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ORIGINAL PAPER

A phase II study of arsenic trioxide in patients with relapsed or refractory malignant lymphoma

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Abstract Limited data have been reported regarding the use of arsenic trioxide (ATO) in the treatment of patients with relapsed or refractory malignant lymphoma; therefore, the present phase II study evaluated the efficacy and toxicity of ATO in such patients. A total of 35 patients were treated with ATO (0.25 mg/kg) infused for 1 h daily, 5 days a week, for a 6-week cycle. Patients were evaluated for the efficacy and toxicity of this regimen. The primary outcome evaluated was the overall response rate (ORR), including the complete and partial response rates. The secondary outcomes evaluated were the overall survival (OS), progression-free survival (PFS), and toxicity. Tumor response data were obtained from all 35 enrolled patients. The ORR was 43 %, including complete responses in four patients (11 %) and partial responses in 11 patients (31 %). The median duration of response was 16 weeks (range 11–23 weeks). The median OS was 79 weeks (range 14–171 weeks), and the median PFS was 55 weeks (range 14–135 weeks). Grade I or II hematological toxicities were the most commonly reported adverse events. The results of this study appear promising for the treatment of relapsed or refractory malignant lymphoma, with well-tolerated ATO toxicity.

Keywords Arsenic trioxide · Lymphoma · Non-Hodgkin lymphoma · Hodgkin lymphoma

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Introduction

Patients with relapsed or refractory malignant non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HD), who are unsuitable for high-dose chemotherapy or have relapsed after such therapy, have a poor prognosis with currently available salvage chemotherapy regimens [1, 2]. Therefore, new approaches are required to improve the prognosis of these patients.

Arsenic trioxide (ATO) has shown significant efficacy in the treatment of acute promyelocytic leukemia [3–7], multiple myeloma [8–13], and myelodysplastic syndromes [14–17]. Several preclinical studies have suggested efficacy of ATO in the treatment of relapsed or refractory lymphoma [18–21]. The mechanism of action of ATO is unclear, and it may differ in different tumor types. In acute promyelocytic leukemia, ATO at low doses appears to induce differentiation of leukemic blasts [22]; in other malignancies, ATO at high doses appears to cause cell death by inducing apoptosis [22, 23]. ATO-induced apoptosis is a H_2O_2-mediated process, and the sensitivity of tumor cells to ATO is correlated with both intracellular levels of H_2O_2 and the activity of enzymes involved in H_2O_2 metabolism, particularly catalase and glutathione peroxidase [24, 25].

On the basis of data from preclinical studies of elapsed or refractory lymphoma, we hypothesized that ATO would be an effective treatment intervention. Herein, we report a phase II study of ATO in patients with relapsed or refractory malignant lymphoma.

Patients and methods

Between June 2008 and May 2011, consecutive patients detected with refractory or relapsed primary malignant

lymphoma at our hospital were enrolled into the study, if they satisfied all the inclusion criteria. Patients' aged ≥18 years with biopsy-confirmed relapsed and refractory classical NHL or HD for which further conventional chemotherapy did not show any potential benefit were recruited into the study. Patients were included only if they also had an absolute neutrophil count >1000/μL, platelet count $>1.0 \times 10^5$/μL, creatinine level ≤1.5 mg/dL (or a creatinine clearance rate >60 mL/min), and bilirubin level <2 mg/mL and seronegativity for hepatitis B, hepatitis C, and human immunodeficiency virus (HIV). Patients were excluded if they were pregnant or breastfeeding, had a history of seizures or active central nervous system disease involvement, active second malignancy or active and uncontrolled infection (including HIV infection), or history of ventricular dysrhythmias, significantly underlying cardiac dysfunction.

This study was designed as a phase II single-center trial of ATO in patients with relapsed or refractory lymphoma. It was conducted at the Department of Hematology, Fourth Affiliated Hospital of Harbin Medical University, Harbin, China. The protocol was approved by the hospital's Medical Ethical Committee: All study patients signed an informed consent form prior to participation in the study.

Patients were treated with ATO (0.25 mg/kg) infused for 1 h daily, 5 days a week for a 6-week treatment cycle. Cycles were repeated until there was evidence of a complete response (CR), a partial response (PR), or stable disease (SD) with two consecutive cycles; progressive disease (PD); or no evidence of a response, unacceptable toxicity, or a patient/physician preference for discontinuation. Patients achieving only SD at reassessment were considered ineligible for continued therapy.

Tumor response was determined according to the 2007 International Harmonization Project criteria for malignant lymphoma by observing the results on computed tomography and [^{18}F] fluorodeoxyglucose–positron emission tomography scans [26]. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 3.0).

The primary outcome evaluated was overall response rate (ORR). The secondary outcomes evaluated were overall survival (OS), progression-free survival (PFS), and toxicity. Treatment failure was defined as SD, PD, or death from any cause. The PFS was recorded from the start of treatment until evidence of progression in patients with relapsed or refractory malignant lymphoma, who achieved PD or SD. The OS was recorded from the beginning of treatment until death or the last follow-up assessment. The duration of response was recorded from the commencement of treatment until evidence of disease progression was seen.

The Simon two-stage design was used to determine the appropriate sample size [27]. Assuming a clinically meaningful ORR of 30 %, an unacceptable response of <10 %, and type I and type II errors of 10 %, three responses among the first 18 enrolled patients were required to proceed to stage two. In stage two, seven responses of 35 patients were required to declare ATO an effective treatment in relapsed or refractory malignant lymphoma. The SPSS software package (version 17.0) was used for statistical analysis. The PFS and OS were estimated by using Kaplan–Meier curves.

Results

Demographic characteristics at the time of enrollment in the study are summarized in Table 1. Patients ranged in age from 31 to 72 years, with a median age of 53 years. In total, 35 patients were evaluated for tumor response after each of the six treatment cycles. Fourteen of the 35 patients had disease that had relapsed following previous chemotherapy regimens; after ATO treatment, one patient achieved CR, five patients showed PR, five patients showed SD, and four patients showed PD. Twenty-one of the 35 patients had disease refractory to previous chemotherapy regimens; after ATO treatment, three patients achieved CR, six patients showed PR, six patients showed SD, and five patients showed PD.

Tumor response data were obtained from all 35 enrolled patients. The ORR was 43 %, including CR in four patients (11 %) and PR in 11 patients (31 %). A total of 66 % of patients achieved tumor reduction (Fig. 1). Considering all

Table 1 Patients demographic characteristics

Patients	35
Sex	
Males	19
Females	16
Age, years	
Median	53
Range	31–72
No. of previous chemotherapy	
Median	3
Range	1–9
Disease status at enrollment	
Relapsed	14
Refractory	21
Histology	
Burkitt's	3
Follicular	7
Diffuse large B cell	5
Mantle cell	5
Nodular sclerosis	8
Mixed cellularity	7

patients, the median OS was 79 weeks (range 14–171 weeks) (Fig. 2), the median duration of response was 16 weeks (range 11–23 weeks), and the median PFS was 55 weeks (range 14–135 weeks) (Fig. 3).

Observed adverse events are listed in Table 2. The most common hematological toxicities were anemia, thrombocytopenia, leucopenia, neutropenia, and hematological-related toxicity of neutropenic fever. The most common non-hematological toxicities were fatigue, dyspnea, dizziness, and pleural effusions. All these toxicities were assessed as being acceptable (Table 2); most of them were classified as grades I, II, or III.

Discussion

Effective salvage regimens for relapsed or refractory malignant lymphoma are clearly needed. In this study, we evaluated the efficacy and toxicity of ATO, which is not usually employed in first-line treatment regimens for malignant lymphoma. However, ATO has already demonstrated a broad range of efficacy in the treatment of acute promyelocytic leukemia [3–7], multiple myeloma [8–13], and myelodysplastic syndromes [14–17].

ATO has been reported to be effective, most importantly for the treatment of acute promyelocytic leukemia [5, 28–30]. Two small-scale trials of ATO in patients with relapsed acute promyelocytic leukemia demonstrated CR rates of 92 and 100 % [28, 29]. In a recent publication examining the role of ATO in the treatment of acute promyelocytic leukemia, 2-year event-free survival rates were 97 % in the ATO-treated group and 86 % in the standard chemotherapy group [5]. A 5-year follow-up assessment of newly diagnosed patients with acute promyelocytic leukemia who received single-agent ATO treatment reported high rates of 5-year disease-free survival and OS [66.7 % ± 4.0 % (mean ± standard error) and 64.4 % ± 4.0 %, respectively] [30].

Modest efficacy of ATO has been reported for the treatment of multiple myeloma and myelodysplastic syndromes. A recent study reported that patients in the treatment group

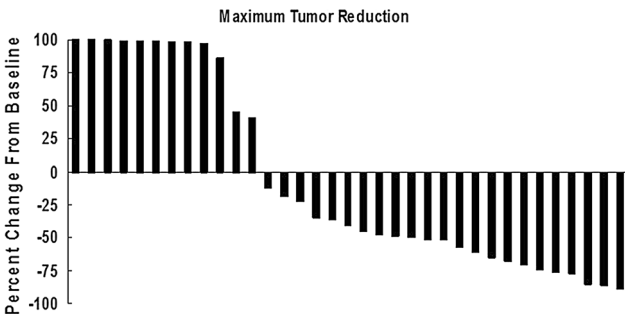

Fig. 1 Maximum tumor reduction

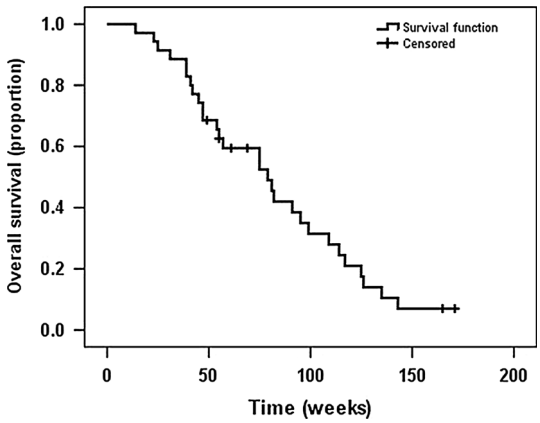

Fig. 2 Overall survival

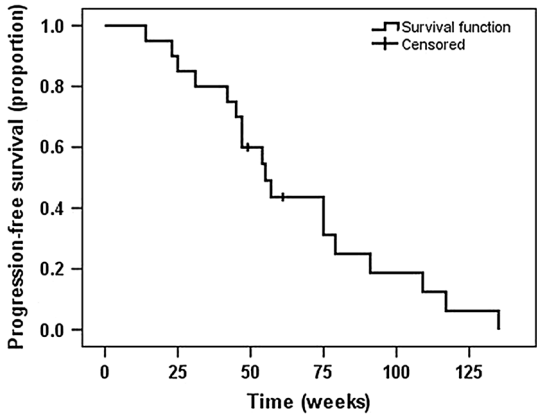

Fig. 3 Progression-free survival

achieved hematological improvement (68.2 vs. 27.3 % in the control group); PFS was longer in the treatment group than in the control group (26 vs. 10 months), and the OS was also longer in the treatment group than in the control group (36 vs. 16 months) [14]. Two other clinical trials demonstrated that ATO had encouraging efficacy in patients with myelodysplastic syndromes; one study showed that hematological improvement was noted in 34 % of low-risk patients and in 6 % of high-risk patients [31], while the other showed hematological response rates of 26 and 17 % in low-risk and high-risk cohorts, respectively [32].

Preclinical studies have suggested ATO to be effective in the treatment of relapsed or refractory lymphoma [33–35]. One study reported that ATO activated glycogen synthase kinase-3beta (via tyrosine-216 phosphorylation) and Ikappa-B kinases alpha/beta (via serine-176/180 phosphorylation); both the activated kinases phosphorylated cyclin D1 at threonine-286, leading to its poly-ubiquitination and degradation by the proteasome [33]. Two other studies found that ATO could substantially inhibit cell proliferation and induce apoptosis in B cell lymphoma cell lines and primary cultures of lymphoma cells [34, 35].

Table 2 Summary of adverse events

Adverse events	Grade (%)				Total (%)
	1	2	3	4	
Anemia	24	14	7	2	47
Thrombocytopenia	22	12	5	2	41
Leukopenia	20	12	5	1	38
Neutropenia	18	10	4	3	35
Neutropenic fever	16	14	4	–	34
Infection	12	4	2	–	18
Hyperglycemia	6	4	1	–	11
Anorexia	12	4	2	–	18
Stomatitis	6	4	4	–	14
Fatigue	18	10	5	1	34
Pain	8	8	2	–	18
Dizziness	10	8	3	–	21
Dyspnea	14	6	2	–	22
Hypoxia	8	6	2	–	16
Pleural effusions	12	6	3	–	21
Edema	10	6	3	–	19
Heart failure	3	1	1	–	5
Cardiac ischemia/ infarct	4	–	2	–	6

Overall, the ATO treatment regimen was well tolerated in patients with relapsed or refractory malignant lymphoma. Although hematological toxicity was common, no serious adverse events were recorded, and other non-hematological toxicities were assessed as being acceptable.

Our results demonstrate that ATO has encouraging efficacy for the treatment of patients with relapsed or refractory malignant lymphoma; future studies will further define the therapeutic role of ATO in these patients.

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Conflict of interest The authors declare that they have no competing interests.

References

1. El Helw LM, Lorigan PC, Robinson MH, Coleman RE, Hancock BW. VEDex (vincristine, epirubicin, dexamethasone): an effective and well tolerated palliative chemotherapy regimen for non-Hodgkin's lymphoma. Int J Oncol. 2000;16:777–82.
2. Shamash J, Lee SM, Radford JA, et al. Patterns of relapse and subsequent management following high dose chemotherapy with autologus haematopoietic supporting relapsed or refractory Hodgkin's lymphoma: a two centre study. Ann Oncol. 2000; 11(6):715–9.
3. Zhu HH, Wu DP, Jin J, et al. Oral tetra-arsenic tetra-sulfide formula versus intravenous arsenic trioxide as first-line treatment ofacute promyelocytic leukemia: a multicenter randomized controlled trial. J Clin Oncol. 2013;31(33):4215–21.
4. Huang BT, Zeng QC, Gurung A, Zhao WH, Xiao Z, Li BS. The early addition of arsenic trioxide versus high-dose arabinoside is more effective and safe as consolidation chemotherapy for risk-tailored patients with acute promyelocytic leukemia: multicenter experience. Med Oncol. 2012;29(3):2088–94.
5. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013;369(2):111–21.
6. Yanada M, Tsuzuki M, Fujita H, et al. Japan AdultLeukemia Study Group. Phase 2 study of arsenic trioxide followed by autologous hematopoietic cell transplantation for relapsed acute promyelocytic leukemia. Blood. 2013;121(16):3095–102.
7. Liu YJ, Wu DP, Liang JY, Qiu HY, Jin ZM, Tang XW, Fu CC, Ma X. Long-term survey of outcome in acute promyelocytic leukemia: a single center experience in 340 patients. Med Oncol. 2011;28(Suppl 1):S513–21.
8. Hussein MA. Arsenic trioxide: a new immunomodulatory agent in the management of multiple myeloma. Med Oncol. 2001;18(4):239–42.
9. Abou-Jawde RM, Reed J, Kelly M, et al. Efficacy and safety results with the combination therapy of arsenic trioxide, dexamethasone, and ascorbic acid in multiple myeloma patients: a phase 2 trial. Med Oncol. 2006;23(2):263–72.
10. Hofmeister CC, Jansak B, Denlinger N, Kraut EH, Benson DM, Farag SS. Phase II clinical trial of arsenic trioxide with liposomal doxorubicin, vincristine, and dexamethasone in newly diagnosed multiple myeloma. Leuk Res. 2008;32(8):1295–8.
11. Berenson JR, Matous J, Swift RA, Mapes R, Morrison B, Yeh HS. A phase I/II study of arsenic trioxide/bortezomib/ascorbic acid combination therapy for the treatment of relapsed or refractory multiple myeloma. Clin Cancer Res. 2007;13(6):1762–8.
12. Wu KL, Beksac M, van Droogenbroeck J, Amadori S, Zweegman S, Sonneveld P. Phase II multicenter study of arsenic trioxide, ascorbic acid and dexamethasone in patients with relapsed or refractory multiple myeloma. Haematologica. 2006;91(12):1722–3.
13. Berenson JR, Boccia R, Siegel D, et al. Efficacy and safety of melphalan, arsenic trioxide and ascorbic acid combination therapy in patients with relapsed or refractory multiple myeloma: a prospective, multicentre, phase II, single-arm study. Br J Haematol. 2006;135(2):174–83.
14. Wei W, Zhou F, Zhang Y, Guo L, Shi H, Hou J. A combination of thalidomide and arsenic trioxide is effective and well tolerated in patients with myelodysplastic syndromes. Leuk Res. 2012; 36(6):715–9.
15. Welch JS, Klco JM, Gao F, et al. Combination decitabine, arsenic trioxide, and ascorbic acid for the treatment of myelodysplastic syndrome and acute myeloid leukemia: a phase I study. Am J Hematol. 2011;86(9):796–800.
16. Sekeres MA, Maciejewski JP, Erba HP, et al. A Phase 2 study of combination therapy with arsenic trioxide and gemtuzumab ozogamicin in patients with myelodysplastic syndromes or secondary acute myeloid leukemia. Cancer. 2011;117(6):1253–61.
17. Roboz GJ, Ritchie EK, Curcio T, et al. Arsenic trioxide and low-dose cytarabine for patients with intermediate-2 and high-risk myelodysplastic syndrome. Leuk Res. 2011;35(4):522–5.
18. Raut LS. Chakrabarti PP. Management of relapsed-refractory diffuse large B cell lymphoma. South Asian J Cancer. 2014;3(1):66–70.
19. Ahn RW, Barrett SL, Raja MR, et al. Nano-encapsulation of arsenic trioxide enhances efficacy against murine lymphoma model while minimizing its impact on ovarian reserve in vitro and in vivo. PLoS ONE. 2013;8(3):e58491.
20. Wang R, Liu C, Xia L, et al. Ethacrynic acid and a derivative enhance apoptosis in arsenic trioxide-treated myeloid leukemia and lymphoma cells: the role of glutathione S-transferase p 1–1. Clin Cancer Res. 2012;18(24):6690–701.

21. Jung HJ, Chen Z, McCarty N. Synergistic anticancer effects of arsenic trioxide with bortezomib in mantle cell lymphoma. Am J Hematol. 2012;87(12):1057–64.
22. Chen GQ, Shi XG, Tang W, et al. Use of arsenic trioxide (As_2O_3) in the treatment of acute promylecytic leukemia (APL): As_2O_3 exerts dose-dependent dual effects on APL cells. Blood. 1997;89: 3345–53.
23. Murgo AJ. Clinical trials of arsenic trioxide in hematologic and solid tumors: overview of the National Cancer Institute Cooperative Research and Development studies. Oncologist. 2001;6(Suppl 2):22–8.
24. Jing Y, Dai J, Chalmers-Redman R, Tatton WG, Waxman S. Arsenic trioxide selectively induces acute promyelocytic leukemia cell apoptosis via a hydrogen peroxide-dependent pathway. Blood. 1999;94:2102–11.
25. Dai J, Weinberg RS, Waxman S, Jing Y. Malignant cells can be sensitized to undergo growth inhibition and apoptosis by arsenic trioxide through modulation of the glutathione redox systems. Blood. 1999;93:268–77.
26. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579–86.
27. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10(1):1–10.
28. Soignet SL, Maslak P, Wang ZG, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med. 1998;339:1341–8.
29. Lazo G, Kantarjian H, Estey E, Thomas D, O'Brien S, Cortes J. Use of arsenic trioxide (As2O3) in the treatment of patients with acute promyelocytic leukemia: the M.D. Anderson experience. Cancer. 2003;97:2218–24.
30. Ghavamzadeh A, Alimoghaddam K, Rostami S, Ghaffari SH, et al. Phase II study of single-agent arsenic trioxide for the frontline therapy of acute promyelocytic leukemia. J Clin Oncol. 2011;29(20):2753–7.
31. Schiller GJ, Slack J, Hainsworth JD, et al. Phase II multicenter study of arsenic trioxide in patients with myelodysplastic syndromes. J Clin Oncol. 2006;24:2456–64.
32. Vey N, Bosly A, Guerci A, et al. Arsenic trioxide in patients with myelodysplastic syndromes: a phase II multicenter study. J Clin Oncol. 2006;24:2465–71.
33. Lo RK, Kwong YL. Arsenic trioxide suppressed mantle cell lymphoma by downregulation of cyclin D1. Ann Hematol. 2014;93(2):255–65.
34. Nie L, Zhang Y, Zhang JJ, Wang SZ. Combinational effects of bcl-2 antisense oligodeoxynucleotides with arsenic trioxide on malignant lymphoma cell lines. China Oncol. 2002;12(3): 197–200.
35. Nie L. Apoptosis induced in malignant lymphoma cells by arsenic trioxide. Ji Nan University, Master's Thesis. 2000; 1–42.