RESEARCH ARTICLE

Glycididazole Sodium Combined with Radiochemotherapy for Locally Advanced Nasopharyngeal Carcinoma

Ming-Yi Li, Jin-Quan Liu*, Dong-Ping Chen, Bin Qi, Yu-Ying Liang, Wen-Jing Yin

Abstract

Background: To evaluate efficacy and side effects of glycididazole sodium (CMNa) combined with chemotherapy (cisplatin plus 5-FU/folic acid, PLF) and radiotherapy in treating patients with locally advanced nasopharyngeal carcinoma. Materials and Methods: Patients with III~IV stage nasopharyngeal carcinoma (NPC),were randomly divided into treatment group (46 patients) and control group (45 patients). Both groups received radiotherapy concomitant with PLF chemotherapy. The treatment group at the same time cwas given CMNa (800 mg/m^2 before radiotherapy), by l h intravenous drip, three times a week. Results: When the dose of radiation was over 60 Gy, complete response rates of nasopharyngeal tumor and lymph node metastases in treatment group were significantly higher than in the control group (93.5% *vs* 77.8%; 89.1% *vs* 93.5%, $p<0.05$). Three months after radiotherapy, complete response rate of nasopharynx cancer and lymph node metastases in treatment group was both 97.8%, again higher than in the control group (84.4% and 82.2%) ($p<0.05$). In the treatment group, 1, 3, 5 year disease-free survival rates were 95.7%, 86.7% and 54.5%; and in control group, the corresponding disease-free survival rates were 93.3%, 66.2% and 38.6%, respectively, the difference being statistically significant (log-rank =5.887, $p=0.015$). One, 3, 5 year overall survival rates in two groups of patients were 97.8%, 93.5%, 70.4% and 95.5%, 88.07%, 48.4%, respectively, again with a statistically significant difference (log-rank=6.470, $p=0.011$). Acute toxicity and long-term radiotherapy related toxicity in the two groups did not differ ($p>0.05$). Conclusions: Glycididazole sodium could improve curative effects without increasing adverse reactions when treating paitents with locally advanced nasopharyngeal carcinoma.

Keywords: Nasopharyngeal cancer - glycididazole sodium - radiotherapy - toxicity - prognosis

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Introduction

Nasopharyngeal carcinoma is one of the common malignant tumor in China. Concomitant radiation and chemotherapy is the most important option in the treatment of patients with locally advanced nasopharyngeal carcinoma (Chen et al., 2012). How to improve efficacy and to reduce side effects of treatment for patients with locally advanced nasopharyngeal carcinoma is still one of the research hot spots. Less study is focused on radiotherapy sensitization glycididazole sodium (CMNa) combined with radio- and chemotherapy in the treatment of patients with locally advanced nasopharyngeal carcinoma. We conducted this comparative study from July 2008 to evaluate the efficacy and side effects of CMNa plus PLF regimen (cisplatin plus 5-FU/folic acid) and concomitant with radiation in treating patients with locally advanced nasopharyngeal carcinoma.

Materials and Methods

Patients

From July 2008 to June 2011, a total of 91 patients with locally advanced nasopharyngeal carcinoma were recruited from Fourth department of radiotherapy, Tumor hospital of Guangzhou medical college. Inclusion eligibility was as follows: (l) patients with nasopharyngeal carcinoma (NPC) aged less than 70 years; (2) general performance status, PS less than or equal to 2. (3) pathologically diagnosed with undifferentiated carcinoma, differentiated squamous cell carcinoma; (4) patients with locally advanced nasopharyngeal carcinoma who were clinical staged III or IV (according to 92 staging system). Exclusion criteria: (l) diagnosed with other malignant tumors or severe heart disease or severe infection, etc. (3) with a history of allergy that is related to treatment (3) pregnant or lactating women.

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Radiotherapy

Patients in two groups were all fixed by the mask, with CT simulation positioning or 3D-CRT. (1) radioactive source: 6 mv X-ray originating from Siemens and Varian linear accelerator was used to irradiate primary tumor bed. And 6 mv X-ray as well as 9~12 mev electron beam to irradiate neck lymphatic drainage area. (2) schedule of radiation therapy: external radiotherapy was conducted from Monday to Friday, once a day. (3) radiation dose: DT 70~76 Gy/7~7.6 weeks for nasopharyngeal primary tumor bed, and DT Gy/6.5~7.4 weeks for neck metastases. (4) radiation field: according to pathological area defined by clinical examination and CT/MRI scan, first with face neck joint portal and anterior neck portal to 36 Gy (2Gy/day), then treated with shrinkaged pre-auricular portal, bounded forward to avoid the spinal cord, lower bound up level, which shall be determined according to the oropharynx invasion, the tangent wild upper anterior portion corresponding increase and wild cohesion in front of the ear. Poststyloid space and posterior triangle of the neck were irradiated by 9~12 mev electron; The wild boundary outside the tumor for at least 1 cm. (5) treatment period: 7~7.6 weeks.

Examination on nasopharyngeal lesion and neck lymphatic area to determin treatment response will be conducted by CT sacn when radiation dose reached 60 Gy. Radiation dose will be set at 76 Gy if treatment response is not satisfactory when the dose of radiation on ear wild to skull base or oropharyngeal invasion reached 70 Gy, or when nasopharyngeal dose reached 70 Gy on nose wild. If primary nasopharyngeal cancer is confined to the nasopharyngeal cavity, and is shallow and small T1 lesion, or is discovered with residual disease after 60 Gy radiation, order a brachytherapy when nasopharyngeal dose reached 70 Gy. Brachytherapy should be conducted by giving a dose of 5 Gy or 10 Gy radiation and by taking submucosal 0.5 cm as a reference points. After irradiation dose reached 60 Gy on lymphatic drainage area around neck, change radiation field to whole neck tangential portal (superior border:along inferior edge of mandibular and earlobe; inferior border: along the edge of supraclavicular; outer border: along the end of clavicle, inside caput humeralis; with a 3 cm wide lead warding off spinal cord along the body middleline.) Adding additional 10 Gy (mev electron line) to a total of 64 Gy to neck lymph node drainage area, if residual disease is diagnosed by ultrasound examination.

Chemotherapy

Patients in both groups were treated with PLF regimen that contains cisplatin 20 mg/m^2 in 500 mL normal saline, intravenously infused from d1 to d4; 5-Fu 2.5 g mg/m^2, of which 0.75 g were intravenously infused on first day, and the rest was infused continuously in 48 hours with an electronic pump; folic acid 200 mg/m^2, added to 500 ml normal saline and intravenously infused from d1 to d3. Chemotherapy was started from the first weekend of radiotherapy, and repeated every five weeks.

CMNa treatment

For treatment group, CMNa 800 mg/m^2, three times/ week and totally for 7~8 weeks (on every Monday, Wednesday and Friday) was infused with l00 ml normal saline within 30 minutes from the first day of radiotherapy (30 minutes before radiotherapy), to a total of 21~24 infusions.

Table 1. Characteristics of Patients

		Treatment group (n=46)	Control group (n=45)	*p* value
Gender (M/F)		31/15	33/12	0.535
Age (y, mean±SD)		46.5±10.2	45.4±11.4	0.783
Pathological type				
Undifferentiated carcinoma		17 (37.0%)	14 (31.1%)	
Keratinizing carcinoma		25 (54.3%)	27 (60.0%)	0.61
Non-keratinizing carcinoma		4 (8.7%)	4 (8.9%)	
T stage	T1	2 (4.3%)	1 (2.2%)	0.773
	T2	18 (39.1%)	19 (42.2%)	
	T3	16 (34.8%)	18 (40.0%)	
	T4	10 (21.7%)	7 (15.6%)	
N stage	N1	15 (32.6%)	14 (31.1%)	0.894
	N2	21 (45.7%)	23 (51.1%)	
	N3	10 (21.7%)	8 (17.8%	
Clinical stage	III	28 (60.9%)	30 (66.7%)	0.565
	IV[a]	18 (39.1%)	15 (33.3%	
Platelet (×10^9/L)		180.5±70.5	178.3±77.5	0.763
Blood urea nitrogen (mmol/L)		5.4±1.7	5.2±1.5	0.47
Serum creatinine (μmol/L)		105.6±11.0	110.4±10.0	0.399
ALT*(U/L)		20.5±10.0	18.5±12.5	0.129
GGT*(U/L)		20.4±15.0	22.3±13.5	0.327
Albumin(g/L)		42.8±4.5	41.0±3.4	0.638
Total bilirubine(mmol/L)		9.87±4.54	10.54±5.64	0.869
PS grade		1.09±0.46	1.02±0.45	0.498

*ALT: Alanine aminotransferase; *GGT: Gamma-glutamyl transpeptidase

Randomization

All patients were randomly divided into the treatment group that patients were treated with PLF and CMNa, as well as control group with only PLF.

Response and toxicities

Response was classified according to the WHO criteria (Gehan et al., 2000) with computed tomography or magnetic resonance scan at baseline and every two cycles by investigators. Toxicity was defined according to RTOG/EORTC Criteria.

Follow-up

All patients were followed regularly in the department of outpatient. Recurrence and metastasis or symptoms associated with disease were recorded at every visit. By the end of March 2014, the median followed up time was 51 months (33-68 months).

Statistical analysis

SPSS 13.0 software package was used for statistical analysis, the analysis of measurement data was conducted by analysis of variance and t test, counting data using rank or chi-square test. Log-rank test was used for comparing differences of disease-free survival and survival rate between two groups, and $p<0.05$ was considered statistically significant.

Results

Patient characteristics

According to pathological diagnosis, 91 patients (64

Table 2. A Comparison on Complete Response Rate (CR) between Treatment and Control Group when the Dose of Radiotherapy Reached 60 Gy

	CR rate	χ^2	*p*
Tumor bed of nasopharynx			
Treatment group	43/46 (93.5%)	4.579	0.032
Control group	35/45 (77.8%)		
Tumor of lymphatic metastasis			
Treatment group	41/46 (89.1%)	4.655	0.031
Control group	32/45 (71.1%)		

Table 3. A Comparison on Complete Response Rate (CR) between Treatment and Control Group 3 Months After Radiotherapy

	CR rate	χ^2	*p*
Tumor bed of nasopharynx			
Treatment group	45/46 (97.8%)	5.08	0.024
Control group	38/45 (84.4%)		
Tumor of lymphatic metastasis			
Treatment group	45/46 (97.8%)	6.215	0.013
Control group	37/45 (82.2%)		

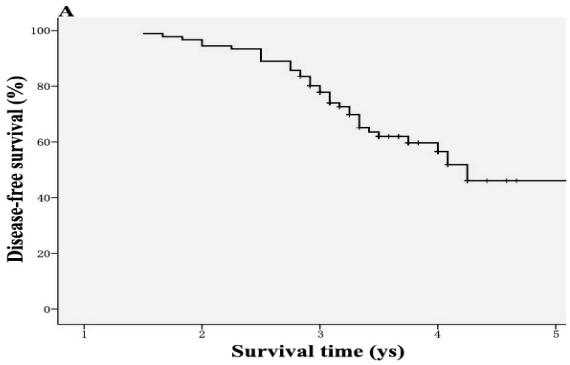

Figure 1. Disease Free Survival of All Patients (n=91)

male, 27 female) were recruited, with a median age of 46.0 years. All patients were locally advanced (n2-3 T3-4 m0, III~IV), with nasopharyngeal carcinoma (NPC), including 31 patients with anaplastic carcinoma, 52 patients with differentiated carcinoma non cornification, 8 patients with squamous cell carcinoma. Fifty-eight patients were diagnosed with clinical stage III, 33 patients with stage IVA. All patients were randomly assigned into treatment group (radiotherapy+PLF+CMNa) and control group (radiotherapy+PLF). Clinical characteristics of two groups were shown in Table 1, no statistically significant difference were detected between two groups (p>0.05).

Response rate

Evaluated by CT/MR on diseases of nasopharyngeal and metastatic sites, (CR+PR) was 100% in both groups when the radiation dose reached 60 gy. Complete response rate (CR) of treatment group was higher than that of control group, and the difference was statistically significant (Table 2).

Three months after radiotherapy, rate of CR was 87.9% (80/91), of PR was 12.1% (11/91). For patients with cancer only in nasopharyngeal area 2 PR (2.2%) were recorded; for patients with cancer in local lymphatic area, 3 patients with PR were documented (3.3%); for those with cancer in nasopharyngeal and local lymphatic area, 6 PR were

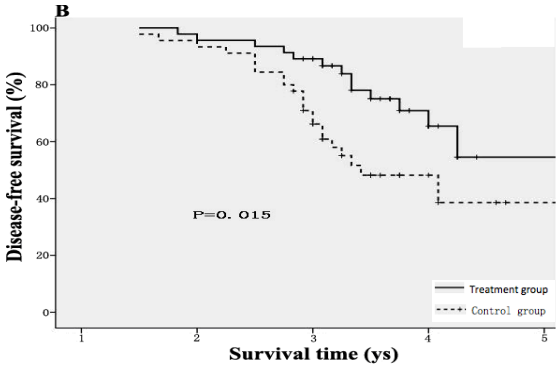

Figure 2. A comparison on Disease free Survival between Treatment and Control Group (log-rank=5.887, p=0.015)

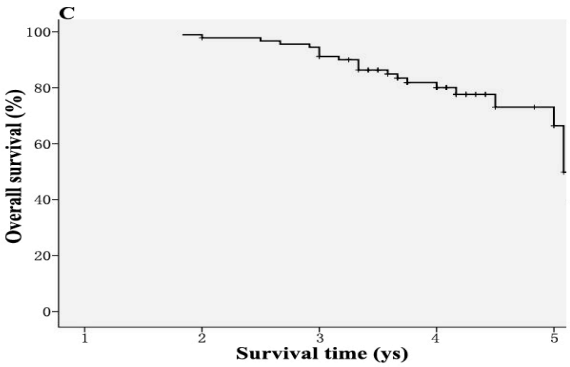

Figure 3. Overall Survival of All Patients (n=91)

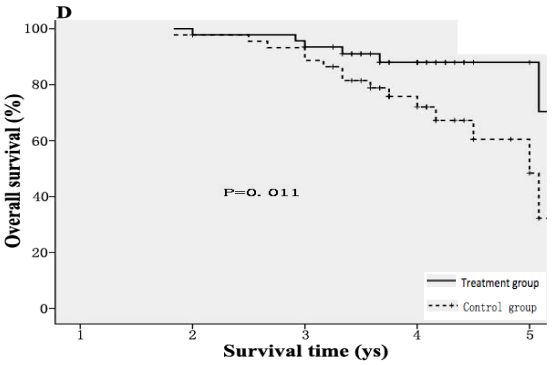

Figure 4. Overall Survival of Patients in Treatment and Control Group (log-rank=6.470, p=0.011)

achieved (6.6%). CR+PR in two groups was 100%, but CR in treatment group was higher than that in control group, the difference was statistically significant (Table 3).

Disease free survival

Till the end of follow-up, median disease-free survival of 91 patients was 39.0 (18.0~66.0) months; 1, 3, 5 year disease-free survival rates were 94.5%, 77.9%, 46.1 respectively (Figure 1). Median disease-free survival in treatment group was 42.0 (22.0~66.0) months, and in control group was 37.0 (18.0~60.0) months. One, 3, and 5 year disease-free survival rates of two groups were 95.7%, 86.7%, 54.5% and 93.3%, 66.2%, 38.6%, respectively, with statistical significance (log-rank=5.887, p=0.015) (Figure 2).

Overall survival

Till the end of follow-up, median survival time of all

Table 4. A Comparison on Acute Side Effects between Treatment and Control Group

Grade		0(%)	1-2(%)	3-4(%)	Statistical value (Mann-Whitney U/χ^2)	*p*
Toxicity						
Skin	Treatment group	0	39 (84.8%)	7 (15.2%)	0.002	0.964
	Control group	0	38 (84.4%)	7 (15.6%)		
Mucosa reaction	Treatment group	0	19 (41.3%)	27 (58.7%)	0.008	0.929
	Control group	0	19 (42.2%)	26 (57.8%)		
Nausea/vomitting	Treatment group	13 (28.3%)	27 (58.7%)	6 (13.0%)	960	0.504
	Control group	15 (33.3%)	25 (55.6%)	5 (11.1%)		
Leukopenia	Treatment group	17 (36.9%)	25 (54.3%)	4 (8.7%)	972	0.574
	Control group	19 (42.2%)	23 (51.1%)	3 (6.7%)		
Anemia	Treatment group	32 (69.6%)	12 (26.1%)	2 (4.3%)	1013	0.83
	Control group	30 (66.7%)	14 (31.1%)	1 (2.2%)		
Thrombocytopenia	Treatment group	43 (93.5%)	2 (4.3%)	1 (2.2%)	1032	0.956
	Control group	42 (93.3%)	1 (2.2%)	2 (4.4%)		
Liver function	Treatment group	44 (95.7%)	2 (4.3%)	0		1.00*
	Control group	44 (97.8%)	1 (2.2%)	0		
Renal function	Treatment group	45 (97.8%)	1 (2.2%)	0		1.00*
	Control group	45(100%)	0	0		

*Fisher's exact test.

Table 5. A Comparison on Long-Term Side Effects between Treatment and Control Group

Grade		0(%)	1-2(%)	3-4(%)	Statistical value (Mann-Whitney U/χ^2)	*p*
Toxicity						
Skin	Treatment group	37 (80.4%)	9 (19.6%)	0	0.48	0.827
	Control group	37 (82.2%)	8 (17.8%)	0		
Mucosa reaction	Treatment group	40 (87.0%)	6 (13.0%)	0	0.002	0.967
	Control group	39 (86.7%)	6 (13.3%)	0		
Xerostomia	Treatment group	29 (63.0%)	17 (37.0%)	0	0.264	0.608
	Control group	26 (56.5%)	19 (43.5%)	0		
Inability to open mouth	Treatment group	23 (50.0%)	20 (43.5%)	3 (6.5%)	992.0	0.700
	Control group	24 (53.3%)	19 (42.2%)	2 (4.5%)		
Hearing loss	Treatment group	26 (56.5%)	13 (28.3%)	7 (15.2%)	1005.5	0.792
	Control group	26 (57.8%)	14 (31.1%)	5 (11.1%)		
Radiation related dental decay	Treatment group	43 (93.5%)	2 (4.3%)	1 (2.2%)	1012.5	0.651
	Control group	43 (95.6%)	2 (4.4%)	0		
Radiation related encephalomyelopathy	Treatment group	45 (97.8%)	1 (2.2%)	0		1.00*
	Control group	45 (100%)	0	0		

*Fisher's exact test.

patients was 45.0 (22.0~66.0) months, and 1, 3, 5 year survival rates were 97.8%, 90.0% and 66.4% respectively (Figure 3). Median survival time of patients in treatment group was 48.0 (24.0~66.0) months, of patients in control group was 45.0 (22.0~62.0) months. One, 3, 5 year survival rates of two groups of patients were 97.8%, 93.5%, 70.4% and 95.5%, 88.07%, 48.4% respectively, with statistical significance (log-rank=6.470, p=0.011) (Figure 4).

Acute toxicities

Acute radiation associated toxicities were recorded according to a standard classification from radiation oncology group (RTOG). All patients could tolerate treatment. No treatment-related death occurred in two groups. Short-term toxicities were caused by concomitant chemoradiation, eg., skin, mucous membrane reaction, nausea and vomiting and a reduction in white blood cells. The difference of incidence for adverse reactions was not statistically significant (p>0.05, Table 4) after the use of CMNa. No adverse reaction of heart and nervous system was detected.

Long-term toxicities

Long-term toxic and side effects in two groups of patients were monitored by follow-up. And these treatment associated toxicities were recorded according to a standard classification from radiation oncology group (RTOG/EORTC). In two groups of patients, long-term toxicities of skin and the mucous membrane, xerostomia, difficulty in opening mouth, hearing loss, radiothreapy associated saprodontia and encephalomyelopathy are shown in Table 5. There was no statistically significant difference between two groups (p>0.05, Table 5).

Discussion

Guangdong is an area with high incidence of NPC. Radiation therapy is a standard treatment for NPC, with 5-year survival rate of 40%~60%. But 5-year survival rate is only 40% and the recurrence rate could reach as high as 42% if only radiotherapy is considered because most patients with nasopharyngeal carcinoma are diagnosed with advanced disease (Guo et al., 2013; Jamshed et al., 2013; Jiao et al., 2013; Kang et al., 2013; Lin et

al., 2013; Li et al., 2013). In recent years, studies have shown that most of local recurrence after radiotherapy of nasopharyngeal carcinoma (NPC) occurred within the field of radiation, and it is estimated that recurrence within the radiation field accounting for 60% of the total number of recurrence (Sun et al., 2013; Xiang et al., 2013; Xie et al., 2013; Abbasi et al., 2014; Cai et al., 2014; Cheah et al., 2014; Chen et al., 2014; Deng et al., 2014; Li et al., 2014). The existence of hypoxic cells may be one of the main factors that cause the failure of radiotherapy. Consensus is reached that to improve the effect of radiation therapy, we should improve tumor hypoxic status and improve the sensitivity of radiation. And among these, one research focus is to combine radiation and chemotherapy. Chemotherapy will kill part of tumor cells, let tumor size to decrease and cells into a status of hypoxia, and demonstrate synergy effect by sensitizing the effect of radiotherapy (Li et al., 2013). Another way to induce tumor cell into a status of hypoxia is by using cell sensitization agent. Nitro imidazoles are considered a research hot topic in this field. It is reported that 3 years survival rate in patients with unresectable advanced pancreatic cancer was increased significantly by using new nitro imidazoles drug as a radiotherapy sensitizer (Karasawa et al., 2008). Our research is to test CMNa that is a new nitro imidazoles compound and a radiation synergistic agent developed in China, to find if it is an agent with high efficiency and low toxicity.In this study, patients with locally advanced nasopharyngeal carcinoma were treated by concomitant radiation and chemotherapy (PLF regimen) with CMNa in the treatment group, and without CMNa in the control group. Between two groups, main patient characteristics, eg., gender, age, basic condition, pathological type, clinical stage, PS score were comparable. Our results demonstrated that the dose of radiation reached 60 Gy, complete remission rates of nasopharyngeal tumor bed or lymph node metastases were significantly higher for treatment group than those for control group (93.5% *vs* 77.8%; 93.5% *vs* 77.8%, $p<0.05$). Patients in treatment group with CMNa, complete response rates were both 97.8% for nasopharyngeal tumor and lymph node metastases higher than the rates in control group (84.4% and 82.2%) with statistical significance. This suggests that CMNa could increase radiosensitivity for patients with locally advanced nasopharyngeal carcinoma when concomitant radiation and chemotherapy was conducted.

Regarding long-term curative effect of CMNa in this study, compared with control group, disease-free and overall survival were significantly improved in treatment group. One, 3, 5 year disease-free survival rates of CMNa treatment group were 95.7%, 86.7% and 54.5%, but in control group were 93.3%, 66.2% and 38.6%, the difference was statistically significant (log-rank=5.887, $p=0.015$). One, 3, 5 year survival rates of two groups were 97.8%, 93.5%, 70.4% and 95.5%, 88.07%, 48.4%, higher in treatment group with statistically significant difference (log-rank=6.470, $p=0.011$). Forty-eight months after treatment, survival curves of two groups trend to be flat, which may be associated with the following factors: (1) the incidence of distant metastasis could be higher than that of local recurrence (21 patients in this study were found distant metastasis, and 14 patients were diagnosed with local recurrence), and distant metastasis in most of patients (82.2% 95.0%) occurred in 3-4 years after radiotherapy. (2) death was declared shortly after distant metastasis and local recurrence occurred. Liu Mengzhong reported that the survival rate was significantly longer for patients with staged III, IV nasopharyngeal carcinoma treated by CMNa and radiotherapy combination than those treated with only radiotherapy ($p=0.009$), but the survival rate was not significantly improved when treating patients with staged I, II nasopharyngeal carcinoma.

In this study, main side effects for patients in treatment and control group included skin and mucous membrane toxicity, nausea/vomiting as well as myelosuppression, but is not statistically different between two groups, suggesting main side effects were caused by concomitant radiation and chemotherapy, probably not by CMNa. In this study, long-term side effects were not increased in CMNa treatment group compared with control group. Liu Mengzhongstudy reported that one patient with nasopharyngeal carcinoma was found with light liver function impairment, after CMNa administration, aminotransferase was elevated to grade IV. This suggests liver function should be monitored during CMNa administration, especially for patients with liver function impairment. In our current research, we did not find CMNa is associated with obvious liver function damage.

In conclusion, CMNa could improve the efficacy of concomitant radiation and chemotherapy for patients with locally advanced nasopharyngeal carcinoma with good tolerance, and not increase adverse reactions. Thus, this regimen is worthy of further clinical application.

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