Jr., Vincent T. DeVita, and George P. Canellos

The clinical significance of an elevated platelet count in the course of chronic granulocytic leukemia was studied in a group of 111 previously untreated patients, whose entire course was evaluated by one clinic. Seventy-one patients (64%) developed a platelet count $>450,000$/cu mm either at diagnosis (56 patients) or in the subsequent course (15 patients). Twenty-nine of the 71 patients had counts in excess of $1 \times 10^9$/cu mm. Four patients had serious thrombohemorrhagic complications. None were fatal, and all occurred in the group with counts over $1 \times 10^9$/cu mm. The occurrence of thrombocytosis as a new observation in the face of previous normal counts (15 patients) was associated with frank blastic crisis (six cases) or heralded its onset with a median duration of 8 mo (nine cases). Thrombocytosis per se was associated with a shorter survival (median 36 mo) as opposed to 45 mo in the group (40 cases) whose count was never elevated.

THROMBOCYTOSIS IS NOT infrequently a hematologic complication of the myeloproliferative disorders. While some reports emphasize the risk of thrombotic or hemorrhagic complications in patients with polycythemia vera (PV) or primary hemorrhagic thrombocythemia, this problem has not been widely studied in chronic granulocytic leukemia (CGL) where thrombocytosis frequently accompanies a marked granulocytic leukocytosis. It has been claimed that thrombocytosis in CGL has an ominous prognostic significance. Aggressive therapeutic maneuvers are employed, at times, to lower platelet counts in patients with myeloproliferative disease. Because of the unpredictable effects of agents such as busulfan, orthophosphate $^{32}$P, and phenylalanine mustard, some patients may be exposed to iatrogenic complications which exceed the potential risk of the hemorrhagic complications of a high platelet count.

The subject of this report is a study of the significance of thrombocytosis in a population of patients with CGL who were followed from diagnosis through their entire course. Correlations with incidence of thrombohemorrhagic complications during the chronic phase of the disease and the relationship to incipient blastic transformation are considered.

MATERIALS AND METHODS

One hundred and eleven consecutive previously untreated patients with Philadelphia chromosome-positive CGL whose entire course has been followed at the National Cancer Institute were studied. Platelet counts were performed in the Clinical Pathology Laboratory using the Coulter Counter. Normal values for this laboratory are 150,000–450,000/cu mm. Chromosome analyses were performed by Dr. J. Whang-Peng, NC! Marrow biopsies were obtained with a Westerman-Jensen needle and prepared by methods previously described. Thrombocytosis was defined as a
platelet count greater than 450,000/cu mm, and marked thrombocytosis was defined as a platelet count greater than 1,000,000/cu mm. The criteria for blastic transformation were defined as (1) the appearance of increasing numbers of blast cells in the marrow (20% - 30%), with or without splenomegaly, (2) progressive leukocytosis with a decreasing percentage of mature granulocytes, decreasing platelet count, and/or anemia unresponsive to previously effective chronic phase therapy.

RESULTS

Incidence and Complications

In the entire series of 111 previously untreated patients, 71 (64%) either presented with or developed thrombocytosis at some time during their course (Table 1). Fifty-six of these 71 presented with thrombocytosis at diagnosis. Despite initial successful reduction of platelet count with chemotherapy for the leukemia, 21 of 56 (38%) of these again developed elevated platelet counts at least once during the course of their illness. Twenty-nine patients in this group of 71 developed platelet counts in excess of 1 x 10^6/cu mm, with the highest platelet count in the series at 7 x 10^6/cu mm. Only four serious thrombohemorrhagic complications in the chronic phase of CGL were noted in the series; severe hemorrhage following dental extraction, massive retroperitoneal hematoma, and one intracranial hemorrhage. One thrombotic complication (priapism) was observed.

None of these was fatal, and all occurred in the group of 29 with marked thrombocytosis. Thus, in the 40 patients with normal platelet counts or those 42 whose counts varied between 450,000 and 1,000,000 platelets, no thrombohemorrhagic complications were observed.

Blastic Transformation

The development of thrombocytosis during the chronic phase of CGL, despite adequate control of the white count, appeared to be associated with acceleration of the disease to the blastic phase. Fifteen of the 71 patients presented with normal platelet counts but subsequently developed thrombocytosis. In nine patients, this preceded frank blastic transformation with a median duration of 8 mo (range, 2-22 mo). Six patients developed elevated platelets coincident with the appearance of the blastic phase of CGL. Twenty-one of the 56 who presented with an elevated platelet count had intermittent thrombocytosis up until the onset of blastic transformation.

Survival

Ninety-eight of the 111 patients studied have died, and all but two died in the accelerated or blastic phase of CGL. With complete followup available, the

<table>
<thead>
<tr>
<th>Table 1. Incidence of Thrombocytosis</th>
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<tr>
<td>Total patients</td>
</tr>
<tr>
<td>Patients with thrombocytosis</td>
</tr>
<tr>
<td>(&gt; 450,000/cu mm)</td>
</tr>
<tr>
<td>At diagnosis</td>
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<tr>
<td>Later in course</td>
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<tr>
<td>Platelet counts &gt; 1,000,000/cu mm</td>
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<td>Thrombohemorrhagic complications</td>
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Table 2. Thrombocytosis and Survival in Chronic Granulocytic Leukemia

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Numbers of Patients</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count elevated at diagnosis</td>
<td>56</td>
<td>36*</td>
</tr>
<tr>
<td>Platelet count elevated in the course of CGL</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>Normal platelet counts through entire course</td>
<td>40</td>
<td>45*</td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
<td>44</td>
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*p value 0.08.

The median survival of those patients (56 patients) presenting with thrombocytosis was 36 mo. This includes six patients who evolved into early blastic crisis. The group of 40 patients who never had a platelet count above 450,000/cu mm had a median survival of 45 mo (Table 2). The differences in survival are significant at a p value of 0.08.

Myelofibrosis

Bone marrow biopsies were performed in 73 of the patients and thus were evaluable for the presence of myelofibrosis. There appeared to be no overall correlation between the presence of myelofibrosis and elevated platelet counts. Forty-five of these patients had elevated platelet counts and of these, 21 (47%) had myelofibrosis. Thirteen (46%) of the 28 patients with normal counts during their course had myelofibrosis.

Therapy

All patients in this series responded to the chemotherapy applied to control the thrombocytosis. In general, all the standard therapies for lowering the white blood cell counts in these patients were also effective in lowering the platelet counts. There was no single agent which appeared superior to any of the others. Fifty-nine of 65 patients with thrombocytosis during the chronic phase of CGL responded to carefully monitored oral alkylating agents including busulfan, dibromomannitol, and phenylalanine mustard. No patient received radioactive phosphorus or splenic irradiation. Six patients responded to oral antimetabolite therapy including hydroxyurea (five cases) and azauridine (one case).

DISCUSSION

Certain comparisons between CGL and the other myeloproliferative disorders are of interest in the light of the present study. Most patients with PV and splenomegaly have elevated platelet counts.1 It is of note that in one series, thrombosis and hemorrhage are the most common complications of PV.3 In that series, 40% of 50 patients had thrombosis and 30% had hemorrhages. In that same series, five of 15 who underwent surgical procedures experienced significant postoperative thrombotic and hemorrhagic complications. In another series of 62 operative procedures in 54 patients with PV, 28 had postoperative complications, 11 of which were fatal.7

Agnogenic myeloid metaplasia (AMM), on the other hand, appears to be
more akin to CGL with respect to thrombocytosis. The combined results of several reported series reveal that of 267 patients with AMM whose platelet counts were recorded, 113 (42%) were elevated. In none of these series, however, are thrombosis and hemorrhage mentioned as causing clinically significant problems. One study reports the results of 18 autopsies on patients with AMM in which there were total of eight thromboses and/or infarcts and nine hemorrhages. No mention is made, however, of the clinical importance of these findings.

A review of the world literature shows that data are consistent with the findings of the present study, namely that hemorrhagic complications of thrombocytosis in CGL are unusual. There are only 13 reported cases in which patients diagnosed as having CGL exhibit a hemorrhagic thrombocythemia-like syndrome. These were isolated cases, since data from large series of CGL patients have not been previously reported. The problem of a definite diagnosis is complicated by the fact that cytogenetic studies were not available in any of the patients.

The low incidence of thrombocytosis-associated complications in CGL may be useful in the management of these patients. Control of the platelet count generally does not require aggressive therapeutic measures, and the risks to the patient of intensive therapy specifically directed at lowering the platelet count may outweigh the small risk of hemorrhagic complications.

The appearance of thrombocytosis during the course of CGL in the absence of previously elevated counts is associated with early appearance of blastic transformation (median, 8 mo). It is possible that thrombocytosis reflects a further defect in stem cell regulation prior to frank blastic transformation. This is suggested by the fact that six patients developed transiently elevated platelet counts coincident with the appearance of increased numbers of blasts.

In an effort to explain the bleeding tendency in patients with myeloproliferative disease, various investigators have examined platelet function tests in these patients. In one study, 12 of 14 patients with CGL had demonstrable abnormalities of their platelet function tests in the absence of significant hemorrhage. In another study, nine patients with CGL all had some abnormality of their platelet function tests. Of those nine, four had clinically apparent bleeding, and of the four who bled, three had elevated platelet counts. Four of the five patients in that study who did not bleed also had elevated platelet counts. In that same study, all eight patients with PV had both abnormal platelet function tests and symptomatic bleeding. Although these studies indicate that it is common for patients with any of the myeloproliferative disorders to have abnormalities of their platelet function, they do not explain the discrepancy between the significance of thrombocytosis in CGL and in the other myeloproliferative diseases. Although there is no clear explanation for the absence of the relationship between thrombocytosis and hemorrhage in patients with CGL, it is important to realize that the appearance of thrombocytosis in a CGL patient may be of some prognostic significance, but does not constitute a medical emergency per se.

REFERENCES
15. Drake CB: Leukemia with thrombocytosis. JAMA 106:1005, 1936
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