¹³¹I therapy for 345 patients with refractory severe hyperthyroidism: Without antithyroid drug pretreatment

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Abstract

The aim of this study is to evaluate the safety and long-term results of ¹³¹I therapy alone for patients with refractory severe hyperthyroidism without antithyroid drug pretreatment. From January 2002 to December 2012, 408 patients with refractory severe hyperthyroidism were treated with ¹³¹I alone. Among them, 345 were followed up for 1 to 10 years for physical examination, thyroid function, and thyroid ultrasound. Complete Blood Count (CBC) liver function, electrocardiogram, echocardiogram, and Emission Computed Tomography (ECT) thyroid imaging were performed as indicated. The 345 patients had concomitant conditions including thyrotoxic heart disease, severe liver dysfunction, enlarged thyroid weighing 80 to 400 g, severe cytopenia, and vasculitis. One to two weeks prior to ¹³¹I therapy, all patients were given low-iodine diet. The dose of ¹³¹I therapy was 2.59 to 6.66 MBq (70 to 180 μ Ci) per gram of thyroid with an average of 3.83 ± 0.6 MBq (103.6 ± 16.4 μ Ci); and the total ¹³¹I activity administered for the individuals was 111 to 3507.6 MBq (3.0 to 94.8 mCi, mean 444 ± 336.7 MBq (12.0 ± 9.1 mCi)). Out of the 408 patients, 283 were cured, 15 with complete remission, and 47 with incomplete remission. No treatment failure or significant clinical worsening was noted in these patients. Our data indicated that ¹³¹I therapy alone for patients with refractory severe hyperthyroidism without antithyroid drug pretreatment is safe and effective.

Keywords: Radioactive iodine, refractory severe hyperthyroidism, without antithyroid drug pretreatment

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Introduction

The current international guidelines for treatment of hyperthyroidism recommend that antithyroid drug (ATD) be considered for patients with severe hyperthyroidism before ¹³¹I treatment to satisfactorily control their hyperthyroidism. This management increases clinical safety with no doubt. However, in clinical dilemmas, patients are often contraindicated to ATD or surgical treatment, due to intolerance to ATD or the patients' critical conditions. Herein, we reported our results of the safety and long-term efficacy of ¹³¹I therapy without ATD pretreatment for refractory severe hyperthyroidism. To our knowledge, this is the first study on ¹³¹I therapy for refractory severe hyperthyroidism without ATD pretreatment.

Materials and methods

Patients and criteria

From January 2002 to December 2012, 408 patients with refractory severe hyperthyroidism were treated with ¹³¹I alone without ATD pretreatment at our hospital.

This clinical study was approved by Ethics Committee of the Affiliated Hospital of Academy of Military Medical Sciences, and informed consent forms were obtained from all the 345 patients.

Among the 408 patients, 345 patients (118 male, 227 female), aged 14 to 83 years, were followed up for 1 to 10 years (on average 3.3 ± 2.5 years) including 282 patients for 1 to 5 years and 63 patients for 5 to 10 years. Individual patients presented with at least one complication. The patients' characteristics are summarized in Table 1.

Severe hyperthyroidism was defined as one or more of the following items: (1) heart rate > 120, loss of weight > 10 kg, the symptoms such as palpitation, weakness, etc., are obvious, $TT_4 > 390$ nmol/L, $TT_3 > 9.24$ nmol/L; (2) hyperthyroid heart disease; (3) complicated with severe liver dysfunction (ALT > 200 IU/L or jaundice); (4) complicated with severe cytopenia (WBC < 3.0×10^9 /L; ANC < 1.0×10^9 /L; PLT < 60×10^9 /L; Hb < 60.0/L); and (5) complicated with renal function failure or other organ function damage.

Refractory severe hyperthyroidism was defined as the recurrence of hyperthyroidism after long-term ATD

Table 1 Characteristics of patients with refractory severe hyperthyroidism (n = 345).

Variables	Number of patients (%)
Gender (%)	
Male	118 (34.2)
Female	227 (65.8)
Age	
Mean $\pm$ SD (year)	39.852 $\pm$ 13.951
Minimum	14
Maximum	83
Complication (%)	
Heart disease	80 (23.2)
Severe liver dysfunction	31 (9.0)
Enlarged thyroid (>80 g)	171 (49.5)
Severe cytopenia	43 (12.5)
Other severe diseases*	20 (5.8)

*Vasculitis induced by PTU, Diabetes, Chronic renal function failure, etc.

treatment and was complicated with at least one of the following items: severe arrhythmia, heart failure, obvious liver dysfunction, severe cytopenia, etc. These patients were not suitable for ATD or surgical treatment.

Criterion for curative effect was: (1) Cure: all symptoms, signs of hyperthyroidism, and the disappearance of complications with the thyroid function returning to normal or to hypothyroidism for more than one year. (2) Complete remission: all symptoms, signs of hyperthyroidism, and thyroid function returned to normal with persistent atrial fibrillation. (3) Incomplete remission: the symptoms and signs of hyperthyroidism and thyroid function were improved, but the hyperthyroidism was not cured. (4) No remission: all symptoms, signs of hyperthyroidism, and thyroid function were not improved.

¹³¹I administration. The administered ¹³¹I activity for each patient was determined by radioactivity meter (CAPINTEC CRC-15R, USA). One to two weeks prior to ¹³¹I therapy, the patients received low-iodine diet. The laboratory tests, EKG, echocardiogram, and bone marrow biopsy were performed on patients when necessary. The weight of thyroid gland was comprehensively evaluated by ^{99m}Tc thyroid scintigraphy, thyroid ultrasonography, and thyroid palpation. After consultation with more than two of the nuclear medicine specialists, the dose for each individual patient was determined and calculated using the following formula: The ¹³¹I therapeutic activity (MBq) = administered ¹³¹I MBq/g of thyroid $\times$ estimated thyroid gland weight(g)/24-h radioiodine highest uptake.

The administered ¹³¹I activity per gram of thyroid was 2.59 to 6.66 MBq (70 to 180 μ Ci), on average 3.83 ± 0.6 MBq (103.6 ± 16.4 μ Ci). The total ¹³¹I activity for individual patients were 111 to 3507.6 MBq (3.0 to 94.8 mCi), on average 444 ± 336.7 MBq (12.0 ± 9.1 mCi). Of the 345 patients, 320 patients received a total of ¹³¹I activity no more than 340 MBq (20 mCi) each, on average 384.8 ± 172.8 MBq (10.4 ± 4.67 mCi), while 25 patients received a total of

Table 2 Outcomes of ¹³¹I therapy without ATD pretreatment for patients with refractory severe hyperthyroidism.

Group	Number of patients	Number of patients (rate, %)		
		Cure	Complete remission	No remission
Group 1	80	65 (81.2)	7 (8.8)	8 (10.0)
Group 2	31	26 (83.9)	2 (6.4)	3 (9.7)
Group 3	171	135 (78.9)	5 (2.9)	31 (18.1)
>80 and $\leq$ 100 g	87	74 (85.1)	2 (2.3)	11 (12.6)
>100 g	84	61 (72.6)	3 (3.6)	20 (23.8)
Group 4	43	40 (93.0)	1 (2.3)	2 (4.7)
Group 5	20	17 (85.0)	0 (0.0)	3 (15.0)
Total	345	283 (82.0)	15 (4.4)	47 (13.6)

ATD: antithyroid drug.

¹³¹I activity more than 340 MBq (20 mCi), on average 1302.4 ± 673.4 MBq (35.2 ± 18.2 mCi). Forty patients received two doses of ¹³¹I and one patient received three doses.

Follow-up

The patients were followed up at 3, 6, and 12 months post ¹³¹I therapy, then once every one to two years for symptoms, physical examination, thyroid function test, and thyroid ultrasound. CBC, liver function, electrocardiogram, echocardiography, and ECT thyroid imaging were performed as indicated.

Statistical analysis

SPSS 16.0 statistic software was used to analyze mean value, standard deviation, and perform t-test for comparison of difference between two groups. $P < 0.05$ was considered as statistically significant.

Results

Based on clinical characteristics, the 345 patients were divided into five groups, and the ¹³¹I therapeutic effects are shown in Table 2. The overall cure rate was 82%, the overall complete remission (CR) rate was 4.4%, and incomplete remission rate (ICR) was 13.6%. No therapeutic failure occurred. No condition worsening or thyroid storm patients were noticed after ¹³¹I therapy. Among the 345 patients, 156 experienced ¹³¹I-induced hypothyroidism, which returned to euthyroidism with proper levothyroxine replacement therapy.

Serum thyroid hormone test results showed that among the 345 patients, 39 with high thyroid hormone levels and thyroids >100 g had gradually decreased serum TT₃, TT₄, FT₃, and FT₄ levels after ¹³¹I treatment. However, the decline of these hormones in patients was not significant on day 3 post therapy, compared with those of the BT group (P all > 0.05); while on day 5 post treatment TT₄ decreased by 10.54% ($P < 0.01$), FT₄ by 12.91% ($P < 0.01$), FT₃ by 23.15% ($P < 0.01$), and TT₃ by 24.60% ($P < 0.01$), compared

with BT. The results revealed no elevation of thyroid hormone concentrations after ^{131}I treatment (Figure 1).

Five representative cases are presented: (1) correction of atrial fibrillation (case 1 Figure 2); (2) recovery of severe jaundice on a background of hepatitis B (case 2, Figure 3); (3) cosmetic advantage of shrinkage of the thyroid to normal size (case 3, Figure 4); (4) recovery of severe thrombocytopenia (case 4, Figure 5); and (5) case 5, a

Figure 1 Decline of serum thyroid hormone levels after ^{131}I treatment in 39 patients with severe hyperthyroidism. "BT": 3–7 days before ^{131}I therapy; "+3d": 3 days after ^{131}I therapy; "+5d": 5 days after ^{131}I therapy. (A color version of this figure is available in the online journal.)

18-year-old female patient complicated with failure of long-term MMI treatment, long-standing proptosis, thyrotoxic heart disease, agranulocytosis, Immunoglobulin A (IgA) renal disease, and Propylthiouracil (PTU)-related vasculitis. ^{131}I therapy not only cured her severe Graves' disease but also corrected her heart, blood, and kidney abnormalities, and she was able to become pregnant and deliver a healthy baby 7.5 years post ^{131}I therapy (Figure 6).

Discussion

^{131}I is the main definitive treatment of hyperthyroidism. However, concerns about multiple aspects of the therapy exist. For example, McDermott et al.¹ proposed that ATD pretreatment should be considered to prevent exacerbations of the thyroid function after ^{131}I therapy for hyperthyroidism patients with high risks, including the elderly, those complicated with cardiovascular disease, diabetes, thyroid gland enlargement, multinodular goiter, and long-term medical history. This approach was incorporated into recent guidelines for management of hyperthyroidism with those conditions.^{2,3} Our data demonstrated that ^{131}I radiotherapy as a sole regimen is safe and effective for refractory hyperthyroidism.

Andrade et al.,⁴ Burch et al.,⁵ and Pirnat et al.⁶ reported that thyroid hormone levels in patients with Graves' disease decreased within five days after ^{131}I therapy, which is

Figure 2 Case (1). Restoration of atrial fibrillation on electrocardiogram (EKG) (Lead II) in a 28-year-old female patient after ^{131}I therapy: (a) eight days before ^{131}I therapy, atrial fibrillation; (b) nine months after ^{131}I therapy, atrial fibrillation; (c) one year after ^{131}I therapy, atrial fibrillation restored to sinus rhythm; (d) two years after ^{131}I therapy, sinus rhythm

Figure 3 Case (2). Recovery of liver function after ^{131}I therapy in a 39-year-old male patient: (a) before ^{131}I therapy, the patient presented with icteric sclera, serum TBil 518.4 $\mu\text{mol/L}$, DBil 213.2 $\mu\text{mol/L}$; (b) six months after ^{131}I therapy, icteric sclera completely disappeared with serum TBil 20 $\mu\text{mol/L}$ and DBil 5.6 $\mu\text{mol/L}$

Figure 4 Case (3). Shrinkage of the enlarged thyroid to normal size after ¹³¹I therapy in a 18-year-old male patient with refractory Graves' disease: (a) the thyroid was five times of normal size before ¹³¹I therapy; (b) the thyroid weight was 176 g as determined by ^{99m}Tc ECT scan before ¹³¹I therapy; (c) The enlarged thyroid returned to normal size; (d) Four years after ¹³¹I therapy, the thyroid weight was 30 g as determined by ^{99m}Tc ECT scan

Figure 5 Case (4). (a) The patient suffered from severe hyperthyroidism complicated with secondary severe thrombocytopenic purpura (PLT $7.0 \times 10^9/L$) and liver damage. After ¹³¹I therapy, severe hyperthyroidism was cured, PLT $79 \times 10^9/L$; (b) picture of bone marrow puncture before ¹³¹I therapy showed reactive hyperplasia of histiocytes

consistent with our data. Pirnat et al.⁶ also stated that ¹³¹I therapy alone was safe for most of the hyperthyroidism patients, but they suggest that severe patients should be pretreated with Methimazole (MMI) until the euthyroid

state is reached before ¹³¹I therapy. However, in the present study, we enrolled patients with hyperthyroidism complicated with apparent thyrotoxic heart disease, severe abnormal liver function, tremendous thyroid enlargement, severe

Figure 6 Case (5). (a) 18-year-old, unmarried. She suffered from Graves' hyperthyroidism complicated with thyrotoxic heart disease, agranulocytosis, PTU-related vasculitis. After ^{131}I therapy, the severe Graves' hyperthyroidism was cured and all of the heart, blood, and kidney complications were restored to normal. (b) 24 June 2010, 7.5 years after ^{131}I therapy, she delivered a healthy baby girl, height 50 cm, body weight 3.4 kg by cesarean section. At present, the girl is four years old with normal growth and development. (A color version of this figure is available in the online journal.)

cytopenia, diabetes, chronic renal failure or aged more than 65 years. These patients were often unsuitable for ATD treatment due to ATD ineffectiveness, intolerance or concomitant critical conditions. In fact, we have investigated the safety and long-term effect of ^{131}I therapy alone without ATD pretreatment for these complicated conditions since 1960. Our follow-up for 2 to 33 years of 68 patients with thyrotoxic heart disease included atrial fibrillation, enlarged heart, heart failure, or angina pectoris demonstrated that the cure rate can reach 80.9%, and the total effective rate is 97%.⁷ From January 1991 to December 2013, we have treated a total of 12,000 patients with hyperthyroidism by ^{131}I without ATD pretreatment. Not a single thyroid storm reaction was ever been observed post ^{131}I therapy.

^{131}I therapy for hyperthyroid patient rarely causes an acute radiation thyroiditis (ART) associated with massive release of stored thyroid hormone into blood, which transiently leads to aggravate the symptoms of hyperthyroidism, or even thyroid storm. The occurrence of ART after ^{131}I therapy mainly depends on the amount of thyroid absorption doses.^{8–12} In the present study, no significant clinical worsening was observed during the first week post ^{131}I therapy, indicating that the administered ^{131}I activities were appropriate.

It is widely accepted that ATD pretreatment is not necessary for most young patients with Graves' disease, but it can be considered for those with severe thyroid dysfunction, or cardiac diseases and for elderly patients.¹³ We individualized ^{131}I therapy for all the 345 patients with refractory severe hyperthyroidism and the clinical outcomes were satisfactory.

It is necessary to emphasize that active supportive measures should be taken to improve the general conditions of such patients prior to ^{131}I therapy, which could accommodate the patients for a timely ^{131}I therapy, which may be the

only possible life-saving treatment for some critical patients with refractory severe hyperthyroidism.

In summary, ^{131}I therapy for patients with refractory severe hyperthyroidism without ATD pretreatment is safe and effective. With supportive treatment, definitive ^{131}I therapy should be considered as therapy of choice for them.

CONTRIBUTORSHIP

YD and JX contributed to the conception and design of the study. All authors participated in the clinical practice, including diagnosis, treatment, consultation and follow up of patients. JX and YW wrote the manuscript. YD and JX revised the manuscript. All authors approved the final version of the manuscript.

DECLARATION OF CONFLICTING INTERESTS

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