Published in final edited form as:

Leuk Lymphoma. 2017 September ; 58(9): 2240–2242. doi:10.1080/10428194.2017.1283030.

Homoharringtonine with Imatinib in Chronic, Accelerated, and Blast Phase Chronic Myeloid Leukemia

Abhishek Maiti, MBBS^{1,2}, Jorge Cortes, MD², Alessandra Ferrajoli, MD², Zeev Estrov, MD², Gautam Borthakur, MD², Guillermo Garcia-Manero, MD², Elias Jabbour, MD², Farhad Ravandi, MD², Susan O'Brien, MD³, and Hagop Kantarjian, MD²

¹Department of Internal Medicine, The University of Texas Health Sciences Center at Houston, TX

²Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

³Chao Family Comprehensive Cancer Center, University of California, Irvine, CA

Keywords

chronic myeloid leukemia; accelerated phase; blast phase; chronic phase; imatinib; homoharringtonine; omacetaxine

To the Editor

Tyrosine kinase inhibitors (TKI) are standard agents for first and subsequent therapy of patients with chronic myeloid leukemia (CML). With TKIs, most patients will have an excellent response and near-normal life expectancy.¹ However, resistance to imatinib develops in approximately 35% of patients with chronic phase (CP) disease, upwards of 45% patients in accelerated phase, and about 90% of patients in blast phase (BP) of the disease.² Despite advances in therapy, prognosis after transformation to AP or BP remains poor with a median survival of approximately 3 years for AP and 9 months for BP.^{3,4}

Homoharringtonine (HHT), a plant alkaloid derived from *Cephalotaxus* species, and its semisynthetic formulation omacetaxine have shown efficacy in CML. In myeloid leukemia and myeloma cell lines these agents inhibit ribosomal protein translation and consequently

Correspondence: Dr. Jorge E. Cortes, MD, Department of Leukemia, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 428, Houston, TX 77030. Phone: +1-713-794-5783 Fax: +1-713-794-4297 jcortes@mdanderson.org.

Clinical trial registration information: <https://clinicaltrials.gov/ct2/show/NCT00114959>

Authorship contribution:

AM collected and analyzed the data, and co-wrote the manuscript. JC designed the clinical trial, treated patients, analyzed the data, and co-wrote the manuscript. AF, ZE, GB, GGM, EJ, FR, SOB, and HK treated patients, acquired data, and revised the manuscript for important intellectual content. All authors reviewed and approved the final version to be published.

Informed consent: obtained

Institutional ethics committee clearance: obtained

Conflict-of-Interest Disclosure:

AM: None; HK: research support from Ariad, BMS, Amgen and Pfizer; AF: none; ZE: none; GB: none; GGM: none; EJ: none; FR: none; SOB: consultant for Pharmacyclis and Janssen; JC: Research support from Ariad, BMS, Novartis, Pfizer, Teva; consultant for Ariad, BMS, Novartis and Pfizer.

induce apoptosis via downregulation of oncoproteins (BCR-ABL1, cyclin D1, cMyc, etc.), mitochondrial disruption, caspase activation, and modulation of transforming growth factor-beta and tumor necrosis factor signaling pathways.^{5,6} Omacetaxine is approved in the United States for treatment of patients with CML in CP or AP after failure of 2 or more TKIs.⁶ Preclinical studies have shown a synergistic effect of HHT with imatinib.⁷⁻⁹ We hypothesized that combining HHT with imatinib might improve outcomes, particularly for patients with advanced-phase disease.

We conducted an open-label phase II trial to evaluate the safety and efficacy of HHT combined with imatinib in the treatment of patients with CML in CP, AP, and BP (NCT00114959). This single-center study enrolled adult patients with CML-CP who were resistant to imatinib, or patients with AP or BP who were either untreated or refractory to imatinib. Patients with Eastern Cooperative Oncology Group performance status 2 or lower and normal organ function were eligible for inclusion. Patients received HHT 2.5 mg/m² by continuous 24-hour intravenous (IV) infusion daily for 5 days every 4 weeks with imatinib 400 mg orally daily for patients in CP, and 600 mg daily for patients in AP or BP. Hematologic efficacy and adverse events (AEs) were assessed prior to and during each cycle. CML phases were defined as per standard criteria and responses were assessed as per the European LeukemiaNet 2006 guidelines.^{10,11} A meaningful response was defined as follows: patients with CML-CP not in complete hematologic response (CHR) must have achieved at least a CHR with study therapy, and patients with CML-CP entering the study in CHR must have demonstrated an improvement in their cytogenetic response (CyR) category; patients in CML-AP or BP at a minimum must have converted to CML-CP. Cytogenetic and molecular evaluations were done every 3 months. Patients who did not achieve a meaningful hematologic or CyR by the end of the fourth cycle were taken off study. Patients who achieved at least a CHR could receive subsequent maintenance cycles with HHT 2.5 mg/m² by continuous 24-hour IV infusions daily for 2 days every 4 weeks and imatinib at the dose received on the last induction cycle. The study was intended to follow a Simon 2-stage design to evaluate 18 patients in each stratum (CP, AP, and BP patients) for efficacy.

We enrolled 15 patients between 10/2005 and 03/2009. Baseline characteristics, prior therapies, number of cycles received, and best responses are shown in the table 1. The median age of the patients was 55 years (range 21–76); 8 patients were male; 1 patient was in CP, 5 in AP, and 9 in BP. These 15 patients received a median of 3 cycles (range 1 to 34) and were on the study for a median duration of 3.1 months (range 1.1 to 36.4). Seven patients completed protocol-defined endpoint of 4 or more cycles for evaluation of response. Overall response rate per study definition was 4/15 (27%) at 1 month and 6/15 (40%) at 4 months. Median survival for all enrolled patients was 4.6 months. Eight of these 15 patients had kinase domain mutations (KDM), T315I mutation in 4 patients, F317L mutation in 2 patients, F359V mutation in 1 patient, and Q252H mutation in 1 patient. Four-month response by stage was: out of 5 AP patients, 2 achieved CHR, out of which 1 patient had CCyR and the other patient had mCyR. Two AP patients went off treatment for losing hematologic response, and 1 AP patient never had any hematologic response. Out of 9 BP patients, 1 patient achieved CHR with sustained MR4.5, 1 patient achieved CHR with PCyR. Six patients had no response, and 1 patient died (from worsening leukocytosis and

infection). One chronic phase patient with complete hematologic response at enrollment was taken off study after 4 cycles due to lack of cytogenetic response.

All 15 enrolled patients reported at least 1 AE. Over the duration of the trial 347 AEs were reported. Most common AEs included thrombocytopenia (3.8%), vomiting (3.5%), anemia (3.2%), nausea (2.8%), and neutropenia (2.8%). Two patients discontinued due to unrelated AEs (1 death due to intracranial hemorrhage (ICH), and 1 fatal car accident). Eleven patients (73%) experienced a total of 37 SAEs, 11 of which were considered possibly, or probably related to study regimen. Grade 3/4 cytopenias including cases of neutropenic fevers were managed with transient treatment interruptions of both imatinib and HHT, which were then resumed after recovery of counts. Blood product transfusions, HHT dose reduction, and growth factors were used when indicated. Thirteen of the 15 enrolled patients died: 6 from BP, 3 from unknown causes, 1 patient in BP died from progressive disease manifested by progressive leukocytosis with an increased number of blasts and infection, 1 from ICH, 1 from neutropenic sepsis and ICH, and 1 in a car accident. Five of these deaths occurred during study period.

This is the first clinical trial to evaluate the combination of HHT with a TKI across all phases of CML. These preliminary observations suggest a possible clinical benefit of this combination in some patients with chronic and advanced stages of CML, including one patient with an MR4.5 sustained for 34 months until study closure. Importantly, most patients with a T315I mutation failed to respond to this combination. All of these patients harboring T315I were in BP. One patient with a F317L mutation in AP initially achieved CHR at 1 month but lost response at 4 months, while another patient in BP with a F317L mutation failed to respond and was taken off trial after 1 cycle. The remaining two patients who failed to respond were 1 with a F359V mutation in CP and another with a Q252H mutation in AP. Tolerance to the HHT-imatinib combination appeared to be acceptable, with most frequent treatment-related AEs being nausea, vomiting, and myelosuppression. The major limitation of our study was low enrollment. The need for 24-hour continuous IV infusions was the primary reason that discouraged patient participation on this trial.

Omacetaxine and HHT are both quite promising agents. HHT has been shown to have *in vitro* activity against a BCR-ABL-positive cell line with an imatinib-resistant E255K mutation.¹² Omacetaxine has been shown to be effective in patients with CML harboring imatinib-resistant T315I mutation and has demonstrated preclinical activity in ponatinib-resistant BCR-ABL-positive cell lines with Y253H, E255K, and T315I mutations.^{13,14} Other clinical studies with omacetaxine have demonstrated synergy with Ara-C, IFN- α , imatinib, second-generation TKI nilotinib, and has also promulgated the idea of re-initiation of second generation TKIs after durable clearance of T315I mutant clones.¹⁵

Given these preliminary observations and potential for different combinations with other TKIs, this approach merits further investigation in a carefully selected group of patients. Future studies need to characterize the subpopulation of patients who would stand to benefit the most from HHT or omacetaxine. Pairing with newer TKIs may make the combination more effective.

Acknowledgments

Funding:

This original research was sponsored by ChemGenex Pharmaceuticals, Ltd (Menlo Park, CA), which is now a wholly owned subsidiary of Teva Branded Pharmaceutical Products R&D, Inc (Frazer, PA). This study was supported in part by the M.D. Anderson Cancer Center Support Grant CA016672 (PI: Dr Ronald DePinho) from the National Cancer Institute, and the CML P01 Grant P01 CA049639 (PI: Dr Richard Champlin)

References

1. Sasaki K, Strom SS, O'Brien S, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. *Lancet Haematol*. 2015; 2(5):e186–193. [PubMed: 26688093]
2. Radich JP, Shah NP, Mauro MJ. Integrating current treatment options for TKI-resistant chronic myeloid leukemia. *Clin Adv Hematol Oncol HO*. 2014; 12(7 Suppl 13):3–17. 1.
3. le Coutre PD, Giles FJ, Hochhaus A, et al. Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. *Leukemia*. 2012; 26(6):1189–94. [PubMed: 22076466]
4. Hehlmann R. How I treat CML blast crisis. *Blood*. 2012; 120(4):737–47. [PubMed: 22653972]
5. Quintás-Cardama A, Kantarjian H, Cortes J. Homoharringtonine, omacetaxine mepesuccinate, and chronic myeloid leukemia circa 2009. *Cancer*. 2009; 115(23):5382–93. [PubMed: 19739234]
6. Rosshandler Y, Shen AQ, Cortes J, Khoury HJ. Omacetaxine Mepesuccinate for Chronic Myeloid Leukemia. *Expert Rev Hematol*. 2016; 9(5):419–24. [PubMed: 26853281]
7. Tipping AJ, Mahon FX, Zafirides G, Lagarde V, Goldman JM, Melo JV. Drug responses of imatinib mesylate-resistant cells: synergism of imatinib with other chemotherapeutic drugs. *Leukemia*. 2002; 16(12):2349–57. [PubMed: 12454739]
8. Kano Y, Akutsu M, Tsunoda S, et al. In vitro cytotoxic effects of a tyrosine kinase inhibitor STI571 in combination with commonly used antileukemic agents. *Blood*. 2001; 97(7):1999–2007. [PubMed: 11264164]
9. Scappini B, Onida F, Kantarjian HM, et al. In vitro effects of STI 571-containing drug combinations on the growth of Philadelphia-positive chronic myelogenous leukemia cells. *Cancer*. 2002; 94(10):2653–62. [PubMed: 12173333]
10. Cortes J, Kantarjian H. How I treat newly diagnosed chronic phase CML. *Blood*. 2012; 120(7):1390–7. [PubMed: 22613793]
11. Baccarani M, Saglio G, Goldman J, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood*. 2006; 108(6):1809–20. [PubMed: 16709930]
12. Chen R, Gandhi V, Plunkett W. A Sequential Blockade Strategy for the Design of Combination Therapies to Overcome Oncogene Addiction in Chronic Myelogenous Leukemia. *Cancer Res*. 2006; 66(22):10959–66. [PubMed: 17108134]
13. Cortes J, Lipton JH, Rea D, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation. *Blood*. 2012; 120(13):2573–80. [PubMed: 22896000]
14. Okabe S, Tauchi T, Tanaka Y, Katagiri S, Kitahara T, Ohyashiki K. Activity of omacetaxine mepesuccinate against ponatinib-resistant BCR-ABL-positive cells. *Blood*. 2013; 122(17):3086–8. [PubMed: 24159169]
15. Heiblig M, Sobh M, Nicolini FE. Subcutaneous omacetaxine mepesuccinate in patients with chronic myeloid leukemia in tyrosine kinase inhibitor-resistant patients: Review and perspectives. *Leuk Res*. 2014; 38(10):1145–53. [PubMed: 24906663]

Table 1Baseline characteristics, prior therapies, number of cycles received, and responses^a

Pts enrolled, n	15		
Age, y, median (range)	55 (21–76)		
Gender, M/F, n	7/8		
Initial CML diagnosis to enrollment, mo, median (range)	40 (0.5–142)		
Diagnosis at enrollment on trial, completed/enrolled, n			
Blast phase	3/9		
Accelerated phase	3/5		
Chronic phase	1/1		
Number of prior therapies, ^b median (range)	3 (1–6)		
Prior imatinib therapy, number of pts	14		
Prior interferon therapy, number of pts	4		
Prior stem cell transplantation, number of pts	3		
Number of cycles received, median (range)	3 (1–34)		
Pts who completed (n=7)	5 (4–34)		
Pts who did not complete (n=8)	2 (1–3)		
Best response (in pts who completed ≥ 4 cycles)	HR (n)	CyR (n)	MR (n)
All pts (n=7) ^c	CHR (6)	mCyR (1) PCyR (1) CCyR (2)	MR4.5 (1)
Chronic phase (n=1)	CHR (1) ^d	No CyR	No MMR
Accelerated phase (n=3)	CHR (3) ^e	CCyR (1) mCyR (1)	No MMR
Blast phase (n=3) ^f	CHR (2) ^f	CCyR (1) PCyR (1)	MR4.5 (1)

^aPer European LeukemiaNet 2006 guidelines;^bIncluding stem cell transplantation;^c3 of the 7 patients who completed at least 4 cycles had detectable mutations as follows:^dThis patient had a F359V mutation;^eOne patient who achieved and later lost CHR had a F317L mutation;^fOne patient who did not respond had a T315I mutation.

CCyR: complete cytogenetic response; CHR: complete hematologic response; CML: chronic myeloid leukemia; CyR: cytogenetic response; HR: hematologic response; mCyR: minor cytogenetic response; MMR: major molecular response; MR: molecular response; PCyR: partial cytogenetic response; pt: patient