

Effect of Homoharringtonine as a Combined Regimen for Acute Myeloid Leukemia

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Abstract

Homoharringtonine (HHT), a cephalotaxus alkaloid has shown promising results in the treatment of several hematological disorders such as chronic myeloid leukemia, acute myeloid leukemia (AML), and myelodysplastic syndrome. It is known for its unique mechanism of action by which it prevents the initial elongation step of protein biosynthesis. Hence, it is used in hematological malignancies where it synergistically potentiates the action of other drugs and induces apoptosis. The relevant studies published were searched using an electronic database from 2002 to 2019. The articles published in English were only considered. Search engines such as PubMed, MEDLINE, Google Scholar, and Semantic scholar were used. In this review, we have discussed the effect of HHT in combination with other chemotherapeutic agents for AML with or without genetic mutation specification and the future perspective of these regimens. Although standard treatment options exist for most of these diseases, still cure rates are low with reported morbidity and the drug resistance emergence is pervasive. Thus, novel treatment approaches are crucial for better outcome. Alternative regimens together with HHT have not been a standard practice, although they have shown a very good potential in AML patients. Many of the combinations were also proved to be safe and effective with very low toxic potential. All these data outcomes of various combinations under different scenarios exhibit that HHT has promising results in the treatment of AML which may lead to its approval in the upcoming years.

Keywords: Cephalotaxus alkaloid, hematological disorders, novel treatment, synergistic effect

INTRODUCTION

Acute myeloid leukemia (AML) is a hematological malignancy identified by a rise in the number of myeloid cells in the bone marrow and an arrest in their maturation, often resulting in hemopoietic insufficiency with or without leukocytosis. Homoharringtonine (HHT)-a cytotoxic alkaloid was known to be isolated from the *Cephalotaxus hainanensis*.^[1] Studies on crystallography of HHT have proven that HHT binds to the peptidyl transferase centre of the ribosome at A-site cleft, by competing with the amino acid side chains of amino acyl-tRNAs (transfer RNAs) and thus prevents the protein biosynthesis.^[2]

HHT has been extensively used in the treatment of chronic myeloid leukemia (CML) as a synergist along with other active chemotherapeutic agents. Even though it has already got approved by the United States Food and Drug Administration (USFDA) in the treatment of tyrosine kinase

inhibitors-resistant CML, it must be approved for the use in the treatment of AML.^[3]

The main aim of this review is to study the effect of HHT in combination with other active agents used in treatment of AML with or without specific genetic mutations.

METHODOLOGY

To find the data for reviewing the effectiveness of HHT in combination with other chemotherapeutic agents in acute

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myeloid leukemia patients, a search was performed using PubMed, MEDLINE, Google Scholar, and Semantic scholar from 2002 to 2019. The keywords used for searching include “homoharringtonine,” “acute myeloid leukemia,” “synergistic effect,” “treatment strategy in AML,” “combined regimen in AML,” “standard chemotherapeutic agents,” “haematological malignancies,” “genetic mutation,” “*de novo* AML,” “leukemia stem cells.” Boolean tags such as “AND,” “OR” and “NOT” were also applied to focus and broaden the search of literatures. Identified and reviewed literatures included research articles, review articles, and editorials. Both abstracts and full text articles in English language were considered [Flow chart 1].

DISCUSSION

Levy *et al.* conducted a phase I dose finding study with 18 patients and a starting dose of 0.5 mg m⁻²–6 mg m⁻² to assess the daily dose. It was reported that 11 of 12 patients achieved blood blast clearance and two achieved complete remission (CR) and one with blast crisis of CML returned in chronic phase. The study concluded that the recommended daily dose ssHHT (subcutaneous semisynthetic HHT) on the 9-day schedule is 5 mg m⁻² day⁻¹.^[4]

A single-center phase II study with 46 patients (refractory/relapsed acute myeloid leukemia) was conducted by Wenjuan Yu *et al.* to determine the effect of HHT in combination with cytarabine and aclarubicin. Eighty percent of patients achieved

CR with an overall survival (OS) rate of 42%. It was concluded that Ara-c, and aclarubicin can be used in combination with HHT to overcome resistance of leukemic cells.^[5]

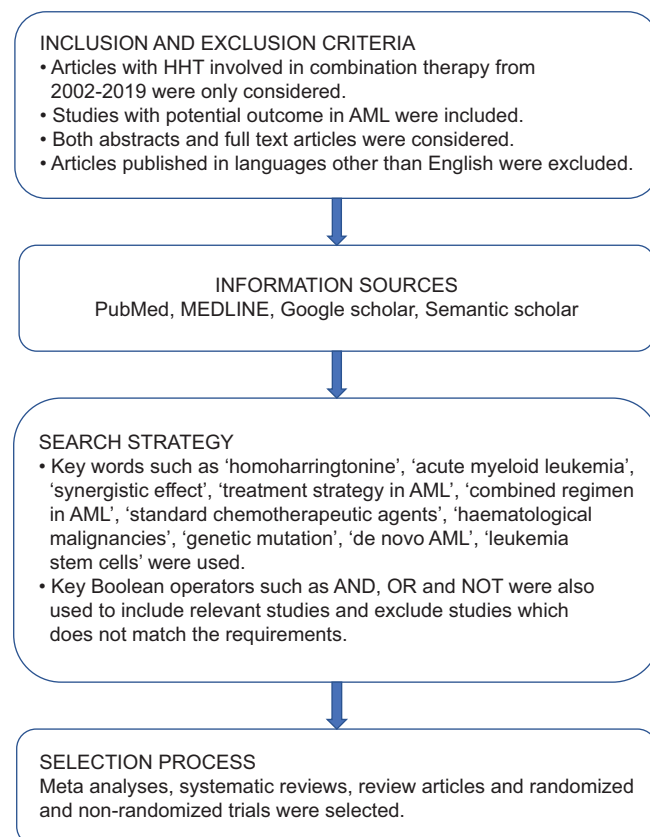
It has been found from a study conducted by Chen *et al.*, that HHT potentiates the antileukemic activity of arsenic trioxide on adhered AML cells both *in vitro* and *in vivo*.^[6] Arsenic from arsenic trioxide kills the leukemia stem cells by directly binding to the cysteine residues of zinc fingers in promyelocytic leukemia protein.^[7,8] The findings suggested that the underlying mechanism might be due to HHT-induced suppression of Mcl-1 protein expression through glycogen synthase kinase-3 β (GSKβ) in AML cells adhered to stromal cells.

The cytotoxicity in AML cells was investigated in a study carried out by Zhang *et al.*, when treated with HHT and Etoposide in synergy.^[9] AML cell lines THP1 and HL60 and primary cells from patients were treated with either HHT and etoposide alone or in combination. The results showed that HHT and etoposide demonstrated cytotoxicity in AML cells lines and primary AML cells *in vitro*, synergistically. On the other hand, HHT gave rise to elevated ROS generation in etoposide-treated AML cells.^[10,11] The uplifted ROS generated by HHT is by disabling thioredoxin-mediated antioxidant defence and depletion of thioredoxin sensitizes AML to etoposide treatment.^[12-14]

FMS-like tyrosine kinase receptor 3-internal tandem duplication (FLT3-ITD) is a mutation in FLT3 with ITD which are associated with increased relapse and overall reduced survival. HHT exhibited potent cytotoxic effect against FLT3-ITD positive cell lines and primary leukemia cells.^[15,16] It also demonstrated a remarkable synergistic antileukemia action *in vitro* and *in vivo* in xenograft mouse models when cotreated with HSP90 inhibitor IPI504, in a study conducted by Wu *et al.*,^[17] Previous studies reported that HSP90 inhibitors as anticancer agents were molecular chaperone of FLT3 highly expressed in FLT3 ITD positive AML.^[19] By inducing apoptosis and cell growth phase (G1 phase) arrest, HHT in combination with IPI504 inhibited the growth of leukemia cells. This synergistic action led to reduction of total and phosphorylated FLT3 (p-FLT3) and also inhibited its downstream signalling molecules such as STAT5, AKT, ERK, and 4E-BP1. It led to a synergistic effect on 55.56% of AML cases, including 3 relapsed/refractory patients.

Similarly, HHT and oridonin synergistically inhibited cell viability and induced significant mitochondrial membrane potential loss and apoptosis.^[20] They also caused remarkable downregulation of C-KIT and its downstream signalling pathways and promotes AE cleavage (AML 1-ETO). HHT elevated the intercellular oridonin concentration by regulating the MRP1 and MDR1 expressions, and thus, it enhanced the effects of oridonin. Further the combination also prolonged the survival of mouse having t(8;21) leukemia.

In a study conducted by Cao *et al.*, SKNO-1 and Kasumi cells with t(8;21) were used and the effect of individual or pairwise



Flow Chart 1: Methodology

administration of HHT, aclarubicin or cytarabine (HAA) was compared.^[21] Out of which HAA revealed the strongest growth inhibition and apoptosis induction in SKNO-1 and kasumi-1 cells. This study proved that HAA synergistically induced apoptosis in t(8;21) leukemia cells and activated the caspase 3 mediated cleavage of the AML1-ETO oncoprotein. Hence, this *in vitro* study has provided a new insight in the treatment of t(8;21) AML. Also, in t(8;21) AML, HAA regimen was highly efficacious as the first course of induction therapy.^[22]

One of the major clinical challenges in the treatment of leukemia remains to be the effective elimination of LSC's (Leukemia Stem Cells) to reduce the chances of remission. A synergistic effect has been observed to inhibit the LSC's proliferation, in KG-1, Kasumi-1, primary CD34⁺ cells from AML patients (Tao *et al.*,) and in an *in vivo* xenograft model by HHT and arsenic trioxide.^[23] Chen *et al.*, discovered that the synergistic effect of HHT and arsenic trioxide contained upregulation of the PI3K/Akt pathway by arsenic trioxide in U937 cells.^[24] Even though only a slight effect of arsenic trioxide is found, it markedly enhances the action of HHT on LSC's at same dose. This further lead to synergic mechanism such as regulation of the Notch, nuclear factor kappa β , and P53 pathways.

Abivertinib – a novel BTK inhibitor causes inhibition of cell proliferation, depletion of colony forming capacity, induction of apoptosis, and cell cycle arrest in AML cells. Predominantly, the AML cells carrying FLT3-ITD mutations which are associated with poor prognosis are sensitive to Abivertinib. Among the AML cell lines studied by Huang *et al.*, MV4-11 and MOLM13 cells carrying FLT3-ITD mutation showed higher sensitivity to abivertinib and this regimen also shows synergistic effects in MV4-11 and MOLM13 cells and also in KASUMI-1 cells which isn't harboring FLT3-ITD mutation.^[25] In both *in vitro* and *in vivo* experiments, abivertinib in combination with HHT was found to be associated with synergistic antileukemic effects.

A reciprocal translocation between chromosomes 9 and 22 (9;22) (q34; q11) is contained in human cell line (K5620) which results in bcr/abl fusion gene and fusion protein with active tyrosine kinase activity. In a study conducted by Cheng *et al.*, susceptibility of K5620 cell lines to idarubicin with or without HHT was examined.^[26] Idarubicin generally promotes caspase 3 activation and cleavage of PARP-1 and these effects may be mediated by HHT induced by BCR-ABL1 activation and mitochondrial apoptotic pathway activation,^[27] enhancing idarubicin induced mitochondrial membrane damage by ROS to promote subsequent apoptosis.

Single agent histone deacetylase (HDAC) inhibitors have shown noticeable anti-leukemic activity in preclinical and clinical studies. The trials were conducted in combination with standard chemotherapeutics. Suberoylanilide hydroxamic acid (SAHA) has shown dual impact on leukemic cells (*In vitro*), provoking apoptosis at high concentrations.^[28] In

a study conducted by Cao *et al.*, a novel strategy where HHT was combined with SAHA, a pan-HDAC inhibitor for treatment of AML.^[29] It was noted that SAHA induced upregulation of DR4 and DR5 (death receptor), while HHT in a dose-dependent manner upregulated-tumor necrosis factor related apoptosis inducing ligand (TRAIL) expression. This synergistic combination was found to impede the growth of leukemia xenografts *in vivo* with elevated apoptosis.

Sorafenib– a notable FLT3 inhibitor^[30-32] may ameliorate the outcome, but only few patients showed long-term responses which raised the need to search for underlying resistance mechanism and therapeutic strategies to curb them. A case study reported CR in primary refractory FLT3-ITD positive AML after successful administration of sorafenib in synergy with low dose HHT as a rescue therapy.^[33]

For treatment of childhood AML, a protocol consisting of HHT based regimen was carried out in patients younger than 14 years diagnosed with AML and with no pretreatment (Jing Yan *et al.*,). This regimen included HHT-3.5 mg/m²/d for 9 days continuously infused for 2–3 h, cytarabine 75 mg/m² subcutaneously every 12 h for 14 dosages totally, etoposide (VP-16) 100 mg/m²/d for 3 days given at induction and consolidation. CR was achieved in 10 of 12 patients (83%) by HHT in synergy with Ara-C and VP-16.^[34]

In a clinical study (Jin *et al.*,) conducted to assess the efficacy and toxicity of HAA (HHT, cytarabine and aclarubicin) regimen as an induction therapy in the treatment of *de novo* AML in younger adult, it was found that HAA regimen has been well tolerated and potent induction regimen for *de novo* AML patients.^[35] The CR rate especially achieved after first course of induction therapy and the OS and relapse free survival at 3 years were promising.

The HCG regimen which consists of HHT and Cytarabine along with simultaneous administration of granulocyte colony stimulating factor has known to possess potentially synergistic effect in eliminating the leukemic cells, especially geriatric patients with threatening Myelodysplastic syndrome (MDS) or AML modified from MDS.^[36,37] However, a study was conducted by Chen *et al.* to evaluate the efficacy and safety of this regimen in geriatric patients with *de novo* AML.^[38] A total of 56 patients aged between 60 and 80 years were enrolled in this study. Based on French-American-British classification and cytogenic analysis, the patients were evaluated for the response. In this study CR was linked with age and karyotype and a higher CR rate has been observed in patients <70 years and with better intermediate risk karyotype. Gene mutations such as NPM1, FLT-ITD, CEBPA, DNMT3 were examined, and clinical analysis was done among patients without recognizable karyotype abnormalities. It was found that CR rate of patients with NPM1 mutation was significant than patients without NPM1 mutation. Further, congestive heart failure and nervous system toxicity were not observed with low dose HHT.

CONCLUSION

Haematological disorders are becoming a high-risk profile disease in most of the developed and developing countries. Synthetic drugs used in chemotherapy mostly have toxic effects. Hence there is high demand for alternative treatments and naturally derived agents which are mostly less toxic compared to the synthetically drugs. Only few secondary metabolites with unique mechanism of action derived from medicinal plants have been labelled as suitable anticancer agents so far. In this regard, HHT has exhibited its synergy along with other chemotherapeutic agents through some the mechanisms such as suppression of Mcl-1 protein expression, generation of ROS, induction of apoptosis and G1 phase arrest, downregulation of C-KIT, regulation of MRP1 and MDR1 expressions, growth inhibition and apoptosis induction in SKNO-1 and kasumi-1 cells, mediation of caspase 3 activation, and cleavage of PARP-1 and upregulation of TRAIL expression. The use of HHT in combination therapy has not only shown compatible results but also proved to be safe and effective with very low toxic potential. Studies have reported that in treatment of acute myeloid leukemia, HHT has shown synergistic effect both *in vitro* and *in vivo* experiments. The use of HHT in treatment of CML has a long track record of the clinical efficacy and safety.

For use in CML patients with resistance to two or more tyrosine kinase inhibitors, HHT has been approved already in the year 2012 by USFDA. It is one of the naturally derived therapeutic agent which has been approved as a commercial drug to treat CML. Currently the focus is to use HHT in Acute Myeloid Leukemia patients having resistance and in those carrying mutations. It is evident from the studies that clinical practice of HHT in AML and other hematological malignancies will result in desired outcome. Even though HHT treatment has shown low toxic potential, it may result in hematologic toxicity like myelosuppression, but this should not restrain the use of the drug. When the benefits exceed the damage, appropriate dose adjustment and patient training for symptoms can limit the damages caused by the drug. Further, studies to investigate the toxic effects of HHT in central nervous system and cardiovascular system must be conducted to confirm its nontoxic nature. All these data outcomes of various combinations under different scenarios exhibit that HHT has promising results in treatment of AML which may lead to its approval in the upcoming years.

The goal is not so far as it is shown by the studies discussed in this review paper. At the same time, high demand for the medicinally important plants will cause a great risk to their biodiversity. Hence, the demand for these naturally derived drugs should be managed to maintain their sustainability. Fortunately, biotechnological solutions and nanotech approaches will provide a new ray of hope in leukemia treatment.

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Conflicts of interest

There are no conflicts of interest.

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