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ORIGINAL ARTICLE

A phase II study of continuous infusion homoharringtonine and cytarabine in newly diagnosed patients with chronic myeloid leukemia: CALGB study 19804

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Abstract
Background Both homoharringtonine (HHT), an alkaloid derivative from the Chinese yew tree that inhibits protein synthesis, and low-dose cytarabine have independent activity in CML and have been used in combination after failure of interferon therapy.
Patients and methods The CALGB performed a phase II trial of HHT (2.5 mg/m^2 per day) plus cytarabine (7.5 mg/m^2 per day), given together via continuous intravenous infusion for 7 days in previously untreated patients with Ph chromosome positive chronic phase CML. HHT/cytarabine cycles were repeated every 28 days if the blood counts were adequate. The primary endpoint was the major cytogenetic response rate after 9 months.
Results Forty of the 44 enrolled patients required reduction in the infusion duration during at least one cycle. Myelosuppression was common; 66% developed neutrophil count <500/μl, but grade 3 infections occurred in only 7%. Thirty-six of 44 patients (82%) achieved a complete hematologic remission; the median duration has not been reached. Only 4 of the 23 patients (17%) having adequate cytogenetic response assessment achieved a major response within nine cycles.
Conclusions Although HHT/cytarabine was generally well tolerated, the cytogenetic response rate did not exceed the level previously seen in patients with interferon-refractory CML and was not nearly as high as associated with imatinib in newly diagnosed patients.

Keywords Chronic myeloid leukemia · Cytarabine · Homoharringtonine

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Introduction

Chronic myeloid leukemia (CML) is a clonal proliferation of bone marrow stem cells harboring the Philadelphia (Ph) chromosomal translocation [t(9;22)] which yields the Bcr-Abl fusion protein, an activated tyrosine kinase [4]. The clinical manifestations of this disease include leukocytosis, basophilia and splenomegaly [2]. The medical therapy of CML has recently been revolutionized by the development of imatinib mesylate, a small molecule Abl kinase inhibitor, which yields a 98% complete hematologic response (CHR) rate and an 83% major cytogenetic response (MCyR) rate when given to newly diagnosed patients with chronic phase CML [3]. However, resistance develops in some patients.

Thus, there is a need for additional non-cross-resistant therapies.

Before the development of imatinib, the mainstay of medical therapy in CML was interferon alfa [21], the first drug to lead to major reductions in the disease burden as measured by the fraction of cells with the Ph translocation. Although interferon led to longer survivals compared with oral chemotherapy [13], it was frequently associated with intolerable constitutional and neuropsychiatric toxicity [7]. Low doses of cytarabine, also known to possess anti-CML activity [17], produced a superior outcome in combination with interferon compared with patients receiving interferon alone [6]. The search for additional active agents in CML led to homoharringtonine (HHT), an alkaloid derivative from the Chinese yew tree [16]. HHT given by continuous intravenous infusion has single agent activity in patients with CML that is resistant to interferon [14]. The main toxicity is mild myelosuppression. Investigators at the MD Anderson Cancer Center performed separate trials of HHT in combination with interferon [15] and with cytarabine in patients with chronic phase CML [10]. HHT and interferon led to a 50% hematologic response rate and to 25% cytogenetic response rate in newly diagnosed patients [15]. In patients who were either intolerant or refractory to interferon, the combination of HHT and cytarabine was well tolerated and led to a 25% likelihood that the fraction of Ph+ metaphase cells would decline [10]. The doses employed in our study were intentionally similar to those used in the MD Anderson HHT/cytarabine combination study [10], which were HHT 2.5 mg/m^2 per day by continuous IV infusion for 5 days (our study included 7 days of HHT at that dose) plus cytarabine 7.5 mg/m^2 per day subcutaneously every 12 h for ten doses (our study used 7.5 mg/m^2 per day by continuous IV infusion for 7 days).

Here, we report the results of a prospective phase II trial of the HHT/cytarabine combination conducted by the Cancer and Leukemia Group B (CALGB) to confirm the MD Anderson findings in less advanced patients and to extend them by performing cytogenetics and molecular monitoring to assess response. After imatinib was approved by the FDA in May 2001, accrual to this upfront trial slowed markedly. Nevertheless, we report here that the combination is feasible and tolerable, albeit with nearly ubiquitous dose modifications due to myelosuppression. However, the rates of cytogenetic responses were lower than expected.

Methods

The primary objective of this trial was to assess the hematologic and cytogenetic response rates for the combination of HHT and cytarabine in recently diagnosed patients with CML. Patients 16 years or above were required to have chronic phase CML with a *BCR/ABL* rearrangement, proven by cytogenetic analysis, immunoblotting, polymerase chain reaction or fluorescent in situ hybridization within 8 weeks of registration. No prior treatment for CML, including HHT, cytarabine, busulfan, interferon, or imatinib was allowed except for hydroxyurea. Candidates for an early allogeneic hematopoietic cell transplant were not eligible, and patients must have declined a potential alternative donor transplant after appropriate counseling. An ECOG performance status of 0–2, bilirubin $\leq 1.5 \times$ the upper limit of normal, and creatinine ≤ 1.5 mg/dl were required. Registration onto the companion studies CALGB 9665 (Leukemia Tissue Bank) and CALGB 28901 (Molecular and Cytogenetic Monitoring of CML) were required. Patient registration and data collection were managed by the CALGB Statistical Center. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The protocol was reviewed and approved by the institutional review board at each trial center.

After signing consent and prior to registration, patients underwent baseline evaluation that included a history and physical exam, a complete blood count (CBC) with differential and routine chemistry evaluation, and a bone marrow aspirate and biopsy for morphology and cytogenetic analysis (centrally reviewed).

Cytarabine (7.5 mg/m^2 per day) and HHT (2.5 mg/m^2 per day) were mixed in an ambulatory pump cassette and were given together as a continuous intravenous infusion for 7 days to outpatients. Cycles were to be repeated every 28 days. If the white blood cell (WBC) recovery from the first cycle reached higher than normal levels before 3 weeks, the second cycle could be started after 22 days, or hydroxyurea could be given.

Dose modification was undertaken by decreasing or increasing the infusion duration in subsequent cycles based on the hematological nadir (Table 1). The minimum number of infusion days was 3, and the maximum was 14. A treatment cycle could begin 28 days after the start of the previous cycle (or later, if necessary), if the following were present: WBC > 4,000/μl, absolute neutrophil count (ANC) > 1,000/μl, and platelets > 50,000/μl. In the event that these parameters were reached after 44 but before 50 days after the previous cycle started, the infusion duration was reduced by one additional day beyond that specified by the nadir counts. If the parameters were reached after day 50, then the infusion duration was reduced by 2 days beyond the time specified by the nadir counts.

Patients underwent blood count measurements weekly for the first 8 weeks and then at the time of the expected nadir and prior to starting each cycle. Bone marrow examinations, including cytogenetic evaluations, were performed after 3 and 9 cycles.

Table 1 Dose adjustments in the infusion duration based on nadir blood counts from the previous cycle

WBC (10^3/μl)	ANC (10^3/μl)	Platelets (10^3/μl)	Infusion duration
>10 and	>5 and	>300	Increase by 2 days
5–10 and	2.5–5 and	150–300	Increase by 1 day
2–4.9 and	1–2.49 and	50–149	No change
<2 or	0.5–0.99 or	>20, <50	Decrease by 1 day
<1 or	<0.5 or	<20	Decrease by 2 days

WBC White blood cells; *ANC* absolute neutrophil count

To continue therapy beyond nine cycles, the post-cycle 9 cytogenetic evaluation was required to show a major cytogenetic response (MCyR; <35% Ph+ metaphase cells). The decision to continue the therapy was based on the findings at the local institution. No response or only a minor response (36–100% Ph+ cells) after nine cycles required removal from protocol therapy. Thereafter, limited long-term follow-up data [including duration of hematological response (normal CBC)] and survival were collected.

Statistical analyses

The primary endpoints were the hematologic and cytogenetic response rates after completion of therapy. Secondary endpoints were the duration of hematologic response and incidence of hematologic progression in all patients, and to assess the duration of cytogenetic response in patients continuing protocol therapy beyond 9 months. Overall survival was defined as the interval from date of registration to the date of death from any cause, or the date of last follow-up exam for living patients. CHR was defined as achieving normal blood counts, with no palpable splenomegaly and <5% marrow blasts. Disease-free survival (DFS) was measured as the interval from date of CHR to the date of relapse or death, or the date of last follow-up exam for patients who were alive and still in remission. Duration of CHR was measured as the interval from the initial date of CHR to the date of clinically documented relapse (loss of normal CBC), or the date of last follow-up exam for patients still in remission. Survival probabilities were calculated using the Kaplan–Meier method. A "reverse Kaplan–Meier" method was also used in which follow-up time is calculated using the Kaplan–Meier estimate of the survival function, but with the meaning of the censoring indicator reversed [11]. Follow-up time was calculated using the potential follow-up method [18]. The Clopper–Pearson method [1] was used in the calculation of 95% confidence intervals for response rates. The planned sample size for the study was a maximum of 60 patients. Two separate single-stage designs were employed, to test the major cytogenetic response rate and the complete cytogenetic response rate. Data quality was ensured by careful review of the data by CALGB Statistical Center staff, the study chairperson, and the CALGB Data Audit Committee. Statistical analyses were performed by CALGB statisticians using the SAS v9.1, S-PLUS v7.0 and StatXact v6.02 software packages. The data were analyzed in July 2007 after a median follow up time of 7 years.

Results

Patients were accrued between 10 May 1999 and 12 April 2001. The accrual goal was 60 patients, but few patients enrolled after the imminent approval of imatinib was anticipated in May 2001, and none after the drug was licensed for use in interferon-refractory or intolerant chronic phase patients. Forty-four patients were enrolled and treated. One additional patient had enrolled but withdrew consent before receiving drug. Demographic data and clinical data are summarized in Tables 2 and 3. Twenty-six (59%) were men, and 21 of the 44 patients (48%) were above the age of 60 years. One patient was determined to be ineligible due to registering for the study a week past the criterion specified in the protocol. One patient had insufficient laboratory data to determine the eligibility. The statistical analysis included available data on all 44 patients who received any protocol therapy.

The most prominent side effect was myelosuppression: 66% developed an ANC <500/μl during at least one cycle, but grade 3 infections occurred in only three patients. Administered cycles, 186 of 389 (48%) were modified, 169 according to protocol-specified criteria. Two patients received a platelet transfusion, and six required a red blood cell transfusion. Forty of the 44 treated patients (91%) required a reduction in the number of treatment days during at least one cycle due to myelosuppression (Table 4). Mild and moderate nausea were common.

Table 2 Demographics for 44 CML patients treated on CALGB 19804

Characteristic	*n* (%)
Age (years)	
<50	9 (20)
50–59	14 (32)
60–69	12 (27)
70–79	9 (20)
Sex	
Male	26 (59)
Female	18 (41)
Race	
White	35 (80)
African American	5 (11)
Asian	2 (5)
Indian Subcontinent	2 (5)

Table 3 Patient peripheral blood and bone marrow differentials at baseline and 3 months following protocol registration

Differential type	Baseline				3 Months			
	N	Median	Min	Max	*N*	Median	Min	Max
WBC ($\times 10^3$)	37	39.4	4.4	313.2	23	4.2	1.0	46.0
Blasts (blood) (%)	35	0	0	11	17	0	0	3
Hemoglobin (gm/100 ml)	36	12.8	7.3	16.6	23	12.4	9.0	14.5
Platelets ($\times 10^3$)	37	337	49	977	23	193	42	572
Blasts (bone marrow) (%)	27	2	0	5	19	2	0	86

Table 4 Summary of dose modifications required by patients enrolled on CALGB 19804

Dose modifications by subject ($n = 44$)		
Subjects with dose modifications	*N*	(%)
No change	2	5
Yes, planned per protocol	41	93
Yes, unplanned	6	14
Yes, both planned and unplanned	5	11

Unplanned dose adjustments refers to dose modifications done because of myelosuppression, but for reasons not precisely specified in the protocol

Thirty-six of 44 patients (82%; 95% CI: 67%–92%) achieved a CHR; 14% experienced a partial hematological response (defined as a decrease in WBC by 50% and to <20,000/μl, or CHR with persistent splenomegaly, immature blood cells, or thrombocytosis). The median duration of the hematological response has not been reached, but exceeds 5 years; all of the patients subsequently received imatinib.

Only 4 of the 23 patients (17%; 95% CI: 5%–39%) having a cytogenetic evaluation after nine cycles achieved a MCyR. Six patients, including three of the four with MCyR, received ten or more cycles (12, 15, and 16 cycles). One patient received a tenth cycle while awaiting the local cytogenetic results, but did not have a MCyR and then discontinued this treatment. Another patient who had no cytogenetic response received 12 cycles in error. No patient had a complete cytogenetic response.

With a median follow-up of 7 years, 14 of the 44 patients (32%) have died, and 30 (68%) are known to be alive. Overall survival is illustrated in Fig. 1. The median overall survival time has not yet been reached. DFS is shown in Fig. 2. Seventeen of 30 patients (57%), who were known to be alive, were in CHR at last contact. The median DFS time was 5.9 years. Since all patients were believed to have switched to imatinib, the reported curves reflect both the efficacy of imatinib and the apparent lack of a deleterious effect of prior HHT/cytarabine exposure.

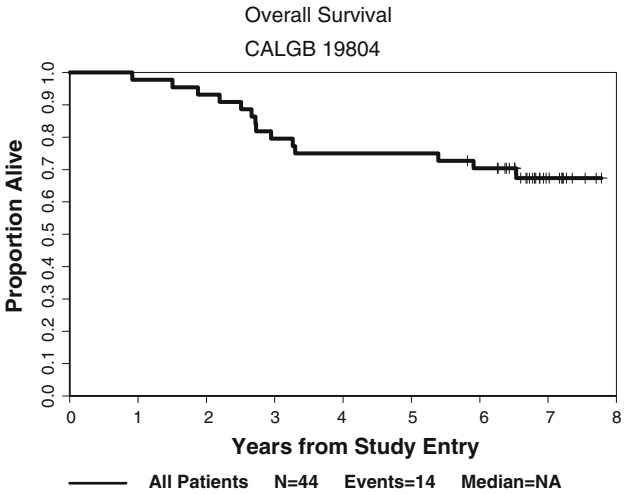

Fig. 1 Survival for 44 CML patients enrolled on CALGB 19804

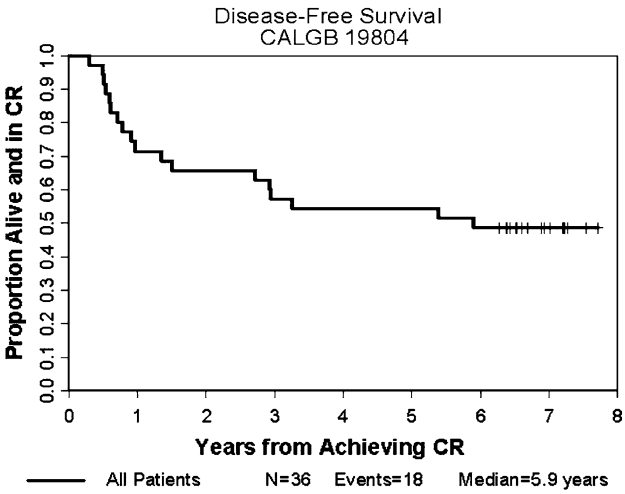

Fig. 2 Proportion of patients alive and continuing in hematologic remission for the 44 CML patients enrolled on CALGB 19804

Discussion

The objective of this study was to determine the cytogenetic response rate in newly diagnosed chronic phase CML patients following 9 months of treatment with a combination of homoharringtonine and cytarabine. We wished to

confirm and extend the results of Kantarjian et al. [10] who showed that patients with CML refractory to interferon had a 50% MCyR rate to these two drugs in combination. In contrast, although we did show that there was a high CHR rate to the combination of HHT plus cytarabine, unfortunately even in our newly diagnosed patients we noted a MCyR in only 4 of 44 patients (10% by intention to treat) after 9 months. It is possible that more prolonged treatment would have resulted in a higher response rate, but there was no apparent justification to continue patients on additional cycles of this infusional therapy. Moreover, the follow-up and accrual to our study was hampered by the development and approval of imatinib, an oral specific Bcr-Abl tyrosine kinase inhibitor which is associated with an 87% CCyR rate in newly diagnosed patients [3]. Thus, even if the results in this trial had been somewhat better than the results reported by Kantarjian et al. [10] in more advanced CML patients, the combination of HHT plus cytarabine would not be a viable upfront strategy due to the relatively cumbersome need for intravenous administration and because of the inferior results compared to those noted with imatinib alone [3].

It remains unclear why our results in early chronic phase patients with CML were inferior to those obtained with a similar regimen in late chronic phase patients. Our patients did not have more adverse prognostic factors than those in the report by Kantarjian et al. Our dose schedule was slightly more intensive and our dose modification criteria was somewhat more rigorous than described in the MD Anderson Cancer Center report, perhaps leading to less drug exposure. We cannot precisely compare the drug exposure in the two studies because that information was not supplied in the MD Anderson report.

Except for frequent myelosuppression and requirements for dose reduction, the combination of HHT plus cytarabine given by continuous IV infusion was generally well tolerated with few serious infections. Whether the combination of HHT plus cytarabine is more effective than HHT or cytarabine alone or interferon/cytarabine would need to be addressed in randomized clinical trials, which are not likely to be performed. However, given its tolerability, non-overlapping mechanism of action, and an appreciable response rate in several studies, one might consider combining HHT plus cytarabine with imatinib or another Bcr-Abl inhibitor, either early in the disease or at the occurrence of primary or secondary resistance as currently defined [19]. Although imatinib leads to a greater than four log reduction in the disease burden as assessed by quantitative real-time PCR analysis [3] in about half of newly diagnosed patients, it remains unproven and perhaps unlikely that imatinib or other tyrosine kinase inhibitors (TKI) will be curative for most patients with CML if given as a single agent. Thus, it may be necessary to combine imatinib with other active drugs. The HHT/cytarabine combination, which we have shown to be feasible, merits testing for activity in CML with a documented T315I *BCR/ABL* mutation, known to be resistant to all available TKIs [5]. Indeed, HHT (now known as omacetaxine mepesuccinate) is currently undergoing clinical evaluation as a single agent for this indication in part because its anti-CML activity is independent of the requirement for an accessible ATP-binding site in *BCR/ABL*. The dose of HHT being developed in this trial (1.25 mg/m^2 subcutaneously twice daily for 14 days every 28 days) [12] is similar to that used in our study.

We planned to measure the degree of tumor reduction resulting from HHT plus cytarabine by means of quantitative PCR analysis of patients achieving a CCyR. Given the lack of such patients, we were unable to accomplish this goal. On the other hand, we had sufficient paired samples to assess correlation between the quantitative PCR levels in the blood and bone marrow [20]. This ancillary study, reported separately, suggests that sequential bone marrow samples in patients with CML can be replaced by sequential assessment of peripheral blood PCR status since the trend of change in each is similar, although the absolute values of Bcr-Abl transcript level in blood and marrow are frequently different at a given time point.

In summary, we found that outpatient treatment of newly diagnosed CML patients with a combination of HHT plus cytarabine by continuous intravenous infusion was tolerable and moderately effective. Further development of this regimen would need to be in conjunction with, or in the setting of resistance to, imatinib mesylate, or a second generation tyrosine kinase inhibitor such as dasatinib [8] or nilotinib [9].

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Appendix

The following institutions participated in this study:

The CALGB Statistical Center, Duke University Medical Center, Durham, NC-Stephen George, Ph.D., supported by CA33601

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