Cancer Letters 277 (2009) 212–217

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Tetra-arsenic oxide (Tetras) enhances radiation sensitivity of solid tumors by anti-vascular effect

Sae-Gwang Park [a,*], Jeong-Joo Jung [a], Hae Jeong Won [a], Mi Seon Kang [b], Su-Kil Seo [a], Il-Whan Choi [a], Choong Ki Eun [c], Ki Jung Ahn [d], Cheol Woo Park [d], Soo-Woong Lee [a], Young S. Lew [e], Ill-Ju Bae [e], In-Hak Choi [a]

[a] Department of Microbiology, Busanpaik Hospital, Inje University College of Medicine, 633-165 Gaegum-Dong, Jin-Gu, Busan 614-735, Republic of Korea
[b] Department of Pathology, Busanpaik Hospital, Inje University College of Medicine, 633-165 Gaegum-Dong, Jin-Gu, Busan 614-735, Republic of Korea
[c] Department of Radiology, Busanpaik Hospital, Inje University College of Medicine, 633-165 Gaegum-Dong, Jin-Gu, Busan 614-735, Republic of Korea
[d] Department of Radiation Oncology, Busanpaik Hospital Inje University College of Medicine, 633-165 Gaegum-Dong, Jin-Gu, Busan 614-735, Republic of Korea
[e] Chunjisan Co. Ltd., 2804 Bangbae-dong, Seocho-gu Seoul 137-853, Republic of Korea

ARTICLE INFO

Article history:
Received 2 October 2008
Received in revised form 5 December 2008
Accepted 8 December 2008

Keywords:
Caner therapy
Tetra-arsenic oxide
Radiation therapy enhancement

ABSTRACT

Tetras (tetra-arsenic oxide, As_4O_6) is a derivative of arsenic used in Korean traditional medicine for the treatment of cancer, but its mechanism remains largely undefined. Recently, a similar arsenic derivative, diarsenic trioxide (As_2O_3, ATO), has been shown to mediate anti-tumor activity, therefore reigniting interest in the therapeutic effect of arsenic compounds. Here we report that Tetras can effectively mediate an anti-vascular effect on tumors, leading to delay in tumor growth and increased survival. Our study demonstrates for the first time the potential use of Tetras as a radiation therapy enhancement agent for solid tumors. These findings reveal an unappreciated role of Tetras in cancer therapy and its potential application to radiotherapy in achieving local tumor control.

1. Introduction

The efficacy of arsenic compounds as potent anti-cancer agents has been well documented in medical history. However acute toxicities and oncogenic effects after prolonged exposure limited its therapeutic application in cancers [1]. Then for the better part of the 20th century the use of arsenic compounds became largely abandoned with the arrival of more reliable antibiotics and chemotherapeutic agents. However, recent success acheiving remission in 85% of adults with refractory acute promyelocytic leukemia (APL) by diarsenic trioxide (ATO, As_2O_3) has revived the idea of using arsenic compounds in cancer therapy and has provided new insights into the pathogenesis and malignancies of cancer [2–4]. ATO has been shown to also mediate anti-tumor activity in APL by the induction of cellular differentiation, tumor cell apoptosis, degradation of specific APL transcripts, inhibition of tumor cell growth, and modulation of redox balance and/or mitochondrial membrane potential [5,6]. Furthermore, on well-established murine solid tumors, such as fibrosarcoma, a high dose of ATO has been shown to abrogate vascular networks and cause blood flow to tumors to shut down, subsequently causing necrosis [7,8]. ATO has also been shown to increase the anti-tumor effects of hyperthermia [9] and radiation *in vivo* [7,10–12]. However, the therapeutic ratio could be further improved if the toxicity of intravenously administered ATO was reduced. Adverse reactions to arsenic containing compounds include elevated serum transaminases, nausea, vomiting, abdominal pain, constipation, electrolyte imbalance, hyperglycemia, dermatitis, and headache [13].

* Corresponding author. Fax: +82 51 891 6004.
E-mail address: micpsg@inje.ac.kr (S.-G. Park).

0304-3835/$ - see front matter Crown Copyright © 2009 Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.canlet.2008.12.012

Tetra-arsenic oxide (Tetras, As_4O_6; 2,4,6,8,9,10-Hexanoxa-1,3,5,7-tetraarsatricyclo[3.3.1.1^{3,7}]decane) (Fig. 1A) is another well documented arsenic compound derivative that has been used as an empirical anti-cancer agent in Korean alternative medicine. A recent report has shown that Tetras shares similar anti-tumor effects as ATO in inhibiting tumor cell proliferation, inducing apoptosis of tumor cells, and inhibiting angiogenesis by arresting cells in the G1 or G2/M phases of the cell cycle [14].

A notable effect of ATO on solid tumors is the synergy with fractionated radiation in abrogating tumor vasculature [7,8,11,12,15]. Controlling primary tumor growth can lead to a better prognosis and preclude the development of metastases which is the primary cause of mortality of many cancer patients. Targeting the primary tumor with radiotherapy as part of a standard treatment has been shown to reduce the local tumor burden, but often fails to elicit complete regression. Established tumors form physical and immunological barriers that hinder targeted destruction by radiotherapy alone. In this study, we show that when local radiation was combined with the administration of Tetras, tumor growth was arrested for 6–7 weeks *in vivo* in not only murine fibrosarcoma, but also in human squamous tumors. This study is the first to report the effects of Tetras on shutting down vascular supply to solid tumors and its potential use as a radiation therapy enhancement agent.

2. Materials and methods

2.1. Mice and tumor cell lines

Balb/c and Balb/c nu/nu female mice, 6–8 weeks of age and weighing 20–25 grams were obtained from Orient bio (Taejun, Korea). WEHI164 tumor cell lines (derived from Meth-A induced fibrosarcoma) and FaDu tumor cell lines (originated from a human nasopharyngeal squamous cancer) were purchased from KCCB (Seoul, Korea). WEHI164 cells (5×10^5) or FaDu cells (1×10^6) in 50 ul MEM were inoculated into the hind leg subcutaneously in either the Balb/c or Balb/c nu/nu mice. Tumor growth was monitored. All animal procedures and care were performed using guidelines approved by the Animal Ethics Committee of the College of Medicine at Inje University.

2.2. Tetra-arsenic oxide (As_4O_6, Tetras)

Tetras supplied from Chunjisan (Seoul, Korea) was dissolved in H_2O by continuous stirring. Tetras solution was kept at 4 °C as a stock solution. Dilution was made with phosphate buffered saline to a final concentration of 0.5 mg/ml. Dextrose was added to a final concentration of 5% to minimize acute arsenic toxicity [16].

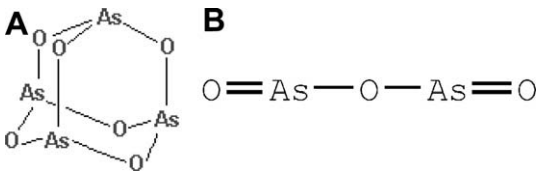

Fig. 1. Structures of arsenic chemicals. (A) Tetra-arsenic oxide (Tetras). (B) Diarsenic trioxide (ATO).

2.3. Radiation and Tetras treatment

Radiation was delivered to tumors using a cobalt-60 unit (Theratron 780; AECL, Kanata, Ontario, Canada) with a secondary collimator of 2-inch-thick cerrobend. A 2 cm-thick tissue-equivalent bolus was used to bring the maximal radiation dose onto the surface of the target tissue. Tetras (8 mg/kg) was administered i.p. 1 h after to each radiation exposure.

2.4. Tumor growth

Tumor volume was assessed two or three times a week. Tumors were measured with a caliper, and tumor volumes were calculated using the formula $a \times b \times h/2$, where a, b, and h are the minor and major dimensions and height from normal skin area, respectively.

2.5. Histopathology

Animals were treated with 8 mg/kg Tetras. At selected time points tumors were excised and fixed in 10% neutral formalin and embedded in paraffin. Paraffin-embedded tissues were sectioned for routine staining with hematoxylin and eosin.

2.6. Confocal microscopy

To examine the effect of Tetras on the tumor vasculature, fluorescein isothiocyanate-labeled dextran (dextran-FITC) (2×10^6 MW, Sigma) were used as previously reported [7]. Briefly, 100 ul of PBS containing 1 mg dextran-FITC was administered intravenously into anesthetized mice with 200 ul of anesthetics (10 mg/ml ketamine and 1 mg/ml xylazine). After 3 min, the tumor tissues, kidney, and normal skins were excised. Resected tissues were embedded in Tissue-Tek (Sakura Finetek, Netherlands) and snap frozen in liquid nitrogen. Fifty micrometer thick cryostat sections were cut and mounted on superfrost plus slides. Tissue-sections were post-fixed for 30 min at room temperature. After drying, tumor cells were stained with propidium iodide (PI) and the slides were mounted in fluoromount-G (Southern Biotechnology Associates Inc., Birmingham, AL), and the fluorescence was visualized using a Zeiss LSM 510 laser scanning confocal device (Carl Zeiss, Germany).

3. Results

3.1. Administration of Tetras to tumor bearing mice can retard tumor growth and prolong survival

To evaluate the direct effect of Tetras on tumor growth, 8 mg/kg of Tetras was administered intra-peritoneally (i.p.) in the Meth-A tumor bearing mice. Repeat administration (R TTO) or single administration (S TTO) of Tetras delayed the tumor growth rate when compared to that of 5% dextrose treated control group ($P < 0.05$) (Fig. 2A). However, the

median survival time of the single administration of Tetras (S TTO) group was comparable to that of the control group (Fig. 2B), while repeat administration of Tetras (R TTO) extended the median survival of mice by more than 10 days when compared to the controls (Fig. 2B).

3.2. Increased incidence of necrosis observed in Tetras treated tumor

Meth-A tumor bearing mice were sacrificed for pathological analysis at indicated times after administration of 8 mg/kg Tetras. Tetras treated tumor revealed varying degrees of tumor cell necrosis (Fig. 3). Extensive necrotic death could be observed in the tumor tissue obtained from the mice sacrificed at 24 and 48 h after Tetras injection (Fig. 3). To test whether evidence of tumor vascular changes are induced by with Tetras, we injected dextran-FITC i.v. 3 min prior to removing the tumor mass from mice (Fig. 4). When vasculature is intact, dextran-FITC can be visualized as distinct clusters, however disruption in vascular permeability allows broad diffusion of dextran-FITC. While dextran-FITC was distinctly separated from the PI stained tumor cells in 5% dextrose treated control groups, FITC was dispersed throughout the tumor tissues in Tetras treated groups. However, this dispersion of FITC within the tumor tissue was short-lived as separation between the dextran-FITC and the PI stained tumor cells became evident at 72 h post Tetras injection. This reversion was likely attributed to the intact tumor vasculature that was left undisrupted even after administering Tetras. To test effects on normal tissues of tetras-induced vascular damage, we remove kidney and non-tumor thigh skins. In the normal tissues, we find FITC were well located in vasculatures (Fig. 4D).

3.3. Tetras treatment can act synergistically with local radiation to inhibit tumor growth

Based on the vascular abrogating effect of Tetras on tumors, we wanted to test whether Tetras can act synergistically with local radiation to reduce the tumor burden and promote local control in either the murine fibrosarcoma (Meth-A) or human squamous tumor (FaDu) models. Balb/c mice bearing Meth-A tumor on the hind legs were treated with fractionated irradiation (12 Gy, once a week for 4 weeks). 8 mg/kg of Tetras was administrated 1 h after each radiation exposure. Local radiation alone did inhibit tumor growth (Fig. 5A), but when used in conjunction with Tetras, tumor growth inhibition was sustained for three additional weeks. To determine whether Tetras can effectively synergize with local radiation in human tumor models, human squamous tumor (FaDu, nasopharyngeal squamous tumor) bearing Balb/c nu/nu mice were treated with 8 mg/kg of Tetras i.p. with or without local radiation. While Tetras

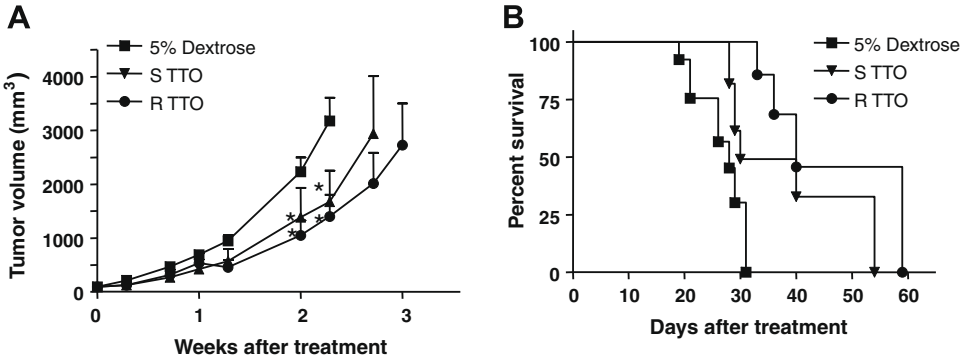

Fig. 2. Anti-tumor effect of Tetras in Meth-A fibrosarcoma mouse model. Balb/c mice with subcutaneous Meth-A tumors on the hind leg were treated with 8 mg/kg of Tetras i.p. one time (triangle) or 4 times weekly (circle), or 5% dextrose (box). (A) Tumor diameters were measured with caliper to assess tumor volume. Each value is the mean ± sd obtained from six mice. ∗ (asterisk) denotes $P < 0.05$ compared with control group (5% dextrose). (B) Mice survival curve for each treatment (each groups $n = 15–14$). Tetras showed the tumor growth inhibition effect and repeat administration of Tetras (R TTO) extended the median survival of mice by more than 10 days than the controls.

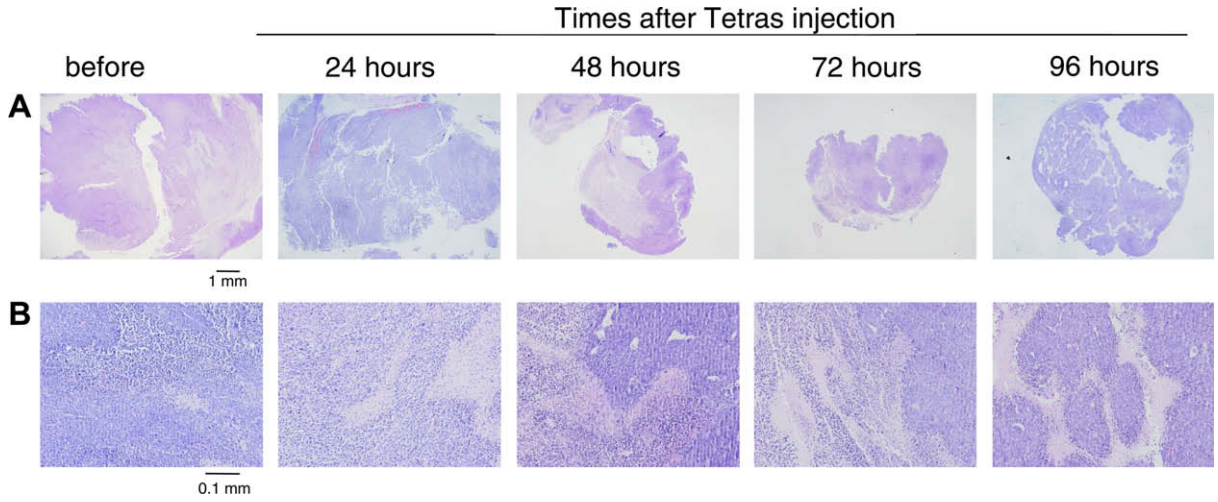

Fig. 3. Histological features of tumors stained with H&E. (A) ×2 magnification. (B) ×20 magnification. Balb/c mice with subcutaneous Meth-A tumors on the hind leg were treated with 8 mg/kg of tetras i.p. At indicated times, tumor tissues were removed and stained with H&E. Tetras induced tumor cell necrosis.

alone did not show any effect, its combination with radiation significantly decreased the tumor growth rate when compared to radiation alone (Fig. 5B and C). Thus these data suggest the synergistic effect of Tetras with radiation in effectively controlling tumor growth.

4. Discussion

The interest in the use of arsenic chemicals as a therapeutic agent against tumors has increased after diarsenic trioxide (ATO) has conclusively been shown to dramatically elicit remission in patients with acute promyelocytic leukemia (APL) [2,4]. While Tetras shares similar characteristics with ATO in inducing apoptosis in tumor cells and inhibiting angiogenesis [14,17–20], its chemical and physical characteristics differ from that of ATO (Fig. 1). Tetras has also been shown to induce 50% apoptosis in U937 leukemic cells *in vitro*, but at a lower concentration (0.5 μM) than ATO (1 μM) [18]. Furthermore, Tetras has been reported to inhibit angiogenesis induced by nerve growth factor (NGF), bFGF, and VEGF, while ATO has been shown to be effective in preventing neovascularization dependent on VEGF and bFGF only [20]. Ahn et al. [17] have also reported that Tetras is more effective than ATO in growth inhibition of established cervical carcinoma cells

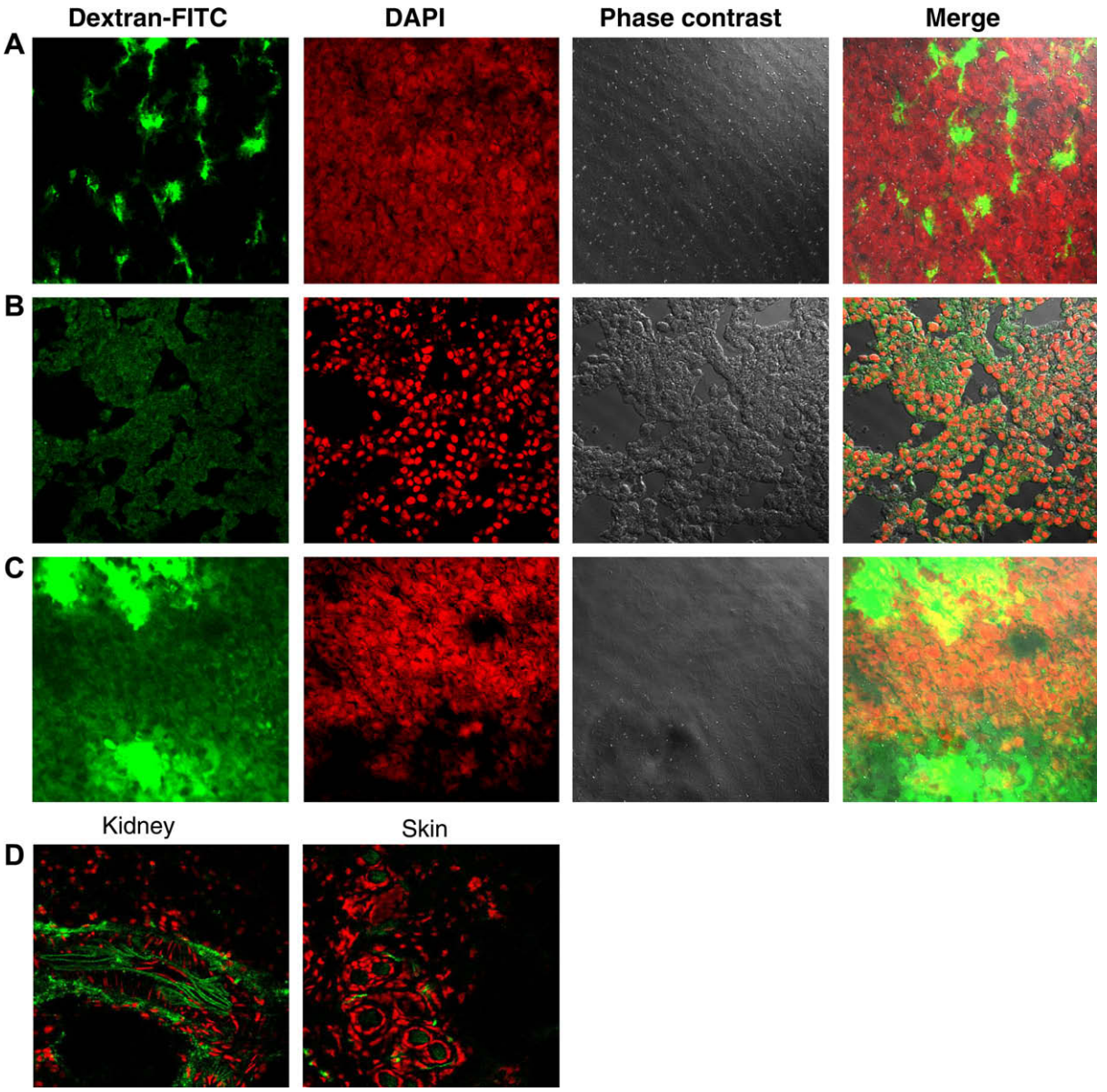

Fig. 4. Laser scanning using confocal microscope. Balb/c mice with subcutaneous Meth-A tumors on the hind leg were treated with 8 mg/kg of tetras i.p. At indicated time (before (A), 48 h after (B, D), or 72 h after (C) Tetras injection), mice were anesthetized with ketamine and xylazine. Fluorescein-labeled (FITC) dextran (1000 kDa) was administered i.v. 3 min prior to surgically removing tumors, kidney, and normal skin. Kidney and skins were removed at 48 h after Tetras injection. Tetras induce vascular permeability change in tumor tissues but not in normal tissues.

(SiHa). In this study, intraperitoneal injections of 8 mg/kg Tetras into Meth-A tumor bearing mice arrested tumor growth for approximately two days, but the growth rate returned to control group levels after two days. This tumor growth pattern is similar to ATO treatment [8]. When ATO was administered at high doses (10 mg/kg), Meth-A fibrosarcoma tumor tissues developed gross necrosis at the center and a reduction in perfusion was observed. However, when tumor bearing mice were treated with Tetras, Meth-A fibrosarcoma tumor tissues did not exhibit gross necrosis but instead had microscopic necrosis (Fig. 2) as shown with H&E staining under high magnification (×2 and ×20). To determine whether the microscopic tumor necrosis was associated with damage to the tumor vasculature, we administered FITC-conjugated dextran intravenously. Within 24 h of Tetras treatment, the FITC-conjugated dextran was dispersed throughout the tumor tissues (Fig. 3) and this observation was readily detected for up to 48 h (data not shown). Increased vascular permeability caused by Tetras peaked at 24 h post treatment and gradually declined to steady state levels 72 h post treatment (Fig. 3).

We propose that vascular disruption induced by Tetras may synergize with the effects of radiation similar to ATO [7,12]. Most vascular targeting agents are hypoxic radiosensitizers, and their effects decrease with reoxygenation during fractionated irradiation [21,22]. To test whether Tetras synergizes with radiation in both murine and human tumor cell lines, we used a murine fibrosacoma (WEHI164) and a human squamous cell carcinoma (FaDu) (Fig. 5). For murine fibrosarcoma model, Tetras showed good radiation-enhancing effects in statistically significant level ($P < 0.05$). Tetras showed radiation-enhancing effect in human squamous carcinoma model also but not statistically significant. It might be caused by starting tumor masses are smaller than murine fibrosarcoma model. If we started with tumor sizes around 150–300 mm^3 like murine fibrosarcoma model and Griffin et al. study [11], Tetras will show better effects than this study. ATO has also been shown to be effective at radiosensitizing tumors at fractionated radiation doses [7,11,12]. However direct comparison between ATO and Tetras in the degree of radiosensitization of tumors is problematic. Even though ATO and Tetras have similar activity in enhancing the radiosensitivity of tumors, Tetras has advantages in the routes of administration. It has been reported that ATO induces severe gastrointestinal toxicity by oral administrations [2], but Tetras does not, even at oral administration of 50 mg/kg per day for 7 days in rats or for 22 days in C57BL/6 mice [19]. For tox-

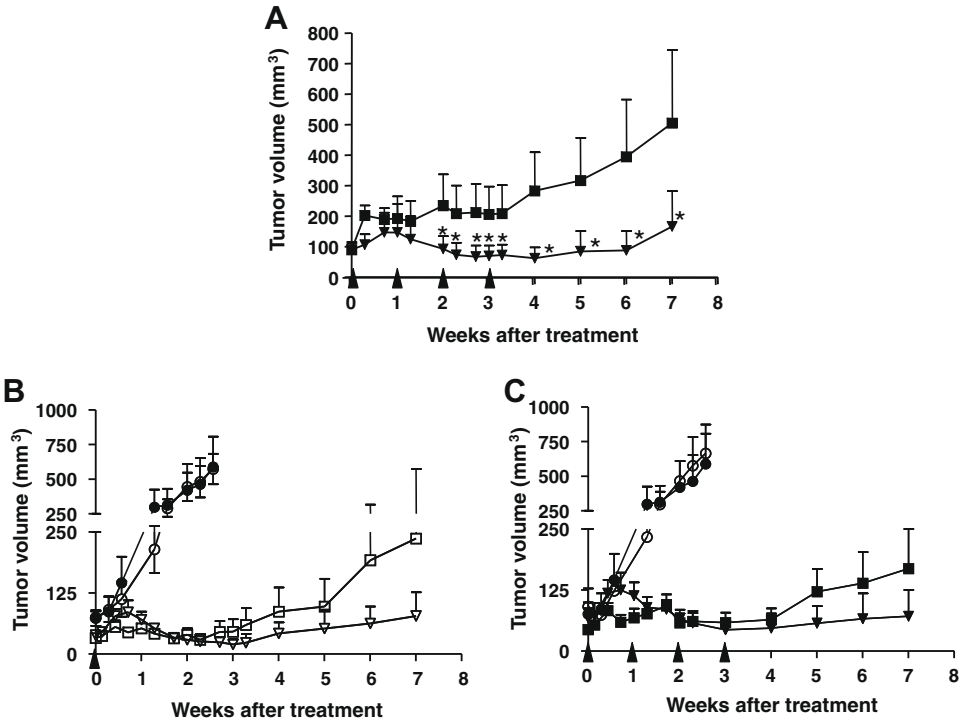

Fig. 5. Tetras as a radiation therapy enhancement agent. Meth-A fibrosarcoma (A) tumor bearing Balb/c mice or human squamous tumor (FaDu) (B and C) bearing Balb/c nu/nu mice were treated with 5% dextrose alone as control (open circles), Tetras alone (filled circles), single high dose of radiation alone (boxes), radiation and Tetras (triangles). Radiation was carried with single high dose at 24 Gy (B) or fractionated radiation at 12 Gy, once a week for 4 weeks (A and C). Tetras was administered in 8 mg/kg doses 1 h after every radiation treatment. Tumor diameters were measured with caliper at least weekly. Each value is the mean ± sd obtained from six mice. *, $P < 0.05$ compared with control group (radiation alone). Tetras showed good radiation-enhancing effects in statistically significant level in Meth-A fibrosarcoma tumor model ($P < 0.05$). In human squamous carcinoma model, combination of radiation and Tetras were more effective than radiation alone, but not statistically significant.

icity problem, we did not do exact experiments but there are no vascular damages in normal tissues especially, kidney and skins (Fig. 4D).

In summary, this report demonstrates for the first time that Tetras functions as a potent anti-cancer agent for solid tumors by disrupting neovasculature and radiosensitizing tumors to control growth of cancers. Further studies are needed to define the mechanism of vascular disruption and to determine the optimal combination course to maximally reduce tumor burden while minimizing toxicity, potentially leading to eradication of tumors.

5. Conflict of interest statement

Y.S. Lew and I.J. BAE work at Chunjisan, the provider of the Tetras reagent.

Other authors have declared that no conflict of interest exists.

Acknowledgement

This work was supported by Chunjisan.

References

[1] Y.L. Kwong, D. Todd, Delicious poison: arsenic trioxide for the treatment of leukemia, Blood 89 (1997) 3487–3488.
[2] Z.X. Shen, G.Q. Chen, J.H. Ni, X.S. Li, S.M. Xiong, Q.Y. Qiu, J. Zhu, W. Tang, G.L. Sun, K.Q. Yang, Y. Chen, L. Zhou, Z.W. Fang, Y.T. Wang, J. Ma, P. Zhang, T.D. Zhang, S.J. Chen, Z. Chen, Z.Y. Wang, Use of arsenic trioxide (As_2O_3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients, Blood 89 (1997) 3354–3360.
[3] S.L. Soignet, S.R. Frankel, D. Douer, M.S. Tallman, H. Kantarjian, E. Calleja, R.M. Stone, M. Kalaycio, D.A. Scheinberg, P. Steinherz, E.L. Sievers, S. Coutre, S. Dahlberg, R. Ellison, R.P. Warrell Jr., United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia, J. Clin. Oncol. 19 (2001) 3852–3860.
[4] S.L. Soignet, P. Maslak, Z.G. Wang, S. Jhanwar, E. Calleja, L.J. Dardashti, D. Corso, A. DeBlasio, J. Gabrilove, D.A. Scheinberg, P.P. Pandolfi, R.P. Warrell Jr., Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide, New Engl. J. Med. 339 (1998) 1341–1348.
[5] J. Dai, R.S. Weinberg, S. Waxman, Y. Jing, Malignant cells can be sensitized to undergo growth inhibition and apoptosis by arsenic trioxide through modulation of the glutathione redox system, Blood 93 (1999) 268–277.
[6] X.H. Zhu, Y.L. Shen, Y.K. Jing, X. Cai, P.M. Jia, Y. Huang, W. Tang, G.Y. Shi, Y.P. Sun, J. Dai, Z.Y. Wang, S.J. Chen, T.D. Zhang, S. Waxman, Z. Chen, G.Q. Chen, Apoptosis and growth inhibition in malignant lymphocytes after treatment with arsenic trioxide at clinically achievable concentrations, J. Natl. Cancer Inst. 91 (1999) 772–778.
[7] J.H. Kim, Y.S. Lew, A. Kolozsvary, S. Ryu, S.L. Brown, Arsenic trioxide enhances radiation response of 9L glioma in the rat brain, Radiat. Res. 160 (2003) 662–666.
[8] Y.S. Lew, S.L. Brown, R.J. Griffin, C.W. Song, J.H. Kim, Arsenic trioxide causes selective necrosis in solid murine tumors by vascular shutdown, Cancer Res. 59 (1999) 6033–6037.
[9] R.J. Griffin, S.H. Lee, K.L. Rood, M.J. Stewart, J.C. Lyons, Y.S. Lew, H. Park, C.W. Song, Use of arsenic trioxide as an antivascular and thermosensitizing agent in solid tumors, Neoplasia 2 (2000) 555–560.
[10] Y.J. Chun, I.C. Park, M.J. Park, S.H. Woo, S.I. Hong, H.Y. Chung, T.H. Kim, Y.S. Lee, C.H. Rhee, S.J. Lee, Enhancement of radiation response in human cervical cancer cells in vitro and in vivo by arsenic trioxide (As_2O_3), FEBS Lett. 519 (2002) 195–200.
[11] R.J. Griffin, B.W. Williams, H.J. Park, C.W. Song, Preferential action of arsenic trioxide in solid-tumor microenvironment enhances radiation therapy, Int. J. Radiat. Oncol. Biol. Phys. 61 (2005) 1516–1522.
[12] Y.S. Lew, A. Kolozsvary, S.L. Brown, J.H. Kim, Synergistic interaction with arsenic trioxide and fractionated radiation in locally advanced murine tumor, Cancer Res. 62 (2002) 4202–4205.
[13] E. Fox, B.I. Razzouk, B.C. Widemann, S. Xiao, M. O'Brien, W. Goodspeed, G.H. Reaman, S.M. Blaney, A.J. Murgo, F.M. Balis, P.C. Adamson, Phase 1 trial and pharmacokinetic study of arsenic trioxide in children and adolescents with refractory or relapsed acute leukemia, including acute promyelocytic leukemia or lymphoma, Blood 111 (2008) 566–573.
[14] S.H. Woo, M.J. Park, S. An, H.C. Lee, H.O. Jin, S.J. Lee, H.S. Gwak, I.C. Park, S.I. Hong, C.H. Rhee, Diarsenic and tetraarsenic oxide inhibit cell cycle progression and bFGF- and VEGF-induced proliferation of human endothelial cells, J. Cell. Biochem. 95 (2005) 120–130.
[15] H. Monzen, R.J. Griffin, B.W. Williams, M. Amano, S. Ando, T. Hasegawa, Study of arsenic trioxide-induced vascular shutdown and enhancement with radiation in solid tumor, Radiat. Med. 22 (2004) 205–211.
[16] F.X. Reichl, H. Kreppel, L. Szinicz, B. Fichtl, W. Forth, Reduction of arsenic trioxide toxicity in mice by repeated treatment with glucose, Arch. Toxicol. 14 (Suppl.) (1991) 225–227.
[17] W.S. Ahn, S.M. Bae, K.H. Lee, Y.W. Kim, J.M. Lee, S.E. Namkoong, I.P. Lee, C.K. Kim, J.S. Seo, J.I. Sin, Y.W. Kim, Comparison of effects of As_2O_3 and As_4O_6 on cell growth inhibition and gene expression profiles by cDNA microarray analysis in SiHa cells, Oncol. Rep. 12 (2004) 573–580.
[18] I.C. Park, M.J. Park, S.H. Woo, H.C. Lee, S. An, H.S. Gwak, S.H. Lee, S.I. Hong, I.J. Bae, K.M. Seo, C.H. Rhee, Tetraarsenic oxide induces apoptosis in U937 leukemic cells through a reactive oxygen species-dependent pathway, Int. J. Oncol. 23 (2003) 943–948.
[19] M.J. Park, I.C. Park, I.J. Bae, K.M. Seo, S.H. Lee, S.I. Hong, C.K. Eun, W. Zhang, C.H. Rhee, Tetraarsenic oxide, a novel orally administrable angiogenesis inhibitor, Int. J. Oncol. 22 (2003) 1271–1276.
[20] M.H. Yoo, J.T. Kim, C.H. Rhee, M.J. Park, I.J. Bae, N.Y. Yi, M.B. Jeong, S.M. Jeong, T.C. Nam, K.M. Seo, Reverse effects of tetraarsenic oxide on the angiogenesis induced by nerve growth factor in the rat cornea, J. Vet. Med. Sci. 66 (2004) 1091–1095.
[21] R. Murata, D.W. Siemann, J. Overgaard, M.R. Horsman, Interaction between combretastatin A-4 disodium phosphate and radiation in murine tumors, Radiother. Oncol. 60 (2001) 155–161.
[22] W.R. Wilson, A.E. Li, D.S. Cowan, B.G. Siim, Enhancement of tumor radiation response by the antivascular agent 5,6-dimethylxanthenone-4-acetic acid, Int. J. Radiat. Oncol. Biol. Phys. 42 (1998) 905–908.