Chemotherapy of the Blastic Phase of Chronic Granulocytic Leukemia: Hypodiploidy and Response to Therapy

By G. P. Canellos, V. T. DeVita, J. Whang-Peng, B. A. Chabner, P. S. Schein, and R. C. Young

Thirty-two patients in the blastic phase of Philadelphia chromosome-positive chronic granulocytic leukemia (CGL) were studied in a prospective randomized trial in which vincristine–prednisone (19 patients) was compared with cytosine arabinoside–6-thioguanine (13 patients). Seven remissions (37%), including two complete remissions, were achieved in the vincristine–prednisone group. Three of the five with predominant hypodiploid blast cell lines treated with vincristine–prednisone had complete or partial remissions. Both complete remitters presented with hypodiploidy consisting of 44 chromosomes. Four patients (30%) who were treated with cytosine arabinoside–6-thioguanine responded with one complete remission. The median survival of the responders was 8 mo, as compared to 1–2 mo for the nonresponders. Crossover to the opposite regimen as secondary therapy following refractoriness or resistance resulted in only 3 partial responses out of 21 treated. All three had previously responded to vincristine–prednisone. Of the 32 cases, 14 had an elective splenectomy during the chronic phase of the disease. Prior splenectomy did not influence the response to chemotherapy, as all three complete remitters occurred in the nonsplenectomized group. Similarly, survival in the blastic phase was not affected by prior splenectomy.

In the vast majority of patients with chronic granulocytic leukemia (CGL), the disease terminates in an acute or blastic phase. Remission of this phase of the disease in most cases is difficult to achieve with chemotherapy. Patients who present in this phase of CGL can have massive splenomegaly, extensive previous alkylating agent therapy, and myelofibrosis, all of which may further complicate chemotherapy. The pancytopenia induced by most combination drug programs effective in the treatment of acute myelogenous leukemia can be severe and prolonged in patients with CGL, resulting in death from sepsis and/or bleeding.

In 1971, we reported our initial experience with the use of vincristine and prednisone alone in the treatment of this disease. The ability of this combination to achieve complete hematologic and cytogenetic remission in 6 of the first 30 cases was encouraging. Further, the data suggested that patients whose blastic phase was characterized by aneuploidy, especially hypodiploidy, were more likely to respond. In order to pursue these observations and correlations further, a prospective randomized trial in which vincristine–prednisone was compared with cytosine arabinoside–6-thioguanine was begun. The latter two drugs had shown promising results in the treatment of acute myelogenous leukemia. In addition, a previously initiated study of elective or “prophylactic”
spleenectomy in the chronic phase of the disease provided the opportunity to examine the effect of prophylactic spleenectomy on the response to chemotherapy and survival in the blastic phase. The results of this prospective trial were correlated with the blastic phase cytogenetics and the prior splenectomy status of the patients.

MATERIALS AND METHODS

Patients

All CGL patients were treated and followed at NCI. The chronic phase of the disease was treated with either busulfan or dibromomannitol (DBM) in all cases as previously described. In addition, those patients (16 cases) whose disease developed acceleration with leukocytosis refractory to busulfan or DBM, but without evidence of frank blastic transformation, were treated with hydroxyurea prior to entrance into the trial. The clinical and hematologic criteria for the diagnosis of the blastic phase of CGL have been previously outlined. Of the 32 cases who entered the trial, 14 had a previous elective spleenectomy during the chronic phase of the disease. Of the 18 cases who did not have the operation, the reasons included: abrupt onset of the acute phase, patient refusal, or other medical contraindications such as advanced age (> 60 yr) or obesity. Splenectomy was performed during the chronic phase of the disease while the patient was in hematologic remission. The median duration of CGL at the time of splenectomy was 12 mo.

Chemotherapy

Since January 1, 1971, patients were randomized by the closed envelope technique to receive one of two regimens.

1) Vincristine sulfate 2.0 mg/sq m was given intravenously each week with prednisone 60 mg/sq m by mouth each day for the first 5 days. Prednisone was not repeated with the subsequent weekly injections of vincristine. In all but one case, at least two doses of vincristine were administered before a patient was judged to be refractory. Those patients who achieved a complete remission were scheduled to receive oral methotrexate 15-20 mg/sq m twice weekly with monthly doses of vincristine until evidence of disease refractoriness. The choice of methotrexate was basically empiric and based on its previous use as maintenance therapy in acute lymphoblastic leukemia. The presumption was that responsiveness to vincristine-prednisone might also be associated with methotrexate sensitivity. The monthly doses of vincristine administered to patients in remission were modified to minimize the neurotoxic effects.

2) Cytosine arabinoside 200 mg/sq m was given intravenously as a 30-min infusion followed in 12 hr by intravenous 6-thioguanine 200 mg/sq m over 30 min (ARA-C/6-TG) each day for at least 5 days. The drugs were continued on a daily basis to bone marrow hypoplasia with < 5% blasts and complete disappearance of abnormal cells from the peripheral blood. Those who achieved remission received intermittent monthly 5-day courses of ARA-C/6-TG even in the absence of recurrent blastic leukemia. Patients were administered allopurinol and platelet transfusions as required. Those cases that were refractory or resistant to one regimen were crossed over to the alternate treatment. Since January 1, 1974, patients who were resistant to both vincristine-prednisone and ARA-C/6-TG received the experimental agent, 5-Azacytidine intravenously (150 mg/sq m/day for 5 days). Patients who received at least one cycle of therapy were evaluable.

Criteria of Response

Complete remission was defined as complete clearance of blasts and promyelocytes from the peripheral blood and less than 5% blasts in bone marrow that showed normal cellularity or granulocytic hyperplasia consistent with the chronic phase of CGL. Peripheral counts returned to > 12 g/100 ml of hemoglobin, white blood count < 12,000/cu mm with less than 5% myelocytes, and a sustained platelet count over 150,000/cu mm. If aneuploidy characterized the blastic phase, then a return of marrow cell cytogenetics to 46 Ph+ characteristic of the chronic phase was required. Partial remission was defined according to the following criteria: (1) reduction in the absolute blast and promyelocyte count in the peripheral blood by 50%, or more; (2) reduction in the
CHEMOTHERAPY OF BLASTIC CGL

Table 1. Chemotherapy of Blastic Transformation of CGL (32 Cases): Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Vincristine-Prendissone</th>
<th>ARA-C/6-TG</th>
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</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Median age</td>
<td>38 (11-64)</td>
<td>37 (21-54)</td>
</tr>
<tr>
<td>M:F</td>
<td>12:7</td>
<td>9:4</td>
</tr>
<tr>
<td>Prior splenectomy</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Acute transition</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Myeloproliferative acceleration</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Aneuploidy</td>
<td>12/19</td>
<td>7/12</td>
</tr>
</tbody>
</table>

percentage of blast cells in the marrow to less than 25%; (3) stabilization and improvement of peripheral red cell and platelet counts but not necessarily a return to the above mentioned levels.

Cytogenetics

All patients had a cytogenetic study of their bone marrow cells during the chronic phase of the disease. All were Philadelphia chromosome positive. Repeat bone marrow cytogenetics were performed at the onset of the blastic phase of the disease prior to randomization. Patients were not stratified according to the cytogenetic findings.

RESULTS

Thirty-two patients were randomized and all were evaluable. The clinical characteristics of the treated patients are shown in Table 1 and were similar in the two treatment groups. The patients were also defined as to the mode of presentation of the blastic phase and were divided into two general groups. Acute transition refers to the abrupt onset of the blastic phase over a period of less than 1 mo. Myeloproliferative acceleration refers to those patients whose blastic phase was preceded by a 3-6 mo period of progressive leukocytosis refractory to increasing doses of alkylating agent; 10% bone marrow blasts; with or without basophilia, reticulin-positive myelofibrosis, massive splenomegaly, and morphological abnormalities of the red cells. Nineteen patients received vincristine-prednisone and 13 ARA-C/6-TG as initial therapy. The results are shown in Table 2. Of the 19 who received vincristine-prednisone, 7 achieved a complete or partial remission (37%). Two achieved a complete hematologic remission with disappearance of their aneuploid blast cells and

Table 2. Blastic Phase of CGL Response to Treatment

<table>
<thead>
<tr>
<th></th>
<th>Vincristine-Prednisone</th>
<th>ARA-C/6-TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>No response</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Crossover therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>0</td>
<td>3 (3)*</td>
</tr>
<tr>
<td>No response</td>
<td>8 (3)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>5-Azacytidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>2 (1)</td>
<td></td>
</tr>
</tbody>
</table>

*Numbers within parentheses denote patients who responded to previous therapy.
return of marrow morphology to normocellularity or granulocytic hyperplasia with normal peripheral and differential blood counts. Five patients had a partial remission of their disease. The two complete remissions were achieved after 2 doses of vincristine in each case and these patients received 11 and 24+ total doses of vincristine. The partial responders received 3, 6, 8, 9, and 10 cycles of therapy, respectively.

Thirteen patients were treated with ARA-C/6-TG and four achieved a complete or partial response (30%). One of these was a complete hematologic response; however, because of the absence of aneuploidy no cytogenetic changes could be documented. Despite the achievement of hypoplasia, after at least one course of 5–12 days of treatment, nine patients failed to improve and had return of blast cells during the post-treatment recovery phase. Five patients had only one cycle of treatment. The toxicity of ARA-C/6-TG was primarily hematologic, although most patients experienced nausea and some vomiting during the first 2–3 days of drug treatment. In general, subsequent doses were tolerated with progressively less nausea.

**Crossover Results**

Thirteen of the 19 who received vincristine–prednisone as initial therapy subsequently were treated with ARA-C/6-TG, resulting in three partial responses of less than 2 mo in patients who previously responded to the primary therapy. Eight patients who received ARA-C/6-TG were crossed over to vincristine–prednisone and none responded. Three patients who failed to respond or were
refractory to either their primary or secondary therapy were treated with multiple courses of 5-Azacytidine, and one patient obtained a 7-mo partial remission after only one course of treatment. The overall survival of the two treatment groups according to their response to primary treatment is shown in Fig. 1. The median survival of nonresponders was between 1 and 2 mo, whereas the responders had a median of 8 mo.

Cytogenetic correlations are shown in Table 3. It is noteworthy that both complete responders to vincristine-prednisone had blast cells with 44 chromosomes Ph1 positive. Four of the eight cases with hypodiploid or pseudodiploid cell lines had a complete or partial remission. The small number of cases and the low remission rate did not allow the possible correlation between response and cytogenetics to be ascertained for the ARA-C/6-TG group. Elective splenectomy did not appear to influence the overall response to chemotherapy. All 3 complete and 4 partial remissions occurred in 18 patients who did not have a prior splenectomy. Of the 14 patients who had a prior splenectomy, 5 achieved a partial response. Further, prior splenectomy per se did not improve survival in the blastic phase (Fig. 2). It should be noted that 3 of 18 patients who did not have splenectomy experienced massive splenic infarction as a terminal event. The survival of each treatment group is shown in Fig. 3. There appeared to be some initial advantage to the vincristine-prednisone group, but by 10 mo there was no difference. In a therapeutic setting where less than half the patients achieved any improvement, the median survival was not a useful figure. Five of the 19 vincristine-prednisone patients survived 12 mo from the onset of therapy.
DISCUSSION

The results of the present study confirm the effectiveness and relative ease of remission induction with vincristine-prednisone in some cases of blastic transformation of CGL. Further, the data confirm and extend the observation that, when the blastic phase is characterized by hypodiploidy, the likelihood of response to these drugs is increased. When our previously published series of vincristine-prednisone-treated patients is combined with the present 19 cases (49 total cases), 7 of the 10 cases with predominant aneuploidy consisting of blast cells with 44 or 45 chromosomes had achieved a complete or partial response. Other workers concur with these therapeutic observations and suggest, in the absence of cytogenetic data, that 9 of 15 patients with “agranular” blasts achieved a complete response. More recent speculation and some experimental data suggest that the blast cells of CGL in some patients may have morphological and enzymatic characteristics of lymphoid cells. The enzyme, terminal deoxynucleotidyl transferase, which catalyzes the addition of deoxyribonucleotide triphosphates to 3’-OH ends of the DNA molecule is characteristic of lymphoid cells of thymic origin. It has been detected in 1 of 4 cases of the blastic phase of CGL as well as 12 of 14 cases of acute lymphoblastic leukemia. It is conceivable that vincristine-prednisone may be effective against such cells. A recent cytochemical and morphological study has demonstrated a marked heterogeneity of the blasts in CGL. One of the three patients in that report, with a high nuclear/cytoplasmic ratio treated with vincristine-prednisone, achieved a complete remission. Based on purely morphological considerations and the possibility that there exists a stem cell that is pluripotential for lymphoid and myeloid cells, it has recently been speculated that there may be a lymphoblastic transformation of CGL. Since only patients with distinctive morphological, cytogenetic, and perhaps biochemical characteristics may have a greater propensity to respond to vincristine-prednisone, this observation might be missed in small series of cases. The absence of myelosuppression has justified the inclusion of these agents in some multiple drug programs that have been reported to produce favorable results in this disease. There is, however, the very real risk that the addition of other myelosuppressive agents may produce prolonged pancytopenia that could obscure a selective therapeutic effect of vincristine for the blast cells.

Our data suggest that there is no advantage to the prophylactic removal of the spleen during the chronic phase if the goal is to facilitate a drug-induced remission of the blastic phase of the disease. Removal of the spleen, however, does eliminate a potential source of great discomfort to the patient in the blastic phase of CGL. It might permit a higher platelet count, facilitate transfusion therapy, and, potentially, bone marrow transplantation. A recent report suggests that elective splenectomy might prolong the duration of the chronic phase. Since half the patients in that study have been followed for less than 2 yr it is too early to assess accurately the impact on survival. Clearly, if one omits to perform the operation on those patients whose disease either presents with or quickly evolves to an accelerated course, the survival curve for elective splenectomy will appear better than previously published series treated in a conventional manner.
Although the overall response rate to ARA-C/6-TG combination is not impressive, despite treatment to hypoplasia, one cannot exclude the possibility that a different schedule of administration might be more effective. Vincristine and prednisone appear to be very effective in patients whose blastic phase is characterized by a predominant hypodiploid cell line. The therapeutic effectiveness of these agents may be limited to such cases, which represent the minority of patients. The data do not exclude the possibility that the addition of ARA-C/6-TG to vincristine-prednisone may increase the duration of response to the latter combination.

REFERENCES

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