Review Article

# Histamine revisited: Role in acute myeloid leukemia

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## ABSTRACT

Histamine dihydrochloride (HDC) is derived from biogenic amine histamine. It suppresses the production of reactive oxygen species which inhibits the stimulation of T cells and natural killer (NK) cells. Co-administration of the cytokine interleukin (IL)-2 and HDC assists the activation of T cells and NK cells by IL-2, causing in the destruction of cancer cells, including those of acute myeloid leukemia (AML). A significantly longer leukemia-free survival (LFS; primary endpoint) was demonstrated in a phase III trial in adult patients with AML in first or subsequent remission, in those who received subcutaneous HDC and concomitant subcutaneous IL-2 as maintenance therapy compared to that of patients receiving no treatment. However, the difference in overall survival (OS) between the two groups was not significant. Patients had acceptable levels of adverse effects. Thus, HDC in addition to IL-2 appears to be a useful maintenance therapy option for adult patients with AML in remission.

**Key words:** Acute myeloid leukemia, histamine dihydrochloride, pharmacodynamics, pharmacokinetics, tolerability

## INTRODUCTION

Acute myeloid leukemia (AML) is a group of neoplastic disorder, complex and heterogenous in nature, characterized by an increase in the number of immature myeloid cells i.e., blasts in the bone marrow with or without the involvement of peripheral blood. The WHO defines AML as blasts ≥20% of the bone marrow or peripheral blood. This results in the failure of the bone marrow leading to anemia, granulocytopenia, and thrombocytopenia. These manifestations could result in fatigue, fever, infection and bleeding, culminating in death within weeks of diagnosis, if untreated.[1-3]

The last 4 decades have seen major developments in understanding the genetic basis of AML, and considerable increases in survival of children and young adults with the disease. An important step forward was the finding that AML cells harbor recurrent cytogenetic abnormalities. The identification of the genes involved in chromosomal rearrangements has provided understandings into the regulation of normal hematopoiesis and how disturbance of crucial transcription factors and epigenetic modulators promote leukemic transformation. Cytogenetics has been extensively accepted to offer the basis for progress of risk-stratified treatment methods to patient management.[4]

AML could either be *de novo* i.e., not resulting from chemotherapy or any previous hematological disorder or secondary if it is due to such condition. Additionally, inherited or acquired genetic mutations too could result in clonal transformation of leukemic blasts in AML.[5-7] AML is of high risk in patients with either myelodysplastic syndrome (MDS) or aplastic anemia.[7]

As per Arora *et al*. 2009, in India, leukemia continues to be the largest contributor to cancer-related deaths in children. Unfortunately, due to the dearth of any nationwide leukemia screening program, the majority of the population of India is still ignorant of this blood disorder. This contributes in late presentation and noncompliance with screening guidelines.[8] However, an attempt to describe the prevalence and risk of leukemia in its varied population by compiling the data of the patients suffering from four main types of Leukemia namely chronic lymphocytic

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leukemia (CLL), chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL), and AML from different hospitals of North Karnataka has been undertaken by Modak H *et al*., 2011.[9]

Results demonstrated that compared to female patients, Hindu males have greater risk of occurrence of leukemia ($P$ = 0.0333). The males of scheduled caste (SC) and Lingayat communities showed a high risk than other communities ($P$ = 0.000). The occurrence of AML showed a significant relationship with ABO blood groups ($P$ = 0.0090). The frequency of leukemia is quite high in Belgaum district when compared to others districts of North Karnataka and totally absent in Bidar district. The reasons need precise molecular and genetical studies of the population. Moreover, since the spectrum of cancer epidemiology seen in India is different from that in developed countries more emphasis should be placed on better development of regional and national registries.[9]

As per the US and UK data, AML frequently afflicts the elderly population.[10,11] Unfortunately, they have a poor prognosis since there is a higher chance of treatment resistance and treatment-induced complications.[12-15] Supporting this is the data from the US suggesting the 5-year survival in patients <65 years is 37.9%, whereas it is only 5.1% in patients ≥65 years.[11] In such a situation, the important prognostic factor could be the assessment of the pre-treatment karyotype, which could either be favorable, intermediate, or adverse.[16] Along with the determination of the pre-treatment karyotype, the management of AML consists of the induction, post-remission (consolidation) and maintenance (post-consolidation) therapy.[17] Maintenance therapy, however, is not always included as a regular treatment protocol.[13,15]

The patient is said to be in complete remission (CR) if there are <5% blasts in the bone marrow.[18,19] This is achieved by providing the induction chemotherapy, which suppresses the leukemic blasts and aims at restoring normal bone marrow function. Post-remission chemotherapy tries to prevent relapse by reducing the concentration of residual blasts assisted by the body's own defense system. Any residual disease is eliminated by the maintenance chemotherapy, which as mentioned earlier, could be a part of standard treatment protocol.[11,13,16,20]

Some patients may benefit from bone marrow transplantation (autologous or allogenic).[13,16,20]

Maintenance therapy though not regularly advocated for AML, has been utilized for other hematological malignancies like ALL and MDS.[20] Certain treatment strategies for maintenance therapy could be continuation of post-remission chemotherapy, demethylating agents (e.g., 5-azacitidine and decitabine), targeted therapies (e.g., tipifarnib), and immunotherapy [e.g., interleukin-2 (IL-2)].[17,20,21]

IL-2 is the major cytokine involved in the stimulation of T cells and natural killer (NK) cells. These cells i.e., T cells and NK cells are cytotoxic lymphocytes responsible for destroying the cancer cells.[22,23] This has been demonstrated by the role of IL-2 in patients with metastatic renal cell carcinoma[24,25] and metastatic melanoma.[24] Unfortunately, IL-2 therapy has not shown any promising benefit in patients of AML.[26-30] Tumor-induced immunosuppression of the T cells and NK cells could probably be the reason for the lack of efficacy of IL-2 in patients of AML.[31] It has been demonstrated that tumor-associated macrophages convert oxygen [mediated by nicotine amide adenine dinucleotide phosphate (NADPH) oxidase] into reactive oxygen species (ROS).[31,32] The ROS in turn produces an unfavorable environment that inhibits the IL-2-mediated activation of both T cells and NK cells.[23,31,33]

Considering the above, any agent which could overcome the ROS-induced inhibition of T cells and NK cells may prove to be of value addition to IL-2 therapy in the management of AML. This article reviews the role of histamine dihydrochloride along with IL-2 as maintenance therapy in patients with AML in remission.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamics

Addition of hydrochloride to histamine generates a synthetic product, i.e., histamine dihydrochloride, with improved water solubility.[23] Histamine dihydrochloride has demonstrated to possess immunomodulatory activity.[34] Studies have shown that histamine dihydrochloride inhibits the production of ROS by tumor-associated macrophages, thereby maintaining the activity of T cells and NK cells.[23,31,33,34] This effect is mediated by the $H_2$ receptors on the surface of the monocytes. To support this claim it has been demonstrated that $H_2$ agonist dimaprit had a similar action, whereas $H_2$ receptor antagonist ranitidine or cimetidine inhibits this activity of histamine dihydrochloride.[35,36] The stimulation of the $H_2$ receptors suppressed the enzyme NADPH oxidase, thus inhibiting the monocyte-induced inactivation of NK cells and T cells.[23,31,33] Additionally, it has been observed that monocytes of patients suffering from chronic granulomatous disease, who lack functional NADPH oxidase, failed to suppress T cells and NK cells;[37] conversely supplementation of catalase, an ROS scavenger, reversed the suppressive action of monocytes on T cells and NK cells.[35] Thus, supplementing histamine dihydrochloride to IL-2 helps the reactivation of T cells and NK cells by IL-2.

Animal studies have demonstrated that histamine dihydrochloride in addition to IL-2 was associated with

reduction of tumor volume,[38] increased clearance of tumor cells,[39] and reduced metastasis.[40] Additionally, phase II and III clinical trials have shown the superiority of the combination of histamine dihydrochloride and IL-2 as compared to that of IL-2 in patients with AML as maintenance therapy.[41-43]

Histamine dihydrochloride acting via $H_1$, $H_2$, and $H_3$ receptors produces a wide range of effects including anaphylaxis ($H_1$), gastric acid secretion ($H_2$), and neurotransmission ($H_3$).[33,34] The discovery of reciprocal regulation of T cell activity by $H_1$ and $H_2$-receptor activation indicating histamine-cytokine cross-talk, as well as the characterization of the fourth histamine receptor ($HR_4$) and its expression on numerous immune and inflammatory cells have prompted a re-evaluation of the actions of histamine. This accounts for a new potential for HR antagonists and agonists in targeting various immunopathological conditions.[44]

Thus histamine dihydrochloride could produce varied adverse effects (discussed subsequently). Furthermore, IL-2 in high doses too produces capillary leakage.[45]

### Pharmacokinetics

There is a high proportion of inter-individual variability in the pharmacokinetic parameters of histamine dihydrochloride. Following subcutaneous administration of histamine dihydrochloride, maximum plasma concentration was achieved in approximately 10 minutes. However, there is no data regarding the absolute bioavailability of histamine dihydrochloride. Administration of IL-2 before histamine dihydrochloride resulted in a significantly lower plasma IL-2 levels and AUC as compared to that of IL-2 alone, hence the recommended schedule of administration is IL-2 followed by histamine dihydrochloride.[46]

Histamine dihydrochloride is metabolized in the kidneys, liver, and other tissues, the metabolites lacking any significant activity. It is primarily excreted via the kidneys, with the mean half-life being 12-13 minutes. Data regarding the distribution of histamine dihydrochloride in the breast milk and placental crossing is lacking; however, its use during pregnancy and lactation is not recommended. The pharmacokinetic parameters of histamine dihydrochloride are not significantly affected by age or bodyweight. Hence, it is not recommended in patients <18 years or >60 years as the data is lacking. No dose adjustments needs to be done based on sex. Although, caution is advised in patients of severe renal impairment as they may develop hypotension, and patients with severe hepatic impairment may experience tachycardia, dosage adjustment is generally not recommended.[47]

## THERAPEUTIC EFFICACY

A large, phase III, 3-year, randomized open-label multicenter trial compared the efficacy of histamine dihydrochloride and IL-2 with no treatment as maintenance therapy in patients with AML who were in first or subsequent complete remission (CR).[43] Included in this trial were adult patients with adequate cardiac, renal and pulmonary functions, (≥18 years) with AML who achieved CR in the previous 6 months and completed post-remission therapy in the previous 3 months.

Patients with active peptic ulcer, asthma and previous hypersensitivity reactions were excluded from this trial. The included patients were randomized in 2 groups i.e., active treatment group or control group (each group $n = 160$). The active treatment group received histamine dihydrochloride and concomitant IL-2, whereas the control group was not given any treatment. The end-point being prevention of leukemia relapse.

Histamine dihydrochloride was administered in a dose of 0.5 mg and IL-2 16,400 U/kg, both given subcutaneously twice a day. The investigators supervised the administration of the first dose; all subsequent doses were taken by the patients at home. The rate of administration of histamine dihydrochloride was 0.1 mg/min., extended by 7-10 minutes if the patients experienced adverse events. If the adverse events failed to be resolved, the dosage was curtailed by 20%; similar to that for IL-2 administration.

The treatment was administered for a total of 10 cycles; each cycle being 3-week duration. The initial 3 such cycles were separated by 3 weeks of no treatment and the remaining 7 cycles were separated by 6 weeks of no treatment. Following the end of treatment phase i.e., 18 months, all patients were followed-up for a further minimum of 18 months.[43]

At baseline in the active treatment and control groups, patients had a mean age of 54 and 55 years (range 18-81 years and 18-84 years). Seventy-three percent and 78% had achieved the current CR in the previous 6 months, and 78% and 76% of patients had completed post-remission in the previous 3 months. Eighty-one percent and 82% respectively, patients were in first complete remission (CR1). The pre-treatment karyotype was favorable in 9% and 8%, intermediate in 59% and 59%, adverse in 6% and 4%, and unknown in 26% and 28%, of patients, respectively. The median follow-up of living patients was 46.7 months and 47.3 months, respectively, in active treatment and control groups.

Results showed that the combination of histamine dihydrochloride and IL-2 therapy was more effective than

no treatment in maintaining remission in patients with AML over the 3-year duration of the study. Leukemia-free survival (LFS) duration was significantly more in the active treatment group than in the control group in the overall population (primary end-point), as well as in the subgroup of patients in CR1, but not in the second or subsequent CR patients (>CR1). However, there was no significant difference between the two groups in terms of the effect on overall survival (OS) [Table 1].

Additionally, the CR1 subgroup receiving active treatment showed numerically lesser relapses as compared to that of no treatment, but the same was not observed in the overall population. The number of patients who remained in CR was numerically greater in the active treatment group compared to that of the control group.

There was no major impact on the Health-Related Quality of Life (HR-QOL) due to the administration of the active treatment.

LFS at 5 years was significantly higher in the CR1 subgroup of patients receiving active treatment (34% vs. 22%; $P$ = 0.024); however the same was not observed in the overall population (30% vs. 21%). At a median follow-up of 7.4 years,[48] a significantly longer LFS duration was observed in the patients receiving histamine dihydrochloride and IL-2 as compared to that of no treatment in both the overall population and the CR1 population

In another trial *post hoc* analyses of efficacy in morphological subtypes of AML among patients participating in the HDC/IL-2 phase III trial showed a non-significant trend toward improvement of LFS for HDC/IL-2-treated patients with FAB-M0/M1 AML versus controls ($P$ = 0.16, $n$ = 41). No benefit of treatment was observed in FAB-M2 AML ($P$ = 0.65, $n$ = 41), while HDC/IL-2 significantly improved LFS among patients with FAB-M4/M5 AML ($P$ = 0.017, $n$ = 58). Treatment efficacy was also improved in patients with non-M2 AML with LFS rates at three years of 52.5% (HDC/IL-2) versus 21.7% $P$ = 0.0089, $n$ = 104).[49]

## TOLERABILITY

Since histamine is a potent vasodilator, its use is commonly associated with headache, flushing, pyrexia, hypotension, tachycardia, injection-site granuloma and injection-site erythema (incidence >30%).[31] As mentioned earlier the frequency and magnitude of histamine-induced adverse events may be reduced by slowing the rate of administration.

### Drug interactions

Histamine dihydrochloride being an $H_2$ receptor agonist containing imidazole ring, simultaneous administration of $H_2$ receptor antagonist with imidazole structure like cimetidine, clonidine, and some systemic steroids must be used with caution or avoided. Similarly, tricyclic antidepressants, antihistaminics, or antipsychotics, because of their affinity to $H_1$/$H_2$ receptors must be restricted.

Potentiation of the hypotensive or cardiotoxic effects can occur due to the co-administration of beta-blockers or other antihypertensive medications; hence these should be used with care. Monoamine oxidase inhibitors may alter the metabolism of histamine dihydrochloride, hence should be avoided in such patients.

Histamine releasers like neuromuscular blockers, narcotic analgesics, and various contrast media used during diagnostic or surgical procedures could aggravate the effects of histamine dihydrochloride, thus caution is advised.[47]

**Table 1: Clinical efficacy of histamine dihydrochloride and interleukin-2 as maintenance therapy in adult patients with acute myeloid leukemia in complete remission***

| Group | No. of patients | Leukemia-free survival % of patients | | | Overall survival % of patients | | | No. of relapses | No. of pts. in CR |
|---|---|---|---|---|---|---|---|---|---|
| | | 12 months | 24 months | 36 months | 12 months | 24 months | 36 months | | |
| All patients | | | | | | | | | |
| Active treatment | 160 | 48 | 41 | 34 | 78 | 55 | 48 | 120 | 49 |
| Control | 160 | 42 | 29 | 24 | 70 | 51 | 44 | 119 | 31 |
| Pts. in first CR | | | | | | | | | |
| Active treatment | 129 | 52 | 45 | 40 | 80 | 61 | 55 | 76 | 46 |
| Control | 132 | 45 | 32 | 26 | 73 | 53 | 46 | 97 | 27 |
| Pts. in second or subsequent CR | | | | | | | | | |
| Active treatment | 31 | 29 | 23 | 10 | 68 | 32 | 19 | NR | NR |
| Control | 28 | 30 | 15 | 15 | 59 | 41 | 33 | NR | NR |

Leukemia-free survival: Primary endpoint, defined as the time from randomization to the date of relapse or death from any cause, Overall survival: Defined as the time from randomization to death from any cause, Relapse: Defined as >5% blast cells in the bone marrow, or extramedullary leukemia, CR: Defined as <5% blast cells in the bone marrow, without evidence of extramedullary leukemia. *Adapted and reproduced from Yang LP, Perry CM. Drugs 2011;71:109-22

## DOSAGE RECOMMENDATION AND ADMINISTRATION

Histamine dihydrochloride is available as a solution containing 0.5 mg/ml for subcutaneous administration. The recommended dosage for adult patients with AML in first remission is 0.5 mg twice daily by slow subcutaneous injection over 5 minutes; with 1-3 minutes, but not simultaneously, after the administration of IL-2.

The recommended treatment duration is a 10-cycle course, with 3 weeks of treatment followed by either 3 weeks (cycles 1-3) or 6 weeks (cycles 4-10) of no treatment. Histamine dihydrochloride is preferably administered on the thigh or abdominal areas, at a site different from the administration of IL-2. The dosage for IL-2 being 16,400 U/kg administered subcutaneously. The second daily dose of either histamine dihydrochloride or IL-2 should be after a gap of at least 6 hours following the first daily dose and the patients should be instructed to lie down for at least 20 minutes following the treatment.

The use of histamine dihydrochloride is contraindicated in patients with hypersensitivity to the active drug or any of its excipients, patients with significant cardiac impairment (NYHA class III/IV); patients receiving H2 blockers, clonidine or systemic steroids; pregnancy, lactation, and patients who are recipients of allogenic stem cell transplantation.[47]

## RECENT DEVELOPMENTS AND FUTURE DIRECTIONS

The current treatment of patients with acute myeloid leukemia yields poor results, with expected cure rates in the order of 30-40% depending on the biological characteristics of the leukemic clone.

Major progress in Molecular and Cellular Biology has resulted in an improved classification and understanding of the biology and prognosis of AML. These accomplishments have given new openings for the development of pioneering, more effective treatments. Innovative agents possibly beneficial in the management of patients with AML include novel formulations of proven drugs, newer nucleoside analogs, molecular target drugs, monoclonal antibodies, and other agents. Three newer nucleoside analogs, clofarabine, troxacitabine, and sapacitabine have been recently studied in patients with AML. Two methylation inhibitors, 5-azacyticline and decitabine are pyrimidine nucleoside analogs of cytidine which can be incorporated into RNA and/or DNA. Reduced doses of these agents are active in AML and have been widely explored, especially in secondary AML and AML in elderly patients. Tipifarnib and lonafarnib are orally available farnesyltransferase inhibitors with *in vitro* and *in vivo* activity against AML. Currently, FLT3 inhibitors, lestaurtinib, tandutinib and PKC 412 have been developed and tested in AML. The preclinical observations and clinical studies show that FLT3 inhibitors are encouraging agents in the treatment of FLT3-mutated AML patients, particularly when used in combinations with chemotherapy. Several newer MDR inhibitors, including valspodar (PSC-833) and zosuquidar trihydrochloride have been also tested for the treatment of relapsed AML.[50]

All are undoubtedly active. Nevertheless, their therapeutic efficacy compared to each other and to regular therapy is uncertain. The future is expected to see combinations of the drugs with each other and with more standard therapies. There also will be a shift away from inquiring which therapy is best for the average patient to inquiring which therapy is best for a given patient with a specific constellation of disease markers.

Therefore, new agents and schemas are intensively planned in order to improve patients' outcomes.

## CONCLUSIONS

Histamine dihydrochloride and IL-2 as post-consolidation therapy significantly prolonged the LFS in patients with AML; hence appears to be a useful maintenance therapy option for adult patients with AML in remission. However, its effects on OS and efficacy in older patients need to be addressed.

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