

Original Article

Glycididazole sodium combined with radioiodine therapy for patients with differentiated thyroid carcinoma (DTC)

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Abstract: The aim of the present study was to evaluate efficacy and side effects of glycididazole sodium (CMNa) combined with radioiodine therapy for patients with DTC cervical metastases. 53 patients of DTC cervical lymph node metastasis were randomly divided into 2 groups, where 24 cases were treated with 4.44 GBq of ^{131}I alone, 29 cases were treated with 800 mg/m² of CMNa combined with 4.44 GBq of ^{131}I . Peripheral blood samples were collected before and after treatment to perform measurements of routine blood test, liver function, renal function, parathyroid hormone (PTH), lymphocyte micronucleus rates and chromosome mutation. The results showed that rates of complete response (CR) in CMNa combined with radioiodine group (65.5%) were significantly higher than that in radioiodine monotherapy group (37.5%). Furthermore, CMNa combined with radioiodine treatment significantly increased the percentage of thyroglobulin (Tg) reduction at 12 weeks after treatment ($P < 0.05$). There is no significant difference in blood routine, liver function, renal function, PTH, lymphocyte micronucleus rates and chromosome mutation rates before and 12 weeks after treatment ($P > 0.05$). These results indicate 4.44 GBq of ^{131}I treatment combined with 800 mg/m² of CMNa could significantly improve clinical efficacy of DTC patients without increasing side effects.

Keywords: CMNa, radioiodine therapy, DTC

Introduction

Differentiated thyroid carcinoma (DTC) is one of the most common malignant tumors and its incidence is increasing in recent years [1]. At present, surgical resection of thyroid combined with radioiodine therapy is the standard therapy protocol for DTC [2]. Radioiodine therapy is one of the best methods in the treatment of patients with DTC cervical lymph node metastasis, however, some patients is not sensitive to the radioiodine therapy which leads to the increasing frequency of radioiodine treatment and poor treatment result [3, 4]. Therefore, how to improve efficacy of radioiodine therapy in DTC is one of the research hot spots.

It is well recognized that improving tumor hypoxic status and the sensitivity of radiation is the key to enhance the clinical efficacy of radiotherapy, and many radiosensitizers were developed and used in radioiodine treatment of solid tumors [5, 6]. Glycididazole sodium (CMNa)

which can increase the sensitization of tumor cell to radiotherapy has been used in radiotherapy of tumors [7, 8]; however, there is little information on CMNa combined with radioiodine treatment in DTC. The present study aimed to evaluate the clinical efficacy and side effects of radioiodine treatment combined with CMNa in the treatment of DTC.

Subjects and methods

Patients

A total of 53 DTC patients who have been treated with total thyroidectomy were recruited from the third hospital of Jilin university. 17 of the patients were males and 36 of them were females. The patients aged between 23 and 68 (mean age: 43 ± 15.5). All the patients were examined by ultrasonography, CT scans and iodine imaging methods to ensure that there are no residual thyroid tissue and other metastasis except cervical lymph node metastasis. A

Table 1. Clinical efficacy of different treatments in DTC patients

Groups	n	CR	PR	Invalid	Rate of CR	Rate of ER
Monotherapy	24	9	13	2	37.5% ^b	91.7%
Combination therapy	29	19	8	2	65.5% ^a	93.1%

Note: Values in the same column with different lowercases indicate statistically significant difference between the two groups. CR=Complete response; PR=partial response ER=CR+PR.

Table 2. Percentage of Tg reduction at 12 weeks and 24 weeks after treatment

Groups	12 W (%)	24 W (%)
Monotherapy	90.32±6.19 ^b	92.66±6.24
Combination therapy	95.41±3.96 ^a	95.95±2.70

Note: Values in the same column with different lowercases indicate statistically significant difference between the two groups.

successful thyroid remnant ablation was defined as the absence of thyroid bed uptake in ¹³¹I neck scan, the thyroglobulin (Tg) value >10 µg/ml and without Tg antibodies in serum. Before the radioiodine treatment, all the patients stopped taking levothyroxine sodium tablets for at least four weeks and subjected to diet without iodine which led to concentration of serum TSH >30 mIU/L. Number of white blood cell (WBC) >4.0×10⁹/L is also a criteria to recruited patients used in this study.

Treatments protocol

53 patients were randomly divided into group A (n=24) and group B (n=29) and then subjected to radioiodine treatment combined with saline (Monotherapy) and radioiodine treatment combined with CMNa (Combination therapy), respectively. All the patients received oral 4.44 GBq (120 mci) of ¹³¹I. In group A, patients received 100 ml of saline by intravenous drip 1 h before the radioiodine treatment every day for 4 consecutive days. In group B, patients received 800 mg/m² (body surface area, BSA) CMNa in 100 ml saline by intravenous drip 1 h before the radioiodine treatment every day for 4 consecutive days. In both groups, patients were treated with levothyroxine sodium tablets (100 µg each day) to carry out suppressive therapy at 24 h after radioiodine treatment.

Evaluation of clinical efficacy

The patients are traditionally carried out with ¹³¹I whole body scan (¹³¹I-WBS) and serum Tg

measurement before radioiodine treatment, 12 weeks and 24 weeks after radioiodine treatment. The treatment effects were then assessed based on ¹³¹I-WBS and serum Tg according to the following criterion. Complete response (CR): negative ¹³¹I-WBS and Tg <1.0 µg/L after radioiodine treatment; partial response (PR): area or quantity of metastatic lesions and serum Tg level decreased after radioiodine treatment; effective response (ER)=CR+PR. Rate of ER and PR were calculated according to the above criterion and results of 24-weeks follow-up examination.

Evaluation of Tg reduction

Serum Tg levels were measured at 12 weeks and 24 weeks after treatment using an immunoradiometric assay (Sanofi Diagnostic Pasteur), with a low detection limit of 0.7 ng/mL. Percentage of Tg reduction was then calculated with the following formula: Percentage of Tg reduction=100%* (A-B)/A.

Where:

A is the Tg level before treatment; B is the Tg level before treatment

Evaluation of side effects

In order to evaluate side effects of the treatments, the following index were determined before and 12 weeks, 24 weeks after the treatments. WBC, red blood cell (RBC) and platelet (Plt) were determined by using automatic hematology analyzer XE-2100. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea Nitrogen (BUN), creatinine (CREA), uric acid (URIC) were determined using the Hitachi 7600 automatic biochemical analyzer. Parathyroid hormone (PTH) was determined using an ELISA kit (Immutopics Inc., San Clemente, California, USA). Chromosome aberration rate and micronucleus rate of peripheral blood lymphocytes were measured using method described in previous study [9].

Statistical analysis

SPSS 18.0 software package was used for statistical analysis. Student test was used to compare the differences between different groups.

Table 3. Effects of different treatments on Blood counts and serum PTH of DTC patients

Index	Monotherapy		Combination therapy	
	Before treatment	After treatment	Before treatment	After treatment
RBC ($\times 10^9/L$)	6.51 $\pm$ 0.12	6.55 $\pm$ 0.26	6.32 $\pm$ 0.23	6.32 $\pm$ 0.32
WBC ($\times 10^9/L$)	4.92 $\pm$ 0.06	4.78 $\pm$ 0.13	4.55 $\pm$ 0.09	4.49 $\pm$ 0.06
Plt ($\times 10^9/L$)	175 $\pm$ 13	180 $\pm$ 15	186 $\pm$ 19	188 $\pm$ 19
PTH (pg/L)	46.3 $\pm$ 1.2	45.5 $\pm$ 2.3	44.2 $\pm$ 2.1	43.6 $\pm$ 4.3

Table 4. Effects of different treatments on function of liver and kidney of DTC patients

Index	Monotherapy		Combination therapy	
	Before treatment	After treatment	Before treatment	After treatment
ALT (IU/L)	6.92 $\pm$ 0.11	6.59 $\pm$ 0.23	6.61 $\pm$ 0.35	6.65 $\pm$ 0.57
AST (IU/L)	4.86 $\pm$ 0.17	4.83 $\pm$ 0.12	4.54 $\pm$ 0.08	4.51 $\pm$ 0.09
BUN (mmol/L)	3.96 $\pm$ 0.35	4.08 $\pm$ 0.26	4.16 $\pm$ 0.21	4.22 $\pm$ 0.12
CREA (μ mol/L)	87.67 $\pm$ 0.98	88.53 $\pm$ 0.23	88.48 $\pm$ 0.28	89.12 $\pm$ 0.35
URIC (μ mol/L)	298.23 $\pm$ 69.12	293.61 $\pm$ 64.58	291.98 $\pm$ 75.45	284.36 $\pm$ 82.71

Table 5. Effects of different treatments on chromosome aberration rate and micronucleus rate of peripheral blood lymphocytes in DTC patients

Index	Monotherapy		Combination therapy	
	Before treatment	After treatment	Before treatment	After treatment
chromosome aberration rate	1.00 $\pm$ 0.22	1.35 $\pm$ 0.75	0.95 $\pm$ 0.26	1.30 $\pm$ 0.76
micronucleus rate	1.10 $\pm$ 0.40	1.30 $\pm$ 0.55	1.10 $\pm$ 0.53	1.25 $\pm$ 0.53

Significant difference was considered at $P < 0.05$.

Results

Clinical efficacy was evaluated at 24 weeks after treatment and the clinical efficacy was shown in **Table 1**. The results showed that radioiodine treatment (4.44 GBq) combined with CMNa (800 mg/m²) could significantly increase the CR rate of DTC patients ($P < 0.05$), compared to radioiodine treatment (4.44 GBq) alone. There is no significant difference for the ER rate in the two groups ($P > 0.05$). Percentage of Tg reduction at 12 weeks and 24 weeks after treatment was shown in **Table 2**. The results showed that radioiodine treatment combined with CMNa could significantly increase percentage of Tg reduction at 12 weeks after treatment ($P < 0.05$), indicating an increase of clinical efficacy, while there is no significant difference at 24 weeks after treatment in the two groups.

In order to investigate side effects of the treatments, blood count, serum PTH, liver function, kidney function, chromosome aberration rate and micronucleus rate in peripheral blood lymphocytes of the DTC patients were evaluated before and 12 weeks after the treatments. The results shown in **Tables 3-5** demonstrated that there is no significant difference between the two groups ($P > 0.05$).

Discussion

Hypoxia, a state of insufficient oxygen, was identified as a microenvironmental component of solid tumors for a long time [10]. Previous studies have shown that hypoxic tumor cells can

be up to three times more resistant to radiotherapy than those in normal oxygen concentrations cells and the root of tumor metastasis and recurrence [11, 12]. Therefore, increasing the sensitivity of hypoxic tumor cells to radiotherapy has been an important approach to improve the radiotherapy outcome of tumor. CMNa, a new nitro imidazoles compound developed in China, could increase the sensitivity of hypoxic tumor cells to radiotherapy and then enhance the cure rate of tumor patients [13]. At present, CMNa has been widely used in treatments of head neck tumors, lung cancer and esophageal cancers [3].

In agreement with previous studies on other cancers [8], results of the present study showed that radioiodine treatment combined with CMNa could significantly increase clinical efficacy of DTC patients. Generally, multiple course of radioiodine treatment is needed in treating DTC. In the present study, rate of CR in radioiodine monotherapy group was 39.1% which is similar

to previous studies [14, 15], while rate of CR in combination therapy group was 66.7%. Tg is a sensitive marker for evaluating recurrence and metastasis of DTC patients, especially those treated with thyroidectomy and adioiodine radiation [16]. In the present study, double-blind treatment was used to measure percentage of Tg reduction at 12 weeks and 24 weeks after adioiodine treatment. The results showed that percentage of Tg reduction in combination therapy group was significantly higher than that in adioiodine monotherapy group at 12 weeks after treatment. These results indicated that CMNa combined with adioiodine treatment could improve the clinical efficacy of DTC patients.

Although previous studies have shown that adioiodine treatment combined with CMNa only affect tumor cells and cause little harm to normal cells, there is still no information in DTC patients. The present study also measured level of WBC, RBC, Plt, ALT, AST, BUN, CREA, URIC, PTH, chromosome aberration rate and micronucleus rate before and after treatment. The results showed that there is no significantly difference between monotherapy group and combination therapy, indicating the harmless of combination therapy to normal cells in treatment of DTC. The present study was limited by the low sample size; therefore, more extensive studies are needed in order to obtain more accurate information.

In conclusion, the present study showed that 4.44 GBq of ^{131}I treatment combined with 800 mg/m² of CMNa could significantly improve clinical efficacy of DTC patients without increasing side effects, compared to 4.44 GBq of ^{131}I monotherapy treatment.

Disclosure of conflict of interest

None.

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References

- [1] Jasim S, Ozsari L and Habra MA. Multikinase inhibitors use in differentiated thyroid carcinoma. *Biologics* 2014; 8: 281-291.
- [2] Chung JK and Cheon GJ. Radioiodine therapy in differentiated thyroid cancer: the first tar-

- geted therapy in oncology. *Endocrinol Metab (Seoul)* 2014; 29: 233-239.
- [3] Schlumberger M, Brose M, Elisei R, Leboulleux S, Luster M, Pitoia F and Pacini F. Definition and management of radioactive iodine-refractory differentiated thyroid cancer. *Lancet Diabetes Endocrinol* 2014; 2: 356-358.
- [4] Dralle H and Machens A. Surgical approaches in thyroid cancer and lymph-node metastases. *Best Pract Res Clin Endocrinol Metab* 2008; 22: 971-987.
- [5] Ren W, Li Z, Mi D, Yang K, Tian J and Zhang Z. [A meta analysis of radiosensitivity on non-small cell lung cancer by metronidazole amino acidum natrium]. *Zhongguo Fei Ai Za Zhi* 2012; 15: 340-347.
- [6] Overgaard J. Hypoxic radiosensitization: adored and ignored. *J Clin Oncol* 2007; 25: 4066-4074.
- [7] Chen L, Hu CS, Chen XZ, Hu GQ, Cheng ZB, Sun Y, Li WX, Chen YY, Xie FY, Liang SB, Chen Y, Xu TT, Li B, Long GX, Wang SY, Zheng BM, Guo Y, Sun Y, Mao YP, Tang LL, Chen YM, Liu MZ and Ma J. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2012; 13: 163-171.
- [8] Li MY, Liu JQ, Chen DP, Qi B, Liang YY and Yin WJ. Glycididazole sodium combined with radiochemotherapy for locally advanced nasopharyngeal carcinoma. *Asian Pac J Cancer Prev* 2014; 15: 2641-2646.
- [9] Bolognesi C, Abbondandolo A, Barale R, Casalone R, Dalpra L, De Ferrari M, Degrossi F, Forni A, Lamberti L, Lando C, Migliore L, Padovani P, Pasquini R, Puntoni R, Sbrana I, Stella M and Bonassi S. Age-related increase of baseline frequencies of sister chromatid exchanges, chromosome aberrations, and micronuclei in human lymphocytes. *Cancer Epidemiol Biomarkers Prev* 1997; 6: 249-256.
- [10] Labiano S, Palazon A and Melero I. Immune Response Regulation in the Tumor Microenvironment by Hypoxia. *Semin Oncol* 2015; 42: 378-386.
- [11] Hammond EM, Asselin MC, Forster D, O'Connor JP, Senra JM and Williams KJ. The meaning, measurement and modification of hypoxia in the laboratory and the clinic. *Clin Oncol (R Coll Radiol)* 2014; 26: 277-288.
- [12] Busk M and Horsman MR. Relevance of hypoxia in radiation oncology: pathophysiology, tumor biology and implications for treatment. *Q J Nucl Med Mol Imaging* 2013; 57: 219-234.
- [13] Liu MZ, He LR, Lu TX, Chen YY, Hu YH, Cui NJ, Xu GZ, Gao L, Xiao GL, Zhang SW, Cai Y, Li DM, Chen LH, Wang FY, Sun Q, Zhu L, Sheng G, Gao

- HJ and Bao YH. [Effect of hypoxic radiosensitizer sodium glycididazole on long-term result of radiotherapy for nasopharyngeal carcinoma]. *Zhonghua Zhong Liu Za Zhi* 2006; 28: 932-937.
- [14] Frasoldati A, Pesenti M, Gallo M, Caroggio A, Salvo D and Valcavi R. Diagnosis of neck recurrences in patients with differentiated thyroid carcinoma. *Cancer* 2003; 97: 90-96.
- [15] Lamartina L, Durante C, Filetti S and Cooper DS. Low-risk differentiated thyroid cancer and radioiodine remnant ablation: a systematic review of the literature. *J Clin Endocrinol Metab* 2015; 100: 1748-1761.
- [16] Mazzaferri EL, Robbins RJ, Spencer CA, Braverman LE, Pacini F, Wartofsky L, Haugen BR, Sherman SI, Cooper DS, Braunstein GD, Lee S, Davies TF, Arafah BM, Ladenson PW and Pinchera A. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. *J Clin Endocrinol Metab* 2003; 88: 1433-1441.