Patient Safety & Quality Improvement Journal
http://psj.mums.ac.ir
PSQI

Efficacy of Hyper-CVAD Drug Regimen in Adult T-Cell Leukemia (ATL) Patients: A Randomized Clinical Trial

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ARTICLEINFO

Article type:
Original Article

***Article History*:**
Received: 16 Mar 2025
Accepted: 30 Sep 2025

Key words:
Adult T-cell leukemia, Hyper-CVAD, Arsenic trioxide, HTLV-I, Therapeutic outcomes

ABSTRACT

Introduction:
Adult T-cell leukemia (ATL), a hematologic malignancy caused by Human T-lymphotropic virus type 1 (HTLV-I) infection, is known for its aggressive course, limited treatment responsiveness, and short survival. This clinical trial compared the therapeutic effects of two treatment approaches-Hyper-CVAD and the combination of arsenic trioxide, interferon-alpha, and zidovudine (As/IFN/AZT)-in newly diagnosed acute ATL patients.

Materials and Methods:
In this randomized study, patients with confirmed HTLV-I infection by ELISA and/or PCR were assigned using block randomization to receive either Hyper-CVAD or As /IFN/AZT over a 60-day treatment period. A total of 29 patients completed the protocol, and therapeutic responses were assessed following completion of therapy.

Results:
Baseline characteristics, including gender distribution, serum lactate dehydrogenase (LDH) levels, and lymphocyte counts, showed no significant differences between the groups ($P > 0.05$). Response rates were 46.67% in the Hyper-CVAD group and 35.71% in the As/IFN/AZT group, without statistical significance ($P > 0.05$). However, survival analysis indicated better outcomes with Hyper-CVAD ($P < 0.05$). Hematologic toxicity was the most common adverse event, with Grade 3 events observed in one patient receiving Hyper-CVAD and three patients receiving As/IFN/AZT.

Conclusion:
While both regimens demonstrated comparable efficacy in overall response, the As/IFN/AZT protocol was associated with higher toxicity. Larger-scale investigations are needed to determine its optimal role and timing as a first-line option for ATL.

► ***Please cite this paper as:***
Kamandi M, Moghaddamnia F, Ataei Azimi S, Moeini Nodeh M. Efficacy of Hyper-CVAD Drug Regimen in Adult T-Cell Leukemia (ATL) Patients: A Randomized Clinical Trial. Journal of Patient Safety and Quality Improvement. 2025; 13(4): 201-207. Doi: 10.22038/psj.2025.86220.1462

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Introduction

Adult T-cell leukemia (ATL) is a rare but highly aggressive malignancy of mature T-lymphocytes that arises secondary to infection with Human T-lymphotropic virus type 1 (HTLV-I) (1,2). The prognosis is generally poor due to the disease's intrinsic resistance to standard chemotherapeutic regimens. ATL presents in a spectrum of clinical subtypes, ranging from indolent forms such as smoldering and chronic types to aggressive presentations, including acute ATL and ATL-associated lymphomas (3,4). Median survival varies substantially-approximately 8 months for acute ATL and up to 55 months in chronic forms (3,4). A characteristic feature in many cases is profound immunosuppression, predisposing patients to opportunistic infections that further compromise survival outcomes (5).

Acute ATL is associated with the shortest survival, typically 6–8 months, and is characterized by clinical manifestations such as marked leukocytosis, cutaneous lesions, lymphadenopathy, hepatosplenomegaly, and elevated serum lactate dehydrogenase (LDH) levels; hypercalcemia is reported in nearly 70% of cases, often accompanied by eosinophilia (6,7).Treatment of ATL is challenging because response rates to conventional chemotherapy are often unsatisfactory, and drug-related toxicity can be substantial (8). Various combination protocols have been explored, including VCAP (vincristine, cyclophosphamide, doxorubicin, prednisone), AMP (doxorubicin, ranimustine, prednisone), As/IFN/AZT (arsenic trioxide, interferon-alpha, zidovudine), and VECP (vindesine, etoposide, carboplatin, prednisone) (9). Clinical evidence suggests that the As/IFN/AZT regimen demonstrates meaningful anti-leukemic activity in ATL, especially in chronic disease, but its use is frequently limited by hematologic toxicities (5,10).

The Hyper-CVAD regimen-comprising cyclophosphamide, vincristine, doxorubicin, and dexamethasone-has been reported as a promising treatment option for aggressive hematologic malignancies, including ATL (11, 12). Available data indicate that Hyper-CVAD may provide therapeutic benefits comparable to or exceeding those of As/IFN/AZT, with a potentially lower toxicity burden. Given the poor long-term survival of ATL patients, this study aimed to directly compare the efficacy and safety profiles of Hyper-CVAD and As/ IFN/ AZT in newly diagnosed acute ATL cases.

Materials and Methods

This randomized clinical trial was conducted on patients newly diagnosed with acute ATL, classified according to the Shimoyama criteria, who were referred to Emam Reza and Qaem Hospitals in Mashhad, Iran. The study was approved by the Ethics Committee of Mashhad University of Medical Sciences (approval code: IR.MUMS. MEDICAL. REC.1400.717) and registered at the Iranian Registry of Clinical Trials (IRCT202107030 51770N1). All procedures complied with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Eligibility Criteria:

Adults aged 18 years or older with acute ATL and confirmed HTLV-I infection—verified via enzyme-linked immunosorbent assay (ELISA) and/or polymerase chain reaction (PCR)—were eligible for inclusion. Patients who withdrew voluntarily or discontinued treatment because of severe toxicity were excluded from the analysis.

Randomization and Baseline Assessment: Block randomization was performed using a sealed opaque envelope method generated on the SEALD ENVELOPE platform (www.sealedenvelope.com) by an independent coordinator not involved in clinical care. Baseline demographic and clinical data, including age, sex, complete blood count (CBC), biochemical tests, and virological profiles, were collected before initiating treatment.

Treatment Protocols:

- Hyper-CVAD Regimen:
- Cyclophosphamide (300 mg/m^2 IV, days 1–3), vincristine (2 mg IV, days 4 and 11), doxorubicin (50 mg/m^2 IV, day 4), and dexamethasone (40 mg orally, days 1–4 and 11–14).
- As/IFN/AZT Regimen: Arsenic trioxide (10 mg/day IV, 5 days per week), interferon-alpha (5 million units/day subcutaneously), and zidovudine (900 mg/day orally in three doses).

Both regimens were administered for 60 consecutive days. Laboratory monitoring

included daily CBC, biochemical profiles, and viral markers. In cases of toxicity, dose adjustments were made: for As/IFN/AZT, interferon-alpha was reduced to 3 million units/day, zidovudine to 600 mg/day, and arsenic trioxide was tapered or discontinued; for Hyper-CVAD, cytotoxic drug doses were proportionally reduced or withheld according to clinical status.

Response Criteria:

Therapeutic response was classified as:

- Complete Response (CR): Absence of leukemic cells in peripheral blood.
- Partial Response (PR): ≥50% reduction in leukemic cell count and measurable tumor size.
- No Response (NR): <50% reduction or evidence of disease progression.

Statistical Analysis:

Data analysis was conducted using Stata version 12 (StataCorp, College Station, TX, USA). Continuous variables were expressed as medians with interquartile ranges and compared using the Mann–Whitney U test.

Categorical data were analyzed using Chi-square or Fisher's exact tests. Survival curves were generated via the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model, with a two-sided p-value <0.05 considered statistically significant.

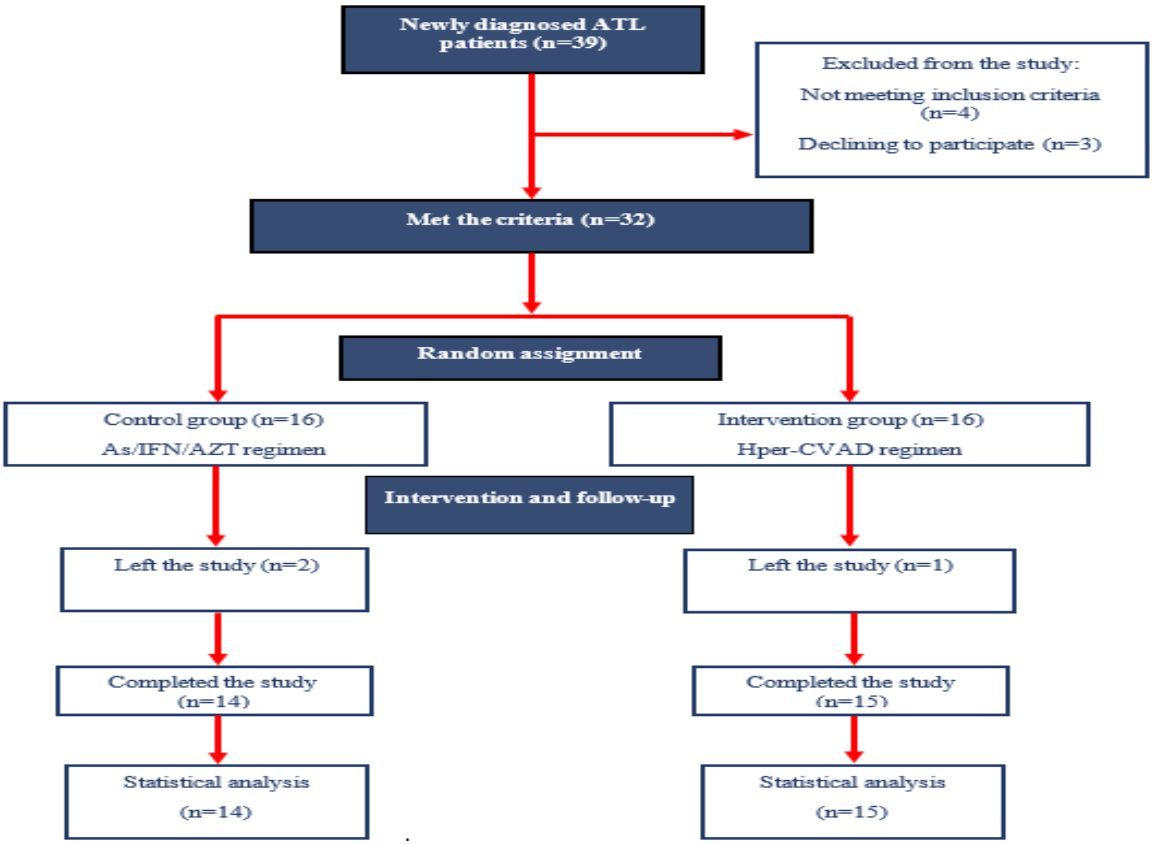

Fig 1. Flowchart of the study

Results

A total of 29 eligible patients were enrolled, with 15 allocated to the Hyper-CVAD group and 14 to the As/IFN/AZT group. Female patients comprised 40% of the Hyper-CVAD arm and 28.57% of the As/IFN/AZT arm; the difference was not statistically significant (P > 0.05). Similarly, baseline serum lactate dehydrogenase (LDH) concentrations and peripheral lymphocyte counts showed no significant variation between groups (P > 0.05).

Response and Survival

The overall treatment response did not differ significantly between the regimens. The Hyper-CVAD group achieved a 46.67% complete response (CR) rate compared to 35.71% in the As/IFN/AZT group (P =

0.715). Relapse occurred in 57.15% of patients in the Hyper-CVAD arm and in 40% of those in the As/IFN/AZT arm (P = 0.450). Mortality rates were 66.67% and 64.28% for Hyper-CVAD and As/IFN/AZT, respectively (P = 0.701). Kaplan–Meier analysis showed no statistically significant difference in overall survival (OS) between groups (log-rank P > 0.05).

However, log-rank testing revealed a significant difference in treatment response rates (P < 0.05).

Table 1. Demographic and clinical information for the Hyper-CVAD and As/IFN/AZT intervention groups

Variable		Hyper CVAD (n=15)	As/IFN/AZT (n=14)	P-value
Age		49 (39-64)	50.5 (46-54)	0.812
Gender (Female)		6 (40%)	4 (28.57%)	0.700
LDH		1025 (753-1334)	802.5 (634-963)	0.744
Initial viral load (copies/ml)		2164 (716-3861)	2483 (931-4106)	0.469
Lymphocyte count (µL)		3411 (1820-4320)	3852 (1985-5465)	0.267
Complete Response	CR	7 (46.67%)	5 (35.71%)	0.715
	NR	8 (53.33%)	9 (64.29%)	
Relapse	Yes	4 (57.15%)	2 (40%)	0.710
	No	3 (42.85%)	3 (60%)	
OS (%)		40%	42.8%	0.938
DFS (Mon)		4	4	0.950
Mortality		10 (66.67%)	9 (64.28%)	0.701
CR: Complete Remission, NR: No Response; DFS: Disease-free survival				

Grade 3 adverse events were reported in 8 patients: 2 from the Hyper-CVAD group and 6 from the As/IFN/AZT group. Hematologic toxicities were the most frequent, with Grade 1 events affecting 14 patients in the Hyper-CVAD arm and 11 in the As/IFN/AZT arm. Grade 3 hematologic toxicity occurred in 1 Hyper-CVAD patient and 3 As/IFN/AZT patients. Extra-hematologic toxicities-such as hepatotoxicity, nausea, and vomiting-were also common. In the Hyper-CVAD group, 14 patients experienced Grade 1 extra-hematologic toxicity, and 1 patient had a Grade 3 event. In the As/IFN/AZT group, 11 patients had Grade 1 and 3 patients had Grade 3 extra-hematologic toxicity. Fatigue was more frequently reported in the As/IFN/AZT group, while fever occurred in only one patient in this arm.

Table 2. Toxicity levels of drug regimens based on WHO criteria

Treatment	Patient Number	Hematological Toxicity				Extra-hematologic Toxicity	
		Cytopenia	Anemia	Neutropenia	Severe Thrombocytopenia	Liver Function	Nausea/Vomiting
Hyper-CVAD	1	1	1	0	0	0	1
	2	0	0	0	1	0	0
	3	0	0	1	0	0	1
	4	1	0	0	0	1	1
	5	1	1	1	0	0	1
	6	0	1	0	0	3	0
	7	1	1	1	1	0	1
	8	0	0	0	1	1	0
	9	0	1	1	0	0	1
	10	1	1	0	3	1	0
	11	0	0	1	0	0	1
	12	1	1	0	0	1	0
	13	0	0	1	0	0	1
	14	1	1	0	0	0	1
	15	0	0	1	0	0	1
As/IFN/AZT	16	1	1	0	1	3	1
	17	0	0	0	1	1	0
	18	0	1	1	0	0	1
	19	1	0	0	0	1	0
	20	1	1	3	0	1	1
	21	0	1	0	3	1	0
	22	0	1	0	0	0	1
	23	1	0	0	0	0	1
	24	0	0	1	0	3	1
	25	0	1	0	0	0	0
	26	0	1	0	1	1	1
	27	0	1	0	0	1	0
	28	0	0	3	0	3	1
	29	1	1	0	0	0	1

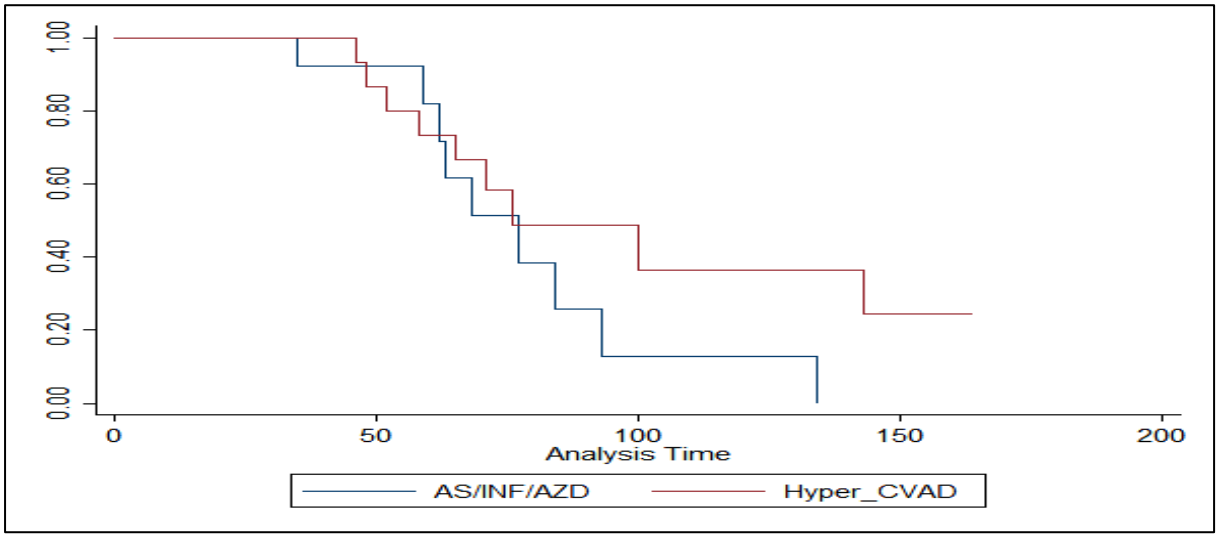

Fig 2. Survival of ATL patients in the Hyper-CVAD and As/INF/AZT groups

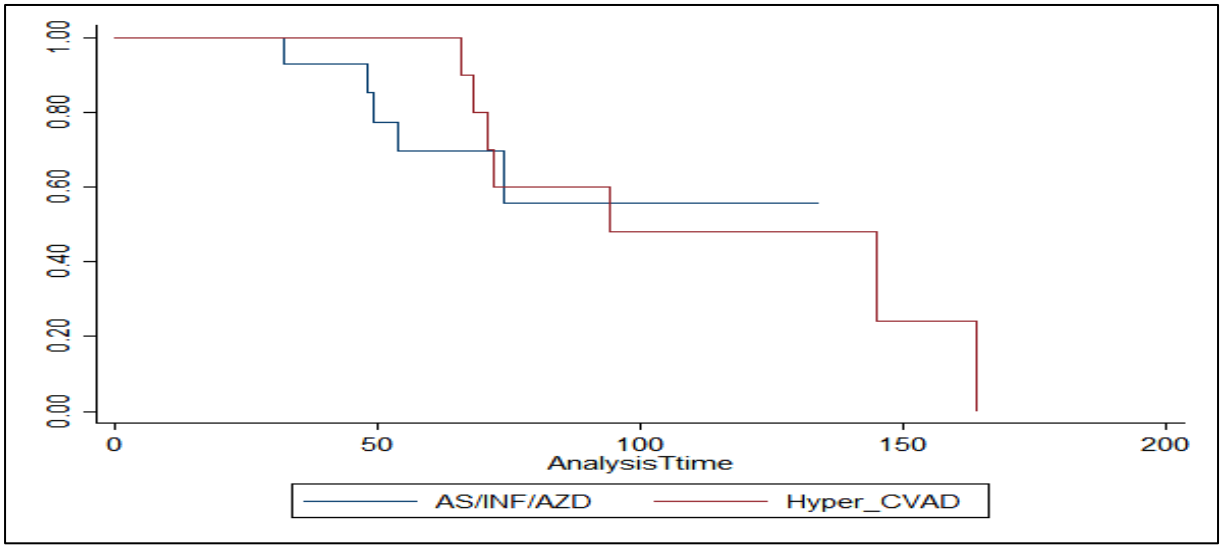

Fig 3. CR rates in the Hyper-CVAD and As/INF/AZT groups

Discussion

The Hyper-CVAD regimen is recognized as an intensive multi-agent chemotherapy protocol that has demonstrated substantial efficacy in a range of hematologic malignancies, including acute leukemias (13–15). In this study, its therapeutic outcomes were compared with those of the As/IFN/AZT protocol in newly diagnosed ATL patients, with particular focus on survival and relapse rates. Although no statistically significant difference was found in remission or relapse between the two regimens, patients treated with Hyper-CVAD demonstrated a survival advantage. Moreover, the toxicity profile of Hyper-CVAD appeared more favorable, aligning with earlier clinical observations (11,12).

Over the past decades, the use of combination cytotoxic regimens has modestly improved long-term survival in ATL, with reported three-year survival rates increasing by approximately 24% (9).

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only treatment with curative potential; however, its applicability is limited by high treatment-related morbidity and mortality, particularly among older individuals or those with advanced disease (16).

Alternative chemotherapy combinations-such as VCAP, AMP, and VECP-have also been evaluated, each offering variable improvements in disease control and patient survival (9). The As/IFN/AZT protocol has shown notable anti-leukemic activity,

especially in chronic ATL. In a phase II trial, Hermine et al. (10) reported meaningful clinical responses, albeit with significant treatment-related hematologic toxicity. Similarly, Kchour et al. (5) achieved near-complete remission rates in chronic ATL using this regimen, with adverse effects predominantly involving the hematopoietic system. In the present study, As/IFN/AZT was associated with a higher incidence of Grade 3 toxicity compared to Hyper-CVAD, consistent with prior reports (5,10,17).

In contrast, Hyper-CVAD has been successfully applied in aggressive hematologic malignancies, including ATL, sometimes in conjunction with HSCT. For instance, Alduaij et al. (11) described complete remission in two ATL cases—one sustained for 18 months post-allogeneic bone marrow transplantation and another for 12 months without transplantation. Such findings suggest that Hyper-CVAD may serve as a viable frontline option, offering comparable efficacy to As/IFN/AZT while minimizing toxicity. However, this trial has limitations that must be acknowledged. The relatively small sample size and short follow-up duration limit the statistical power and the generalizability of the results. Future investigations should include larger, multicenter cohorts and incorporate extended monitoring periods. Furthermore, the integration of molecular and immunological biomarkers into clinical trials could help refine patient selection and optimize treatment strategies, ultimately clarifying the specific role of each regimen in both acute and chronic ATL.

Conclusion

The present findings indicate that, although overall survival favored the Hyper-CVAD regimen, there were no statistically significant differences between Hyper-CVAD and As/IFN/AZT in terms of treatment response or relapse rates. Both protocols were associated with moderate adverse effects; however, hematologic toxicity was more pronounced with As/IFN/AZT. Future investigations should focus on optimizing the timing and sequencing of As/IFN/AZT administration, as well as evaluating its role as a frontline therapy with strategies aimed at minimizing toxicity.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Funding

This work was financially supported by Mashhad University of Medical Sciences, Mashhad, Iran.

Data Availability

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

Ethics Statement

The protocols were approved by the Ethics Committee of the Mashhad University of Medical Sciences, Iran. In addition, informed consent was obtained from all the participants included in this study according to the committee regulations.

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