Homoharringtonine Therapy Induces Responses in Patients With Chronic Myelogenous Leukemia in Late Chronic Phase

By Susan O'Brien, Hagop Kantarjian, Michael Keating, Miloslav Beran, Charles Koller, L.E. Robertson, Jeane Hester, MaryBeth Rios, Michael Andreeff, and Moshe Talpaz

Homoharringtonine (HHT) is a plant alkaloid with potent myelosuppressive activity and little toxicity when used in a continuous infusion schedule. The antileukemic efficacy of HHT has been shown in acute myeloid leukemia, but has not been investigated in chronic myelogenous leukemia (CML). Seventy-one patients with Philadelphia chromosome-positive (Ph+) CML in late chronic phase (time from diagnosis to therapy longer than 12 months) were treated with a continuous infusion of HHT at a daily dose of 2.5 mg/m² for 14 days for remission induction and for 7 days every month for maintenance. The median number of courses given was 5 (range, 1 to 35) and 21 patients (30%) continue on treatment. Forty-two of 58 patients (72%) evaluable for hematologic response achieved a complete hematologic remission, and 9 (16%) had a partial hematologic remission. Twenty-two of 71 patients (31%) developed a cytogenetic response; it was major (Ph⁻ cells less than 35%) in 11 (15%) and complete (Ph⁻ cells 0%) in 5 (7%). Significant myelosuppression occurred in 39% of induction courses and 9% of maintenance courses. Fever or documented infection was present in 26% of induction courses and in only 8% of maintenance courses. Nonmyelosuppressive toxicity was minimal. Homoharringtonine produced hematologic remissions in the majority of patients with advanced chronic-phase CML. Cytogenetic response occurred in some patients without an association with myelosuppression, and these responses may be prolonged. Future studies investigating homoharringtonine in combination with other active agents in CML, such as interferon, are warranted. © 1995 by The American Society of Hematology.

A LLOGENEIC BONE MARROW (BM) transplantation is curative in patients with chronic myelogenous leukemia (CML), but is limited to only 20% of patients because of restrictions on age and donor compatibility. Interferon α (IFN-α) treatment in early chronic-phase CML results in a hematologic response in 70% to 80% of patients and in complete suppression of the Philadelphia chromosome (Ph), or complete cytogenetic response, in 15% to 25% of patients. These complete cytogenetic responses are long lasting, with 80% of patients remaining alive and in remission at 8 years. Confirmation that the survival benefit is conferred by the cytogenetic response has been shown by landmark analysis that analyzed survival from 12 months to therapy by response at 12 months; and by multivariate analysis that identified major cytogenetic response (introduced as a time varying factor after pretreatment prognostic factors were identified) to be an independent prognostic factor for survival. An Italian randomized study also showed by landmark analysis the prognostic significance for survival of achieving a cytogenetic response with IFN-α.

When the CML becomes resistant to IFN-α, therapeutic options are limited, and palliative treatment such as hydroxyurea is commonly used. Based on the hypothesis that suppression of the Ph chromosome will prolong survival, we have searched for other agents that can produce both hematologic and cytogenetic remissions in CML.

Homoharringtonine (HHT) is a plant alkaloid derived from the Cephalotaxus fortunei tree. A mixture of HHT and harringtonine was first used in the treatment of leukemia by the Chinese, who reported activity in both acute myelogenous leukemia (AML) and CML. Cytochrome responses were not described in those studies. Subsequent phase I studies in the United States using a bolus schedule of HHT showed hypotension and myelosuppression to be the dose-limiting toxic effects. To abrogate the hypotensive side effects, HHT was given as a continuous infusion for AML, and occasional responses were seen. However, hypotension still occurred frequently at daily doses above 5 mg/m². Using a lower daily dose of 2.5 mg/m² and prolonging the infusion to 14 to 21 days reduced the incidence rate of hypotension to only 3% and with this schedule, the only dose-limiting toxic effect was prolonged myelosuppression. Because of its potent myelosuppressive effects, we investigated HHT in the treatment of CML. Study patients were ineligible for related BM transplants and in most cases had failed to respond to therapy with IFN-α. Herein, we describe our results using HHT in patients with CML in late chronic phase.

PATIENTS AND METHODS

Study population. Seventy-one patients with CML in late chronic phase (defined as a period from diagnosis to therapy longer than 12 months) were treated after written informed consent was obtained according to institutional guidelines. The 12-month treatment cut-off was chosen based on known differences in response to therapy of CML patients beyond this point. Patients with a disease duration of more than 1 year have inferior hematologic and cytogenetic response rates to IFN-α. Similarly, patients with CML who receive an allogeneic BM transplant at more than 1 year from diagnosis have significantly inferior survival compared with those patients transplanted within 1 year.

Treatment eligibility criteria included a Zubrod performance status ≤2 and normal renal and hepatic functions. Patients with severe heart disease (cardiac classes III and IV) were excluded. Patient characteristics are outlined in Table 1. The median patient age was 46 years (range, 23 to 71 years), and 48% were women. All but three patients had a Zubrod performance status ≤2. The median time from diagnosis of CML to treatment with HHT was 37 months (range, 4 to 148 months). Five patients (7%), were treated within 1 year of diagnosis, all of whom had previously received
HOMOHARRINGTONINE IN CML

Promyelocytes, or myelocytes; a platelet count
quired a WBC count
the 71 patients (30%) continue on treatment. Toxicity was graded
according to National Cancer Institute criteria.

number of courses of HHT given was 6 (range, 1 to
2,500/pL and the platelet count to above 100
intervals provided the granulocyte count had recovered to above

HHT could not be evaluated in those patients, but they were included
in the analysis for evaluation of cytogenetic response. All 13 of
these patients had 100% Ph+ metaphases, and 4 of the 13 had addi-
tional clones.

Therapy. Homoharringtonine was given as a continuous infusion
through a central venous catheter at a daily dose of 2.5 mg/m² over
14 days on an outpatient basis. Patients who achieved complete
hematologic remissions received maintenance therapy with 2.5 mg/
m² HHT for 7 days every month. In subsequent courses, the dose
was held constant, but the number of days could be adjusted to
achieve a nadir granulocyte count of about 1,000/µL and a nadir
platelet count above 50 × 10³/µL. Courses were given at monthly
intervals provided the granulocyte count had recovered to above
2,500/µL, and the platelet count to above 100 × 10³/µL. Most patients
who achieved remission did so with one 14-day course. Fourteen
patients (20%) required two courses, four patients (6%) required
three courses and one patient received five induction courses. The
median time from the start of HHT therapy (14-day induction) to
the maintenance courses was five weeks (range, 2 to 18). The median
number of courses of HHT given was 6 (range, 1 to 35), and 21 of
the 71 patients (30%) continue on treatment. Toxicity was graded
according to National Cancer Institute criteria.

Response criteria. Response criteria were those previously de-

Partial hematologic remission (P-HR) required a peripheral WBC
count = 10 × 10³/µL, and ≥ 50% reduction of palpable splenomeg-
aly and thrombocytosis but residual immature cells were allowed.

RESULTS

Active disease. Of the 58 patients who had active dis-
ease, 42 (72%) achieved CHR with HHT therapy (Table 2). Nine
patients (16%) achieved a PHR. Of the 42 patients
attaining CHR, 16 patients (38% of CHR patients, 28% of
total patients with active disease) achieved a cytogenetic
response. This response was minimal in 9, partial in 2, and
complete in 5 patients. Thus, 7 cytogenetic responders devel-
aped a majority population of normal diploid cells. Of the 16
patients with active disease and clonal evolution, 11 (69%)
achieved CHR and 5 (29%) achieved P-HR. A cytogenetic
response occurred in 3 (27%) of the 11 CHR patients, being
minimal in 2 patients and complete in 1. In 4 (25%) of
the 16 patients with active disease and clonal evolution,
metaphases remained 100% Ph+, but clonal evolution re-
solved with HHT therapy.

Cytogenetic response in patients in remission. Thirty
patients had normal blood counts when they began therapy
with HHT. All 13 had 100% Ph+ metaphases and 4 had
additional clones in 16% to 91% of metaphases. Of the 13
patients, 2 had an increase in their blood counts while receiv-
ing HHT and were considered therapy resistant. One patient
maintained normal blood counts, but was not considered to
be in continuing CHR because immature cells were present
in the blood. Of the remaining 10 patients, 6 developed a
cytogenetic response that was minimal in 2 patients and
partial in 4 patients (Table 2). Two patients who achieved a
partial cytogenetic response had clonal evolution that re-
solved.

Table 1. Patient Characteristics (n = 71)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;50 (yr)</td>
<td>46 (23-71)</td>
</tr>
<tr>
<td>Time from diagnosis to HHT &gt;3 yr</td>
<td>37 (52)</td>
</tr>
<tr>
<td>Prior interferon therapy</td>
<td>56 (82)</td>
</tr>
<tr>
<td>Interferon resistant</td>
<td>41 (58)</td>
</tr>
<tr>
<td>Palpable splenomegaly</td>
<td>18 (32)</td>
</tr>
<tr>
<td>Clonal evolution</td>
<td>20 (28)</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>58 (82)</td>
</tr>
<tr>
<td>Hematologic remission, 100% Ph+</td>
<td>13 (18)</td>
</tr>
</tbody>
</table>

Patients with active disease (n = 58)

Table 2. Response to HHT

<table>
<thead>
<tr>
<th>CML patients with active disease (n = 58)</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic response</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>42 (72)</td>
</tr>
<tr>
<td>Partial</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Resistant</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Lowest Ph status (% metaphases)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (9)</td>
</tr>
<tr>
<td>1-34</td>
<td>2 (3)</td>
</tr>
<tr>
<td>35-95</td>
<td>9 (16)</td>
</tr>
<tr>
<td>100</td>
<td>26 (46)</td>
</tr>
<tr>
<td>Patients in hematologic remission with</td>
<td></td>
</tr>
<tr>
<td>100% Ph+ metaphases (n = 13)</td>
<td></td>
</tr>
<tr>
<td>Lowest Ph status (% metaphases)</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>7 (54)</td>
</tr>
<tr>
<td>35-95</td>
<td>2 (15)</td>
</tr>
<tr>
<td>1-34</td>
<td>4 (31)</td>
</tr>
</tbody>
</table>
bocytopenia was noted in courses (Table 4). Thrombocytopenia below 30 × 10^9/L with an AGC below 100 pL during remission induction tenth cycle of HHT when bigeminy was noted. He received 33% of induction cycles, but was usually mild (grade 1) and often required no intervention. All side effects diminished was given for only 7 days. Although occasional patients below 500 × 10^9/L developed and 20% had severe neutropenia (Table 5).

"Toxicity." Side effects of HHT, shown in Table 3, were mild. Diarrhea, the most common toxic effect, occurred in 33% of induction cycles, but was usually mild (grade 1) and often required no intervention. All side effects diminished with the subsequent maintenance courses in which HHT was given for only 7 days. Although occasional patients complained of vague chest pain or tachycardia (11%), an arrhythmia was documented in only one patient during his tenth cycle of HHT when bigeminy was noted. He received five more cycles of HHT without experiencing further arrhythmias. No patient had significant hypotension.

In 39% of patients, an absolute granulocyte count (AGC) below 500/μL developed and 20% had severe neutropenia with an AGC below 100 pL during remission induction courses (Table 4). Thrombocytopenia below 30 × 10^9/μL occurred in 25% of induction courses. No serious bleeding episodes occurred. With the reduction in days of HHT on the maintenance phase of the therapy and adjustment in subsequent courses to reduce myelosuppression, granulocytopenia below 500/μL was noted in 9% of courses, and thrombocytopenia was noted in 5%.

Fever or documented infection occurred in 18 induction courses (26%); 12 (67%) were associated with granulocytopenia (Table 5). During the shorter maintenance courses, fever or infection occurred in only 8% of courses. An association with granulocytopenia was less common (21%), and severe infections (sepsis or pneumonia) occurred in only 2% of courses.

Two patients (3%) died during HHT therapy. One patient was a 63-year-old man who began treatment with a performance status of 2 and pneumonia. Progressive pneumonia developed and he died on day 7 of his first course. The other patient was a 55-year-old woman in whom BM aplasia developed after three courses of HHT. The BM was unresponsive to growth factors, and the patient died on day 115 with pneumonia.

"Follow-up results." Fifty patients (70%) have had HHT therapy discontinued for various reasons (Table 6); in 41%, hematologic resistance or disease evolution had developed. The median survival of the whole population is 30 months (Fig 1).

The course of patients who achieved a major cytogenetic response is shown in Table 7. Four patients have been taken off the study and seven patients continue to receive HHT. Patient 6 had no evidence of Ph+ cells after the first course of HHT, but later showed gradual loss of cytogenetic response and developed hematologic resistance after 18 courses of HHT; 1 month later, blast crisis occurred. Patient 9 had Ph+ status after four cycles of HHT; he refused further therapy, and blastic phase CML developed 20 months later; no therapy had been given in the interim. Patient 10 had 10% Ph+ metaphases after receiving two courses of HHT, but experienced prolonged and severe myelosuppression with both courses and did not receive further therapy. Eleven months later, his blood counts were normal, but another 6 months blastic-phase CML developed. Patient 11 showed 100% diploid cells after receiving one course of HHT, but severe pneumonia developed and performance status decreased after the first course, and he received no further therapy. He remains alive more than 30 months later with chronic-phase CML. Thus, three of the four patients who came off study have developed blastic phase CML and died at 23, 24, and 30 months from the start of HHT.

The remaining seven patients have now received 7 to 35 courses of HHT. Three patients (patients 1, 4, 7) continue to have a major cytogenetic response, with one patient (pa-
DISCUSSION

Although 95% of patients with CML show the Ph chromosome on cytogenetic analysis, the question remains as to whether this is a secondary event or whether the presence of the p210 protein encoded by this translocation is responsible for the development of the disease. Recent evidence suggesting a causal relationship includes the fact that introduction of the bcr/abl message into normal hematopoietic cells results in their malignant transformation. In addition, when murine BM was infected with a retrovirus encoding p210 bcr/abl and then transplanted into irradiated mice, the recipients of this BM developed hematologic malignancies that in some cases appeared similar to the chronic phase of CML. Clinical evidence supporting the Ph translocation as the etiology of CML includes the fact that patients who do achieve a significant cytogenetic response with IFN-α have a longer interval before disease evolution and prolonged survival. Thus, the impetus for achieving a cytogenetic remission is established. IFN-α is the only agent to date that can elicit significant cytogenetic responses in patients with Ph+ CML. However, once the disease becomes resistant to IFN-α, no therapeutic modalities are available to treat these patients other than in a palliative mode. Autologous BM transplant may be feasible in some patients who, after chemotherapy, have a reduction in the percent of Ph+ cells. However, the effectiveness of this in vivo purging is less in patients with long-standing disease.

In this study, we have shown the significant anti-CML efficacy of HHT. Used in a low-dose, continuous-infusion schedule, HHT induced hematologic remissions in two thirds of patients with late chronic-phase CML. More important, 11 (15%) of 71 patients achieved significant cytogenetic responses, and these have been maintained in 3 patients, all of whom have completed more than 1 year of therapy. All patients who achieved a cytogenetic response had normalization of blood counts. However, there was no correlation between severe myelosuppression and achievement of a cytogenetic response. This is in keeping with the finding that most myelosuppression occurred during the initial course and that the incidence rate of significant granulocytopenia in a subsequent courses was only 9%. The use of high-dose chemotherapy for early-stage CML may result in cytogenetic responses in up to 60% of patients. However, these responses are transient and follow a prolonged period of myelosuppression as is seen with acute leukemia therapy. This suggests that the temporary disturbance of the BM pool initially benefits the normal stem cells in terms of recovery time, but that, inevitably, the malignant clone will exert its preferential growth advantage. Interferon is the only agent for which significant cytogenetic responses have been described in association with the lowering of blood counts to normal range, but without significant myelosuppression.

The beneficial effects of interferon are most pronounced in patients who are treated within 1 year of diagnosis. The use of IFN-α in patients with late chronic-phase CML results in CHR in 28% and in Ph suppression in 5%. No major cytogenetic responses are seen. HHT produced significantly more hematologic responses (72%) and cytogenetic responses (31%) in these late chronic-phase CML patients. Moreover, 58% of the patients treated with HHT had disease that was resistant to IFN-α, and thus, these patients represented a poor-prognosis group.

In summary, HHT produces hematologic remissions in the majority of patients with advanced chronic-phase CML. Cytogenetic responses may occur without an association with myelosuppression in a minority of patients, and these responses may be prolonged in some patients. Future studies investigating HHT in combination with other active agents such as IFN-α for CML are warranted.

REFERENCES


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