Short-term bone marrow suppression in differentiated thyroid cancer patients after radioactive iodine treatment

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Abstract. After thyroidectomy in differentiated thyroid cancer (DTC), radioactive iodine (RAI) treatment is often used for remnant ablation. However, RAI treatment has been associated with bone marrow suppression, and leukopenia, anemia, and thrombocytopenia may occur after a single RAI administration. In this study, we examined the change in complete blood counts at 1 week after RAI administration; this is less well studied. A group of 189 DTC patients who received RAI treatment and underwent blood tests before and after treatment, were included. Peripheral blood counts at baseline were compared to those obtained at 1 week, 1–6 months, and 6–12 months after RAI treatment in order to test for bone marrow suppression. At 1 week after RAI treatment, there was a significant decrease in the white blood cell count (WBC, 5.8 ± 1.6 × 10⁹/L vs. 5.4 ± 1.5 × 10⁹/L, p < 0.001) and hemoglobin level (Hb, 13.5 ± 1.7 g/dL vs. 13.3 ± 1.4 g/dL, p = 0.001). The WBC decrease was mostly due to lymphocyte counts (2.2 ± 0.6 × 10⁹/L vs. 1.6 ± 0.5 × 10⁹/L, p < 0.001), with no decrease in the neutrophil count. Although not significantly changed at 1 week, platelet counts were altered within 6 months (265 ± 69 × 10⁹/L vs. 239 ± 53 × 10⁹/L, p < 0.001). The decline in the WBC count recovered within 6 months; lymphocyte and platelet counts recovered within 12 months. In conclusion, RAI treatment after a thyroidectomy was associated with a statistically significant but temporary decline in WBC counts and Hb levels at 1 week. Physicians treating DTC patients should not decrease usage of moderate dose RAI treatments.

Key words: Differentiated thyroid cancer, Radioactive iodine, Bone marrow, White blood cell, Lymphocyte

DIFFERENTIATED THYROID CANCER (DTC) is the most common endocrine malignancy, and in Korea, most DTC includes papillary thyroid cancer (PTC) [1-3]. Radioactive iodine (RAI) treatment has been used in patients with DTC after thyroidectomy, either for ablation of the postoperative thyroid remnant or for treatment of recurrent and metastatic disease [4]. RAI treatment is associated with a significantly lower rate of recurrence, metastatic disease, and overall mortality in DTC patients [5, 6]. However, RAI treatment also is associated with several adverse effects on the gonads, salivary and lacrimal glands, and hematopoietic systems [7-10]. Furthermore, cumulative administration of treatments have been associated with an increased risk of secondary malignant neoplasms, including bone and soft-tissue sarcomas, salivary gland and digestive tract cancers, and leukemia [11].

Peripheral blood counts were studied to evaluate bone marrow suppression after RAI treatment, as it is known that it can cause leukopenia, anemia, and thrombocytopenia [12-14]. A significant decrease in white blood cell (WBC) and platelet counts at 1 year after single RAI treatment has been reported [15]. Post-treatment platelet and leukocyte counts have also been shown to temporarily decrease and normalize to baseline levels within 5 years [16]. However, previous studies focused on the changes of bone marrow suppression at 1 year after RAI treatment; no studies have investigated the immediate acute changes. Therefore, we evaluated the impact of a single dose of RAI on the complete blood count 1 week after the treatment.

Materials and Methods

Study design, subjects, and data collection

The electronic records at Pusan National University Hospital, a tertiary medical center, were retrospectively reviewed for all patients who were treated with RAI...
between 2012 and 2013. Since no individual patient information is discussed, consent from participants was not needed according to the Institutional Review Board of Pusan National University Hospital (IBR No. H-2004-014-089). The inclusion criteria for the study were as follows: patients with documented DTC who were treated with thyroidectomy, access to complete electronic medical records, and data on complete blood counts (CBC) on the day of RAI treatment, at 1 week after RAI, and within one year following treatment. Patients were excluded from the study if they were taking any medications known to affect the CBC, if they received a second dose of RAI during the first year of follow-up, if they were known to have any hematological conditions, if they had active concomitant malignancy, or received current chemotherapy or immunotherapy, or if they had recent hemorrhage (within six months before RAI) with a decrease in hemoglobin (Hb) levels by ≥1.5 g/dL.

The following data were collected from the patients’ files: age at the time of treatment, body weight, sex, tumor size and histology, tumor-node-metastasis (TNM) stage according to the American Joint Committee on Cancer (AJCC) 7th edition, preparation with recombinant human thyroid-stimulating hormone (rhTSH) or thyroid hormone withdrawal (THW), administered RAI dose, and CBC before and after the RAI treatment.

The primary endpoints of the study were the hematologic changes after 1 week of RAI treatment in DTC patients. All serum blood tests were performed by the automated Sysmex XE-2100 and Sysmex XN-3000 (Sysmex Corp) machines. Intervals assessed for bone marrow function were baseline values (on the day of RAI treatment), 1 week, 1–6 months, and 6–12 months after RAI treatment. The normal values for Hb in males were 13–17 g/dL and 11.5–16 g/dL for females. The normal WBC values were 4.0–11.0 × 10^9/L, and the normal platelet values were 160–400 × 10^9/L.

Statistical analysis

Data have generally been presented as the mean ± standard deviation (SD). A paired t-test was used to compare blood counts at each time point with baseline blood counts.

Lymphocyte counts declined rapidly in this study; we therefore focused on lymphocyte counts at 1 week for analysis of risk factors. The characteristics of patients with lymphocyte count reduction from pre-treatment values at 1 week after completion of RAI treatment were compared with those without lymphocyte count reduction.

In order to evaluate the characteristics of patients with and without lymphocyte count reduction, the χ^2 test was performed to compare patients’ sex, TNM stage, RAI dose, and preparation methods (with rhTSH or THW). For similar reasons, we analyzed age and RAI dose per kg body weight using the parametric t-test, and performed logistic regression analyses to identify variables associated with lymphocyte counts reduction. All statistical analyses were performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp, Armonk, NY). A two-sided p-value of <0.05 was considered statistically significant for all analyses.

Results

Patients

A total of 189 DTC patients who were treated with RAI after total thyroidectomy had their CBC data available for review. The mean age at RAI treatment was 49.8 ± 11.4 years, with a median age of 51 years. The majority of the patients were female (81.0%). All had undergone total thyroidectomy, and tumor histology showed that they all had PTC. TNM staging (based on AJCC classification, 7th edition) revealed that a higher proportion of patients were in stage I (45.5%) and stage III (47.1%) than in stage II (0.5%) and stage IV (6.9%). None of the patients in this study had distant metastases. The patients in stage IV either had T4 or N1b disease according to the AJCC 7th edition. The majority of patients were prepared for RAI treatment with rhTSH (59.8%), the administered RAI dose was 100 mCi (54.5%) or 150 mCi (45.5%), and the RAI dose per kg body weight was 2.0 ± 0.5 mCi/kg (Table 1).

Bone marrow function

The results of the CBC findings at baseline and after RAI treatment are shown in Table 2. The mean follow-up at 1–6 months was 4 months, and the mean follow-up at 6–12 months was 10.5 months. At 1 week after RAI treatment, there was a statistically significant decrease in WBC (5.8 ± 1.6 vs. 5.4 ± 1.5 × 10^9/L, p < 0.001), and Hb (13.5 ± 1.7 vs. 13.3 ± 1.4 g/dL, p = 0.046), but the change in platelets showed no significant difference (265 ± 69 vs. 264 ± 57 × 10^9/L, p = 0.857). The decline of the WBC count was mostly due to lymphocyte counts (2.2 ± 0.6 vs. 1.6 ± 0.5 × 10^9/L, p < 0.001); other components of the WBC count (neutrophil and monocyte counts) were not decreased.

The decreases in lymphocyte counts remained at 1–6 months, but the change in the WBC count was not statistically significant. At 6–12 months, the change in lymphocyte counts was no longer significant. Platelets decreased at 1–6 months (264 ± 69 vs. 239 ± 53 × 10^9/L, p < 0.001) and recovered at 6–12 months (265 ± 69 vs. 260 ± 63 × 10^9/L, p = 0.062).
CBC findings analyzed by gender

WBC was significantly decreased in females; in males, the decline in the WBC count was not observed. Nevertheless, lymphocyte counts in both males and females were significantly decreased at 1 week (2.3 ± 0.7 to 1.7 ± 0.5, \( p < 0.001 \); 2.2 ± 0.6 to 1.6 ± 0.5, \( p < 0.001 \)).

Hb showed a significant decrease in the total patient population, but the decrease in males and females did not persist when categorized by sex (15.0 ± 1.2 to 14.7 ± 1.3, \( p = 0.136 \); 13.1 ± 1.6 to 13.0 ± 1.2, \( p = 0.138 \) (Table 3).

Risk factors for impairment of bone marrow function at 1 week

The lymphocyte counts at 1 week after RAI treatment were decreased in 168 patients. There were no significant differences in terms of age, sex, TNM stage, RAI dose, preparation methods, and RAI dose per kg body weight between patients with and without lymphocyte reduction (Table 4). On logistic regression analysis, the variables in this study were not associated with lymphocyte count reduction at 1 week after RAI treatment (Table 5).

Discussion

In this study, we showed that a single moderate dose (100 mCi or 150 mCi) of RAI treatment was associated with bone marrow suppression at 1 week after RAI therapy. There was a statistically significant decline in the WBC count, mostly lymphocytes, and in Hb levels, but platelets were reduced only at 1–6 months. All blood components recovered within 12 months. The decline in Hb was no longer statistically significant when categorized by sex. This pattern of marrow suppression is in agreement with those of previous studies, demonstrating a significant decrease in platelets and WBC, with relative sparing of Hb [15-19].

Our study is the first to show effects of RAI treatment on bone marrow function within a very short period. RAI treatment for ablation of postoperative thyroid remnants or for treatment of recurrent and metastatic disease has been found to be associated with bone marrow suppression, but the small change was not found to be clinically significant for adverse events (such as severe neutropenia or anemia, requiring transfusion or administration of

| Table 1 | Baseline characteristics of the trial patients |
|---------|---------------------------------|
| Number of patients | 189 |
| Gender | |
| Female | 153 (81.0%) |
| Male | 36 (19.0%) |
| Age, mean ± SD | 49.8 ± 11.4 |
| Body weight (Kg), mean ± SD | 62.4 ± 9.2 |
| Extent of surgery | |
| Total thyroidectomy | 189 (100%) |
| Histology | |
| PTC | 189 (100%) |
| TNM Stage | |
| I | 86 (45.5%) |
| II | 1 (0.5%) |
| III | 89 (47.1%) |
| IV | 13 (6.9%) |
| Preparation | |
| rhTSH | 113 (59.8%) |
| THW | 76 (40.2%) |
| Administered activity | |
| 100 mCi | 103 (54.5%) |
| 150 mCi | 86 (45.5%) |
| RAI dose per body weight (mCi/Kg), mean ± SD | 2.0 ± 0.5 |

SD, standard deviation; PTC, papillary thyroid cancer; RAI, radioactive iodine; TNM, tumor-node-metastasis; THW, thyroid hormone withdrawal; rhTSH, recombinant human TSH.

| Table 2 | Blood counts baseline and after RAI treatment |
|---------|---------------------------------|
| WBC (10^9/L) | Baseline \((n = 189)\) | 1 week \((n = 189)\) | 1–6 Months \((n = 150)\) | 6–12 Months \((n = 105)\) |
| Neutrophil (10^9/L) | 3.1 ± 1.2 | 3.3 ± 1.2 | 3.2 ± 1.3 | 3.2 ± 1.2 |
| Lymphocyte (10^9/L) | 2.2 ± 0.6 | 1.6 ± 0.5 | 1.9 ± 0.5 | 2.2 ± 0.6 |
| Monocyte (10^9/L) | 0.37 ± 0.24 | 0.38 ± 0.16 | 0.44 ± 0.36 | 0.35 ± 0.13 |
| Hemoglobin (g/dL) | 13.5 ± 1.7 | 13.3 ± 1.4 | 13.3 ± 1.4 | 13.7 ± 1.5 |
| Platelets (10^9/L) | 265 ± 69 | 264 ± 57 | 239 ± 53 | 260 ± 63 |

Numbers in each column relate to number of available CBCs at that time point (in parentheses). P-values relates to comparison with baseline CBC only for patients included at each time point (and not to mean ± SD at baseline). 

Paired \(t\) test compared to baseline levels.

WBC, white blood cell.
colony-stimulating factors) [15-19]. However, previous studies evaluating the association of RAI treatment with bone marrow suppression have shown the relationship at 3 months or more after RAI treatment. In our institution, patients with RAI treatment (RAI dose above 30 mCi) were routinely evaluated using CBC at 1 week after treatment and were regularly monitored for hematologic changes. Owing to this monitoring protocol, we were able to evaluate bone marrow suppression at 1 week after RAI treatment and show that a single treatment was associated with a rapid decline in blood counts.

Some statistical results of this study differed from those of previous studies. One of the findings was a decline in Hb at 1 week after RAI treatment. Prinsen et al. showed that Hb in each gender decreased statistically significant at 3 months after RAI treatment, and Hu et al. showed that significant decline in Hb at 6 months after treatment in each gender [16, 18]. However the decrease of Hb in each gender was not statistically significant in this study. These results may be explained by the smaller number of subjects in each gender compared to the total population. Another finding was that the decreased WBC count recovered within 1 year. However, previous studies showed a significant decline in leukocytes at 1 year [15, 16]. Compared to those in previous studies, participants in our study received lesser RAI doses. Duskin-Bitan et al. found that WBC and Hb were suppressed with administered RAI doses of ≥150 mCi [17]. In two dosimetrically guided RAI treatment studies, high cumulative activities of RAI administered under dosimetric guidance (mean activity >250 mCi) were associated with statistically significant decreased blood counts [19, 20].

Table 3  Blood counts changes baseline and after RAI treatment according to gender at 1 week

|                     | Male (n = 36) | Female (n = 153) |
|---------------------|--------------|------------------|
| **Baseline**        |              |                  |
| WBC (10⁹/L)        | 6.2 ± 1.5    | 5.8 ± 1.7        |
| Neutrophil (10⁹/L) | 3.3 ± 1.1    | 3.1 ± 1.2        |
| Lymphocyte (10⁹/L) | 2.3 ± 0.7    | 2.2 ± 0.6        |
| Monocyte (10⁹/L)   | 0.48 ± 0.45  | 0.35 ± 0.16      |
| Hemoglobin (g/dL)  | 15.0 ± 1.2   | 13.1 ± 1.6       |
| Platelets (10⁹/L)  | 248 ± 0.6    | 269 ± 0.7        |
| **1 week**         | 5.9 ± 1.4    | 5.3 ± 1.6        |
|                     | 3.5 ± 1.0    | 3.2 ± 1.3        |
|                     | 1.7 ± 0.5    | 1.6 ± 0.5        |
|                     | 0.47 ± 0.26  | 0.36 ± 0.13      |
|                     | 14.7 ± 1.3   | 13.0 ± 1.2       |
|                     | 245 ± 0.5    | 269 ± 0.6        |
| **p-value**        | 0.187        | <0.001           |
|                     | 0.305        | 0.186            |
|                     | <0.001       | 0.314            |
| **p-value**        |              |                  |

* Paired t test compared to baseline levels.

WBC, white blood cell.

Table 4  Characteristics of patient with and without lymphocyte count reduction at 1 week

|                                | With lymphocyte count reduction (n = 168) | Without lymphocyte count reduction (n = 21) | p-value |
|--------------------------------|-------------------------------------------|-------------------------------------------|---------|
| Age, mean ± SD                 | 49.6 ± 11.4                               | 51.6 ± 11.4                               | 0.454   |
| Gender                         |                                           |                                           |         |
| Female                         | 139 (82.7%)                               | 14 (66.7%)                                | 0.077   |
| Male                           | 29 (17.3%)                                | 7 (33.3%)                                 |         |
| TNM Stage                      |                                           |                                           |         |
| I–II                           | 78 (46.4%)                                | 9 (42.9%)                                 | 0.757   |
| III–IV                         | 90 (53.6%)                                | 12 (57.1%)                                |         |
| RAI dose                       |                                           |                                           |         |
| 100 mCi                        | 88 (52.4%)                                | 15 (71.4%)                                | 0.098   |
| 150 mCi                        | 80 (47.6%)                                | 6 (28.6%)                                 |         |
| Preparation                    |                                           |                                           |         |
| rhTSH                          | 98 (58.3%)                                | 15 (71.4%)                                | 0.249   |
| THW                            | 70 (41.7%)                                | 6 (28.6%)                                 |         |
| RAI dose per body weight       | 2.03 ± 0.5                                | 1.87 ± 0.4                                | 0.169   |

RAI, radioactive iodine; TNM, tumor-node-metastasis; THW, thyroid hormone withdrawal; rhTSH, recombinant human TSH.
The majority of patients were treated with doses of 100 mCi (54.5%) in this study; therefore, the WBC count at 1 year after RAI treatment was not significantly decreased.

The characteristic sensitivities of the various blood cells to radiation have been evaluated in several studies. Among all hematopoietic cells, small lymphocytes have the greatest radiosensitivity; therefore, declines in lymphocyte and granulocyte counts occur over hours and days, respectively [21]. Previously, Mauch et al. found that lymphopenia occurs almost immediately after marrow radiation exposure, followed by neutropenia, and thrombocytopenia and anemia in 2–3 weeks and months, respectively [22]. In this study, the decline in lymphocyte counts occurred at 1 week after RAI treatment. The decline in platelets followed that in lymphocytes. On logistic regression analysis, none of the variables evaluated in this study were associated with lymphocyte reduction (age, sex, TNM stage, RAI dose, preparation methods, and RAI dose per kg body weight).

This study has several limitations. First, the RAI was mostly administered at a moderate dose (100 mCi or 150 mCi). At our medical center, low-risk patients were administered low RAI doses (30 mCi RAI activity). In cases of low-dose RAI treatment, the baseline CBC was evaluated on the day of RAI treatment, but the next follow-up evaluation was not performed for more than 3 months. However, a previous study on low-dose RAI treatment (<100 mCi) associated with bone marrow suppression found no significant dose-response relationship [15]. Second, bone marrow suppression within 1 year after RAI treatment cannot exclude the risk of long-term damage to bone marrow. However, Prinsen et al. showed that both, platelet and leukocyte counts normalized to baseline levels at five years after RAI treatment; this implies that bone marrow toxicity is temporary [16]. Finally, the predictors for bone marrow suppression were not found. A previous study showed that the most pronounced suppression occurred in patients treated with doses of >150 mCi [17]. In our cohort, all patients had PTC tumor histology and were treated with moderate doses of RAI. It is possible that on evaluation of RAI-treated patients receiving low (<100 mCi) or high (>150 mCi) doses, the RAI dose would show an association with bone marrow suppression at 1 week after treatment.

In conclusion, moderate dose RAI treatment (activities between 100 mCi and 150 mCi) after total thyroidectomy in DTC patients is associated with a statistically significant decrease in the WBC count (mostly lymphocyte) at 1 week, but not in platelet counts. However, all blood components recovered within 1 year. Thus, physicians treating DTC patients should not decrease the use of moderate dose RAI treatment when the benefits of ablation are likely to outweigh the risks.

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Disclosure

The authors declare that no competing interests exist.

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