RESEARCH ARTICLE

Evaluation on Efficacy and Safety of Arsenic Trioxide Plus Transcatheter Arterial Chemoembolization Versus Transcatheter Arterial Chemoembolization alone for Unresectable Primary Liver Cancer

Haitao Yang[1], Sijing Zhou[1], Ruifen Shen[1], Shuimei Luo[1], Lina Li[1], Heng Lin[1,2], Huijuan Chen[1], Ziyuan Liao[1], Wanzun Lin[1], Xianhe Xie[1]*

Abstract

Currently, some clinical trials of arsenic trioxide (As203) plus transcatheter arterial chemoembolization (TACE) in the treatment of unresectable primary liver cancer (PLC) had been conducted, but the results were controversial. Therefore, we performed a meta-analysis on 14 clinical trials (1076 cases) to evaluate efficacy and safety of As203 plus TACE versus TACE alone for unresectable PLC. The primary end points included objective response rate (ORR), karnofsky performance score (KPS) improvement rate, and 1-year survival rate. The second end points were adverse events consisting of leukopenia, liver dysfunction, nausea/vomiting, fever, myelosuppression and pain. Our study showed that, compared with TACE alone, As203 plus TACE appeared a significant benefit on ORR (RR = 1.32, 95% CI: 1.15,1.50, P < 0.0001), KPS improvement rate (RR = 1.24, 95% CI: 1.03,1.48, P = 0.02) and 1-year survival rate (RR = 1.31, 95% CI: 1.15,1.49, P < 0.0001). Additionally, no remarkable difference of adverse events were observed between two arms: leukopenia (RR = 1.44, 95% CI: 0.90,2.32, P = 0.13), liver dysfunction (RR = 0.96, 95% CI: 0.76,1.21, P = 0.71), nausea/vomiting (RR = 1.10, 95% CI: 0.84,1.44, P = 0.48), fever (RR = 1.15, 95% CI: 0.82,1.61, P = 0.43), myelosuppression (RR = 1.07, 95% CI: 0.74,1.56, P = 0.72) and pain (RR = 0.88, 95% CI: 0.57,1.36, P = 0.57). This study demonstrated that As203 plus TACE produced a favorable efficacy without enhancing adverse events and was a promising combination therapy option for unresectable PLC.

Keywords: primary liver cancer- As203- TACE- meta-analysis

Asian Pac J Cancer Prev, **18 (10)**, 2695-2701

Introduction

Primary liver cancer (PLC) is one of the diseases severely threatening human life with a high incidence of 782451 new cases each year worldwide and 394770 cases in China (Chen et al., 2014; Ferlay et al., 2013). Due to insidious onset, high malignancy and invasive fast-growing, a large number of patients are diagnosed as unresectable PLC. With regard to the treatment of unresectable PLC, except for radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE) is also an effective approach (Qin et al., 2011). However, the compensatory circulation derived from TACE counteracts its anticancer effect (Ni et al., 2012; Ranieri et al., 2015). Thus, it is urgent to explore appropriate drugs combining with TACE to maximize efficacy of unresectable PLC. Arsenic trioxide (As203), a potent and cost-effective drug, after Zhang et al., (1995) reporting the favorable efficacy of As203 on acute promyelocytic leukemia (APL), many studies (Yua et al., 2014; Zhang et al., 2015) on its anticancer effect and molecular mechanism were conducted. Owing to its broad pattern of inhibiting proliferation, inducing apoptosis of tumor cell and suppressing intimal hyperplasia (Huang et al., 2005; Jiang et al., 2014), As203 was increasingly used to deal with several solid tumors, especially for PLC. In the past decades, some clinical trails involving As203 plus TACE had been performed in an attempt to produce synergetic effects against unresectable PLC (Cui et al., 2005; Cui et al., 2006; He et al., 2015; Hou et al., 2015; Hu et al., 2014, Nian et al., 2015; Qian et al., 2014; Tang et al., 2006; Xie et al., 2007; Xing et al., 2012; Yan et al., 2013; Zhang et al., 2010; Zhou et al., 2007; Zhuang et al., 2006), but the results were controversial (Zhang et al., 2010; Zhuang et al., 2006). Thereby, we performed this meta-analysis to evaluate the efficacy and safety of As203 plus TACE in managing unresectable PLC.

*[1]Department of Chemotherapy, The First Affiliated Hospital, Fujian Medical University, Fuzhou, Fujian, 350005, [2]Department of Oncology, Fuzhou Pulmonary Hospital, Fuzhou, 350008, China. *For Correspondence: xiexianhe@yahoo.com. Haitao Yang and Sijing Zhou have equal contribution in this study.*

Materials and Methods

Search strategy

Relevant trials were identified from PubMed, Embase, Cochrane Library, WanFang, CNKI and VIP databases from their inception till January 2017. The searching words were primary liver cancer, hepatocellular carcinoma, arsenic trioxide, As203, transcatheter arterial chemoembolization, TACE, locoregional therapy and LRT. The search was performed without any language limitation.

Study selection

Initially, the study selection was executed by finding duplications via EndNote X7 software. Then, other pertinent articles were identified by screening titles or abstracts. Two reviewers selected articles independently according to the inclusion criteria. Disagreement on whether an article should be included was resolved by the third reviewer.

Inclusion and exclusion criteria

All projects which met the following criteria were eligible: (1) clinical control trials; (2) cases were pathologically or imageologically plus clinical manifestation and AFP level confirmed as PLC; (3) the intervention of experiment group was As203 plus TACE while control group was TACE alone. Single arm trials, animal experiments and trials with other interventions were excluded.

Data extraction

The basic information included author, year, study type, method, number of patients, gender, median/mean age, child-pugh stage, AFP positive rate, objective response rate (ORR), 1-year survival rate and karnofsky performance score (KPS) improvement rate. The primary end points included ORR, KPS improvement rate and 1-year survival rate. The second end points were adverse events consisting of leukopenia, liver dysfunction, nausea /vomiting, fever, myelosuppression and pain. All data were extracted independently by two reviewers. When the extracted data were not uniform, discussion was performed to make a final determination.

Definition

ORR was defined as complete response (CR) plus partial response (PR). The treatment responses were categorized according to World Health Organization criteria (1979) or Response Evaluation Criteria in Solid Tumors (RECIST). KPS improvement was defined as KPS improved ten or more points. Unresectable PLC were these patients: moderate/advanced PLC; inability or refusal to receive surgical therapy.

Quality assessment

The qualities of all available trials were evaluated based on the Cochrane Handbook for Systematic Reviews of intervention (Version 5.3.0), which contains seven aspects (random sequence generation, allocation concealment, blind of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias). The bias of each trial based on the criteria listed above was marked as 'low risk', 'high risk' or 'unclear risk'. Trials were judged as low risk of bias (i.e. A rating) when all criteria were assessed as low risk; trials were judged as moderate risk of bias (i.e. B rating) or high risk of bias (i.e. C rating) when one or more criteria were assessed as unclear risk or high risk, respectively. Ten of fourteen trials (Cui et al., 2006; He et al., 2015; Hou et al., 2015; Hu et al., 2014; Qian et al., 2014; Xie et al., 2007; Xing et al., 2012; Zhang et al., 2010; Zhou et al., 2007; Zhuang et al., 2006) mentioned the term of randomization, but only 2 (Zhou et al., 2007; Zhuang et al., 2006) referred to the ways of randomization and 1 (He et al., 2015) allocated patients to experimental group and control group randomly according to the odevity of the last number of the hospital numbers. Moreover, fourteen trials (Cui et al., 2005; Cui et al., 2006; He et al., 2015; Hou et al., 2015; Hu et al., 2014; Nian et al., 2015; Qian et al., 2014; Tang et al., 2006; Xie et al., 2007; Xing et al., 2012; Yan et al., 2013; Zhang et al., 2010; Zhou et al., 2007; Zhuang et al., 2006) did not mention double blind and selection bias. As shown in Figure 1, 9 trials (Cui et al., 2006; Hou et al., 2015; Hu et al., 2014; Qian et al., 2014; Xie et al., 2007; Xing et al., 2012; Zhang et al., 2010; Zhou et al., 2007; Zhuang et al., 2006) were judged as B quality scores and 5 (Cui et al., 2005; He et al., 2015; Nian et al., 2015; Tang et al., 2006; Yan et al., 2013) as C quality scores. Publication bias was assessed via funnel plot (Figure 2).

Methods of statistics

Review Manager 5.3 was applied to analyze data. Chi-square and I-square tests were employed to measure the heterogeneity of different trials (Higgins et al., 2003). Significant heterogeneity was found if $P < 0.1$ and $I^2 > 50\%$, a random effect model was utilized, otherwise, a fixed-effect model was applied (Ford et al., 2014). Risk ratio (RR) with 95% confidence interval (95% CI) represented the overall results of each end point.

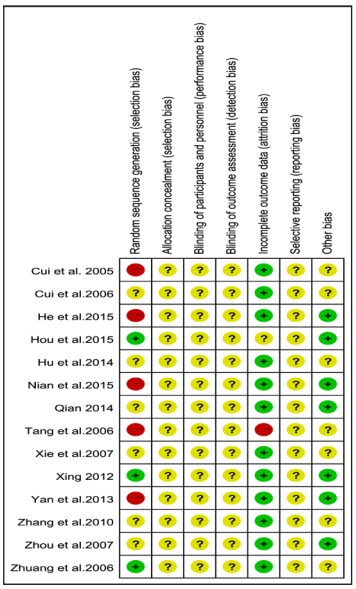

Figure 1. Bias Risk and Quality Assessment of Included Studies

Table 1. The Characteristic of the Studies in the Meta-Analysis

Study ID	Study types	Methods	Patients	Man/Female	Median/Mean age	Child-Pugh A%	AFP+%	ORR%	1-year survival rate	KPS improvement rate
Cui et al.2005	E	TACE+As203	9	6/3	39(22-57)	88.89	88.89	55.56	NA	55.56
	C	TACE	30	26/4	45(20-68)	83.33	83.33	20	NA	20
Cui et al.2006	E	TACE+As203	26	21/5	52±13	73.08	73.08	34.62	80.77	NA
	C	TACE	29	25/4	52±15	75.86	68.97	31.03	51.72	NA
He et al.2015	E	TACE+As203	36	22/14	58.1±4.5	61.11	NA	61.11	77.78	NA
	C	TACE	36	25/11	(28-81)	52.78	NA	36.11	55.56	NA
Hou et al.2015	E	TACE+As203	63	35/28	56.5±3.8	NA	NA	74.6	NA	NA
	C	TACE	63	33/30	54.5±3.5	NA	NA	39.68	NA	NA
Hu et al.2014	E	TACE+As203	28	21/7	59(31-80)	NA	100	64.29	67.86	50
	C	TACE	25	17/8	51(28-70)	NA	100	52	40	52
Nian et al.2015	E	TACE+As203	81	96/60	57.6(45-76)	NA	NA	NA	76.54	NA
	C	TACE	75			NA	NA	NA	68	NA
Qian 2014	E	TACE+As203	40	32/8	52(33-81)	NA	82.5	57.5	NA	72.5
	C	TACE	40	35/5	50(31-68)	NA	87.5	47.5	NA	57.5
Tang et al.2006	E	TACE+As203	26	21/5	39(22-57)	73.07	73.08	34.62	80.77	34.62
	C	TACE	30	26/4	45(20-68)	83.33	83.33	20	51.72	20
Xing 2012	E	TACE+As203	23	18/5	55.43±10.49	78.26	NA	52.17	80.3	NA
	C	TACE	25	23/2	54.84±8.24	84	NA	52	51.4	NA
Xie et al.2007	E	TACE+As203	33	25/8	52(21-70)	NA	72.73	51.52	NA	60.61
	C	TACE	32	23/9	51(21-70)	NA	68.75	43.75	NA	53.13
Yan et al.2013	E	TACE+As203	30	26/4	52(29-72)	83.33	56.67	20	46	50
	C	TACE	32	26/6	53(31-74)	81.25	56.25	15.63	52	43.75
Zhang et al.2010	E	TACE+As203	30	24/6	52(28-72)	NA	NA	60	NA	66.67
	C	TACE	30	25/5	50(31-68)	NA	NA	46.67	NA	56.67
Zhou et al.2007	E	TACE+As203	41	35/6	51(27-75)	85.37	63.41	14.63	NA	NA
	C	TACE	45	40/5	50(23-74)	82.22	75.56	8.89	NA	NA
Zhuang et al.2006	E	TACE+As203	62	44/18	(26-76)	45.16	74.19	77.42	61.29	NA
	C	TACE	56	36/20	(24-79)	44.64	75	78.57	39.29	NA

C, control group; E, experiment group; NA, not available; TACE, transcatheter arterial chemoembolization; As203, arsenic trioxide; ORR, objective response rate; AFP+%: AFP positive rate

Results

209 relevant articles were identified from 6 databases. Initially, after checking duplications and reading the titles or abstracts, 68 duplication, 112 ineligible and 9 republished articles were excluded. Then, 6 articles were excluded after performing discussion: 1 article processing beta-ultrasound guided percutaneous As203 injection to the lesions of PLC, 4 administering As203 by intravenous drip and another 1 using As203 both through the catheter of TACE and intravenous drip. Eventually, 14 trials (Cui et al., 2005; Cui et al., 2006; He et al., 2015; Hou et al., 2015; Hu et al., 2014; Nian et al., 2015; Qian et al., 2014; Tang et al., 2006; Xie et al., 2007; Xing et al., 2012; Yan et al., 2013; Zhang et al., 2010; Zhou et al., 2007; Zhuang et al., 2006) (1076 patients) of As203 plus TACE versus TACE alone for unresectable PLC were included (Figure 3). In these trials, As203 was mostly administered by: (1) continuous regional infusion As203 through the chemotherapy pump placed beneath the skin by femoral

Table 2. Adverse Events

Types of adverse events	Included trials	Experiment group	Control group	Statistical model	Heterogeneity test		Meta-analysis result	
		n/N	n/N		I^2	p	RR(95% CI)	P
Leukopenia	4	33/134	24/141	fixed effect model	35%	0.2	1.44(0.90,2.32)	0.13
Liver dysfunction	6	115/248	130/247	random effects model	75%	0.001	0.96(0.76,1.21)	0.71
Nausea/vomiting	5	62/152	57/155	fixed effect model	0%	0.71	1.10(0.84,1.44)	0.48
Fever	4	47/129	41/130	fixed effect model	0%	0.84	1.15(0.82,1.61)	0.43
Myelosuppression	3	32/150	29/143	fixed effect model	40%	0.19	1.07(0.74,1.56)	0.72
Pain	6	84/233	89/230	fixed effect model	0%	0.54	0.88(0.57,1.36)	0.57

N, the total number of patients; n, the total number of events.

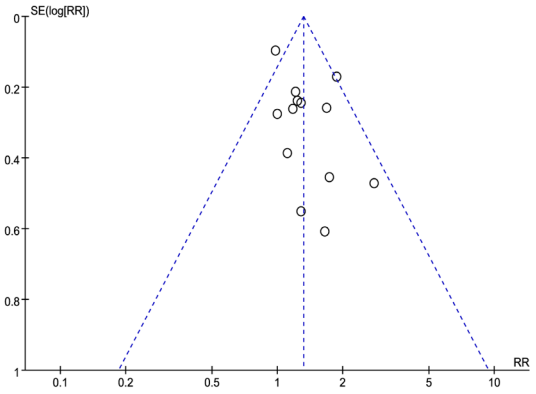

Figure 2. The Funnel Plot of Objective Response Rate

Figure 3. Flowchart for Study Selection

artery transcatheter, 20 mg, qd×7, and repeated every four weeks; (2) chemotherapy embolism with As203 (20 mg) + lipiodol (10-20ml) by femoral artery transcatheter, and repeated every month. Characteristics of these trials were shown in Table 1.

Objective response rate

Thirteen of 14 trials (Cui et al., 2005; Cui et al., 2006; He et al., 2015; Hou et al., 2015; Hu et al., 2014; Qian et

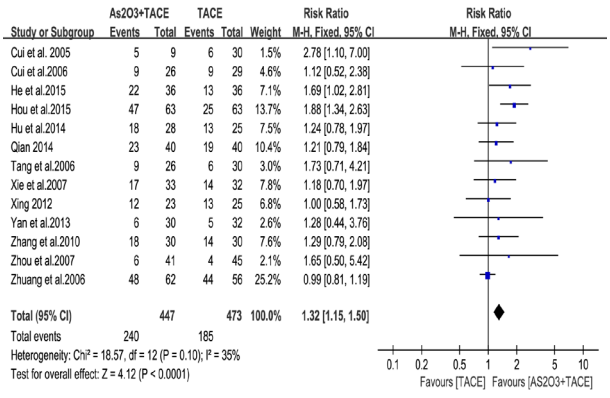

Figure 4. Objective Response Rate of the Study

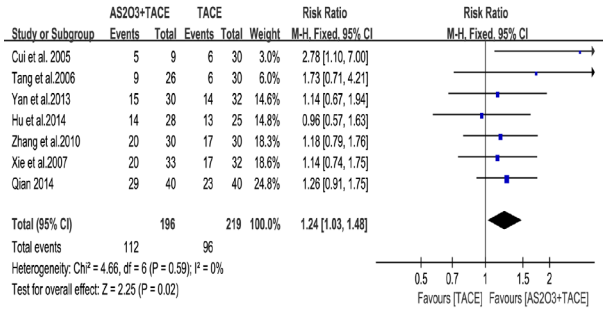

Figure 5. KPS Improvement Rate of the Study

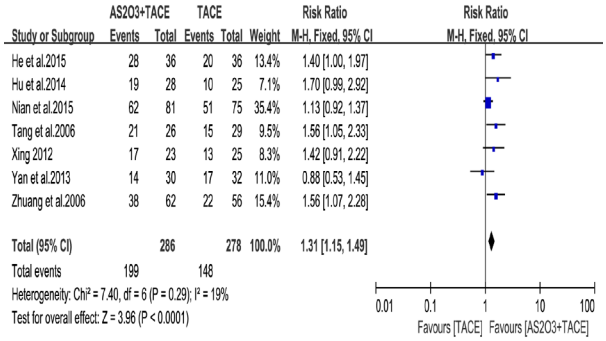

Figure 6. One-Year Survival Rate of the Study

al., 2014; Tang et al., 2006; Xie et al., 2007; Xing et al., 2012; Yan et al., 2013; Zhang et al., 2010; Zhou et al., 2007; Zhuang et al., 2006) referred to ORR of As203 plus TACE for unresectable PLC. Due to no heterogeneity in these trials (P =0.10 I^2 = 35%), a fixed effect model was applied. The result showed that compared with TACE alone, As203 plus TACE possessed noticeable superiority for unresectable PLC (RR = 1.32, 95% CI: 1.15,1.50, P < 0.0001) (Figure 4).

KPS improvement rate

Seven of 14 trials (Cui et al., 2005; Hu et al., 2014; Qian et al., 2014; Tang et al., 2006; Xie et al., 2007; Yan et al., 2013; Zhang et al., 2010) referred to KPS improvement rate of As203 plus TACE for unresectable PLC. A fixed effect model was used to analyze KPS improvement rate because heterogeneity did not exist (P = 0.59, I^2 = 0%). The result displayed that compared with TACE alone, As203 plus TACE significantly improved quality of life (RR = 1.24, 95% CI: 1.03,1.48, P = 0.02) (Figure 5).

One-year survival rate

Seven trials (He et al., 2015; Hu et al., 2014; Nian et al., 2015; Tang et al., 2006; Xing et al., 2012; Yan et al., 2013; Zhuang et al., 2006) concerning 1-year survival rate were included. Owing to no heterogeneity existed in these trials (P = 0.29 I^2 = 19%), a fixed effect model was applied and the result demonstrated that As203 plus TACE arm obtained a favorable benefit compared with TACE alone arm (RR = 1.31, 95% CI: 1.15,1.49, P < 0.0001) (Figure 6).

Adverse event

The common adverse events were leukopenia, liver dysfunction, nausea/vomiting, fever, myelosuppression and pain. The data for each type of adverse events extracted from eligible trials were evaluated by a fixed effect model or a random effect model based on heterogeneity value (Table 2). No distinct difference in adverse events were observed between two arms. On the whole, adverse events were mild (grade ≤ II) and tolerable.

Discussion

Based on data from 14 trials incorporating 1076 patients, our study demonstrated that compared with TACE alone, the regimen of As203 plus TACE possessed superior ORR, KPS improvement rate and 1-year survival rate in unresectable PLC without enhancing toxicity profile. These desirable results could be explained by synergistic effects of TACE and As203.

Current treatment strategies for unresectable PLC, including RFA, microwave ablation (MWA), TACE, and systematic treatment (sorafenib, FOL-FOX 4 and As203), do not yield satisfactory outcomes. TACE, one of the most widely used approaches, exerts effect through increasing the local cytotoxic agent concentration and blocking blood supply of tumor. However, it can induce the overproduction of vascular endothelial growth factor (VEGF), and promote disease progression or metastasis, which counteracts its anticancer effect (Ni et al., 2012; Qin et al., 2011). Consequently, highly efficient agent combining with TACE is urgently needed to overcome the limitations and maximize efficacy. As203, a miraculous and traditional agent, gradually comes into sight in managing unresectable PLC. Some studies (Chen et al., 2013; Tan et al., 2005; Wang et al., 2008; Wang et al., 2012; Xu et al., 2004; Yin et al., 2009, Yuan et al., 2012; Zhou et al., 2009; Zhang et al., 2011; Zhang et al., 2012) showed that it possessed a broad antitumor activity which was based on following three evidence levels: at cellular level (Chen et al., 2013; Wang et al., 2008; Wang et al., 2012; Yin et al., 2009; Yuan et al., 2012; Zhang et al., 2011; Zhang et al., 2012; Zhou et al., 2009), As203 was able to inhibit many types of tumor cells, such as SMMC-7721 (Zhou et al., 2009), HepG2 (Wang et al., 2008), MDA-MB-231 (Zhang et al., 2012), T cell lymphoma cell line Hut-78 (Zhang et al., 2011), burkitt lymphoma cells (Chen et al., 2013), colorectal cancer stem cells (Yuan et al., 2012), multiple myeloma cells (Wang et al., 2012), neuroblastom cell (Yin et al., 2009); at animal trial level, many experiments (Tan et al., 2005; Xu et al., 2004) proved that As203 was a promising agent against many types of cancers; at clinical trial level, studies (Cui et al., 2005, Cui et al., 2006, He et al., 2015, Hou et al., 2015, Hu et al., 2014, Nian et al., 2015, Qian et al., 2014, Tang et al., 2006, Xie et al., 2007, Xing et al., 2012, Yan et al., 2013, Zhang et al., 1995, Zhang et al., 2010, Zhou et al., 2007, Zhuang et al., 2006) involving As203 in APL as well as solid tumors, such as PLC, acquired definite efficacy.

Furthermore, the molecular mechanism of As203 in treating APL was elaborated by down-regulating the key protein which was able to drive APL progress (Shen et al., 2015). Meanwhile, studies (Cui et al., 2006; Huang et al., 2005; Jiang et al., 2014; Li et al., 2003; Liu et al., 2000; Liu et al., 2001; Liu TF et al., 2001; Liu et al., 2008; Tang et al., 2005; Tang et al., 2009; Wang et al., 2008; Yua et al., 2014; Zhang et al., 2004) showed the anti-hepatoma molecular mechanisms probably were as follows: (1) triggering apoptosis: down-regulating the expression of Bcl-2 and Bcl-XI genes, up-regulating the expression of Bax, Bcl-Xs and p53 genes, activating p21 gene, increasing CDK's activity and enhancing the expression of Fas, Fas-L (Li et al., 2003, Liu et al., 2000, Liu et al., 2001; Yua et al., 2014; Zhang et al., 2004); (2) restricting tumor angiogenesis via suppressing the expression of VEGF (Liu et al., 2008; Jiang et al., 2014; Tang et al., 2009); (3) inhibiting proliferation of tumor cell through arresting cell cycle at G1/S or G2/M phase (Huang et al., 2005; Tang et al., 2005; Wang et al., 2008; Zhang et al., 2004); (4) repressing tumor metastasis by down-regulating the expression of CD44 (Liu TF et al., 2001); (5) promoting demethylation of tumor suppressor gene via blocking the activity of DNA methyltransferase and the mRNA expressions of DNA methyltransferase 1, resulting in the death of cancer cells (Cui X et al., 2006).

With regard to the safety, our study showed no remarkable difference of adverse events between two arms. The probable mechanisms were based on: (1) due to the local administration of As203, its concentration was much higher in liver than in other tissues and blood which may partly account for the enhancing efficacy of TACE without aggravating adverse events; (2) rapid decline of As203 in blood can further explain its mild adverse events (Song et al., 2000; Wang et al., 2003; Zheng et al., 2004).

However, we encountered two limitations: first, owing to particularity of As203, the study population was only limited in Chinese; second, because of the limitation of data, the endpoints were only including the ORR, KPS improvement rate and 1-year survival rate and adverse events, but OS, PFS can not be evaluated. Thereby, more well designed trails involving different races and long-term outcomes are critical to further validate the value of this strategy in coping with unresectable PLC.

Briefly, our study demonstrated that As203 plus TACE achieved a favorable efficacy without increasing adverse events and was a promising combination therapy option for unresectable PLC.

Disclosure of Potential Conflicts of Interest

There is no conflict of interest.

Funding

None.

References

Chen YJ, Li HM, Lu W, et al (2013). Blocking effect of arsenic trioxide on the proliferation and cell cycle of human Burkitt lymphoma cells and Its related mechanism. *Exp Hematol Oncol*, **21**, 1454-9.

Chen WQ, Zhang SW, Zeng HM, et al (2014). Report of cancer incidence and mortality in China, 2010. *China Cancer*, **23**, 1-9.

Cui SZ, Song T, Wang LK, et al (2005) Clinical observation on transcatheter arterial chemoembolization combined with arsenic trioxide in treatment of patients with primary liver cancer. *Mod Dig Inter*, **10**, 89-91.

Cui SZ, Wu YB, Wang JK, et al (2006). Clinical research of arsenic trioxide (As_20_3) continuous regional hepatic arterial infusion in the treatment of primary hepatic carcinoma. *J Mod Clin Med Bioeng*, **12**, 433-6.

Cui X, Wakai T, Shirai Y, et al (2006). Arsenic trioxide inhibits DNA methyltransferase and restores methylation-silenced genes in human liver cancer cells. *Hum Pathol*, **37**, 298-311.

Ferlay J, Soerjomataram I, Ervik M, et al (2013). GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC Cancer Base No. 11 [DB/OL].Lyon: International Agency for Research on Cancer. 2013. Available http://globocan.iarc.fr.

Ford AC, Forman D, Hunt RH, et al (2014). Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ*, **348**, g3174.

He JM, Huang CY, Xu JX (2015). Effect of arsenic trioxide combined with oxaliplatin and gemcitabine arterial chemoembolization for hepatocellular carcinoma recurrence and metastasis ability. *J Xiangnan Uni Med Sci*, **17**, 12-5.

Higgins JP, Thompson SG, Deeks JJ, et al (2003). Measuring inconsistency in meta-analyses. *BMJ*, **327**, 557-60.

Hou YB, Liu Q, Duan GF, et al (2015). Interventional treatment effects of arsenic trioxide for advanced primary liver cancer. *J North Pharm*, **12**, 24-5.

Hu Q, Wei YM, Guan R, et al (2014). Clinical effect of transcatheter arterial chemoembolization combined with arsenic trioxide in treatment of primary liver cancer. *Mod Oncol*, **22**, 2679-81.

Huang JF, Tan B, Wei Q, Zhang H, Ni RZ (2005). Anti-hepatoma effect of arsenic trioxide on rat liver cancers induced by 2-acetamidofluorene. *Chin J Hepatol*, **13**, 623-5.

Jiang F, Wang XX, Liu QQ, et al (2014). Inhibition of TGF-b/SMAD3/NF-kB signaling by microRNA-491 is involved in arsenic trioxide-induced anti-angiogenesis in hepatocellular carcinoma cells. *Toxicol Lett*, **231**, 55-61.

Li JT, Qu QJ, Liu YB, Wang XB, Xu B (2003). Significance of expression of bcl-2 mRNA and bax mRNA in arsenic trioxide-induced apoptcsis of hepatocellular carcinoma cells. *Chin J Hepatobiliary Surg*, **9**, 241-7.

Liu L, Qin SK, Chen HY, et al (2000) An experimental study on arsenic trioxide-selectively induced human hepatocarcinoma cell lines apoptosis and its related genes. *Chin J Hepatol*, **8**, 367-9.

Liu LX, Jiang HC, Zhuan AL, et al (2001). Arsenic trioxide induces apoptosis in hepatocellular carcinoma cells and to elucidate the possible mechanism. *Natl Med J China*, **81**, 1526-7.

Liu TF, Cheng BL, Guan YG, Liang T (2001). Study on relationship between expressions of CD44 and inhibition effect of arsenic trioxide on carcinoma. *J Harbin Med Univ,* **35**, 111-2.

Liu L, Qin SK, Chen BA, et al (2008). Effect of arsenic trioxide on the anti-angiogenesis of hepatocarcinoma. *J Southeast Univ (Med Sci Edi)*, **27**, 330-5.

Ni JY, Huang KH, Xu LF (2012). Relationship between HIF-1α expression after TACE and recurrence and metastasis of hepatoma. *Int J Med Radiol*, **35**, 349-52.

Nian DF, Yan AF, Hou LY, Yu YC (2015). Clinical application of arsenic trioxide combined with transcatheter arterial chemoembolization treatment of advanced primary liver cancer. *Chin Imaging J Integr Tradit West Med*, **13**, 211-3.

Qin SK, Fan J, Shen F, et al (2011). Diagnosis, management, and treatment of hepatocellular carcinoma (V2011). J *Clini Hepatol*, **27**, 1141-59.

Qian LK (2014). Clinical observation on arsenic trioxide combined with transcatheter arterial chemoembolization in treatment of patients with primary liver cancer. China Medical University, 1-33. Available online: http://istic.wanfangdata.com.cn/Search/Detail?db=zw_xw&uniqueId=0620151100549217

Ranieri G, Ammendola M, Marech I, et al (2015). Vascular endothelial growth factor and tryptase changes after chemoembolization in hepatocarcinoma patients. *World J Gastroenterol*, **21**, 6018-25.

Shen Y, Fu YK, Zhu YM, et al (2015). Mutations of epigenetic modifier genes as a poor prognostic factor in acute promyelocytic leukemia under treatment with all-trans retinoic acid and arsenic trioxide. *EBio Medicine*, **2**, 563-71.

Song YX, Du X, Jin Y, Zhang Y (2000). Pharmacokinetics of As203 in rabbit after iv administration with different dose. *Chin J Hosp Pharm*, **20**, 27-8.

Tan B, Huang JF, Wei Q, Zhang H, Ni RZ (2005). Anti-hepatoma effect of arsenic trioxide on experimental liver cancer induced by 2-acetamidofluorene in rats. *World J Gastroenterol*, **11**, 5938-43.

Tang YH, Tian YG, Liu TF, et al (2005). Inhibitory effect of arsenic trioxide on proliferation of hepatoma cells in mice. *WorId Chin J Digestol*, **13**, 2074-7.

Tang RJ, Cui SZ, Tan ZM, et al (2006). Arsenic trioxide continuous regional hepatic arterial infusion after TACE in the treatment of primary hepatic carcinoma; a report of 26 cases. *J Chin Med Res*, **6**, 925-6.

Tang YH, Shang GY, Liang T (2009). Effect of As203 on VEGF and COX-2 expression in mouse hepatocacinoma. *J Harbin Med Univ*, **43**, 435-40.

Wang SS, Zhang T, Wang XL, Hong Li, Qi QH (2003). Effect of arsenic trioxide on rat hepatocarcinoma and its renal cytotoxicity. *World J Gastroenterol*, **9**, 930-5.

Wang XJ, Liu XM, Zeng CY, Zhang Y, Liang XQ (2008). Apoptosis and cell cycle-blockade of human hepatocarcinoma HepG2 cells induced by arsenic trioxide. *J Beijing Univ Tradi Chin Med*, **31**, 404-7.

Wang MM, Hu JP, Ou LF, et al (2012). Effects of arsenic trioxide on intracellular SOCS-1gene methylation and P-STAT3 expression in multiple myeloma cells. *J Int Oncol*, **39**, 633-6.

Xing R (2012). Randomized controlled study of lipiodol-arsenic trioxide emulsion in the treatment of primary hepatic carcinoma. China Medical University, 1-33. Available online: http://d.g.wanfangdata.com.cn/Thesis_Y2092205.aspx

Xie YR, Zhou YF, Ying XL (2007). Efficiency evaluation on arsenic trioxide containing regimen in treatment of patients with middle or advanced hepatocellular carcinoma by intervention. *Zhejiang Clin Med J*, **9**, 1161-2.

Xu HY, Yang YL, Liu SM, Li B, Chen SX (2004). Effect of arsenic trioxide on human hepatocarcinoma in nude mice. *World J Gastroenterol*, **10**, 3677-9.

Yan TH, Xu WD, Gu WL, Yu JY (2013). Clinical observation of arsenic trioxide combined with transcatheter arterial chemoembolization treatment of advanced primary liver cancer. *Chin J Clin Oncol Rehabil*, **20**, 1377-80.

Yin H, Tang SQ, Feng C, Yu F (2009). Experimental study on effect of arsenic trioxide on suppression of neuroblastom cell invasion. *J Appl Clin Pediatr*, **24**, 209-15.

Yua ZY, Wu FL, Chen L, et al (2014). ETME, a novel β-elemene derivative, synergizes with arsenic trioxide in inducing apoptosis and cell cycle arrest in hepatocarcinoma cells via a p53-dependent pathway. *Acta Pharm Sin B*, **4**, 424-9.

Yuan HM, Cheng HM (2012). Arsenic trioxide induced

colorectal cancer stem cells apoptosis and inhibited clonal hyperolasia. *Acta Acad Med Xuzhou*, **32**, 281-5.

Zhang P, Wang SY, Hu LH, et al (1995). The Clinical observation and mechanism discussion of "713" in the treatment of 117 cases acute promyelocytic leukemia. *J Harbin Med Univ,* **29**, 243.

Zhang X, Wang PL, Tao XH (2004). Study on arsenic trioxide induced apoptosis in hepatoma cells and its molecular mechanism. *J Chongqing Med Univ,* **29**, 444-7.

Zhang XB, Xie JG, Tan ZM, et al (2010). Clinical study of arsenic trioxide in the treatment of primary hepatic carcinoma by interventional ways. *Contemporary Med*, **16**, 112-3.

Zhang XM, Wang T, Li XJ, Zhao L, Li HM (2011). Effect of arsenic trioxide on proliferation of T cell lymphoma cell line Hut-78. *J Clin Rehabil Tissue Eng Res*, 15, 4325-9.

Zhang WJ, Xu DF, Fan QX, et al (2012). Arsenic trioxide restores ERα expression in ERα-negative human breast cancer cells and its treatment efficacy in combination with tamoxifen in xenografts in nude mice. *Chin J Oncol*, **34**, 645-51.

Zhang HN, Yang LN, Ling JY, et al (2015). Systematic identification of arsenic-binding proteins reveals that hexokinase-2 is inhibited by arsenic. *Proc Natl Acad Sci U S A*, **112**, 15084-9.

Zheng MY, Yu XD, Wang T, et al (2004). Hepatic toxicity of arsenic trioxide on rabbits with hepatic Vx-2 carcinoma by transcatheter arterial chemoembolization. *J Chin Physician*, **6**, 1465-7.

Zhou ZT, Lin XJ, Cui BK, Li GH (2007). Clinical study on arsenic trioxide-containing regimen in treatment of patients with middle or advanced hepatocellular carcinoma by TACE. *Chin J Cancer Prev Treat*, **14**, 1094-6.

Zhou Y, Yu JW, Wu HX, Yu ZJ (2009). Apoptosis induced by arsenic trioxide and its effects on OPN expression in human hepatocellular carcinoma SMMC-7721 cell. *Shandong Med J*, **49**, 7-9.

Zhuang XL, Wu XQ, Wu WY (2006). Efficacy of hepatic artery infusion of arsenic trioxide in treatment of hepatocellular carcinoma. *Chin J Cancer Prev Treat*, **13**, 1106-7.