Phase 2 study of the efficacy and safety of the combination of arsenic trioxide, interferon alpha, and zidovudine in newly diagnosed chronic adult T-cell leukemia/lymphoma (ATL)

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Adult T-cell leukemia/lymphoma (ATL) is resistant to chemotherapy and carries a dismal prognosis particularly for the acute and lymphoma subtypes. Promising results were obtained with the combination of zidovudine and interferon-alpha. Chronic ATL has a relatively better outcome, but poor long-term survival is noted when patients are managed with a watchful-waiting policy or with chemotherapy. In ATL cell lines, arsenic trioxide shuts off constitutive NF-κB activation and potentiates interferon-alpha apoptotic effects through proteasomal degradation of Tax. Clinically, arsenic/interferon therapy exhibits some efficacy in refractory aggressive ATL patients. These results prompted us to investigate the efficacy and safety of the combination of arsenic, interferon-alpha, and zidovudine in 10 newly diagnosed chronic ATL patients. An impressive 100% response rate was observed including 7 complete remissions, 2 complete remissions but with more than 5% circulating atypical lymphocytes, and 1 partial response. Responses were rapid and no relapse was noted. Side effects were moderate and mostly hematologic. In conclusion, treatment of chronic ATL with arsenic, interferon-alpha, and zidovudine is feasible and exhibits an impressive response rate with moderate toxicity. Long-term follow up will clarify whether this will translate to disease cure. Overall, these clinical results strengthen the concept of oncogene-targeted cancer therapy. (Blood. 2009; 113:6528-6532)

Introduction

Adult T-cell leukemia/lymphoma (ATL) is an aggressive proliferation of mature activated $CD4^+$ T cells associated with the human T-cell lymphotropic virus type I (HTLV-I).[1] Leukemia develops after a very long latency period and is preceded by oligoclonal expansions of HTLV-I–infected activated T cells.[2] These clonal expansions result from the expression of the viral transactivator protein Tax, which activates various cellular genes[3] and creates an autocrine loop involving interleukin-2, interleukin-15, and their cognate receptors.[4] The diversity in clinical features and prognosis of ATL patients has led to its subclassification into smoldering, chronic, lymphoma, and acute subtypes.[5] Patients with aggressive ATL (acute and lymphoma subtypes) generally have a very poor prognosis because of intrinsic chemoresistance of malignant cells, a large tumor burden with multiorgan failure, hypercalcemia, and/or frequent infectious complications due to a profound T-cell immune deficiency.[6,7] Patients with indolent ATL (ie, the chronic or smoldering subtypes) have a better prognosis.[6] However, data from Japan showed poor long-term survival results when these patients are managed with a watchful-waiting policy until disease progression or with chemotherapy.[8] Indeed, 4-year survival in chronic ATL is less than 30%.[6] We and others showed that high response rates are achieved in ATL patients with the combination of the antiretroviral nucleotide analog zidovudine (AZT) and interferon alpha (IFN).[9-14] However, most patients eventually relapse, which underlines the need for new therapeutic approaches.

Arsenic trioxide (As) is a very effective treatment of acute promyelocytic leukemia (APL),[15] a distinct subtype of acute myeloid leukemia that is characterized by unique clinical characteristics and a specific cytogenetic abnormality, t(15;17), which results in a reciprocal translocation between the *PML* gene on chromosome 15 and the retinoic acid receptor α (RAR-α) gene on chromosome 17.[16,17] Clinically, As directly targets and degrades PML/RARA fusion protein, inducing clinical remission of APL patients.

In ATL cells, we have previously shown that As synergizes with IFN to induce cell cycle arrest and apoptosis.[18] At the molecular level, the combination of As/IFN specifically induces proteosomal degradation of the HTLV-1 oncoprotein Tax and reversal of NF-κB activation.[19,20] Such specific targeting of the viral oncoprotein by IFN/As treatment, reminiscent of As targeting of PML/RAR in APL, provides strong rational for combined IFN/As therapy in ATL patients. In that sense, we previously reported the results of a phase 2 trial of As/IFN combination in 7 patients with relapsed/refractory

Submitted March 18, 2009; accepted April 22, 2009. Prepublished online as *Blood* First Edition paper, May 1, 2009; DOI 10.1182/blood-2009-03-211821.

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Table 1. Patient characteristics at initiation of treatment

Patient no.	Age, y	Sex	LDH, xN	Lymphocyte count/μL	$CD4^+CD25^+$, %
1	47	F	1.2	7000	41
2	53	M	1.8	1320	15
3	36	M	1.9	4230	45
4	53	M	< 1	2160	22
5	46	F	< 1	5100	42
6	63	F	< 1	5050	29
7	51	F	< 1	4350	14
8	77	M	1.7	7980	54
9	68	F	1.6	4990	40
10	58	F	1.2	185700	52

The last column indicates the percentage of total lymphocytes that is $CD4^+$ and $CD25^+$.
LDH indicates lactate dehydrogenase; and ATL, adult T-cell leukemia/lymphoma.
All patients had chronic ATL and did not have hypercalcemia.

aggressive ATL after AZT, IFN, and chemotherapy.[21] One patient achieved complete remission, 3 achieved partial remission, and 3 progressed. The patient in complete remission (CR) is still alive after more than 5 years of follow up. These results indicate that treatment with As and IFN is feasible and exhibits an antileukemic effect in vivo in these selected aggressive ATL patients with poor prognosis. However, the slow pharmacokinetics of As (duration to obtain maximum levels, low maximum levels) that we observed in our previous study, and the refractory status of these patients to many drugs including IFN, argue for the use of As and IFN earlier in the course of the disease, either as maintenance therapy or in association with AZT/IFN as first-line therapy of ATL. Similarly, a transient response to As/IFN combination was reported in Japan in 2 patients with refractory acute ATL.[22]

In this prospective phase 2 study, in line with our previous findings, we investigated the efficacy and safety of the treatment with the combination of As, IFN, and AZT in 10 newly diagnosed chronic ATL patients from the region of Mashhad in northeast Iran. We show that this combination treatment is feasible and exhibits a remarkably high response rate with moderate side effects.

Methods

Patients' characteristics

Ten newly diagnosed, previously untreated, chronic ATL patients were included in this prospective phase 2 study after giving informed consent. Patient enrollment started in 2007. These patients were referred to the hematology-oncology department of Ghaem and Imam Reza hospitals, Mashhad University of Medical Sciences. All ATL patients had serologic evidence of HTLV-I infection by enzyme-linked immunosorbent assay (ELISA) and confirmation of HTLV-I positivity by standard polymerase chain reaction (PCR; data not shown). Flow cytometric analysis of peripheral blood at diagnosis showed that tumor cells were $CD4^+$, $CD8^-$, and $CD25^+$ (Table 1). All patients had chronic ATL according to the Shimoyama classification criteria for ATL.[5] The patient's characteristics are shown in Table 1. This study was approved by the ethical committee of Mashhad University of Medical Sciences and patient informed consent was obtained in accordance with the Declaration of Helsinki.

Study design and treatment schedule

Treatment consisted of intravenous As (10 mg/day, 5 days/wk), subcutaneous IFN (Pooyesh Darou Pharmaceutical, Tehran, Iran; 5 million units/day), and oral AZT (900 mg/day). Arsenic was initially planned for a duration of 60 days. However, after poor tolerance in the first patient who received 60 days of As together with AZT and IFN, the protocol was amended to 30 days of As. In case of toxicity, AZT and IFN were either transiently interrupted or their dose was reduced to 600 mg/day and 3 million units per day, respectively. Arsenic dose was not reduced in case of toxicity, but As treatment was transiently interrupted. Details about treatment dose, treatment duration, and treatment interruption are listed in Table 2. Treatment of nonresponders was at the discretion of the investigator.

Response criteria

Complete remission (CR) was defined as a normalization of the complete blood count (CBC) associated with a disappearance of all measurable

Table 2. Treatment schedule

Patient no.	As dose, mg/d	As duration, d	As interrupt Y/N (duration)	IFN dose, MIU/d	IFN duration, d	IFN interrupt Y/N (duration)	AZT dose, mg/d	AZT duration, d	AZT interrupt Y/N (duration)
1	10	60	Y (15 d)	5	440	Y (15 d)	900	455	Y (15 d)
2	10	30	N	5	450	N	900	30	N
							600	420	N
5	10	30	N	5	90	N	900	90	N
				3	195	N	600	180	N
6	10	30	N	5	180	N	900	180	N
7	10	30	N	5	75	Y (15 d)	900	75	Y (15 d)
				3	165		600	165	N
8	10	30	N	5	75	N	900	75	N
9	10	30	N	5	90	N	900	90	N
				3	105	N	600	160	N
10	10	30	N	5	90	N	900	90	N
				3	105	N	600	150	N
11	10	30	N	5	90	N	900	90	N
				3	45	N	600	60	N
13	10	30	N	5	75	N	900	75	N

As indicates arsenic trioxide; IFN, interferon alpha; AZT, zidovudine; Y, yes; N, no; interrupt, interruption; d, days; and MIU, million international units.

Table 3. Toxicity (WHO grade)

Patient no.	Anemia	Neutropenia	Thrombocytopenia	Liver function	Nausea/vomiting	Other
1	1	1	0	2	1	0
2	0	0	0	0	1	0
5	1	3	0	0	1	Fever
6	0	0	0	0	1	0
7	1	3	3	1	1	0
8	0	0	0	0	0	0
9	1	0	0	0	1	0
10	1	0	3*	0	0	0
11	1	3	1	0	0	0
13	0	0	1	0	1	0

WHO indicates World Health Organization.
*Thrombocytopenia present before starting treatment

tumors lasting at least 1 month. Patients with persistence of less than 5% atypical lymphocytes were, however, considered in CR because this situation may be seen in healthy carriers of HTLV-I. Very good partial response (VGPR) was defined as a normalization of the CBC associated with a disappearance of all measurable tumors lasting at least 1 month, but with persistence of more than 5% atypical lymphocytes on peripheral blood smear. Partial response (PR) was defined as a decrease of more than 50% in the number of leukemia cells and in the size of all measurable tumors. No response (NR) was defined as less than 50% decrease in the number of leukemia cells or in the size of any measurable tumor, or as disease progression. Progression-free survival (PFS) was defined as the period between initiation of treatment and the date of disease progression, death, or last follow-up. Overall survival (OS) was defined as the period between initiation of treatment and the date of death or last follow-up.

Proviral load

The HTLV-I viral copy number per microliter of blood was calculated from the cell count and the average viral copy number per cell as assessed by quantitative PCR. Real-time quantitative PCR was performed on DNA extracted from peripheral blood mononuclear cells as previously described, using primers and Taqman probe positioned on *tax* gene and *albumin* gene for normalization.[23] TaqMan amplification was carried out in reaction volumes of 25 μL, with the use of the qPCR MasterMix (Eurogentec, Leuven, Belgium). Each sample was analyzed in triplicate with the use of 250 ng DNA in each reaction. Thermal cycling was initiated with a 2-minute incubation at 50°C, followed by a first denaturation step of 10 minutes at 95°C and then by 45 cycles at 95°C for 15 seconds and 58°C for 1 minute for *tax* (or 60°C for 1 minute for *albumin*).

Results

Toxicity and dose adjustment

Toxicity (WHO > 3) occurred in 4 patients (Table 3). Most patients experienced hematologic toxicity, especially at the end of the first month of treatment (grade > 1 [6 patients], grade > 3 [3 patients]). Extrahematologic toxicities (grade > 1 [7 patients], grade > 2 [1 patient]) included gastrointestinal (nausea and vomiting) and hepatic (cytolysis and cholestasis) signs. Overall, toxicity resulted in dose reduction or transient discontinuation of treatment in 7 patients. In addition to these objective toxicities, we noted that most patients experienced severe fatigue during the last week of arsenic therapy. This was rapidly reversible after arsenic discontinuation.

Most patients could achieve the initially planned duration of arsenic treatment (30 days) and are still receiving maintenance therapy with AZT and IFN, albeit at reduced dose as shown in Table 2. Overall, AZT was transiently interrupted in 2 patients or given at a reduced dose in 6 patients. Similarly, IFN was transiently interrupted in 2 patients or given at a reduced dose in 5 patients. Finally, As was transiently interrupted in one patient.

Response and survival

All patients initially presented with symptomatic chronic ATL. The most frequent symptoms were cutaneous manifestations with maculopapular rash, severe itching, and skin ulcerations (Figure 1). Treatment with As, IFN, and AZT resulted in an impressive 100% response rate (Table 4). At day 30, 5 patients achieved PR and 5 patients achieved VGPR defined as a normalization of the CBC associated with a disappearance of all measurable tumors lasting at least 1 month, but with persistence of more than 5% of atypical lymphocytes on peripheral blood smear. Impressively, within 2 to 4 weeks, skin lesions almost disappeared (Figure 1). Interestingly, in the 7 patients for whom initial and day-30 DNA was available, HTLV-I proviral load significantly decreased from an average of 1415 copies/μL blood to 226 copies/μL ($P < .05$; Table 5). All patients continued to improve their response (Table 4; Figure 1). Indeed, disease evaluation at last follow up showed that 7 patients were in CR, 2 patients were in VGPR (solely because of the presence of 6% and 8% of atypical lymphocytes on peripheral blood smear, respectively), and 1 patient was in PR (after a short follow up of 2 months, his lymphocytosis decreased from 185 000 × 10^9/L to 6400 × 10^9/L). After a median follow-up of 8 months (range, 2-15 months), all patients are still alive; none of them relapsed or progressed.

Discussion

In this prospective phase 2 study, we show promising clinical results of an As/IFN/AZT combination in 10 newly diagnosed chronic ATL patients from northeast Iran. An impressive 100% response rate was observed, including 7 patients who achieved CR, 2 patients who achieved VGPR (clinical and biologic CR except for the presence of more than 5% atypical lymphocytes on peripheral blood smear), and 1 achieved PR (after a short follow-up of 2 months, lymphocytosis decreased by more than 95%). Although this impressive response rate could be partly explained by the presence of AZT and IFN in the As/IFN/AZT triple combination, it is noteworthy that the response rate and particularly the CR rate with AZT/IFN alone in published studies[9-14] is less than what is observed in this study. Moreover, the highest rates of response were previously reported with the use of high doses of AZT and high doses of IFN (6 million units/m^2), whereas most of our patients received a much lower dose of IFN (total dose of 5 to 3 million

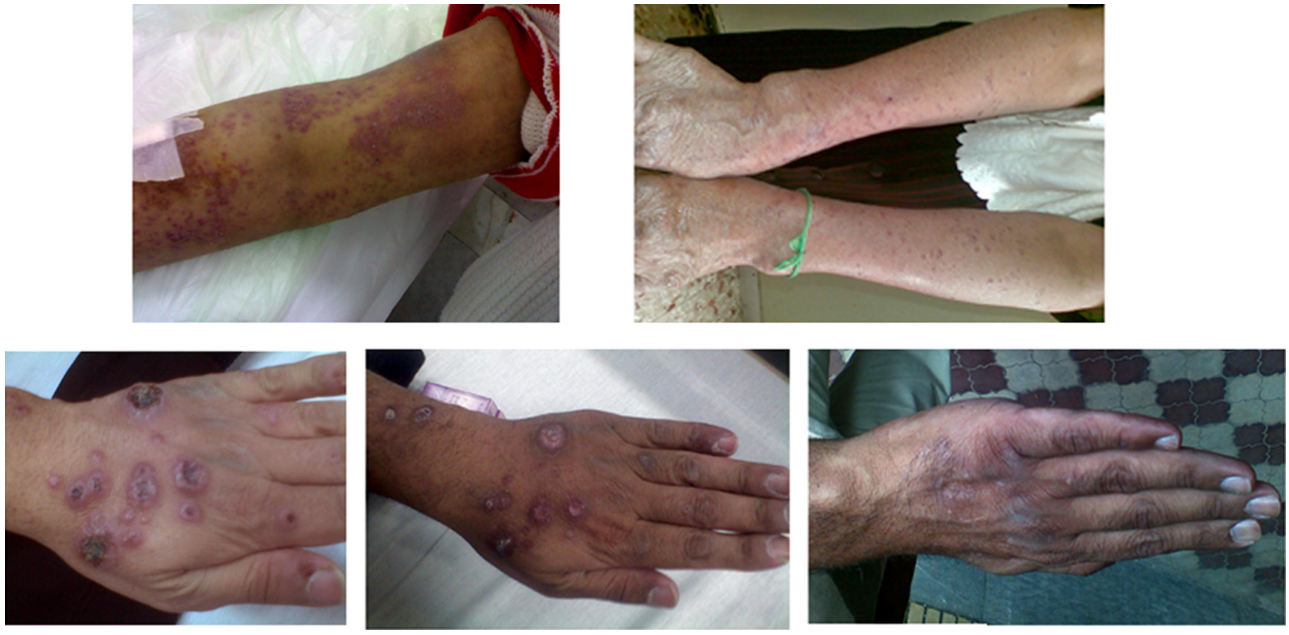

Figure 1. Treatment with arsenic, interferon, and zidovudine results in rapid resolution of ATL skin manifestations. (Top panels) Representative skin manifestations in patient 1 at diagnosis (left) and after 1 month of therapy (right). (Bottom panels) Representative skin manifestations in patient 3 at diagnosis (left), after 2 weeks of therapy (middle), and after 8 months of therapy (right).

units). Finally, although the follow-up of our study is relatively short (median follow-up of 8 months), none of the patients relapsed or progressed. Altogether, these results strongly suggest that As significantly improved the response rate of AZT/IFN.

The triple combination of As/IFN/AZT was feasible with moderate and manageable side effects. Hematologic toxicity necessitated transient treatment interruption or dose reduction in some patients. Extrahematologic toxicity consisted mainly of gastrointestinal discomfort. However, it is noteworthy that severe fatigue was noted during the last week of arsenic therapy in most patients. This was rapidly reversible after arsenic discontinuation. Hence, a shorter duration of arsenic (3 weeks) may be associated with increased tolerance and should be explored in future trials. Overall, based on this study, in patients with chronic ATL, the recommended starting dose of the 3 agents during the first month of treatment would be AZT (900 mg/day), IFN (5 million IU/day), and As (10 mg/day). Dose reduction of AZT (to 600 mg/day) and IFN (to 3 million IU/day) should be done in case of severe toxicity. This should be followed by maintenance AZT/IFN at the same dose. However, a phase 1 study is now recommended to establish the maximal tolerated dose for each drug in this highly effective combination regimen.

As for the mechanism of action, we have previously shown that, ex vivo, the combination of As and IFN selectively kills HTLV-I–infected cells, through reversion of the constitutive activation of NF-κB and degradation of the Tax oncoprotein by the proteasome.[18-20] Proteasome-mediated degradation of Tax by As/IFN is reminiscent of the proteasome-mediated degradation of PML-RAR by As in APL. After many years of controversy, it is now established that the viral transactivator Tax plays a critical role in initiating the leukemic process, because *Tax* mice transgenics develop a disease with striking ATL features.[24] We recently demonstrated that As and IFN cooperate to cure mouse ATL derived from these *Tax* transgenics (H.E.H., M. El-Sabban, H. Hasegawa, G. Zaatari, S. Saab, A. Janin, R. Mahfouz, R. Nasr, Y. Kfoury, C. Nicot, O. Hermine, W. Hall, H.d.T., and

Table 4. Response and follow-up

Patient no.	Response day 30	PFS, mo	Status at last F/U	Survival, mo
1	VGPR	15+	CR	15+
2	PR	15+	CR	15+
5	VGPR	12+	VGPR*	12+
6	PR	10+	CR	10+
7	VGPR	8+	CR	8+
8	PR	3+	CR	3+
9	PR	8+	CR	8+
10	VGPR	4+	CR	4+
11	VGPR	5+	VGPR†	5+
13	PR	2+	PR‡	2+

All patients were alive at end of study; no patient had relapse/progression.

CR indicates complete remission; PR, partial response; VGPR, very good partial response; PFS, progression-free survival; and F/U, follow-up.

*Eight percent atypical lymphocytes on peripheral blood smear.

†Six percent atypical lymphocytes on peripheral blood smear.

‡Lymphocytosis decreased from 185 000 to 6400.

Table 5. Variation of HTLV-I proviral load between initiation of treatment and day 30

Patient no.	Initial viral load, copy/μL	Viral load at day 30, copy/μL	Viral load at day 30, % from initial
1	1990	336	17
2	84	33	40
3	999	838	84
6	1081	63	6
7	196	64	33
8	3747	182	5
9	1805	65	4
Average	1415	226*	27
SD	1256	290	29

The viral copy number per microliter of blood was calculated from the cell count and the average viral copy number per cell as assessed by quantitative PCR as described in "Proviral load."

SD indicates standard deviation.

*$P < .05$.

A.B., unpublished results, May 2009). Surprisingly, this combination does not trigger an immediate growth arrest or apoptosis but rather selectively eradicates leukemia-initiating cells (LICs). This strongly suggests that LICs, rather than the bulk of the leukemia, are addicted to continuous oncogene expression. Hence, addition of As to AZT/IFN, through elimination of LICs, may result in long-term disease eradication and eventual cure. The short follow-up of our study does not allow conclusive evidence regarding overall survival. Long-term follow-up of patients treated by the combination of As/IFN/AZT will demonstrate whether this high rate of complete remission will translate in terms of disease eradication and patients cure.

In aggressive ATL, preliminary results from 2 acute ATL patients suggest that addition of As to AZT/IFN during the induction phase may result in severe tumor lysis syndrome. Hence, an attractive strategy in that setting would be induction therapy with AZT/IFN to decrease the tumor bulk followed by addition of arsenic at low tumor burden to achieve CR, in a clinical situation similar to chronic ATL patients.

In conclusion, treatment of ATL with As, IFN, and AZT is feasible and exhibits an impressive response rate with moderate toxicity in patients with chronic ATL. Although the follow-up was relatively short (8 months), none of the patients have relapsed, raising hopes that extinction of viral replication (AZT) and Tax degradation (As/IFN) may eradicate the disease. These clinical results strengthen the concept of oncogene-targeted cancer therapy.

Acknowledgment

This study was supported by funds from the research council of the Mashhad University of Medical Sciences.

Authorship

Contribution: G.K. and M.T. performed diagnostic and molecular analysis and patient follow-up and participated in study design, data analysis, and writing the paper; M.-M.K., H. Rahimi, M. Maleki, M.T.Y., and A.S. treated patients; H.E.H., E.W., M. Mahmoudi, H. Rafatpanah, and S.A.R.R. performed diagnostic and molecular analysis; H.H. analyzed data; H.d.T., and O.H. participated in study design, data analysis, and writing the paper; R.F. performed diagnostic and molecular analysis and participated in study design, data analysis, and writing the paper; and A.B. designed the study and wrote the paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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2009 113: 6528-6532
doi:10.1182/blood-2009-03-211821 originally published online May 1, 2009

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Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.