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ORIGINAL PAPER

Radiation sensitization with sodium nitrite in patients with brain metastases: a pilot randomized controlled trial

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Abstract Systemic administration of nitrite anion seems to be a practical way to produce local burst of nitric oxide, a hypoxic cell radiosensitizer in solid tumors. This randomized controlled pilot study assessed radiologic objective response rate (ORR) in patients suffered from brain metastases treated by whole-brain radiotherapy (WBRT) concurrent with intravenous infusion of sodium nitrite versus WBRT alone. Twenty patients were randomized into the following groups: Ten patients treated by WBRT (30 Gy in ten fractions over 2 weeks) concomitant with 2-hour intravenous infusion of sodium nitrite (267 μg/kg/h) before each fraction of radiation (WBRT + SN arm) and ten patients received the same schedule of WBRT, alone (control arm). ORR was measured according to response evaluation criteria in solid tumors (RECIST version 1.1). There were four radiologic objective responses in WBRT + SN arm compared with three in the control group without significant statistical difference ($P = 1.00$). In contrast, age $\leq$ 65years ($P = 0.05$) and presence of extra-cranial metastases ($P = 0.01$) were predictor factors of ORR. In conclusion, intravenous infusion of sodium nitrite with this dose and schedule to patients with brain metastases concurrent with radiotherapy did not show any major benefit in terms of radiologic response.

Keywords Nitric oxide · Sodium nitrite · Radiation-sensitizing agents · Radiotherapy · Brain neoplasm

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Introduction

Radiosensitizers are pharmacologic agents that potentiate the lethal effects of ionizing radiation on cancer cells. Oxygen (O_2) is the most potent radiosensitizer and acts by fixing the radiation-induced DNA damage and making it unrepairable. Therefore, partial pressure of oxygen (pO_2) in solid tumors plays an important role in clinical response to radiation therapy (RT), and hypoxia is a major cause of treatment failure. Oxygen deficiency in tumors is a result of inadequate perfusion and also increased oxygen consumption [1].

Enhancing the tumor pO_2 by vasoactive agents and oxygen consumption modifiers is a promising approach to increase the therapeutic benefits of RT. Multiple preclinical studies have been shown that the bioregulatory free radical nitric oxide (NO) can efficiently enhance the effects of ionizing radiation on hypoxic cells. Most probable mechanisms are mimicking the effects of oxygen and stabilization of radiation-induced DNA damage, inhibition of mitochondrial respiration and sparing of the natural radiosensitizer oxygen and finally by increasing tumor blood flow and oxygenation. [2–4].

Pharmacological delivery of adequate concentrations of short-lived gaseous NO to solid tumors is problematic because of its vasoactive complications. Recent evidence suggests that nitrite anion (NO_2^-), the inert end product of the NO oxidative metabolism, under low pO_2 and acidic pH can

be reconverted into biologically active NO and thus systemic intravenous (IV) infusion of nitrite as a NO donor could produce a local burst of NO in acidic microenvironment of solid tumors in contrast to normal tissues with physiologic pH, and this can result to a selective radiosensitization of malignant cells with minimal systemic toxicity. [5, 6].

To test this hypothesis in a clinical setting, this pilot study assessed whether IV infusion of sodium nitrite ($NaNO_2$) (SN) concomitant with conventional whole-brain radiation therapy (WBRT) was able to obtain a higher radiologic objective response rate (ORR) (complete response plus partial response) than WBRT alone in patients suffered from brain metastases.

Materials and methods

Study design

We conducted a pilot single-blind, prospective randomized controlled trial (RCT) at a single institution (Clinical Oncology Department of Golestan Hospital, Ahwaz Jundishapur University of Medical Sciences, Ahvaz, Iran). Registration was done in Iranian Registry of Clinical Trials (IRCT.ir) (number IRCT2013101515026N1), and informed consent was obtained from all individual participants included in the study. The study started in October 2013 and closed in September 2014. Patients with brain metastasis were randomly assigned into two groups. In the first group, patients were treated with WBRT alone (control arm), and in the second group (intervention arm), patients received WBRT with concomitant sodium nitrite. The primary endpoint was radiologic ORR.

Eligibility

Eligible patients were 18–80 years of age with a histopathologically confirmed extra-cranial malignancy and at least one brain metastasis more or equal to 1 cm in size demonstrated on an axial gadolinium-enhanced T1 sequence magnetic resonance scan (MRI). Patients must have an estimated survival of at least 4 weeks and ECOG performance status of 0–3. Patients were ineligible if they had major medical illnesses or psychiatric impairments which, in the investigator's opinion, will prevent completion of the protocol therapy, previous radiotherapy to the head, patients who cannot be regularly followed and leptomeningeal involvement.

Treatment

In both arms of this study, WBRT was delivered using parallel opposed 6 MV photon beams to a total dose of 30 Gy in ten fractions, five times weekly in two consecutive weeks. The dose was calculated in the mid plane along the central axis. Sodium nitrite (diluted in half liters of normal saline) was administered to the intervention group intravenously in 2 hours and at a dose rate of 267 μg/kg/h before each fraction of radiation [7]. Steroids and anticonvulsant agents were allowed as needed and at the lowest dose possible to maintain neurologic function and prevent seizures, respectively. [8, 9].

Radiologic response measurement

For evaluation of the radiologic objective response, two gadolinium-enhanced T1 sequence brain MR scans were obtained from the enrolled patients, first one at baseline within 2 weeks prior to initiation of treatment and the second one 4–6 weeks after completion of WBRT. After comparing the baseline to the second MRI, patients classified into four groups including complete responders (CR), partial responders (PR), progressive and stable disease (PD and SD) according to response evaluation criteria in solid tumors version 1.1 (RECIST). CR was defined as disappearance of all target lesions. PR was defied as at least 30 % decrease in the sum of the longest diameters (SLD) of target lesions. PD was defined as at least 20 % increase in the SLD of target lesions and an absolute increase in SLD of at least 5 mm or the appearance of new lesions. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient enlargement to qualify for PD. [10].

Statistical analysis

Patients were stratified according to sex (male vs. female), age (<65 vs. ≥ 65 years), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0, 1 vs. 2, 3), number of brain metastases (≤ 4 vs. >4), type of primary tumor (breast vs. other), extracranial metastases (presence vs. absence) and history of pervious chemotherapy (presence vs. absence). Objective responses and other categorical variables were compared between arms of this study using two-sided Fisher's exact test. Statistical calculations were carried out with the online GraphPad QuickCalcs (www.graphpad.com/quickcalcs).

Results

Twenty consecutive patients were enrolled in this trial from October 2013 to September 2014. Ten patients randomly assigned to the intervention arm (WBRT + SN) and ten patients to the control arm (WBRT). Demographic, Clinical and histopathologic features of the patients are outlined in Table 1 and are not statistically different between the

study arms. Treatment was well tolerated in the both groups, and no symptomatic acute toxicity was observed.

There was four radiologic objective responses in WBRT + SN arm compared with three responses in the control group which did not reach statistical significance ($P = 1$). In the univariate analysis, age <65 years ($P = 0.05$) and presence of extracranial metastasis ($P = 0.01$) were OR predictive factors. Details of response evaluation are shown in Tables 2 and 3 for the WBRT + SN and WBRT arms, respectively.

Discussion

Enhancing the biologic effects of ionizing radiation on cancer cells and at the same time protecting normal tissues from toxicity with less toxic pharmacologic interventions is of particular interest in modern radiation oncology [11]. Many preclinical studies suggest that the free radical nitric oxide is a potent hypoxic cell radiosensitizer with an approximate enhancement ratio of 2.5 [12, 13]. Also, it seems that intravenous administration of sodium nitrite as a NO donor is a practical way for delivering adequate concentrations of nitric oxide to solid tumors. [5–7].

Our preliminary small clinical trial which tried to test this hypothesis in patients with brain metastases did not show any major improvement in radiologic objective response rate in WBRT + SN arm compared with the control group. Because of small sample size and heterogeneous characteristics of participants including primary tumor histopathology, this study was not sufficiently powered to demonstrate small statistically significant benefits, and it clearly establishes that there is no major difference between the two arms of this trial in terms of radiologic ORR. One explanation for this negative result is administration of insufficient doses of sodium nitrite to the intervention group. However, Pluta et al. [7] in their dose finding study showed that sodium nitrite can be safely infused intravenously at the maximal tolerated dose rate of 267 μg/kg/h for prolonged intervals without symptomatic toxicity, and it seems reasonable and feasible to use much higher IV bolus doses before each fraction of radiotherapy for radiation sensitization purposes with minimal side effects.

We observed a 30 % response rate in the control group compatible to what is reported in the literature for patients with brain metastases who treated with radiotherapy. For example in a meta-analysis of eight RCT's involving 2,317 patients suffered from brain metastases and treated with WBRT ± radiosensitizer, Viani et al. [14] reported a 24.6 % ORR in evaluable patients who received RT alone. Also similar to results of this study, multiple clinical trials showed that younger age is a favorable predictor of radiologic response. [15].

Table 1 Patient characteristics

Characteristic	WBRT + SN arm ($n = 10$)	WBRT arm ($n = 10$)	P value
Gender			
Male	3	5	0.65
Female	7	5	
Age (median)	52 years	57 years	
Range	30–73 years	36–75 years	
<65years	7	7	1
≥65years	3	3	
ECOG PS			
0, 1	3	6	0.37
2, 3	7	4	
Brain Mets (n)			
≤4	8	8	1
>4	2	2	
Primary tumor			
Breast	4	4	1
Other	6	6	
Extra-cranial Mets			
Presence	8	5	0.35
Absence	2	5	
Previous CHT			
Presence	9	8	1
Absence	1	2	

ECOG PS Eastern Cooperative Oncology Group performance status, *Mets* metastases, *CHT* chemotherapy

Table 2 Details of response analysis in WBRT + SN arm

Patient No.	Primary tumor	TL LD/SLD (Before treatment) (mm)	TL LD/SLD (After treatment) (mm)	TL LD/SLD change (%)	TL response	Non-TL response	New lesion	Overall response
1	CUP	33 + 10 = 43	20 + 0=20	−53.5	PR	Non-CR/PD	–	PR
2	Breast	17	11	−35	PR	–	–	PR
3	NSCLC	25 + 12 = 37	10 + 11 = 21	−40.5	PR	Non-CR/PD	–	PR
4	Uterine	48	43	−10.5	SD	–	–	SD
5	NSCLC	66 + 28 = 94	61 + 20 = 81	−14	SD	Non-CR/PD	–	SD
6	Breast	18	21	+16.5	SD	Non-CR/PD	–	SD
7	Breast	15 + 15 = 30	10 + 11 = 21	−30	PR	Non-CR/PD	–	PR
8	CRC	17	15	−12	SD	–	–	SD
9	TCC	16 + 15 = 31	16 + 17 = 33	+6.5	SD	Non-CR/PD	–	SD
10	Breast	18	15	−16.5	SD	–	–	SD

TL target lesion, *LD* longest diameter, *SLD* sum of longest diameters, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CUP* cancer with unknown primary site, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *CRC* colorectal cancer, *TCC* transitional cell carcinoma

Table 3 Details of response analysis in WBRT arm

Patient No.	Primary tumor	TL LD/SLD (Before treatment) (mm)	TL LD/SLD (After treatment) (mm)	TL LD/SLD change (%)	TL response	Non-TL response	New lesion	Overall response
1	Hemangiopericytoma	48	65	+35.5	PD	–	–	PD
2	NSCLC	14	13	−7	SD	Non-CR/PD	–	SD
3	TCC	30	30	0	SD	–	–	SD
4	Breast	14	11	−21.5	SD	–	–	SD
5	Breast	11	0	−100	CR	CR	–	CR
6	NSCLC	26 + 17 = 43	20 + 17 = 37	−14	SD	–	–	SD
7	Breast	14 + 10 = 24	0 + 0=0	−100	CR	Non-CR/PD	–	PR
8	Breast	19 + 12 = 31	16 + 10 = 26	−16	SD	Non-CR/PD	–	SD
9	SCLC	26	11	−57.5	PR	–	–	PR
10	CRC	13	13	0	SD	Non-CR/PD	–	SD

TL target lesion, *LD* longest diameter, *SLD* sum of longest diameters, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CUP* cancer with unknown primary site, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *CRC* colorectal cancer, *TCC* transitional cell carcinoma

Important limitations of our study were small patient sample size with heterogeneous characteristics that preclude finding small differences in ORR, using relatively low doses of sodium nitrite because of insufficient data regarding safe higher bolus doses of this drug in human binges and also that other important oncologic end points such as overall and neurologic progression-free survival as well as late toxicity were not evaluated.

We suggest that despite this negative result, well-designed larger-scale randomized clinical trials with more homogenous patient population and using higher doses of sodium nitrite or other ways of delivering NO to cancer concurrent with radiotherapy should be done based on encouraging evidence provided by many preclinical studies.

In conclusion, 2-h IV infusion of NO donor sodium nitrite at a dose rate of 267 μg/kg/h as a radiosensitizer to patients diagnosed with brain metastasis before each fraction of radiotherapy did not show any statistically significant major benefit in terms of radiologic ORR.

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Conflict of interest None.

Ethical approval The Ahvaz Jundishapur University of Medical Sciences ethics and scientific committees approved the study protocol according to the Helsinki declaration (ajums.REC.1392.170).

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