INTERNAL MEDICINE

□ CASE REPORT □

Outpatient ^{131}I Treatment for a Patient with Graves' Disease Receiving Hemodialysis

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Abstract

A patient presented with hyperthyroidism and end-stage renal disease requiring hemodialysis that was difficult to control despite increased dosages of anti-thyroid drugs. The condition could finally be controlled by ^{131}I radioactive iodine therapy (RIT) and hemodialysis provided under a hospital-linkage system. During three hemodialysis sessions after the oral administration of ^{131}I, we measured the radioactivity released from the patient and the radioactivity of the devices/tools used. The radioactivity of the devices/tools was managed by allowing the isotope to decay into non-radioactive elements. Our experience suggests that outpatient RIT may provide a safe and convenient means of treating Graves' disease, even in patients receiving hemodialysis.

Key words: ^{131}I therapy, hyperthyroidism, hemodialysis, end-stage renal disease, a hospital-linkage system, radioactivity measurement

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Introduction

In 1942, Hertz et al. first reported the treatment of Graves' disease by ^{131}I radioactive iodine therapy (RIT) (1, 2). RIT has since been used extensively as an effective means of treating Graves' disease (3). As of the end of 2011, 304,600 patients in Japan with end-stage renal disease (ESRD) (2,380/million population) were receiving chronic dialysis therapy, with the number of such patients increasing by about 6,000/year (4).

In Graves' disease patients with comorbid ESRD, RIT should preferably be applied at facilities that have both isotope treatment and hemodialysis equipment. However, the number of such facilities in Japan is small. Outpatient RIT was approved in Japan in June 1998, with the upper limit of the dose set at 13.5 mCi (5). When RIT is applied, the radiation dose must be managed at 30 μSv/hour or less, and special care must be taken in handling the devices and tools contaminated by ^{131}I, to mitigate the effect on the public. We herein report a Graves' disease patient on chronic hemodialysis who received RIT at a clinic without dialysis facilities, in cooperation (under the hospital-linkage system) with a hospital providing hemodialysis.

Case Report

The patient was a 35-year-old man. He had been diagnosed with chronic renal failure at 10 years of age and began to receive hemodialysis at 12 years of age. At 13 years of age, the patient underwent kidney transplantation from a live donor (father); however, the graft was rejected and hemodialysis was resumed at 19 years of age. At 30 years of age, he was diagnosed with Graves' disease. The disease was poorly controlled by thiamazole (MMI) treatment, with signs of hyperthyroidism (FT_3 8.1 pg/mL, FT_4 2.54 ng/dL) persisted despite an increase in the MMI dose to 60 mg/day. Furthermore, his blood pressure remained poorly controlled. Although multiple drugs were used to treat his hypertension (40 mg nifedipine, 40 mg carvedilol, 16 mg azelnidipine, 10 mg amlodipine besilate, 4 mg doxazosin mesilate and 40 mg olmesartan medoxomil were used simultaneously), his blood pressure remained difficult to control and was consistently approximately 200/120 mmHg thus requiring the concomitant use of intravenous nicardipine hydrochloride. Muscular catabolism was stimulated by the persistent hyperthyroidism, resulting in leg muscle weakness and leg pain while walking that made it difficult for the patient to work. Thus, the pa-

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tient desired to achieve an early remission of Graves' disease and thus requested treatment with RIT. Because the thyroid function remained elevated despite oral treatment with MMI, 50 mg potassium iodide (38 mg inorganic iodine) was added to the therapeutic regimen. As a result, hyperthyroidism was temporarily alleviated, with FT_3 and FT_4 values of 5.5 pg/mL and 1.91 ng/dL respectively, measured 13 days before RIT. RIT therapy was applied under these improved conditions.

Methods

Potential problems that are encountered before and after RIT include: (i) those related to RIT, (ii) radioactivity released by the patient after oral ^{131}I treatment, and (iii) radioactivity from ^{131}I in the blood remaining on the devices/tools used for hemodialysis, thus requiring the proper disposal of such devices/tools.

i) RIT

As estimated by ultrasonography, the thyroid volume was approximately 88 mL, with no evidence of a visible nodule. When examined in advance by an ophthalmologist specializing in Graves' disease, no signs of active ophthalmopathy were noted, and the Clinical Activity Score (CAS) was 1. One week before RIT, the patient started an iodine-limited diet, and suspended oral treatment with anti-thyroid drugs. The day after a hemodialysis session, the patient visited our outpatient clinic to undergo an evaluation of the percent ^{123}I thyroid uptake by the thyroid 3 hours after a dose and scintigraphy. After the 3-hour uptake measurement, ^{131}I (13.5 mCi) was orally administered, followed by hemodialysis the following day (26 hours after dose administration). The effective half-life of ^{131}I was calculated from the percent radioactive iodine uptake by the thyroid one day after and one month after RIT.

ii) Radioactivity measurement in the patient following oral ^{131}I intake

According to the standards for discharge of patients following RIT in Japan, radioactivity measured at a distance of 1 m from the patient's body surface must be 30 μSv or less before the patient is allowed to leave the facility (5). To ascertain whether this standard had been met, gamma rays were measured with an ionization chamber at a distance of 1 m from the body surface during three hemodialysis sessions (conducted on the following day, the 4th day, and the 6th day after RIT).

iii) Measurement of ^{131}I radioactivity contained in the blood remaining on devices/tools used for hemodialysis, and the disposal of these devices/tools

Radioactivity was measured in the hemostatic cotton, dialysis columns, dialysis circuits, and disposable gloves used in each of the three hemodialysis sessions after RIT. This measurement was performed at a distance of 10 cm with a Geiger-Muller (GM) survey meter. The GM survey meter can measure the count per minute, but it is not capable of measuring radioactivity. For this reason, the measurement of radioactivity (in μSv/hour) was simultaneously performed using a scintillation survey meter. Background counts were calibrated with both detectors, and the conversion was 1,264 cpm = 1 μSv. Because the physically effective half-life of ^{131}I is 8.04 days, the radioactivity in these devices/tools was measured 13 days after RIT, i.e., at a time point when some degree of radioactive decay was anticipated.

Laboratory methods

The FT_3, FT_4, TSH, and thyrotropin receptor antibody (TRAb) levels were measured by an electrochemiluminescence immunoassay kit (Roche Diagnostics, Basel, Switzerland); Elecsys (reference ranges: FT_3: 2.2-4.3 pg/mL, FT_4: 0.8-1.6 ng/dL TSH: 0.2-4.5 μU/mL, TRAb: <2.0 IU/L).

Results

RIT

Fig. 1 shows the protocol for RIT and hemodialysis. The percent thyroid uptake of ^{123}I at 3 hours after an oral dose was 18%. Scintigraphy revealed diffuse accumulation in the thyroid. ^{131}I was administered at a dose of 486.6 megabecquerel (MBq), and the percent thyroid uptake 24 hours after RIT was 50%. The effective half-life was 7.5 days, and the actual absorbed dose was 81.9 gray (Gy).

Radioactivity measurement following oral ^{131}I intake

The radioactivity measured at a distance of 1 m from the patient was 27 μSv/hour when analyzed 26 hours after RIT and prior to the hemodialysis session. When the measurement was repeated 3 hours after the hemodialysis session, the radioactivity was 25.5 μSv/hour (Table).

Measurement of ^{131}I radioactivity contained in blood remaining on devices/tools used for hemodialysis

Thirteen days after RIT, the radioactivity in the devices/tools contaminated by the patient's blood during the hemodialysis sessions was measured. The measurements revealed high levels of radioactivity in the hemostatic cotton, dialysis columns, dialysis circuits, and disposable gloves (550 cpm, 200 cpm, 60 cpm and 60 cpm, respectively; Table). The radioactivity on the first day of hemodialysis after RIT was estimated to be 1,830 cpm for hemostatic cotton and 660 cpm for the dialysis column, based on disintegration calculations using the half-life of ^{131}I which is known to be 8.04 days. Therefore, the combined total radioactivity in the blood-contaminated hemostatic cotton and dialysis column was 2,490 cpm, equivalent to about 2 μSv when calculated with a scintillation survey meter. The radioactivity in these highly contaminated devices/tools would be expected to decrease to a level close to background counts by approximately the 35th day following exposure. Thus, the devices/tools were stored for 35 days and then were disposed of after confirmation of sufficient decay into non-radioactive elements.

Course of treatment

Fig. 2 illustrates the course of treatment after RIT. The thyroid function remained elevated for about 6 months after RIT, necessitating a temporary increase in the daily dose of MMI from 60 mg to 90 mg and potassium iodide from 38 mg to 56 mg. Thereafter, the thyroid function gradually re-

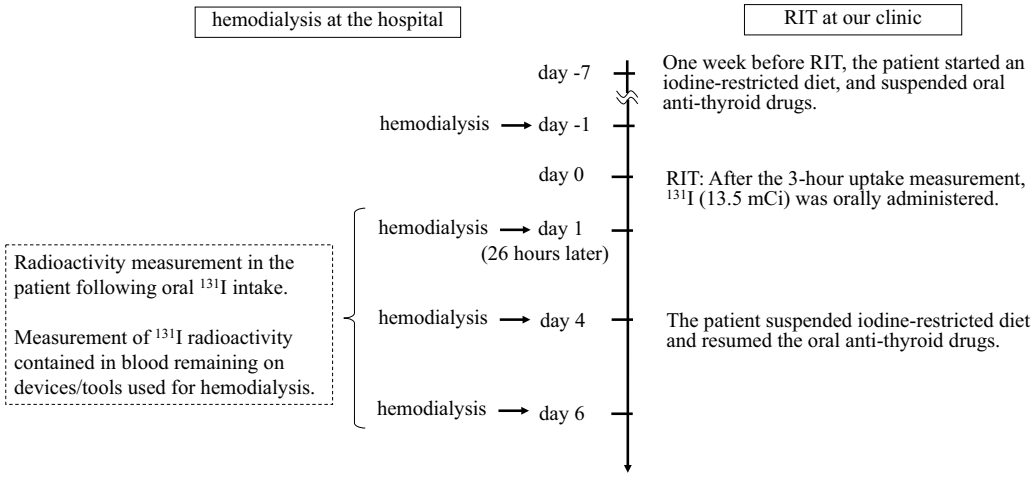

Figure 1. **RIT and hemodialysis protocol.**

Table. **Radioactivity Measurement in the Patient Following Oral ^{131}I Intake, and Measurement of ^{131}I Radioactivity Contained in Blood Remaining on Devices and Tools Used for Hemodialysis.**

Length of time after RIT	Radioactivity measurement following oral ^{131}I intake(μSv/hour)		The hemostatic cotton (cpm)	The dialysis column (cpm)	The dialysis circuit (cpm)	The disposable gloves (cpm)
	Prior to the hemodialysis	3 hours after hemodialysis				
Next day	27	25.5	1,830* (550)	660* (200)	60	60
4th day	19	16	100	60	60	60
6th day	15.5	14.5	60	60	60	60

* The radioactivity based on disintegration calculations using the half-life of ^{131}I which is known to be 8.04 days.

turned to the normal range, and a normal thyroid function, in the absence of oral MMI treatment, was documented approximately 3 years later. The estimated thyroid volume decreased from 88 mL (at initiation of RIT) to 10 mL (3 years later).

Although the thyroid function remained normal, the blood pressure fluctuated markedly before and after hemodialysis sessions. The doses of hypertensive agents were reduced (to 40 mg nifedipine, 20 mg carvedilol, 40 mg olmesartan medoxomil and 10 mg imidapril hydrochloride), but oral treatment with these agents is still necessary at present. The patient's at-home systolic blood pressure measurements decreased to 120-130 mmHg. However, prior to dialysis his blood pressure was elevated to 189/116 mmHg, and after dialysis the blood pressure remained elevated at 156/108 mmHg 35 months after RIT.

Discussion

The remission rates of anti-thyroid drugs for patients with Graves' disease vary between 40% and 80% for cases not complicated by ESRD (6-10). RIT or surgery is recommended if a goiter is large, the TRAb level is high, or adverse reactions to anti-thyroid drugs are noted.

The percentage of ESRD patients with Graves' disease is reportedly similar to the prevalence of Graves' disease in the general population (11); therefore, some patients are likely to require ^{131}I therapy or surgery in addition to anti-thyroid drug therapy.

RIT plan

When RIT is performed at our facility, the ^{131}I dosages level is adjusted depending on the estimated thyroid volume, with the expected absorbed dose increasing with enlargement of the thyroid gland. The expected absorbed dose is also higher in patients unable to receive anti-thyroid drugs because of adverse reactions. In the present case, the estimated thyroid volume was 88 mL and the expected absorbed dose was 108 Gy based on our facility's calculations. Thus, at the highest dosage of ^{131}I possible for outpatients [13.5 mCi (500 MBq)], the expected absorbed dose is calculated to be 80.6 Gy based on the Marinelli-Quimby equation (assuming the effective half-life = 6.0 days and the percent thyroid uptake at 24 hours = 60%). Therefore, in this case, RIT was administered at a dosage of 13.5 mCi, which is the highest level possible for outpatients. The actual absorbed dose was 81.9 Gy, lower than the expected absorbed dose (108 Gy). For patients with Graves' disease, a second session of RIT should be scheduled 6 months or more after the first session. Multiple RIT sessions are reported to be effective, particularly for patients with large goiters receiving outpatient treatment (12). In this case, the estimated thyroid volume was approximately 88 mL, and we initially considered a second RIT session 6 months or more after the first.

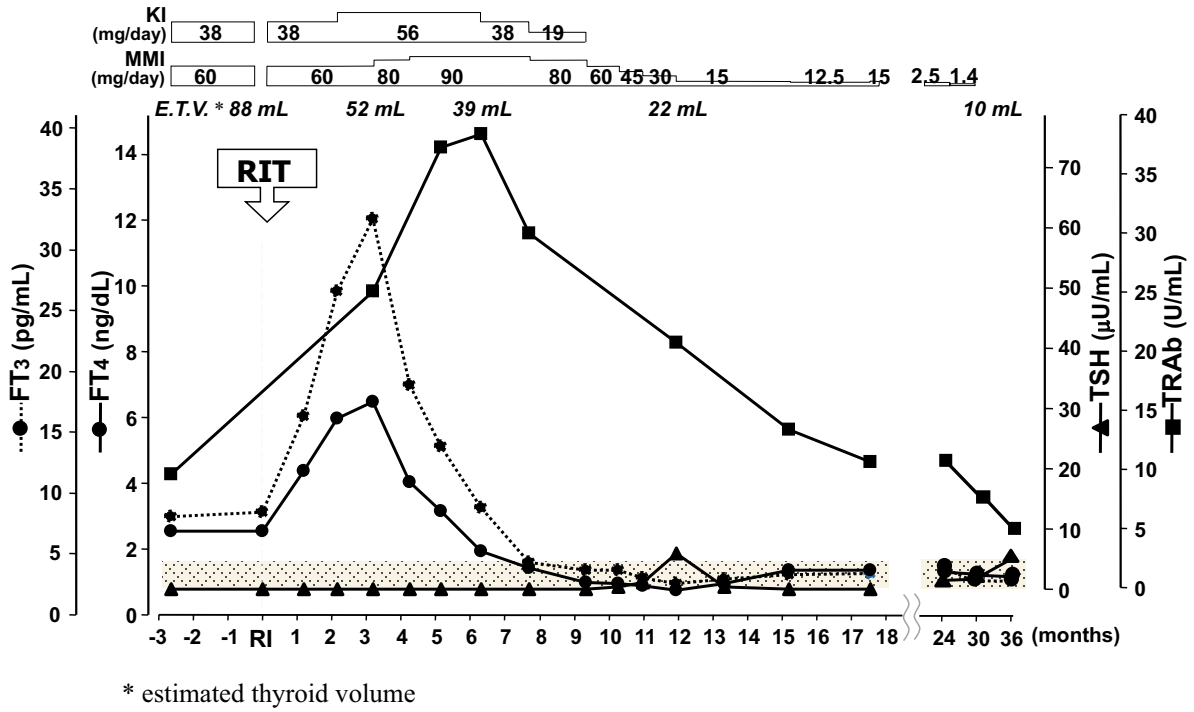

Figure 2. **Course of the thyroid function and blood pressure following RIT.**

However, the goiter in this case diminished following RIT, and treatment with anti-thyroid drugs was continued. When RIT is applied using our protocol, some patients achieve disease remission by 5 years after treatment (13). Anti-thyroid drug treatment was discontinued 2 years and 8 months after RIT, thus allowing us to conclude that RIT was successful in this case.

Standards for discharge of patients after RIT

In accordance with the recommendations from the International Commission on Radiological Protection (ICRP; 1990), the Japanese regulatory authority established standards for the discharge of patients from clinical radioisotope rooms of hospitals following radiotherapy (Notification No. Iyakuan-70, Safety Division Manager, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, June 30, 1998) (5). According to these standards, the limit for the effective dose is 1 mSv per year, in order to limit public exposure to radiation. The exposure limit for caregivers is 5 mSv/case. The ^{131}I dose limit is set at 500 MBq, and the limit for a 1-cm dose equivalent at a distance of 1 m from the patient's body surface is 30 μSv/hour.

In patients receiving RIT for Graves' disease or toxic multinodular goiter, safety is reportedly a concern, given the influence of radiation exposure on individuals surrounding the patient during hemodialysis (14-17). In this study, the radioactivity was 27 μSv/hour during the first hemodialysis session after an oral dose of ^{131}I, satisfying the aforementioned patient discharge standard. According to our calculations, the exposure level for caregivers surrounding the patient would only exceed the limit (1 mSv) if the caregivers were located at a distance of 1 m from the patient for a period of 37 hours. If they were to remain at this distance for 185 hours, then the calculated exposure level would be 5 mSv (without taking the decay of ^{131}I into account). Thus, our data indicate that the caregivers in this case did not receive any significant radiation exposure, and our observations are consistent with those of previous reports.

^{131}I radioactivity measurement of devices/tools used for hemodialysis and their disposal

If patients receiving tests with radioactive substances use diapers, then the disposal of such diapers must be carried out after confirmation of radioactivity decay in those diapers to background counts (18). The length of time for which materials with radioactivity equal to or higher than background counts remain in substances excreted by the patient vary considerably depending on the type, dosage, and pharmacokinetics of the radioactive drugs used, as well as the patient's characteristics and other factors. Therefore, measurement with a radioactivity counter is necessary. The devices/tools used for hemodialysis may have been contaminated by blood containing ^{131}I, and thus required confirmation of ^{131}I decay into non-radioactive elements. In this case, we collected the circuits and blood-contaminated materials used during the three hemodialysis sessions after RIT to measure their radioactivity. Those used in the first session had the highest level of residual ^{131}I, while those used in the other two sessions had lower radioactivity. In accordance with the aforementioned standards, we disposed of the devices/tools used for these hemodialysis sessions after confirming radioactive decay to background radiation counts. Our experience in this case indicates that the disposal of materials contaminated by radioactivity is not problematic if the radiation dose does not exceed 13.5 mCi (the highest dose allowable for outpatients).

RIT in a hospital-linkage system

In patients with Graves' disease, the following aspects of accompanying ESRD may affect the therapeutic effects of ^{131}I: residual kidney function (affecting ^{131}I excretion from the kidneys), and time until the next hemodialysis session after RIT (14, 15, 19). Theoretically, RIT is more effective if applied immediately after a hemodialysis session, with the interval until the next session set to be as long as possible. However, there are only a limited number of facilities where both dialysis and radiotherapy for inpatients are available. Furthermore, in Japan, facilities capable of performing radiotherapy for inpatients tend to prioritize the treatment of thyroid cancer, and it is often difficult for patients such as the one in this case to gain admission to such hospitals. Furthermore, because the maximum thyroid uptake period for ^{131}I is known to be 10 hours, it has been recommended that the first hemodialysis session after RIT be scheduled at least 10 hours after RIT (14). In this case, RIT was administered on the day following hemodialysis, and the next hemodialysis session was 26 hours after RIT. Thus, if RIT is applied under a hospital-linkage system, then patients capable of moving between the hospital and the clinic can receive treatment in a highly convenient way without the need for hospitalization; however, such an arrangement requires sufficient coordination between the patient, the dialysis facility, and the radiotherapy facility.

Our experience suggests that RIT on an outpatient basis may provide a safe and highly convenient means of treatment, given the appropriate application and radioactivity measurement and management, in patients with Graves' disease receiving hemodialysis.

The authors state that they have no Conflict of Interest (COI).

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