Original Article

Effectiveness and safety of different amifostine regimens: Preliminary results of a phase II multicenter randomized controlled trial

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Abstract

Objective: The radioprotective effects of amifostine remain uncertain in patients with nasopharyngeal carcinoma (NPC), and adverse effects and cost limit generalization of its classical everyday regimen. This phase II multicenter randomized controlled trial aimed to explore whether amifostine could ameliorate the toxicities of NPC patients in the era of intensity-modulated radiotherapy (IMRT), and to compare different regimens of amifostine on effectiveness and safety.

Methods: Patients with stage I–IVB NPC were involved prospectively from January 1st, 2013. All patients received radical treatment based on IMRT. After a randomization stratified by their stage, these patients were allocated into 3 groups: the group treated without amifostine, the group treated with the everyday regimen of amifostine, and the group treated with the every-other-day regimen. The 3 groups of patients were compared on radiotherapy-related acute toxicities, treatment effects of NPC, and amifostine-related complications. This trial was registered on the clinicaltrials.gov (ID: NCT01762514).

Results: Until August 31st, 2017, totally 187 patients completed experimental intervention. Only amifostine of everyday regimen appeared to reduce the patient proportion of mucositis (79.1% *vs*. 96.8%, P=0.002). Hypocalcemia was less common in patients treated without amifostine than in those treated with amifostine (22.6% *vs*. 53.4% *vs*. 41.8%, P=0.002). Neither complete remission rates nor the survivals were affected by amifostine.

Conclusions: Amifostine of everyday regimen could reduce mucositis in NPC patients who received IMRT, though it also had the possibility to cause more hypocalcemia.

Keywords: Nasopharyngeal carcinoma; amifostine; intensity-modulated radiotherapy; acute toxicity

Submitted Nov 13, 2017. Accepted for publication May 07, 2018.
doi: 10.21147/j.issn.1000-9604.2018.03.03
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2018.03.03

Introduction

The nasopharyngeal carcinoma (NPC) is one of the most common cancers in South China (1,2) and mainly treated through radiotherapy (RT) (3). The intensity-modulated radiotherapy (IMRT) brings a 5-year overall survival (OS) of 85.0% (4). Contrarily, there are still many patients suffering from severe RT-related toxicities. The total incidence of grade 3/4 acute toxicities during RT is as high as 33.2% (5). And late toxicities (incidence, 9.0%) remained the main adverse factors affecting life quality of the patients after RT (6). Because reducing the toxicities might help to ameliorate tolerance of RT and life quality of the long-term survivors, radioprotection has now become one of the research hotspots.

Amifostine (AMF) is one of the most frequently used radioprotectors. It has been proved *in vitro* that AMF could protect normal cells from deoxyribonucleic acid (DNA) damage, and simultaneously inhibit DNA repair of the cancer cells (7). A series of clinical studies have also revealed that AMF could reduce toxicities of RT in some solid tumors, such as head and neck (HN), ovarian, breast and lung cancers (8-10), without influencing the treatment effects (11). Oppositely, the radioprotective effects of AMF were not seen in some studies (12,13). Furthermore, the clinical value of AMF remains uncertain in NPC. Therefore, this phase II trial aimed to explore the protective and the adverse effects of AMF in NPC patients treated with IMRT. Additionally, the side effects and the high cost of the classical everyday regimen limit generalization of AMF (14), especially in the developing countries like China. This trial also aimed to compare the every-other-day regimen with the standard everyday regimen on effectiveness and safety.

Patients and methods

Registration and ethical information

This trial was registered on the clinicaltrials.gov (ID: NCT01762514). It was approved by the Institutional Review Boards of the participating centers. Written informed consent was obtained from all individual participants involved in this trial.

Study design and patients

This trial is a multicenter, randomized parallel controlled, unblinded phase II clinical trial. The details of design referred to the protocol on the clinicaltrials.gov. The patients were enrolled into this trial if they had: 1) diagnosis of untreated stage T1–4N0–3M0 [the 7th edition of the Union for International Cancer Control/American Joint Cancer Committee TNM staging classification (15)] NPC after the trial started (January 1st, 2013); 2) age between 18 and 75 years old; 3) Karnofsky performance score ≥60; and 4) expected survival time ≥3 months. The exclusion criteria included: 1) prior history of alcohol or drug abuse; 2) pregnant or lactating women; 3) treatment with other radioprotective drugs currently; 4) regular application of anti-hypertension drugs; 5) severe hypocalcemia; 6) heart, lung, liver, kidney or hematopoietic dysfunctions unsuitable for RT; 7) severe neurological, mental or endocrine diseases; 8) prior allergic reactions to AMF; or 9) participation in clinical trials of other drugs within 3 months.

Randomization

A randomization stratified by stage was applied centrally in this trial, to allocate the patients into the control group (Group A), the every-other-day AMF group (Group B), and the everyday AMF group (Group C), at a ratio of 1:1:1. The allocation was unblinded for the researchers and the patients. The procedure of the randomization is summarized in *Figure 1*.

Cancer treatment

The treatment strategies of all the patients were decided according to the guidelines of the National Comprehensive Cancer Network and our hospital, which was the sponsor center. Stage I–II disease was treated with RT alone, and stage III–IVB disease was treated with RT plus concurrent chemotherapy (CCT). The RT technique for all the patients was IMRT. The CCT was performed uniformly with the nedaplatin plus 5-flurouracil regimen.

AMF administration

The patients in Group A were planned to receive only the cancer treatment (RT plus CCT or not). The patients in Group B were planned to receive the cancer treatment plus AMF of every-other-day regimen (400 mg on Day 1, 3 and 5, every week for totally 6–7 weeks). And the patients in Group C were planned to receive the cancer treatment plus AMF of everyday regimen (400 mg on Day 1–5, every week for totally 6–7 weeks).

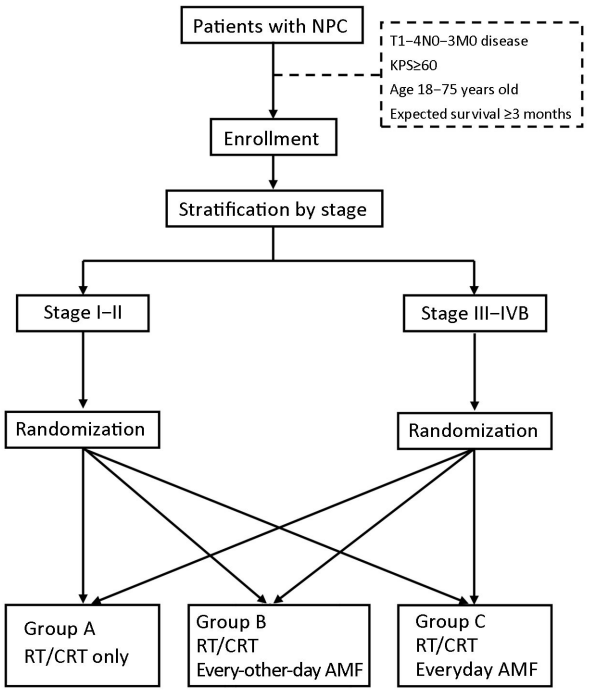

Figure 1 Procedure of randomization. NPC, nasopharyngeal carcinoma; KPS, Karnofsky performance score; RT, radiotherapy; CRT, chemoradiotherapy; AMF, amifostine.

Study measurements

Before treatment, all the patients underwent a series examinations assessing baseline clinical profiles, including naspharyngoscope, physical examination (PE) and magnetic resonance imaging (MRI) of HN, thoraco-abdominal computed tomography (CT), and whole-body bone scan (or positron emission tomography).

When the RT was performed 10, 20 and 30 fractions, HN CT and nasopharyngoscope were performed for each patient to evaluate the regression of the primary tumor. The regression grade was determined based on the Response Evaluation Criteria in Solid Tumors version 1.1 (16).

HN PE, complete blood count and serum biochemistry profile were assessed once a week during RT and a week after RT. The RT-related toxicities and the AMF-related complications were decided on basis of Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (17).

The follow-up of disease status was made through outpatient interview every 3 months for the first 3 years after treatment. In the 4th and 5th years, the patients were followed up by outpatient interview or telephone semi-annually. And the patients were followed up annually thereafter, until death from NPC or August 31st, 2017, whichever came first.

Endpoints

The primary endpoints of this trial were: 1) proportions of patients with the most common RT-related acute toxicities of NPC (myelosuppression, xerostomia and mucositis); and 2) OS, which was defined as the percentage of patients who survived after a certain time period from pathological diagnosis (the survival patients and those lost to follow-up were regarded censored).

The secondary endpoints included: 1) proportions of patients with the grade 3/4 acute toxicities mentioned above; 2) complete remission (CR) rates at 30 fractions of RT and 3 months after RT; 3) disease-free survival (DFS), which was defined as the percentage of patients who had no death, local recurrence or distant metastasis after a certain time period from pathological diagnosis (the patients without these events and those lost to follow-up were regarded censored); and 4) proportions of patients with the most common AMF-related complications, including upper gastrointestinal (GI) reactions, hypotension and hypocalcemia.

Statistical analysis

The baseline clinical profiles, patient proportions, and CR rates among the 3 groups were compared by a Chi-square test. The survivals were calculated through the Kaplan-Meier approach, in which a log-rank test is performed to assess the differences among the 3 groups. If a statistical significance is attained, multiple comparisons between any 2 of the 3 groups will be performed.

All statistical analyses were done by IBM SPSS software (Version 23.0; IBM Corp., New York, USA). A difference with a two-sided P value of less than 0.05 was considered to be statistically significant. But for the multiple comparisons, the P value threshold was adjusted as 0.017 according to the Bonferroni correction (18).

Results

Baseline characteristics

Until August 31st, 2017, a total of 189 patients were enrolled. Of those, 2 patients (1 case in the Group B and 1 case in the Group C) quitted the trial before RT, according

to the will of the patients. Finally, 187 patients (98.9%) completed experimental intervention and were eligible for analysis. The median age of these patients was 46 (range, 18–75) years old. The numbers of the patients with stage I–II disease and those with stage III–IVB disease were 51 (27.3%) and 136 (72.7%), respectively. There were 62 (33.2%), 58 (31.0%) and 67 (35.8%) patients in the Groups A, B and C respectively. Baseline characteristics were balanced among the 3 groups (*Table 1*).

Protective effects of AMF

The proportions of patients with mucositis were 96.8%, 94.8% and 79.1% in the Groups A, B and C (P=0.001), respectively (*Table 1*). The proportions of patients with xerostomia were 87.1%, 89.7% and 86.6% (P=0.858), respectively. And the figures of myelosuppression were 66.1%, 70.7% and 64.2% (P=0.735), respectively. Multiple comparison showed that the Group C had less patients with mucositis than the Groups B and A (P=0.011 and 0.002, respectively) (*Figure 2*). The Groups A and B had similar patients with mucositis (P=0.594). Nevertheless, there was no difference in proportions of patients with grade 3/4 mucositis, myelosuppression or xerostomia among the 3 groups (P=0.444, 0.561 and 0.958, respectively) (*Table 1*, *Supplementary Figure S1*).

Treatment results

No difference was seen in CR rates among the 3 groups at 30 fractions of RT, or 3 months after RT (P=0.279 and 0.974, respectively). After a median follow-up time of 41 (range, 6–56) months, 14 out of 187 patients (7.5%) were lost to follow-up. There was no difference either in the OS or in the DFS among the 3 groups (P=0.354 and 0.448, respectively) (*Figure 3*).

AMF-related complications

Hypocalcemia was less common in the Group A than in the Groups B and C (P=0.002). But there was no difference in patient proportion of GI reactions or hypotension among the 3 groups (P=0.321 and 0.222, respectively) (*Table 1*). Further multiple comparison showed that the Group B had more patients with hypocalcemia than the Group A (53.4% *vs*. 22.6%, P<0.001). No difference was shown between the Group C and the Group B, or between the Group C and the Group A (P=0.193 and 0.020, respectively) (*Supplementary Figure S2*).

Discussion

AMF of the everyday regimen (400 mg/d, 5 d per week) concurrently with RT was proved in this trial to decrease the patient proportion of mucositis, compared with RT alone (79.1% *vs*. 96.8%, P=0.002). The result was reliable because the trial was a multicenter randomized controlled trial enrolling relatively large scale of NPC patients. For NPC, there was no such strong evidence before. Considering mucositis has been reported as the most common acute toxicity (incidence, 99.0%–99.4%) during RT (5,19), AMF might help to improve RT tolerance of NPC patients. Additionally, a recent study by You *et al*. indicated that combining chemotherapy with agents targeting epidermal growth factor receptor could further elevate the survival of locally advanced NPC, as well as the risk of mucositis (20). It conferred broader prospect of application to AMF. However, in this trial, the proportion of patients with grade 3/4 mucositis was not influenced by AMF.

Prior to our study, there were a series of approaches which also showed radioprotective effects of AMF in HN cancers. A study by Münter *et al*. indicated that AMF could relieve decline in excretion rate of salivary glands after RT (21). Büntzel *et al*. also showed in a prospective cohort study involving 851 patients that AMF could ameliorate late xerostomia and altered taste significantly (22). Furthermore, Gu *et al*. made a meta-analysis summarizing 17 trials until January 2012 to demonstrate that AMF could decrease the risk of developing grade 3/4 acute mucositis, xerostomia and dysphagia (23). In addition, a study by Saavedra *et al*. revealed that AMF had a potential to alter radio-induced apoptosis of peripheral blood cells (24).

Yet, evidences on application of AMF are unconsistent. In a phase II randomized controlled trial of Haddad *et al*., AMF did not bring improvement of acute xerostomia or mucositis to patients who received chemoradiotherapy (25). The protective effects of AMF on acute or late xerostomia were not seen in a systemic review by Riley *et al*., either (14). In our study, neither myelosuppression nor xerostomia was reduced when AMF was administrated. Therefore, more evidences are needed to validate the radioprotection from AMF, particularly the strong evidences from randomized controlled trials.

AMF itself could also cause some complications. The most common grade 3/4 side effects of AMF are hypocalcemia, emesis, nausea, hypotension and allergic reactions (incidences were 8.6%, 6.0%, 5.0%, 4.0% and

Table 1 Baseline profiles, treatment effects and complications (N=187)

Factors	n (%)			χ^2	P
	Group A	Group B	Group C		
Total number	62	58	67		
Baseline profiles					
Age (year)					
<46	30 (48.4)	31 (53.4)	26 (38.8)	2.808	0.246
≥46	32 (51.6)	27 (46.6)	41 (61.2)		
Gender					
Male	50 (80.6)	44 (75.9)	45 (67.2)	3.170	0.205
Female	12 (19.4)	14 (24.1)	22 (32.8)		
Stage					
I–II	20 (32.3)	16 (27.6)	15 (22.4)	1.586	0.453
III–IVB	42 (67.7)	42 (72.4)	52 (77.6)		
RT toxicities					
Mucositis					
No	2 (3.2)	3 (5.2)	14 (20.9)	13.306	0.001
Yes	60 (96.8)	55 (94.8)	53 (79.1)		
Xerostomia					
No	8 (12.9)	6 (10.3)	9 (13.4)	0.306	0.858
Yes	54 (87.1)	52 (89.7)	58 (86.6)		
Myelosuppression					
No	21 (33.9)	17 (29.3)	24 (35.8)	0.616	0.735
Yes	41 (66.1)	41 (70.7)	43 (64.2)		
Grade 3/4 mucositis					
No	47 (75.8)	40 (69.0)	44 (65.7)	1.624	0.444
Yes	15 (24.2)	18 (31.0)	23 (34.3)		
Grade 3/4 xerostomia					
No	57 (91.9)	56 (96.6)	63 (94.0)	1.155	0.561
Yes	5 (8.1)	2 (3.4)	4 (6.0)		
Grade 3/4 myelosuppression					
No	59 (95.2)	55 (94.8)	63 (94.0)	0.087	0.958
Yes	3 (4.8)	3 (5.2)	4 (6.0)		
Treatment effects					
CR rate at 30 fractions					
No	20 (32.3)	12 (20.7)	15 (22.4)	2.550	0.279
Yes	42 (67.7)	46 (79.3)	52 (76.6)		
CR rate at 3 months					
No	8 (12.9)	7 (12.1)	9 (13.4)	0.052	0.974
Yes	54 (87.1)	51 (87.9)	58 (86.6)		
AMF complications					
GI reaction					
No	23 (37.1)	15 (25.9)	18 (26.9)	2.275	0.321
Yes	39 (62.9)	43 (74.1)	49 (73.1)		

Table 1 (*continued*)

Table 1 (*continued*)

Factors	n (%)			χ^2	P
	Group A	Group B	Group C		
Hypotension					
No	55 (88.7)	45 (77.6)	53 (79.1)	3.009	0.222
Yes	7 (11.3)	13 (22.4)	14 (20.9)		
Serum calcium (mmol/L)					
<2.11	14 (22.6)	31 (53.4)	28 (41.8)	12.330	0.002
≥2.11	48 (77.4)	27 (46.6)	39 (58.2)		

CR, complete remission; RT, radiotherapy; AMF, amifostine; GI, gastrointestinal.

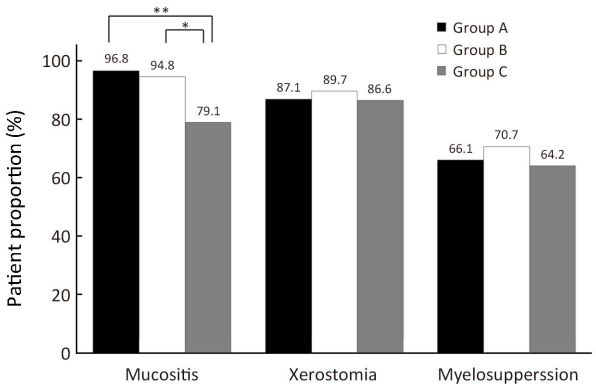

Figure 2 Multiple comparison in mucositis, xerostomia and myelosuppression. *, P<0.05; **, P<0.01.

4.0%, respectively) (23,26). Some rare complications such as Stevens-Johnson syndrome and toxic epidermal necrolysis were also reported (27). In our study, AMF did not increase incidence of GI reactions or hypotension. Nevertheless, compared with RT alone, concomitant AMF of every-other-day regimen presented to cause more hypocalcemia (53.4% *vs*. 22.6%, P<0.001). And though statistical significance was not achieved, the everyday regimen still had a potential possibility to increase hypocalcemia (41.8% *vs*. 22.6%, P=0.020). Additionally, subcutaneous injection of AMF was reported to cause fewer complications than intravenous injection. Meanwhile, the protective effects of the former might be weaker as well (23,28). Admittedly, it is another concern whether AMF influences the treatment effects of RT. Our study showed that neither CR rates (at 30 fractions of RT or at 3 months after RT) nor the survivals (OS or DFS) were affected by AMF. These results were in accordance with the previous

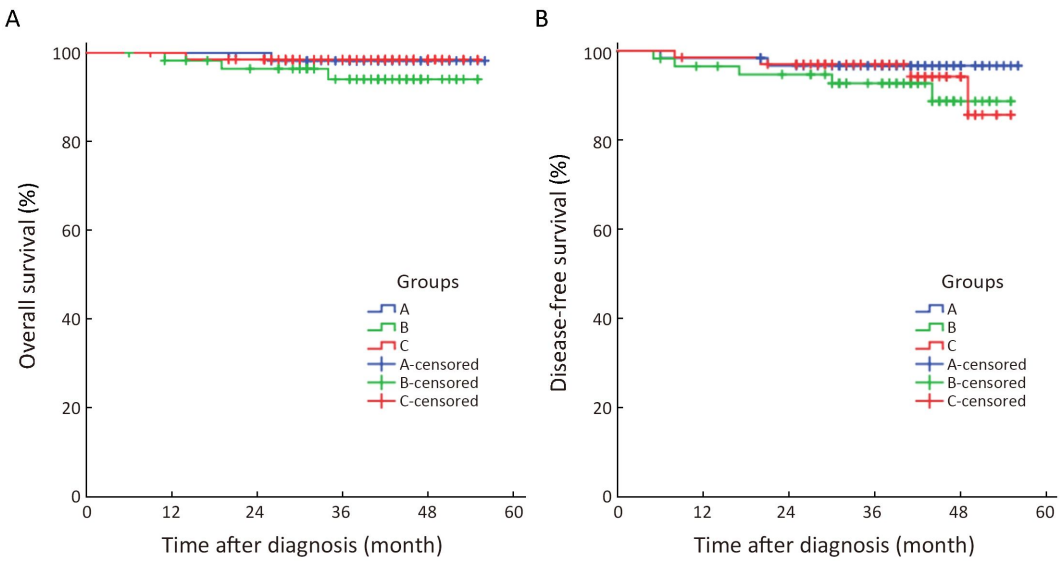

Figure 3 Survival curves of the 3 groups of patients. (A) Overall survival (OS). The OS of the Groups A, B and C were 98.4%, 94.8% and 98.5%, respectively (P=0.354); (B) Disease-free survival (DFS). The DFS of the Groups A, B and C were 96.8%, 91.4% and 94.0%, respectively (P=0.448).

studies performed in HN and lung cancers (11). Hence, AMF was a safe choice for radioprotection of NPC patients.

Indeed, there were some limitations in our study. First, it was not done in a double-blind manner because enough financial and technical support was lacked. Second, late toxicities were not compared among patients with different regimens of AMF. It was because that this trial focused mainly on the acute toxicities, which were the main factors affecting the RT tolerance. Last, the follow-up time was relatively short for NPC, which had an ideal long-term outcome. The follow-up will be continued to report more exact results of prognosis.

Conclusions

AMF of everyday regimen appeared to reduce mucositis in NPC patients who received IMRT, though it also had the possibility to bring more hypocalcemia. And we still recommended that the results of our study be further verified by a phase III trial with a longer follow-up before generalization.

Acknowledgements

We are grateful to Prof. Qing Liu (Department of Preventive Medicine, Sun Yat-sen University Cancer Center) for his technical help in the statistical procedure. This study was supported by the grants of the Hi-Tech Research and Development Program of China (Grant No. 2006AA02Z4B4) and the National Key Projects of Research and Development of China (Grant No. 2016YFC0904600). The funding sources had no role in the study design, data collection, analysis, interpretation or writing of the manuscript.

Footnote

Conflicts of Interest: The authors have no conflicts of interests to declare.

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Cite this article as: Chang H, Yi W, Wang X, Tao Y, Yang X, Chen C, Zhang W, Zhou S, Liu S, Li X, Ding S, Li J, Li G, Shao X, Liu Y, Song W, Xia Y. Effectiveness and safety of different amifostine regimens: Preliminary results of a phase II multicenter randomized controlled trial. Chin J Cancer Res 2018;30(3):307-314. doi: 10.21147/j.issn.1000-9604.2018.03.03

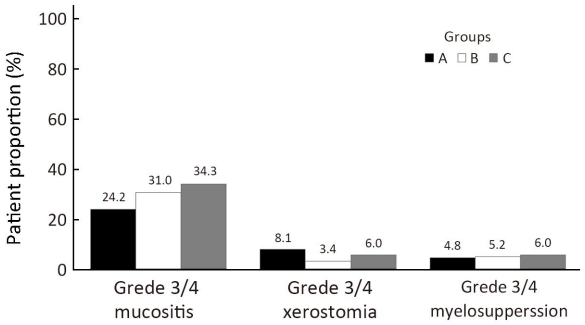

Figure S1 Multiple comparison in grade 3/4 mucositis, xerostomia and myelosuppression. There was no statistically significant difference in proportions of patients with grade 3/4 mucositis, xerostomia or myelosuppression among the 3 groups.

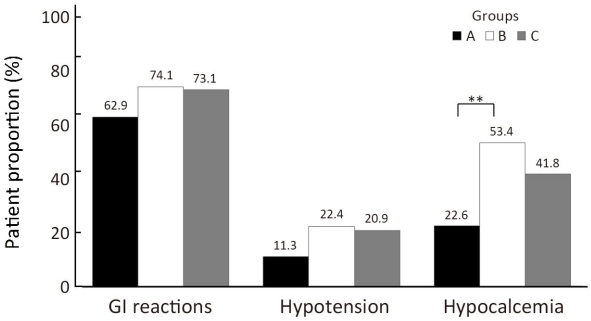

Figure S2 Multiple comparison in gastrointestinal (GI) reactions, hypotension and hypocalcemia. **, P<0.01.