

Clinical Research Article

Transient Leukopenia After Radioactive Iodine Treatment in Patients With Graves' Disease: A Retrospective Cohort Study

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Abbreviations: ATD, antithyroid drugs; BMI, body mass index; DDD, defined daily dose; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FT4, free thyroxine; MMI, thiamazole; RAI, radioactive iodine; TSH, thyrotropin (thyroid-stimulating hormone); WBC, white blood cell.

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Abstract

Context: Radioactive ¹³¹I (RAI) for the treatment of differentiated thyroid cancer is known to induce bone marrow suppression, which occurs approximately 1 month after treatment. However, it is unknown whether RAI therapy for Graves' disease causes bone marrow suppression.

Objective: This study aimed to evaluate the short- and long-term effects of RAI therapy on bone marrow function in patients with Graves' disease.

Methods: In this retrospective cohort study, we included patients with Graves' disease who received RAI therapy only once between 2003 and 2019 at Tokyo Women's Medical University. Blood cell counts at baseline were compared with counts at 1, 2, 4, 12, 24, 48, 144, and 240 weeks after RAI therapy. Moreover, changes in white blood cell (WBC) count and leukopenia at 1 week after RAI treatment were compared by baseline patient characteristics.

Results: We enrolled 48 patients. Leukopenia was observed in 6 patients at 1 week after RAI treatment, and the overall WBC count significantly decreased ($P < 0.001$) 1 week after the therapy; however, the values were not significantly lower after 2 weeks. Neither red blood cell nor platelet count were significantly altered. Moreover, independent of other factors, the neutrophil count at the baseline was significantly negatively associated with changes in WBC count or the occurrence of leukopenia 1 week after the RAI treatment.

Conclusion: These data showed that RAI treatment induced transient reduction in the WBC count 1 week after treatment, although WBC levels were subsequently restored.

Key Words: bone marrow suppression, hyperthyroidism, leukopenia, radioactive isotope, white blood cell count

Graves' disease is one of the most common endocrine disorders with autoimmune pathophysiology, where antibodies stimulate the thyroid-stimulating hormone (TSH) receptor and cause hyperthyroidism. The treatment of Graves' disease includes antithyroid drugs (ATD), radioactive iodine 131 (¹³¹I) (RAI), and thyroidectomy. In the United States, RAI therapy has been the most preferred treatment for Graves' disease. A survey among clinical endocrinologists in the United States in 2011 showed that 59.7% of respondents from the United States selected RAI therapy as the first-line treatment for an uncomplicated case of Graves' disease [1]. Most patients respond to RAI therapy within 4 to 8 weeks, as indicated by the normalization of values on thyroid function tests and the improvement of clinical symptoms. However, early and late adverse effects of RAI treatment may occur. Transient exacerbation of hyperthyroidism due to the destruction of the thyroid gland is an early adverse effect that occurs within 1 to 4 weeks after treatment completion [2]. Hypothyroidism is a delayed adverse effect, which may occur from 4 to 16 weeks after treatment [3].

Furthermore, RAI therapy may be postoperatively administered after thyroidectomy for differentiated thyroid cancer to ensure ablation of remnant tissues [4]. The recommended ¹³¹I dose for thyroid cancer is 30 to 200 mCi (1110-7400 MBq) [4-6]. Treatment with ¹³¹I is known to potentially cause bone marrow suppression at approximately 1 month post treatment [7]. In contrast, the RAI dose for Graves' disease is calculated by the size of the thyroid and is usually 8 to 10 mCi (296-370 MBq) [2], which is less than one-tenth of the RAI dose for cancer. However, it remains unclear whether this dose causes bone marrow suppression.

Therefore, the present study was conducted with an aim to investigate the effect of RAI treatment for Graves' disease on bone marrow function.

Methods

Patients

This study was conducted at the Department of Endocrinology and Hypertension, Tokyo Women's Medical University Hospital, Tokyo, Japan. The institutional ethics committee approved the study protocol (approval no. 5468). A retrospective chart review showed that 48 patients were treated with RAI only once for Graves' disease between March 2003 and August 2019 and had data

available on the blood cell count at baseline and at least once during the follow-up period. We defined leukopenia as a white blood cell (WBC) count <3000/ μ L, which has been stipulated by the Common Toxicity Criteria [8] as a marker of impaired bone marrow function.

RAI Treatment and Follow-Up

Patients were restricted from consuming iodine-containing foods for 1 week before the RAI treatment, and the ATD treatment was stopped 3 days prior to the treatment if the patients were on ATD [2]. The appropriate ¹³¹I dose was calculated by the Marinelli-Quimby formula as previously described [9]. Patients were treated with RAI in the hospital or at the outpatient clinic, depending on their individual requirements. After RAI treatment, patients returned for follow-up at the outpatient clinic.

Data Collection

Data on patient characteristics, such as sex, smoking, alcohol use, and history of type 1 diabetes mellitus (DM) and agranulocytosis (defined as neutrophil count <1500/ μ L) [10], ¹³¹I dose and uptake% in 24h, ATD use, thiamazole (MMI) use, and duration of ATD, maximum dose of ATD, were retrospectively derived from medical charts. The body mass index (BMI) was calculated as a person's weight in kilograms divided by the square of the height in meters. The age at RAI treatment was recorded as the patient's age. Blood cell counts and creatinine were measured using standard laboratory methods at our clinical laboratory. The estimated glomerular filtration rate (eGFR) was calculated using the following equation: $eGFR \text{ (mL/min/1.73m}^2\text{)} = 194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} (\times 0.739, \text{ if female})$ [11]. Serum TSH and free thyroxine (fT4) levels were measured with an electrochemiluminescence immunoassay using ECLusys TSH and FT4 (Roche Diagnostics K.K.). Laboratory reference ranges in healthy Japanese adults are: TSH, 0.50 to 5.00 IU/L; and fT4, 0.90 to 1.70 ng/dL.

Statistical Analysis

Data are expressed as mean \pm SD or as median with interquartile range (IQR), as appropriate. Baseline characteristics were compared by the chi-square or Fisher's test between 2 groups of patients whose WBC count was either <3000/ μ L or \geq 3000/ μ L 1 week after RAI therapy.

Blood cell counts after the RAI treatment were compared with those at baseline by using the Wilcoxon signed-rank test. The Spearman's rank correlation test was conducted to compare the following characteristics with change in WBC count (Δ WBC count) and leukopenia 1 week after RAI treatment: age, sex, smoking, alcohol use, history of type 1 DM and agranulocytosis, blood cell counts, serum free T4 level, eGFR, the ^{131}I dose, 24-hour ^{131}I uptake (%), history of ATD use and thiamazole (MMI) use, duration of ATD use, and maximum dose of ATD. Maximum dose of ATD was calculated using the defined daily doses (DDD) according to those set by the World Health Organization [12]. We subsequently undertook logistic regression analyses to identify variables that are associated with leukopenia. We used the forward Akaike Information Criterion (AICc) stepwise analyses to select variables from the abovementioned characteristics of age, sex, smoking, alcohol use, history of type 1 DM and agranulocytosis, blood cell counts, serum fT4 level, eGFR, and ^{131}I dose and ^{131}I uptake (%) in 24 hours, history of ATD use and MMI use, duration of ATD use, and maximum dose of ATD. The selected variables were then subjected to regression analysis. Significance was defined as $P < 0.05$. All statistical analyses were carried out in JMP pro version 12 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

Table 1 shows the baseline characteristics of the patients included in the final analysis dataset; 38 patients (81%) were female (age, median [IQR], 44 [36–54 years]), and the mean \pm SD ^{131}I dose was 356.5 ± 64.5 MBq. Single correlation analyses showed that the baseline WBC count was significantly positively correlated with BMI, hemoglobin level, and platelet count and was significantly negatively correlated with the baseline fT4 level (Table 2).

Short- and Long-Term Effects on Bone Marrow Function

Figure 1 shows the changes in mean blood cell counts from before RAI therapy and up to 5 years after the RAI therapy. A follow-up period of 3 months was completed for 45% of the patients after the RAI treatment and 10 patients were followed until 5 years after the RAI treatment. The WBC count significantly decreased 1 week after the therapy ($P < 0.001$) but did not remain significantly low at 2 weeks after RAI therapy ($P = 0.7704$, compared with baseline values). Neutrophil, erythrocyte, and platelet counts were not significantly altered from the baseline. Six patients

Table 1. Baseline Characteristics

	All participants (n = 48)	WBC < 3000/ μL at 1 week (n = 6)	WBC \geq 3000/ μL at 1 week (n = 42)	P value
Age, years	44 (36–54)	39 (30–47)	46 (36–55)	0.1650
Sex, female	38 (81%)	5 (83%)	33 (80%)	0.8686
Alcohol use	9 (20%)	0 (0%)	9 (23%)	0.1883
Smoking	10 (22%)	1 (17%)	9 (23%)	0.7251
BMI, kg/m^2	21.1 ± 0.5	20.1 ± 2.6	21.3 ± 3.5	0.4955
Type 1 DM	1 (2%)	0 (0%)	1 (2%)	0.6990
Agranulocytosis	14 (30%)	3 (50%)	11 (27%)	0.2464
WBC, per μL	5297 ± 1712	3690 ± 573	5532 ± 1699	0.0053
NEUT, per μL	2390 (1613–3325)	1913 (1284–2647)	2457 (1741–3407)	0.2070
RBC, $\times 10^6/\mu\text{L}$	5.04 (4.31–5.04)	4.34 (4.11–5.13)	4.67 (4.32–5.04)	0.3388
Hb, g/dL	12.9 (12.0–14.2)	12.3 (11.5–13.9)	13.0 (12.2–14.3)	0.3632
Plt, $\times 10^4/\mu\text{L}$	23.9 ± 8.3	21.0 ± 4.1	24.3 ± 8.7	0.4537
fT4, ng/dL	4.46 ± 2.40	3.66 ± 2.20	4.59 ± 2.43	0.3254
TSH, $\mu\text{U}/\text{mL}$	0.03 ± 0.17	0.17 ± 0.41	0.007 ± 0.003	0.6568
eGFR, $\text{mL}/\text{min}/1.73\text{m}^2$	125.5 ± 47.3	118.0 ± 45.6	126.6 ± 48.0	0.8608
^{131}I dose, MBq	356.5 ± 64.5	362.8 ± 16.1	355.8 ± 68.2	0.9474
^{131}I uptake in 24h (%)	64.5 ± 16.3	79.1 ± 4.4	62.7 ± 16.3	0.0440
ATD use	43 (91%)	6 (100%)	37 (90%)	0.4238
MMI use	36 (77%)	6 (100%)	30 (73%)	0.1471
Duration of ATD (weeks)	74.9 ± 177.7	114.8 ± 173.2	65.4 ± 180.9	0.0729
Max dose of ATD (DDD)	236.8 ± 157.5	283.3 ± 194.1	228.1 ± 151.8	0.7569

Data are expressed as mean \pm standard deviation, median (interquartile range), or n (%).

Abbreviations: ATD, antithyroid drug; BMI, body mass index; DDD, defined daily dose; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; fT4, free thyroxine; Hb, hemoglobin; MMI, thiamazole; NEUT, neutrophil; Plt, platelet; RBC, red blood cell; TSH, thyroid-stimulating hormone; WBC, white blood cell.

Table 2. Single Correlation Analyses With Baseline WBC and Baseline Characteristics

	ρ	P value
Age	0.0871	0.5560
Sex	-0.0463	0.7547
Smoking	0.1070	0.4841
BMI	0.3328	0.0359
Type 1 DM	-0.1316	0.3725
Agranulocytosis	-0.1980	0.1773
RBC	0.2246	0.1249
Hb	0.3434	0.0169
Plt	0.2914	0.0444
fT4	-0.4061	0.0062
TSH	0.2895	0.0822
eGFR	-0.2208	0.1316
ATD use	-0.2043	0.1636
MMI use	-0.1268	0.3905
Duration of ATD	-0.2293	0.2146
Max dose of ATD	0.1985	0.2323

Abbreviations: ATD, antithyroid drug; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; fT4, free thyroxine; Hb, hemoglobin; MMI, thiamazole; NEUT, neutrophil; Plt, platelet; RBC, red blood cell; TSH, thyroid-stimulating hormone; WBC, white blood cell.

showed leukopenia (WBC count $<3000/\mu\text{L}$) 1 week after the RAI treatment (Tables 1 and 3). Baseline WBC count was significantly lower in patients with leukopenia than in patients without leukopenia (3960 ± 573 vs 5532 ± 1699 , respectively; Table 1). The percentage of ^{131}I uptake in 24 hours was significantly higher in patients with leukopenia ($P = 0.0440$; Table 1). The details of the 6 patients with leukopenia are shown in Table 3; 3 of these patients underwent RAI treatment as they had agranulocytosis due to ATD, and 2 of the remaining patients received RAI treatment because they were refractory to ATD (defined as those who experienced multiple recurrences or those who did not cure even though they were taking ATD for more than 3 years) and 1 had RAI treatment because the patient was had a heart failure condition (Table 3).

Association With Leukopenia

Single correlation analyses showed that leukocyte and neutrophil counts and hemoglobin level at baseline and the ^{131}I dose were significantly negatively correlated and fT4 level at baseline was significantly positively correlated with the ΔWBC count (Table 4, Fig. 2); the leukocyte count at baseline was significantly negatively associated and percentage of ^{131}I uptake in 24 hours was significantly positively associated with leukopenia 1 week after the RAI treatment (Table 4). To determine whether the correlation between WBC count at baseline and ΔWBC count is independent of other factors, we conducted stepwise multiple regression

analyses that tested the parameters of age, sex, WBC count, neutrophil count, hemoglobin level, serum fT4 concentration, and the ^{131}I dose and ^{131}I uptake in 24 hours showed significant associations with ΔWBC (Table 5). The neutrophil count and hemoglobin level at baseline were identified as possibly independent variables, and both variables showed a significant negative correlation with the ΔWBC count. Similarly, to investigate whether the correlation between WBC count at baseline and leukopenia at 1 week post-RAI treatment is independent of other factors, we used stepwise multiple regression analyses, but none of the variables was independent from other factors (data not shown). A low neutrophil count and low hemoglobin level were associated with a significant decrease of WBC count.

Discussion

This study undertook a novel investigation and showed short- and long-term changes in blood counts after RAI treatment for Graves' disease. We found that RAI treatment induced transient reduction of WBC count at 1 week after the treatment, and the WBC counts recovered thereafter (Fig. 1). In addition, baseline neutrophil count and hemoglobin level were significantly and independently associated with decreased WBC count (Table 5). These data indicated a risk for leukopenia after RAI treatment, especially in patients with low WBC count at the time of RAI treatment.

Bone marrow suppression is a known side effect of RAI therapy for thyroid cancer and occurs within 1 month after treatment completion [7, 13]. The ^{131}I dose used for Graves' disease is less than one-tenth the dose that is used for the treatment of thyroid cancer. The International Commission on Radiological Protection (ICRP) 2009 reported that the threshold dose for induction of acute bone marrow suppression is 0.5 Gy [14]. The absorbed RAI dose per unit activity administered into the red marrow when thyroid uptake was 55% was reported to be 0.12 mGy/MBq on posttreatment Day 8 [15]. In our study population, the median thyroid uptake after 24 hours was $64.5\% \pm 16.3\%$, and the mean ^{131}I dose was 356.5 ± 64.5 MBq (Table 1). Red marrow absorption of the radioiodine was calculated to be 0.0041 mGy, which is one-thousandth lower than the threshold dose for acute bone marrow suppression. This leads to a clear inference that ^{131}I therapy for Graves' disease does not affect bone marrow function. Surprisingly, however, our study sample showed decreased WBC count about 1 week after RAI therapy (Fig. 1) ($2240/\mu\text{L}$ minimum, Table 3). This diminished WBC count resolved without any treatment within 4 weeks and no long-term bone marrow suppression was detected over 5 years (Table 3, Fig. 1). In our study, the neutrophil count and hemoglobin level were significantly and negatively correlated with ΔWBC count,

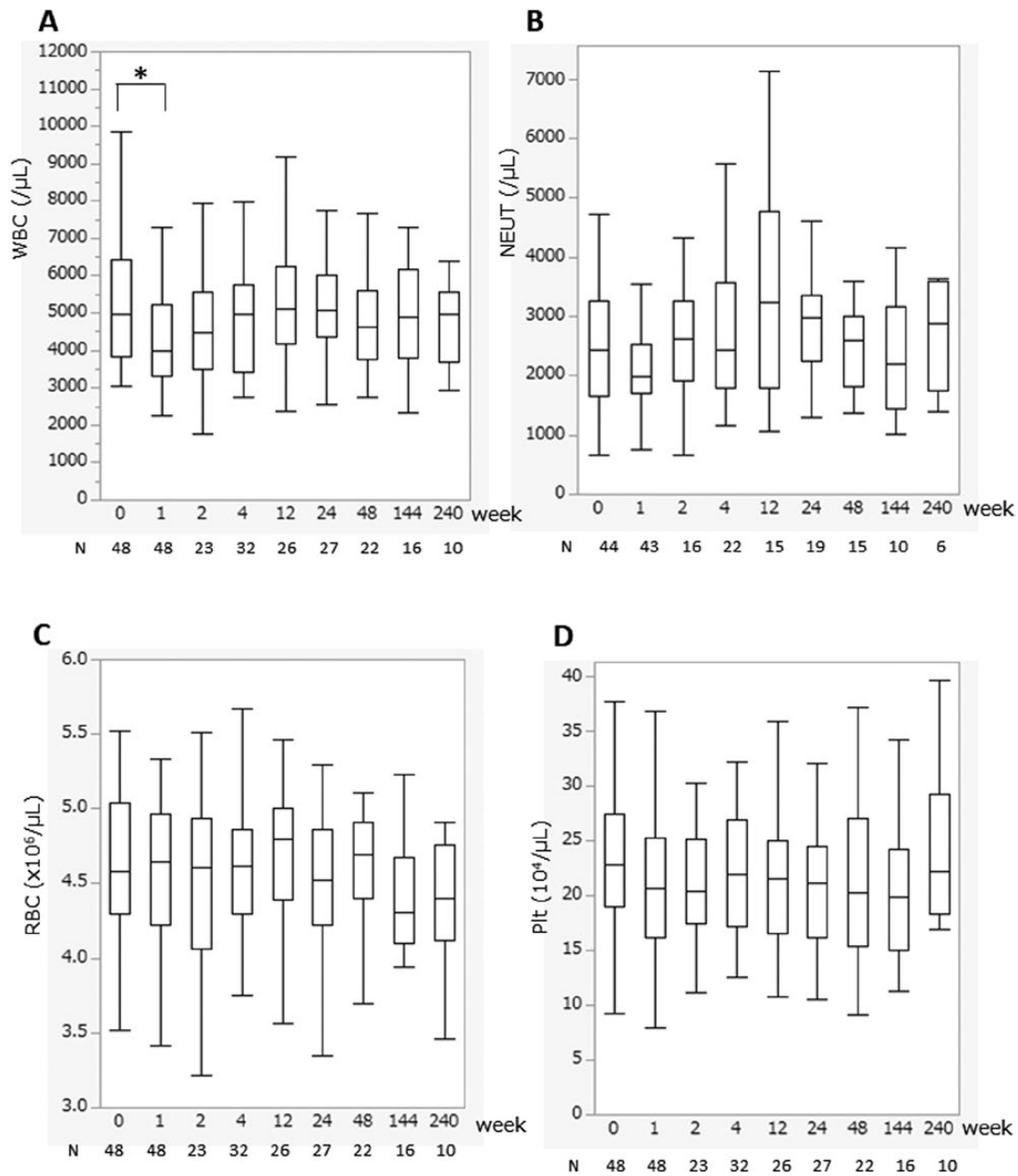


Figure 1. Blood counts during follow-up. Counts of **A**, white blood cells, **B**, neutrophils, **C**, red blood cells, and **D**, platelets. * $P < 0.001$. Abbreviations: NEUT, neutrophil; Plt, platelet; RBC, red blood cell; WBC, white blood cell.

independent of other factors, suggesting that low neutrophil count and hemoglobin level are the independent risk factors for decreased WBC count at 1 week after treatment (Table 5). Hematologic abnormalities are frequently seen in the setting of thyrotoxicosis. It is known that patients with thyrotoxicosis may have increased RBC mass, with microcytosis, leukopenia, anemia, and, rarely, pancytopenia [16-18]. Aggarwal et al reported that hyperthyroidism by Graves' disease is associated with neutropenia [19]. In the hyperthyroid state, gene expression of the thyroid hormone receptor is downregulated in hematopoietic progenitor

cells, and apoptosis of the hematopoietic cells is increased [20]. However, neither fT_4 level at baseline nor ^{131}I dose was independently associated with ΔWBC in the present study (Table 5). Prior to RAI treatment, restrictions on iodine-containing food and ATD are usually required [2]. Interruption of ATD may cause hyperthyroidism; therefore, clinicians need to be vigilant about the occurrence of leukopenia. In our study, there was no significant correlation between the history of agranulocytosis and reduction of WBC count. However, agranulocytosis could be a risk factor for suppressed bone marrow function; therefore, it may be

Table 3. Clinical Features of the Patients With Leukopenia

No.	Age (yrs)	Sex	Smoking	Alcohol use	BMI (kg/m ²)	WBC at baseline (/ μ L)	WBC at 1wk (/ μ L)	WBC at 2wk (/ μ L)	WBC at 4wk (/ μ L)	WBC at 12wk (/ μ L)	TSH (μ U/mL)	fT4 (ng/dL)	eGFR (mL/min/1.73 m ²)	¹³¹ I dose (MBq)	¹³¹ I uptake in 24h (%)	Reasons
1	31	M	-	-	22.7	3110	2240	1760	2840	2370	0.006	4.74	110.4	370	77.8	Agranulocytosis due to MMI Max dose 15 mg, duration 14 wk
2	33	F	-	-	19.0	3640	2470	N/A	3240	4180	0.005	6.74	176.8	370	N/A	Agranulocytosis due to MMI Max dose 15 mg, duration 15 wk (nadir NEUT 750/ μ L)
3	26	F	-	-	22.0	4500	2760	N/A	3330	N/A	1.010	0.93	138.2	370	85.4	Resistance to MMI (recurrence) Max dose 45 mg, duration 234 wk (nadir NEUT 112/ μ L)
4	44	F	-	-	16.4	3060	2760	2450	2920	2970	0.005	4.84	108.0	334	75	Resistance to MMI (not cure) Max dose 20 mg, duration 417 wk
5	45	F	-	-	22.4	4190	2870	4050	4410	8740	0.005	3.15	134.7	370	N/A	Heart failure
6	54	F	-	-	18.2	3640	2930	N/A	3300	4000	0.005	1.53	39.9	N/A	87	Agranulocytosis due to MMI Max dose 15 mg, 1 wk (nadir NEUT 1409/ μ L)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; fT4, free thyroxine; MMI, thiamazole; N/A, not available; NEUT, neutrophil; TSH, thyroid-stimulating hormone; WBC, white blood cell.

Table 4. Single Correlation Analyses With Δ WBC and WBC <3000 at 1 Week

	Δ WBC at 1 week		WBC <3000 at 1 week	
	ρ	P value	ρ	P value
Age	0.1263	0.3923	-0.2117	0.1486
Sex (female)	0.0056	0.9701	0.0388	0.7936
Alcohol use	-0.0043	0.9778	-0.1961	0.1967
Smoking	-0.1152	0.4509	-0.0524	0.7324
BMI	-0.2528	0.1155	-0.1062	0.5143
Type 1 DM	0.0474	0.7491	-0.0551	0.7098
Agranulocytosis	0.0298	0.8408	0.1732	0.2390
WBC at baseline	-0.4216	0.0028	-0.4116	0.0037
NEUT at baseline	-0.4855	0.0008	-0.1982	0.1972
RBC at baseline	-0.2601	0.0742	-0.1228	0.4057
Hb at baseline	-0.3694	0.0098	-0.1160	0.4322
Plt at baseline	0.1014	0.4929	-0.0932	0.5286
ft4 at baseline	0.3245	0.0316	-0.1463	0.3432
TSH at baseline	-0.1326	0.4342	-0.0648	0.7034
eGFR at baseline	0.0146	0.9217	0.0341	0.8180
^{131}I dose	-0.4960	0.0005	0.0063	0.9668
^{131}I uptake in 24h	-0.0664	0.6962	0.3424	0.0380
ATD use	-0.1871	0.2029	0.1289	0.3826
MMI use	-0.0955	0.5184	0.2182	0.1362
Duration of ATD (weeks)	0.0796	0.6702	0.3274	0.0722
Max dose of ATD (DDD)	-0.0672	0.6883	0.0509	0.7615

Abbreviations: ATD, antithyroid drug; BMI, body mass index; DDD, defined daily dose; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ft4, free thyroxine; Hb, hemoglobin; NEUT, neutrophil; Plt, platelet; RBC, red blood cell; TSH, thyroid-stimulating hormone; WBC, white blood cell.

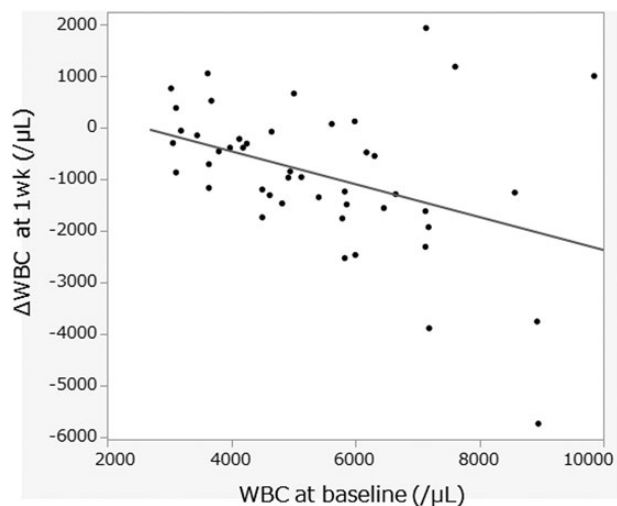


Figure 2. Linear correlation between basal WBC and Δ WBC at 1 week after the treatment. $R^2 = 0.1615$, $P = 0.0046$. Abbreviations: WBC, white blood cell.

desirable to wait for the normalization of WBC count in patients with agranulocytosis before RAI treatment.

It remains unknown why patients with low WBC at baseline developed leukopenia after RAI treatment. However, single correlation analyses with baseline WBC count showed a significantly negative correlation with baseline ft4 ($\rho = -0.4061$, $P = 0.0062$; Table 2). Low

Table 5. Multiple Regression Analyses With Δ WBC at 1 Week

	Δ WBC at 1 week	
	β (95% CI)	P value
Age	-	-
Sex (female)	-	-
WBC at baseline	-	-
NEUT at baseline	-0.48 (-0.0008, -0.0002)	0.0027
Hb at baseline	-0.31 (-0.4360, -0.0100)	0.0408
ft4 at baseline	-	-
^{131}I dose	-	-
^{131}I uptake in 24h	-0.20 (-0.0323, 0.0063)	0.1792

$R^2 = 0.4008$, $P = 0.0014$ for Δ WBC at 1 week.

Abbreviations: ft4, free thyroxine; Hb, hemoglobin; NEUT, neutrophil; WBC, white blood cell.

baseline WBC count due to a postagranulocytic status or hypermetabolism of the blood cells due to hyperthyroidism, as previously discussed, might be causally related to the occurrence of transient reduction of WBC count.

Limitations

This study has some limitations. First, the study sample was relatively small, full follow-up was not possible for every patient, and this was a single-center study. One of the reasons

for the small sample size in this study may be low frequency of the RAI treatment selection in Japan [21]. Only 6 patients (14% of the sample studied) developed leukopenia. Second, the retrospective cohort design of this study and missing data for the follow-up period proves a limitation. Investigations in larger-scale prospective studies are required to elucidate the association of leukopenia with RAI outcomes.

Conclusion

RAI treatment induced a significant but transient reduction of WBC count 1 week after the treatment, and WBC counts subsequently recovered without therapeutic interventions. Furthermore, the baseline neutrophil count was significantly and independently negatively associated with changes in WBC count 1 week after the treatment. There is a need for clinical vigilance with regard to the risk of leukopenia after RAI treatment, especially in patients with pretreatment low neutrophil count as these patients need careful posttreatment follow-up to prevent infections.

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Additional Information

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Disclosures: All authors report nothing to disclose.

Data Availability: Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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