Arsenic trioxide (As$_2$O$_3$) as a maintenance therapy for adult T cell leukemia/lymphoma

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Abstract

**Background:** Adult T-cell leukemia-lymphoma (ATL) is an aggressive and mature lymphoid proliferation associated with poor prognosis. Standard of care includes chemotherapy and/or the combination of zidovudine and interferon-alpha. However, most patients experience relapse less than 6 months after diagnosis. Allogeneic stem cell transplantation is the only curative treatment, but is only feasible in a minority of cases. We previously showed in a mouse model that Arsenic trioxide (As$_2$O$_3$) targets ATL leukemia initiating cells.

**Results:** As$_2$O$_3$ consolidation was given in 9 patients with ATL (lymphoma n = 4; acute n = 2; and indolent n = 3), who were in complete (n = 4) and partial (n = 3) remission, in stable (n = 1) and in progressive (n = 1) disease. Patients received up to 8 weeks of As$_2$O$_3$ at the dose of 0.15 mg/kg/day intravenously in combination with zidovudine and interferon-alpha. One patient in progression died rapidly. Of the remaining eight patients, three with indolent ATL subtype showed overall survivals of 48, 53 and 97 months, and duration of response to As$_2$O$_3$ of 22, 25 and 73 months. The other 5 patients with aggressive ATL subtype had median OS of 36 months and a median duration of response of 10 months. Side effects were mostly hematological and cutaneous (one grade 3) and reversible with dose reduction of AZT/IFN and/or As$_2$O$_3$ discontinuation. The virus integration analysis revealed the regression of the predominant malignant clone in one patient with a chronic subtype.

**Conclusion:** These results suggest that consolidation with As$_2$O$_3$ could be an option for patients with ATL in response after induction therapy and who are not eligible for allogeneic stem cell transplantation.

**Keywords:** Arsenic trioxide, ATL
with chemotherapy [4]. The combination of zidovudine (AZT) and interferon-alpha (IFN) may induce long term response in indolent and a small proportion of acute type [5]. Allogeneic stem cell transplantation is the only curative treatment in responding patients but its use is limited to a minority of patients [6]. The anti-CCR4 antibody mogamulizumab showed interesting results in relapsed patients, but a randomized trial in newly diagnosed ATL showed no benefit of its addition to chemotherapy in term of progression-free survival (PFS) and overall survival (OS), despite an increase response rate [7, 8].

In prior ex vivo studies, we showed that arsenic trioxide synergizes with IFN to selectively induce ATL cell apoptosis through the degradation by the proteasome of the oncoprotein Tax [9, 10]. This combination showed some signals of efficacy but a low rate of response in relapsed or refractory ATL patients [11]. A pilot study reported 100% response rate including 70% complete remission in newly diagnosed chronic ATL patients treated with the combination of arsenic, IFN and AZT [12]. We recently showed that this combination cures ATL developed in Tax-transgenic mice through selective targeting of leukemia-initiating cell (LIC) activity [13], suggesting that the best use of arsenic and IFN may be as a consolidation or maintenance therapy. Thus, we performed a retrospective study analyzing the outcome of patients treated with the combination of arsenic trioxide and AZT/IFN as consolidation after induction therapy with chemotherapy or antiviral therapy.

Results and discussion

Response criteria and overall survival
Response evaluation was performed according to consensus published criteria [15]. Overall survival (OS) was defined as the period between initiation of treatment and the date of death or last follow-up.

HTLV-i proviral load and clonality assay
DNA extraction was done using Invitrogen kit (QiAmp or blood and cell's DNA extraction kit) and performed according to manufacturer’s instructions. HTLV DNA was quantified by real-time PCR in the pX region as previously described [16]. High-throughput sequencing for the genome-wide identification and quantification of proviral integration sites was performed as previously described [17].

Patients and methods

Patients and diagnosis criteria
This retrospective study included nine newly diagnosed, previously untreated ATL patients. Patients’ characteristics are described in Table 1. This study was approved by the local ethic committee (CNIL: number 1692254 and CPP IRB registration number 000001072). TP53 status was evaluated in seven patients by a functional assay as previously described [14].

Treatment schedule

After induction with chemotherapy (mainly anthracyclin-based regimen including LSG and CHOP like regimen) and/or AZT/IFN, patients received up to 8 weeks of arsenic at the dose of 0.15 mg/kg/day intravenously (Table 1) in combination with oral zidovudine (AZT; 600 mg/day) and subcutaneous recombinant IFN (Roferon, ROCHE® 3 millions/day) or pegylated IFN (PEG-IFN Virafeeron MSD® 1.5 µg/kg/week). During the consolidation phase, patients could receive only IFN/AZT combination between the arsenic infusions.

In case of hematological toxicity, growth factors such as GCSF or EPO were used, or the antiviral therapy dose was reduced as per physician choice.
## Table 1 Patient’s characteristics

| Patient | Sex | Age at diagnosis | Clinical subtype | p53 activity | First line treatment | Interval between induction therapy and As$_2$O$_3$ consolidation (months) | Disease status at time/after of As$_2$O$_3$ | Treatment duration (weeks) | OS since diagnosis (months) | Death OS since arsenic (months) | Duration of response since As$_2$O$_3$ (months) | Progression |
|---------|-----|------------------|------------------|--------------|----------------------|-----------------------------|-----------------------------|--------------------------|-----------------------------|----------------------------------|------------------------------------------|-------------|
| ATL 6   | M   | 51.6             | Chronic          | F            | AZT-IFN-VP16         | 24.4                        | SD/SD                      | 4                        | 53                          | Yes                              | 28                        | 22          | Yes         |
| ATL 9   | M   | 50.6             | Chronic          | F            | CHOP like            | 20.1                        | CR/CR                      | 6                        | 48                          | Yes                              | 28                        | 25          | Yes         |
| ATL 11  | M   | 27.7             | Chronic          | F            | LSG 15 + AZT-IFN     | 13.2                        | VGR/CR                     | 6                        | 97                          | Yes                              | 83                        | 73          | Yes         |
| ATL 7   | F   | 59.8             | Acute            | F            | CHOP like            | 6.2                         | PD/PD                      | 4                        | 8                           | Yes                              | 1                         | NA          | Yes         |
| ATL 14  | F   | 35.1             | Acute            | NF           | Alemtuzumab-CHOP     | 2.2                         | CR/CR                      | 4                        | 12                          | Yes                              | 10                        | 5           | Yes         |
| ATL 43  | F   | 66.3             | Lymphoma         | F            | CHOP like            | 6.3                         | CR/CR                      | 8                        | 19                          | Yes                              | 12                        | 5           | Yes         |
| ATL 44  | F   | 54.8             | Lymphoma         | F            | CHOP like            | 3.8                         | VGR/CR                     | 8                        | 36                          | Yes                              | 32                        | 29          | Yes         |
| ATL 64  | M   | 63.1             | Lymphoma         | ND           | CHOP/DHAOx           | 13                          | CR/CR                      | 8                        | 65                          | No                               | 51                        | 51          | No          |
| ATL 65  | M   | 54.4             | Lymphoma         | ND           | CHOP                | 4                           | PR/PR                      | 16                       | 41                          | Yes                              | 36                        | 10          | Yes         |

M, male; F, female; CHOP, cyclophosphamide, doxorubicine, oncovin, prednisone; DHAOx, dexamethasone, aracynite high dose, oxaliplatine; CR, complete response; PR, partial response; VGPR, very good partial response; SD, stable disease; PD, progressive disease

F, functional; NF, non functional (this patient was found to have a p.V274A variant of TP53)

* Clone switch
before relapsing with a new tumoral clone as described below. The three indolent ATLs had an OS of 48, 53 and 97 months and duration of response to As$_2$O$_3$ of 22, 25 and 73 months. The six aggressive ATLs had a median OS of 27.5 months (range 8–65 months) and a median duration of response to As$_2$O$_3$ of 10 months (5–55 months).

Longitudinal analysis of the HTLV-I proviral load (PvL) revealed no difference during treatment except in one patient (ATL 14) with acute ATL, who showed a dramatic decrease of proviral load after chemotherapy. Viral integration clonality analysis was assessed in 2 patients. One patient (ATL 11) who had a normal lymphocyte count but with an excess of phenotypically abnormal T-cells and one dominant clone representing 92% of infected cells exhibited 1 month after As$_2$O$_3$ treatment a regression of the predominant malignant clone and restoration of an oligoclonal architecture, both in proportion and in absolute count, while the proviral load remained stable. Interestingly, this patient remained in remission 86 months after initiation of arsenic and 97 months from diagnosis but finally relapsed with a different clone, as demonstrated by the finding of a different TCR rearrangement as previously published [18]. In contrast, another patient (ATL 9), with a chronic subtype initially treated with chemotherapy had a normal lymphocyte count with an excess of abnormal phenotype T cells with one dominant clone that represented 91% of infected cells, which remained unchanged after completion of As$_2$O$_3$ treatment. This patient progressed to an acute subtype 2 years later and died (Fig. 1).

Taken together, as predicted by our mice model and our previous clinical study with the triple induction with As$_2$O$_3$/AZT/IFN in chronic ATL, this retrospective clinical analysis shows that As$_2$O$_3$ consolidation in combination with low-dose AZT/IFN maintenance may enhance

![Figure 1](image-url)
long-term disease control also in ATL lymphoma with moderate side effects [12, 13]. In addition, although based on a small number, our data suggest that sequential analysis of proviral load and architecture of the virus clonality could serve as a good surrogate marker of long-term response rather than the viral load and lymphocyte count.

However, despite prolonged responses in some cases, most patients ultimately relapsed, suggesting that one cycle of arsenic consolidation may not be sufficient. Future trials are warranted to investigate whether or not multiple cycles of arsenic consolidation are needed in ATL to prevent relapses.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12977-020-0513-y.

Additional file 1: Table S1. Toxicity.

Abbreviations
ATL: Adult T-cell leukemia-lymphoma; HTLV-1: Human T cell leukemia virus type 1; AZT: Zidovudine; INF: Interferon-alpha; PFS: Progression free survival; OS: Overall survival; LIC: Leukemic initiating cells; WT: Wild type; PEG-INF: Pegylated interferon; TCR: T-cell receptor.

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Authors’ contributions
AM, AB, HdT, FS and OH designed research, AM, LC, AW, VA, VAF, HDt, CB, OH, FS performed research and analyzed data, AM, RD, MC, DS, LF, OH, FS treated patients and provided data. AM, AB, OH and FS wrote the first draft of the paper. All authors read and approved the final manuscript.

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Availability of data and materials
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Ethics approval and consent to participate
The local ethic committee approved this study (CNIL: number 1692254 and CPP IRB registration number 000001072) and all surviving patients gave their consent.

Consent for publication
All authors contributed to paper correction and editing.

Competing interests
The authors declare no conflict of interests related to this work.

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