Published in final edited form as:
Clin Lymphoma Myeloma Leuk. 2013 October ; 13(5): 530–533. doi:10.1016/j.clml.2013.03.017.

Homoharringtonine/Omacetaxine Mepesuccinate: The Long and Winding Road to Food and Drug Administration Approval

Hagop M. Kantarjian, **Susan O'Brien**, and **Jorge Cortes**
The University of Texas M.D. Anderson Cancer Center, Department of Leukemia, Houston, TX

Abstract

Homoharringtonine/omacetaxine is a unique agent with a long history of research development. It has been recently approved by the Food and Drug Administration for the treatment of chronic myeloid leukemia after failure of 2 or more tyrosine kinase inhibitors. Research with this agent has spanned over 40 years, with many instructive lessons to cancer research, which are summarized in this review.

Introduction

Homoharringtonine (HHT) is a natural plant alkaloid derived from *Cephalotoxus fortunei*. HHT and related compound esters of cephalotaxine were described first in 1970,[1] and were the subject of intensive research efforts by Chinese investigators to clarify their role as anticancer and antileukemic agents from the 1970s until the present.[2–6] Omacetaxine mepesuccinate is a semisynthetic purified HHT compound (99.7% purity) used in recent studies in chronic myeloid leukemia (CML), and approved by the Food and Drug Administration (FDA) in October 2012 for the treatment of CML in chronic or accelerated phase after failure of 2 or more tyrosine kinase inhibitors (TKIs).[7] In our experience, omacetaxine, milligram for milligram, is more myelosuppressive than HHT.

Homoharringtonine-omacetaxine probably holds the dubious record for the longest time of development of an anticancer agent until FDA approval, almost more than 40 years. The saga of HHT-omacetaxine from its original discovery until FDA approval is an interesting story of drug development in cancer.[8–11]

The Past

Over several decades, Chinese investigators have identified HHT as an active anticancer agent in acute myeloid leukemia (AML),[1–6,12,13] myelodysplastic syndrome (MDS),[14] acute promyelocytic leukemia (APL),[15] polycythemia vera,[16] and as intrathecal therapy for central nervous system (CNS) leukemia.[17] In AML, they reported single-agent HHT to result in complete response (CR) rates of 25%. In combination in frontline AML therapy with daunorubicin or aclarubicin and cytarabine, the CR rates were 70% to 90%, and survival

Address for correspondence: Hagop M. Kantarjian, MD, The University of Texas M.D. Anderson Cancer Center, Department of Leukemia, 1400 Holcombe Blvd, Unit 428, Houston, TX 77030, hkantarj@mdanderson.org.

Disclosure
H. Kantarjian and J. Cortes received research grants from ChemGenex.

rates were 30% to 40%.[8,9,12] These efforts culminated in a recent randomized study demonstrating that the addition of HHT to standard AML chemotherapy significantly improved the CR and survival rates. In a phase III study, 620 patients younger than 60 years old were randomized to cytarabine 100 mg/m^2 daily for 7 days and daunorubicin 40 to 45 mg/m^2 daily for 3 days, cytarabine daunorubicin (DA) and HHT 2 mg/m^2 intravenously (HAD), vs. cytarabine aclarubicin (an improved anthracycline) 40 mg/m^2 daily for 3 days and HHT (HAA).[13] The CR rate after 1 course was greater with the addition of HHT (66% vs. 54%; $P = .005$ for HAA versus DA; $P = .03$ for HAD vs. DA) at the expense of a higher induction mortality (6% vs. 1%). The 3-year event-free survival rates were greater with the addition of HHT: HAA 35% vs. DA 23%; $P = .002$; HAD 33% vs. DA 23%; $P = .08$. Survival and relapse-free survival were also better for HAA vs. DA in patients with favorable or intermediate cytogenetic categories ($P = .014$ for survival; $P = .02$ for relapse-free survival).[13]

In the Chinese studies, the HHT doses ranged from 2 to 8 mg given as short intravenous infusion or intramuscularly. Cardiovascular complications (severe hypotension, arrhythmias) were significant. The studies in China used mixtures of HHT and other alkaloid compounds, which might explain some differences of efficacy and toxicity profiles.

Encouraged by these findings, the studies in the United States started in the early 1980s, using purified alkaloid formulations, under the auspices of the National Cancer Institute (NCI), Clinical Trials Evaluation Program (CTEP). The early studies used short intravenous infusions, which were dose-limited by severe cardiovascular complications.[8–11,18] Later studies in leukemia used continuous infusion schedules over 24 hours at dose ranges of 5 to 9 mg/m^2 daily for 7 to 9 days. These confirmed the results of Chinese investigators, reporting CR rates of 15% to 20%. Serious cardiovascular complications were still noted in 30% of patients.[19–22] The drug was also confirmed to be active in MDS.[23] Lower doses and longer exposure schedules of HHT 2.5 to 3 mg/m^2 daily for 14 days eliminated the cardiovascular complications.[24] At these dose schedules, significant and delayed myelosuppression became the dose-limiting toxicity. These findings led to a shift of the HHT research in the United States to CML. Through the 1980s and 1990s, HHT was investigated as a single agent,[25] and in combination with low-dose cytarabine, with interferon-α, and with both,[25–30] in late[25,27] and early chronic phase CML.[26,28–30] These studies, summarized in several previous reviews, confirmed the anti-CML efficacy of HHT (Table 1).[8,9,16,17,25–27,29–32]

The supply of HHT until 1996 was through the NCI-CTEP. After the results on its anti-CML activity, reported through the M.D. Anderson Cancer Center studies, confirmatory studies were planned. In 1995, the NCI issued a Cooperative Research and Development Agreement for future development of HHT, awarded to American Bioscience but not further developed. In 1998 OncoPharm, a Houston-based small biotech company developed the semisynthetic HHT product.[7]

The (New) Present

The development of HHT was delayed by several obstacles: difficult production and unreliable source supply; toxicity profile of the original dose schedules; difficulties in reproducing the original Chinese studies; large quantities of bulk of cephalotoxus trees required; the success of TKIs; and the uncertainty regarding a potential role of HHT in the context of TKIs.

In 1998, Dr. Jean-Pierre Robin, OncoPharm founder, reported on the first semisynthetic formulation of HHT.[7] This was followed by multiple pilot studies confirming the efficacy of the semisynthetic HHT, known later as omacetaxine.[33–39] In 2001, Dr. Dennis Brown,

founder of ChemGenex, provided a stable source of omacetaxine for future studies. Together with the M.D. Anderson Cancer Center investigators, ChemGenex developed, conducted, and completed the FDA pivotal trials of omacetaxine in CML after treatment failure of several TKIs and in the setting of CML and T315I mutations.[31] In a phase II study, omacetaxine was given at 1.25 mg/m^2 subcutaneously twice daily for 14 days during induction and for 7 days during maintenance, to 62 patients in chronic phase CML with the T315I mutation. A complete hematologic response was achieved in 77%; the median response duration was 9.1 months. Twenty-three percent of patients achieved a major cytogenetic response, which was complete in 16%. The estimated 3-year survival rate was 60%.[31] An updated analysis concerned 122 patients who had previously received 2 or more TKIs (including imatinib). Among 81 patients treated in chronic phase, 16 (20%) achieved a major cytogenetic response (CR in 10%, partial in 10%). The median duration of major cytogenetic response was 18 months. Four patients (5%) had a minor cytogenetic response. The median overall survival was 34 months. Among 41 patients in the accelerated phase, 11 (27%) had a major hematologic response for a median duration of 9 months. Six patients (14%) had a cytogenetic response. The median overall survival was 16 months.

The original submission to the FDA and review resulted in a negative Oncology Drug Advisory Committee vote for omacetaxine approval in patients with CML and the T315I mutation, because of the lack of a standardized molecular test for T315I. The subsequent FDA submission for omacetaxine in the setting of CML after failure of 2 or more TKIs resulted in FDA approval on October 26, 2012. By then, ChemGenex had been acquired by Cephalon Oncology, which was later acquired by Teva Pharmaceutical Industries.

The Future

Although HHT is part of the standard AML therapy in China, the FDA approval of omacetaxine for the narrow indication of CML in chronic or accelerated phases after failure of 2 or more TKI therapies has salvaged this drug from oblivion. This is a very important step, and probably the beginning for the real research into different potential uses of omacetaxine in leukemia.

The high activity of omacetaxine in CML, and its efficacy against dormant CML clones[40] makes it ideal to eradicate residual CML disease and to cure CML. Studies have shown its efficacy in CML and minimal residual disease.[33] Future studies should investigate the addition of omacetaxine to TKIs in patients with CML in complete cytogenetic response with persistent molecular disease. The end point of these studies would be the achievement of complete molecular response after 6 to 12 months of omacetaxine therapy in 1 to 3 days subcutaneous dosages every month.

The Chinese experience in AML advocates reinvigorating research with omacetaxine for different indications. Omacetaxine could be investigated as low intensity therapy in combination with low-dose cytarabine or hypomethylating agents in older patients with AML not fit for intensive chemotherapy, or in whom intensive chemotherapy is not beneficial. Combinations of omacetaxine with standard chemotherapy in younger patients with AML should be further explored, during induction or as consolidation-maintenance therapy to eradicate minimal residual disease.

In MDS, omacetaxine has shown reasonable activity. It could be evaluated in patients in whom hypomethylating agent therapy has failed, and in whom the expected median survival is approximately 6 months It might also be useful in combination therapy with hypomethylating agents in frontline MDS therapy.

As already discussed in this review, omacetaxine might have additional roles in the setting of APL, myeloproliferative conditions such as polycythemia vera, and importantly as intrathecal therapy for resistant CNS leukemia. The role of omacetaxine in other hematologic disorders including chronic lymphocytic leukemia and lymphomas has not been addressed. Finally, omacetaxine might have additional potential roles outside the context of cancer, for example, as a treatment for resistant malaria.

The story of HHT-omacetaxine continues. Through multiple obstacles related to schedule, toxicities, shifting research priorities, drug supplies and purities, financial hardships, and several almost fatal misses, it has taken many decades to salvage the drug as a beneficial treatment for leukemia. Two issues to be addressed are the high price of the drug ($24,000 for induction; $12,000 for maintenance), and the FDA mandate that it cannot be self-administered (even though previous studies were on self-administered subcutaneous omacetaxine, without any safety concerns). Studies of single daily dose omacetaxine, allowing for patient self-administration, and oral formulations[41] will improve access and compliance, and reduce the cost of care.

References

1. Powell RG, Weisleder D, Smith CR Jr, et al. Structures of harringtonine, isoharringtonine, and homoharringtonine. Tetrahedron Lett. 1970; 11:815–8. [PubMed: 5436615]
2. Cephalotaxine esters in the treatment of acute leukemia. A preliminary clinical assessment. Chin Med J (Engl). 1976; 2:263–72. [No authors listed]. [PubMed: 825360]
3. Leukemia Research Group of the Chinese Liberation Army 187th Hospital. An analysis of 72 cases of leukemia treated with cephalotaxus ester alkaloid [in Chinese]. J Chin Acad. 1978; 58:163–6. 1978 [NIH library translation (NIH Pub No. 79-479)].
4. Zhang Z, Hou C. Clinical analysis of the therapeutic effects of semisynthetic harringtonine in treating 55 cases of non-lymphocytic leukemia [in Chinese]. Chin J Intern Med. 1981; 20:667–9. [NIH library translation (NIH Pub. No. 87-168)].
5. Shang Z. Treatment of acute leukemia with harringtonine, semisynthetic harringtonine or total alkaloids of cephalotaxus hainanesis: analysis of curative results in 46 cases [in Chinese]. Chung Hua Erh K O Tsa Chi. 1981; 19:abstract 233. [NIH library translation (NIHPub. No. 87-166)].
6. Zhang ZY, Hou CH, Zhu YF. A preliminary therapeutic analysis of 82 cases of chronic granulocytic leukemia treated with harringtonine [in Chinese with English abstract]. Chin J Intern Med. 1986; 25:156–7.
7. Robin J, Dhal R, Dujardin G, et al. The first semi-synthesis of enantiopure homoharringtonine via anhydrohomoharringtonine from a preformed chiral acyl moiety. Tetrahedron Lett. 1999; 40:2931–4.
8. Grem JL, Cheson BD, King SA, et al. Cephalotaxine esters: anti-leukemic advance or therapeutic failure? J Natl Cancer Inst. 1988; 80:1095–103. [PubMed: 3045335]
9. Kantarjian HM, Talpaz M, Santini V, et al. Homoharringtonine. History, current research, and future directions. Cancer. 2001; 92:1591–605. [PubMed: 11745238]
10. Quintas-Cardama A, Kantarjian H, Cortes J. Homoharringtonine, omacetaxine mepesuccinate, and chronic myeloid leukemia circa 2009. Cancer. 2009; 115:5382–92. [PubMed: 19739234]
11. O'Dwyer PJ, King SA, Hoth DF, et al. Homoharringtonine—perspective on an active new natural product. J Clin Oncol. 1986; 4:1563–8. [PubMed: 3531426]
12. Liu J, Mi Y, Fu M, et al. Intensive induction chemotherapy with regimen containing intermediate dose cytarabine in the treatment of de novo acute leukemia. Am J Hematol. 2009; 84:422–7. [PubMed: 19484734]
13. Jin J, Wang J, Chen F, et al. Homoharringtonine-based induction regimens for patients with de novo acute myeloid leukemia: a multicenter randomized controlled phase 3 trial. Blood. 2012; 120:abstract 45.
14. Wu L, Li X, Su J, et al. Effect of low-dose cytarabine, homoharringtonine and granulocyte colony-stimulating factor priming regimen on patients with advanced myelodysplastic syndrome or acute

leukemia transformed from myelodysplastic syndrome. Leuk Lymphoma. 2009; 50:1461–7. [PubMed: 19672772]

15. Ye JS, Wang XH, Feng GH, et al. Small-dose harringtonine induces complete remission in patients with acute promyelocytic leukemia. Leukemia. 1988; 2:427–9. [PubMed: 3164799]
16. Li LH, Lin SP, Liang YY, et al. Harringtonine in treatment of polycythemia vera [in Chinese]. Chin J Intern Med. 1984; 23:413–5. [NIH library translation (NIH Pub. No. 4-415)].
17. Hou CH, Zhang ZY. Chinese People's Liberation Army 187th Hospital. Intrathecal injection of harringtonine and homoharringtonine in treating central nervous system leukemia –clinical analysis in 26 cases [in Chinese]. J Chin Acad. 1981; 61:530–2. [NIH library translation (NIH Pub. No. 87-43)].
18. Legha SS, Keating M, Picket S, et al. Phase I clinical investigation of homoharringtonine. Cancer Treat Rep. 1984; 68:1085–91. [PubMed: 6478448]
19. Warrell RP Jr, Coonley CJ, Gee TS. Homoharringtonine: an effective new drug for remission induction in refractory nonlymphoblastic leukemia. J Clin Oncol. 1985; 3:617–21. [PubMed: 3889229]
20. Arlin Z, Feldman E, Biguzzi S, et al. Phase I/II trial of homoharringtonine in acute leukemia. Proc Am Soc Clin Oncol. 1987; 6:160.
21. Stewart JA, Cassileth PA, Bennett JM, et al. Continuous infusion homoharringtonine (NSC 141633 in refractory acute nonlymphocytic leuikemia. An ECOG pilot study. Am J Clin Oncol. 1988; 11:627–9. [PubMed: 3189228]
22. Feldman E, Arlin Z, Ahmed T, et al. Homoharringtonine is safe and effective for patients with acute myelogeous leukemia. Leukemia. 1992; 6:1185–8. [PubMed: 1434802]
23. Feldman EJ, Seiter KP, Ahmed T, et al. Homoharringtonine in patients with myelodysplastic syndrome (MDS) and mMDS evolving to acute myeloid leukemia. Leukemia. 1996; 10:40–2. [PubMed: 8558935]
24. Kantarjian HM, Keating MJ, Walters RS, et al. Phase II study of low-dose continuous infusion homoharringtonine in refractory acute myelogenous leukemia. Cancer. 1989; 63:813–7. [PubMed: 2914287]
25. O'Brien S, Kantarjian H, Keating M, et al. Homoharringtonine therapy induces responses in patients with chronic myelogenous leukemia in late chronic phase. Blood. 1995; 86:3322–6. [PubMed: 7579434]
26. O'Brien S, Kantarjian H, Koller C, et al. Sequential homoharringtonine and interferon-alpha in the treatment of early chronic phase chronic myelogenous leukemia. Blood. 1999; 93:4149–53. [PubMed: 10361112]
27. Kantarjian HM, Talpaz M, Smith TL, et al. Homoharringtonine and low-dose cytarabine in the management of late chronic-phase chronic myelogenous leukemia. J Clin Oncol. 2000; 18:3513–21. [PubMed: 11032593]
28. Stone RM, Donohue KA, Stock W, et al. Cancer and Leukemia Group B, a phase II study of continuous infusion homoharringtonine and cytarabine in newly diagnosed patients with chronic myeloid leukemia: CALGB study 19804. Cancer Chemother Pharmacol. 2009; 63:859–64. [PubMed: 18670778]
29. O'Brien S, Talpaz M, Cortes J, et al. Simultaneous homoharringtonine and interferon-alpha in the treatment of patients with chronic-phase chronic myelogenous leukemia. Cancer. 2002; 94:2024–32. [PubMed: 11932905]
30. O'Brien S, Giles F, Talpaz M, et al. Results of triple therapy with interferon-alpha, cytarabine, and homoharringtonine, and the impact of adding imatinib to the treatment sequence in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in early chronic phase. Cancer. 2003; 98:888–93. [PubMed: 12942553]
31. 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; 120:2573–80. [PubMed: 22896000]
32. Cortes J, Nicollini F, Wetzler M, et al. Subcutaneous omacetaxine in chronic or accelerated chronic myeloid leukemia resistant to two or more tyrosine-kinase inhibitors including imatinib. Blood. 2011; 118(suppl 1):abstract 2761.

33. Marin D, Kaeda JS, Andreasson C, et al. Phase I/II trial of adding semisynthetic homoharringtonine in chronic myeloid leukemia patients who have achieved partial or complete cytogenetic response on imatinib. Cancer. 2005; 103:1850–5. [PubMed: 15786422]
34. Quintas-Cardama A, Kantarjian HM, Wierda W, et al. A phase II study of intravenous (IV) homoharringtonine (HHT) and imatinib (IM) in patients (pts) with chronic myeloid leukemia (CML). Blood. 2006; 108:abstract 2174.
35. Quintas-Cardama A, Kantarjian H, Garcia-Manero G, et al. Phase I/II study of subcutaneous homoharringtonine in patients with chronic myeloid leukemia who have failed prior therapy. Cancer. 2007; 109:248–55. [PubMed: 17154172]
36. Maloisel F, Rousselot P, Morariu R. Subcutaneous hemisynthetic homoharringtonine (HHT) in combination with imatinib mesylate (Gleevec) in patients (PTS) with STI-resistant chronic myelogenous leukemia (CML): preliminary results of a pilot study. Blood. 2003; 102:abstract 909a.
37. Burton C, Ranger A, Nedal E, et al. Semi-synthetic homoharringtonine (Myelostat®) for chronic myeloid leukemia in accelerated phase after imatinib failure. Blood. 2003; 102:abstract 908a.
38. de Lavallade H, Khorashad JS, Davis HP, et al. Interferon-alpha or homoharringtonine as salvage treatment for chronic myeloid leukemia patients who acquire the T315I BCR-ABL mutation. Blood. 2007; 110:2779–80. [PubMed: 17881650]
39. Legros L, Hayette S, Nicolini FE, et al. BCR-ABL (T315I) transcript disappearance in an imatinib-resistant CML patient treated with homoharringtonine: a new therapeutic challenge? Leukemia. 2007; 21:2204–6. [PubMed: 17541396]
40. Chen Y, Hu Y, Michaels S, et al. Inhibitory effects of homoharringtonine on leukemic stem cells and BCR-ABL induced chronic myeloid leukemia and acute lymphoblastic leukemia in mice. Blood. 2007; 110:abstract 2912.
41. Brown, D.; Michaels, S. Design and evaluation of oral delivery dosage forms of homoharringtonine. Proceedings of the 98th Annual Meeting of the American Association for Cancer Research; April 14–18, 2007; Los Angeles, CA. 2007. p. abstract 4730

Table 1

Summary of Homoharringtonine-Omacetaxine Patient Studies

Study	Disease	Therapy	n	Outcome
Chinese Studies[8,9]	AML	HHT	350	CR 24%
Li[16]	Polycythemia vera	HHT	12	CR 100%
Hou[17]	CNS leukemia	HHT	26	CR 78%
Chinese Studies[8,9]	AML	Combos	286	CR 45% to 88%
O'Brien[25]	CML, late CP	HHT	73	CG response, 30%; CG major response, 15%
Kantarjian[27]	CML, late CP	HHT with ara-C	100	CG response, 32%; CG major response, 15%
O'Brien[26,29]	CML, early CP	HHT with or without IFN	127	CG response, 57% to 60%; CG major response, 27% to 43%
O'Brien[30]	CML, early CP	HHT with IFN and ara-C	97	CG response, 75%; CG major response, 45%
Cortes[31]	CML, CP, T315I	Omacetaxine	62	CG major response, 23%
Cortes[32]	CML, CP with 2 or more TKI treatment failures	Omacetaxine	81	CG major response, 20%; median survival, 34 months
Cortes[32]	CML, AP with 2 or more TKI treatment failures	Omacetaxine	41	CG response, 14%; median survival, 16 months

Abbreviations: AML = acute myeloid leukemia; AP = accelerated phase; ara-C = cytarabine; CG = cytogenetic; CML = chronic myeloid leukemia; CNS = central nervous system; combos = HHT combination chemotherapy; CP = chronic phase; CR = complete response; HHT = homoharringtonine; IFN = interferon-α; TKI = tyrosine kinase inhibitor.