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Single dose planning for radioiodine-131 therapy of Graves' disease

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Objective: Patients with Graves' disease were studied one year after radioiodine-131 therapy to assess the relationship between the effectiveness of the therapy and the radioiodine doses used. ***Methods:*** Patients were classified into three groups according to thyroid function as hyperthyroidism, euthyroidism and hypothyroidism at one year after I-131 therapy. In these groups we compared the mean values of dose, dose per thyroid weight calculated with I-123 uptake before the therapy (pre D/W), dose per thyroid weight calculated with therapeutic I-131 uptake (post D/W), and absorbed dose. ***Results:*** No significant differences were found between the three groups in terms of dose or pre D/W. The mean values of post D/W and absorbed dose in the non-hyperthyroid (euthyroid and hypothyroid) group were significantly greater than those in the hyperthyroid group. Post D/W of 6.3 MBq/g was a threshold separating the non-hyperthyroid group from the hyperthyroid group. There was no correlation between pre D/W and post D/W; however, the mean post D/W was significantly greater than the mean pre D/W. All patients with pre D/W above 6.3 MBq/g showed non-hyperthyroidism at one year after the radioiodine treatment. ***Conclusions:*** No indicators before the radioiodine therapy had significant relationships with the effectiveness of the therapy at one year after the treatment. However, the single therapy planned for setting the pre D/W above 6.3 MBq/g will certainly make the patients non-hyperthyroid. As this proposal of dose planning is based on a small number of patients, further study is needed.

Key words: I-131 therapy, Graves' disease, dose per thyroid weight

INTRODUCTION

FOR TREATMENT of Graves' disease, we have three options: surgery, antithyroid drugs and radioiodine therapy. The first choice of treatment differs from country to country (antithyroid drugs in Europe and Japan,[1,2] radioiodine therapy in the U.S.[3]) Radioiodine therapy is safe, non-invasive, and cost effective; however, there has been no general agreement on the applied dose. Some institutions have been using fixed doses, while others have determined applied doses based on estimated fixed doses per thyroid weight or estimated fixed absorbed doses. Several studies have reported on optimal doses aiming at euthyroidism after radioiodine therapy, and noted that it is difficult with individualized doses.[4–9] Therefore, fixed dose regimens aiming at complete ablation of the thyroid gland have been suggested by some authors.[10–12]

We studied patients with Graves' disease at one year after radioiodine therapy to assess the relationship between the effectiveness of the therapy and radioiodine doses. One year after the therapy seemed appropriate for the assessment since transient hypothyroidism within several months has been often observed,[13–15] and the annual incidence of hypothyroidism beyond one year is independent of the radioiodine dose.[16–19]

MATERIALS AND METHODS

From February 1996 to March 2001, 92 patients with Graves' disease were referred to Kanazawa University Hospital to be considered for I-131 therapy. Out of them,

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Table 1 A comparison of factors known before and after the radioiodine treatment

	Hyperthyroidism	Euthyroidism	Hypothyroidism	P value*
Number of patients	4	8	8	
Dose	875 ± 455 MBq	608 ± 277 MBq	671 ± 392 MBq	NS
Thyroid weight	122 ± 82 g	55 ± 32 g	54 ± 36 g	NS
24-hr I-123 uptake	60.6 ± 19.3%	45.6 ± 12.4%	41.3 ± 13.9%	NS
Pre D/W	4.4 ± 1.3 MBq/g	5.4 ± 1.2 MBq/g	5.4 ± 1.8 MBq/g	NS
24-hr I-131 uptake	57.1 ± 22.0%	64.6 ± 13.2%	68.6 ± 11.3%	NS
Effective half-life	3.8 ± 1.6 days	5.0 ± 1.8 days	5.6 ± 0.6 days	NS
Post D/W	4.1 ± 1.7 MBq/g	7.6 ± 1.0 MBq/g	9.1 ± 2.4 MBq/g	< 0.01
Absorbed dose	79 ± 45 Gy	173 ± 51 Gy	235 ± 60 Gy	< 0.005

* Kruskal-Wallis test NS = not significant

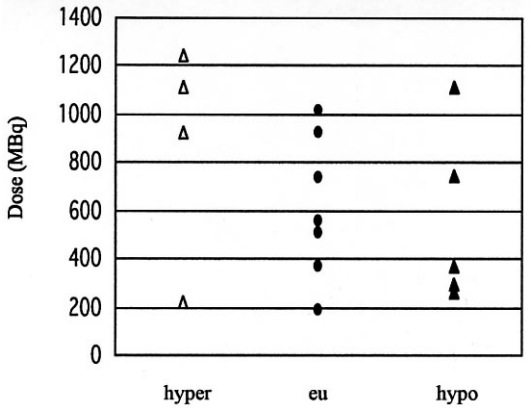

Fig. 1 Comparison of dose against the treatment outcome. hyper = hyperthyroidism, eu = euthyroidism, hypo = hypothyroidism

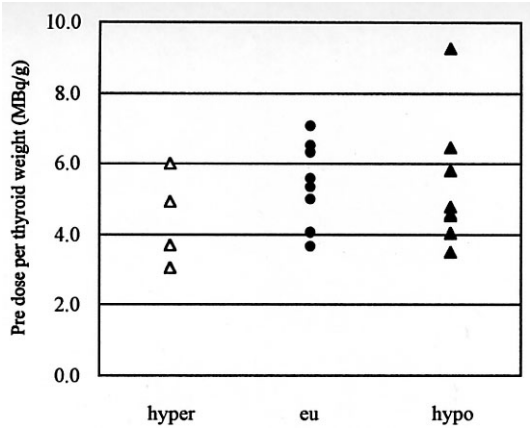

Fig. 2 Comparison of pre dose per thyroid weight against the treatment outcome. hyper = hyperthyroidism, eu = euthyroidism, hypo = hypothyroidism

we could trace only 20 patients to determine their hormonal status at one year after I-131 treatments. The mean age at I-131 therapy was 44.5 (range 19–68) years. They were 15 females and 5 males. In all patients, antithyroid drugs had been administered and were withdrawn before the therapy.

The therapeutic I-131 doses were empirically intended to induce absorbed doses around 120 Gy (mean value ± standard deviation: 122 ± 34 Gy). A modified Marinelli-Quimby formula[20] was used for calculation of doses.

$$\text{Dose (MBq)} = \frac{21.4AW}{UTe}$$

where A is absorbed dose (Gy), W is thyroid weight (g), and U is 24-hr I-123 uptake (%), and Te is effective half-life, which was assumed to be 5 days.

Thyroid weight was estimated based on the volume obtained with ultrasonography. The density of thyroid gland was assumed to be 1 g/m*l*. The volume of each thyroid lobe was calculated using the following formula based on an ellipsoid model:

$$\text{Volume (m}l\text{)} = \frac{\pi abc}{6}$$

where a is length (cm), b is width (cm), and c (cm) is thickness.

The total thyroid volume was obtained by adding the volume of both lobes.

The studies with 3.7 MBq I-123 were performed after iodine restriction for at least seven days.

Dose per thyroid weight was obtained by the following formula.

$$\text{Dose per thyroid weight (MBq/g)} = \frac{DU}{100W}$$

where D is administered dose (MBq), W is thyroid weight (g), and U is 24-hr radioiodine uptake (%).

Dose per thyroid weight calculated with the I-123 uptake (pre D/W) and dose per thyroid weight calculated with the therapeutic I-131 uptake (post D/W) were obtained. Time interval between the I-123 studies and the therapeutic I-131 administration differed from patient to patient (range 3 to 30 days).

The thyroid gland radioactivity was routinely measured at 24, 48, 72, 144 hours after the oral administration of therapeutic I-131. The effective half-life was determined by linear regression analysis on a semi-logarithmic scale. Then, the absorbed dose was calculated by the

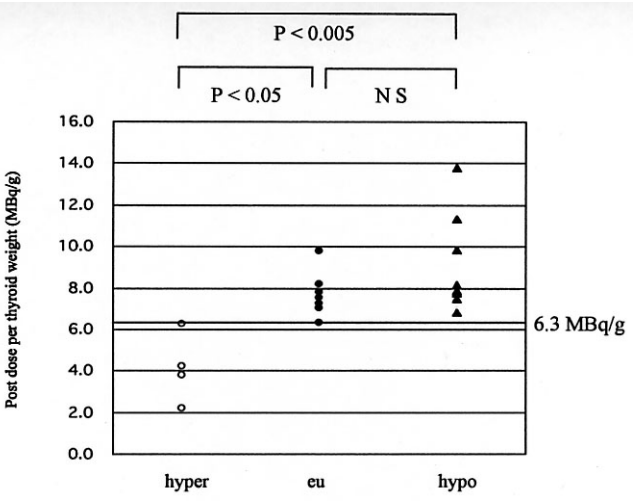

Fig. 3 Comparison of post dose per thyroid weight against the treatment outcome. The Scheffe test was used for comparing each combination of two groups. hyper = hyperthyroidism, eu = euthyroidism, hypo = hypothyroidism, NS = not significant

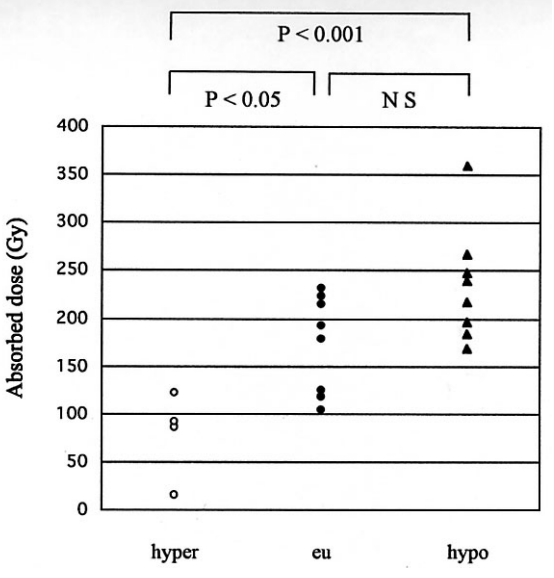

Fig. 4 Comparison of absorbed dose against the treatment outcome. The Scheffe test was used for comparing each combination of two groups. hyper = hyperthyroidism, eu = euthyroidism, hypo = hypothyroidism, NS = not significant

modified Marinelli-Quimby formula.

At one year after the treatments, the patients were classified into three groups according to the thyroid function as hypothyroid (subnormal thyroid function or euthyroid on thyroxine substitution), or euthyroid (normal free thyroxine and free triiodothyronine without any thyroid medication), or hyperthyroid (elevated free triiodothyronine and/or elevated free thyroxine, and euthyroid state with antithyroid drug ingestion).

In these groups we compared the mean values of dose, pre D/W, post D/W, and absorbed dose.

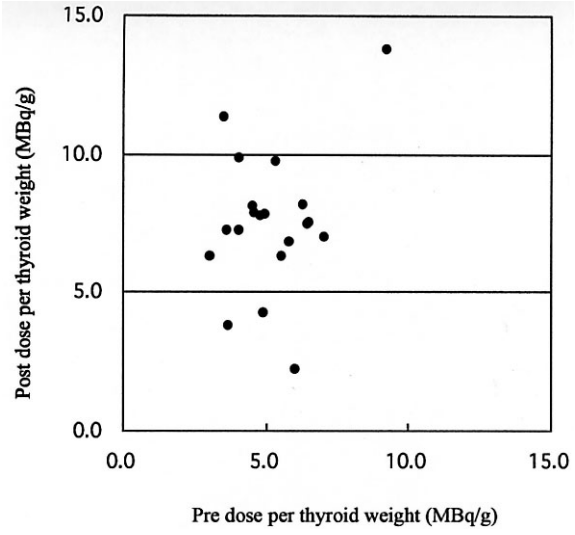

Fig. 5 Comparison of pre dose per thyroid weight with post dose per thyroid weight.

Statistical Analysis

Statistical analysis was done using Statcel97 PC software (OMS, Saitama, Japan). Comparisons of dose, thyroid weight, 24-hr uptake, effective half-life, dose per thyroid weight and absorbed dose between the three groups were performed with the Kruskal-Wallis test and the Scheffe test. Data were reported as the mean ± standard deviation. The Spearman's correlation coefficient by rank test and paired t test were used when appropriate. Statistical significance was set at $p < 0.05$.

RESULTS

The factors known before I-131 treatment were dose, thyroid weight, 24-hr I-123 uptake, and pre D/W. No significant differences in any of these factors were found between the three groups (Table 1 and Figs. 1, 2).

The factors obtained after the treatment were 24-hr I-131 uptake, effective half-life, post D/W, and absorbed dose. As shown in Table 1, both mean values of post D/W and absorbed dose were significantly different between the three groups (Kruskal-Wallis test).

The mean effective half-life (Te) measured with therapeutic radioiodine for the 20 patients was 5.0 ± 1.5 days (range 1.5–7.3 days).

The mean value of post D/W in the non-hyperthyroid (euthyroid and hypothyroid) group was significantly greater than that in the hyperthyroid group (Fig. 3). There was a threshold of 6.3 MBq/g separating the non-hyperthyroid group from the hyperthyroid group. There was no significant difference in the mean values of post D/W between the euthyroid and hypothyroid groups.

The mean value of absorbed dose in the non-hyperthyroid (euthyroid and hypothyroid) group was significantly

greater than that in the hyperthyroid group (Fig. 4). There was some overlap in absorbed dose between the euthyroid group and the hyperthyroid group. The maximum absorbed dose was 122 Gy in the hyperthyroid group. Like post D/W, absorbed dose did not differ significantly between the euthyroid and hypothyroid groups.

There was no correlation between pre D/W and post D/W (Spearman's correlation coefficient by rank test) (Fig. 5). However, the mean value of post D/W was significantly greater than that of pre D/W (paired t test, $p < 0.0005$) since the mean therapeutic I-131 uptake was significantly greater than the mean I-123 uptake (paired t test, $p < 0.001$).

All patients with pre D/W above 6.3 MBq/g (the threshold determined from the comparison between the three groups in terms of post D/W) became non-hyperthyroid at one year after the radioiodine treatment (Fig. 2).

DISCUSSION

We assessed the relationship between the effectiveness of the therapy and radioiodine doses. In the relationship with the effectiveness at one year after the treatment, no significant indicators were found before the therapy. After the treatment, two factors, post D/W and absorbed dose, were related to effectiveness.

In dose planning, we could use 6.3 MBq/g as a reference value. Post D/W was significantly greater than pre D/W and the post D/W of 6.3 MBq/g separated the non-hyperthyroid group from the hyperthyroid group. Therefore, the single dose planned for setting the pre D/W above 6.3 MBq/g will certainly make the patients non-hyperthyroid. In fact, it was observed that all patients with pre D/W above 6.3 MBq/g became non-hyperthyroid at one year after the treatment.

As the therapeutic radioiodine uptake was significantly higher than the diagnostic radioiodine uptake, the post D/W was made significantly greater than the pre D/W. It is speculated that the greater values of the therapeutic uptake were caused by the longer time interval of iodine restriction as well as withdrawal from antithyroid drugs.

There was a close relationship between the absorbed doses obtained after the therapy and the treatment effect. Although the mean Te measured with therapeutic I-131 was 5.0 days and is equal to our assumption, the Te differed from patient to patient showing a broad range of 1.5–7.3 days. Therefore, our dose planning based on the fixed Te of 5 days was not correct. It is suggested that measurement of individual Te as well as uptake before the therapy is necessary to determine the dose based on the absorbed dose speculation. Since we have not clarified the relationship between the speculated absorbed dose and the actual one, it is not possible to determine the therapeutic dose based on the absorbed dose at this time. Additionally, no studies reporting the relationship between the speculated and actual absorbed doses were found.

On the other hand, both post D/W and absorbed dose could be used as indicators predicting the effects of therapy. All patients with post D/W above 6.3 MBq/g or absorbed dose above 122 Gy became non-hyperthyroid at one year after the therapy. Since both post D/W and absorbed dose are known within a week after the therapy, they must be the earliest indicators of the effects. Absorbed dose could be a better indicator since its degree of significance was superior to that of post D/W in the comparison between the three groups ($p < 0.005$ versus $p < 0.01$, as shown in Table 1).

Number of data in this study was small and so we need to obtain further data to investigate whether this proposal of dose planning is sufficient to cure hyperthyroidism.

CONCLUSIONS

No indicators before the radioiodine therapy had significant relationships with the effectiveness of the therapy at one year after the treatment. However, the single therapy planned for setting the pre D/W above 6.3 MBq/g will certainly make the patients non-hyperthyroid. As this proposal of dose planning is based on a small number of patients, further study is needed.

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