Effect of ¹³¹I Therapy on Complete Blood Count in Patients with Differentiated Thyroid Cancer

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Background: The aim of this study was to investigate the effects of ¹³¹I therapy on complete blood count (CBC) in patients with differentiated thyroid cancer (DTC).

Materia/Methods: We analyzed CBC in 542 patients with DTC who were grouped according to treatment cycles and cumulative dose and then subdivided by sex and age. The effects of ¹³¹I therapy among the different groups and subgroups were analyzed.

Results: After sorting patients by treatment cycles and doses, ¹³¹I therapy was found to have different effects on CBC depending on patient sex and age. The effect on white blood cell (WBC) counts persisted longer in women, while increases in hemoglobin (Hb) were more significant in men. The influence on red blood cell (RBC) counts was short-lived in patients aged 45 to 54 years. Monocyte counts were significantly decreased only in patients aged 55 years and older who had undergone 3 or 4 treatment cycles. In men, CBC was more affected by cumulative dose. ¹³¹I therapy only influenced platelet and monocyte counts in patients aged 55 years or older. Hb was significantly decreased and increased in the high- and low-dose groups, respectively. No significant complications were observed during follow-up.

Conclusions: ¹³¹I therapy had a greater impact on WBC counts in women, while changes in RBC counts and Hb were more obvious in men. During ¹³¹I therapy, clinicians should pay attention to different CBC indicators based on a patient's sex and age, but risks associated with an altered CBC are unlikely to outweigh the benefits of ¹³¹I. The results of the present study may help alleviate the concerns of a large proportion of patients with DTC and their families about the effects of ¹³¹I therapy on CBC.

Keywords: ABO Blood-Group System • Dose Fractionation • Iodine • Thyroid Neoplasms • Treatment Outcome

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CLINICAL RESEARCH

Background

The incidence of thyroid cancer has rapidly increased worldwide in recent decades [1-4]. Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprises the vast majority (>90%) of all thyroid cancers [5]. [131]I therapy is a conventional method of treating DTC after thyroidectomy that can successfully ablate remnant or recurrent thyroid carcinoma cells in both primary and metastatic lesions [5, 6]. Although ^{131}I is widely accepted to be safe, it still has adverse effects that negatively affect patient quality of life, although they are rarely life-threatening [7]. They include transient neck pain and edema, gastritis, radiation thyroiditis [7], salivary gland dysfunction [8], and nasolacrimal obstruction [9]. Knowledge about the adverse effects of ^{131}I is essential for both considering preventative measures before and managing complications after treatment.

[131]I therapy also leads to bone marrow toxicity and can cause bone marrow dysfunction [10]. Some studies have shown that both a single dose and multiple doses of ^{131}I therapy can change complete blood count (CBC) [11,12]. However, the influence of ^{131}I therapy on CBC in patients with DTC is debatable. A large proportion of patients with DTC are concerned about the effects of bone marrow toxicity. However, few studies have investigated the influences of cumulative doses and treatment cycles of ^{131}I and analyzed the influence of age and sex on CBC. Therefore, we evaluated the effects of ^{131}I therapy on CBC in patients grouped by treatment cycles and cumulative doses, with a focus on sex and age.

Material and Methods

Patients

We reviewed the clinical records of patients with DTC who were treated in the Nuclear Medicine Department of Tianjin Medical University General Hospital between January 2009 and June 2018. All patients underwent total thyroidectomy and dissection of central lymph nodes and lymph nodes on the affected side and then were given at least 1 cycle of postoperative ^{131}I therapy in our department. To avoid the influence of confounding factors, patients were excluded from the study if they: (1) had taken any medications known to affect CBC; (2) were known to have any baseline hematologic diseases or any abnormalities in CBC prior to initial ^{131}I therapy; (3) received external beam radiation therapy and/or chemotherapy before or during the treatments; (4) had postoperative blood loss that impacted CBC; or (5) received more than 4 cycles of ^{131}I therapy, because the size of our cohort was limited.

Methods

All patients underwent traditional thyroid hormone withdrawal preparation before ^{131}I therapy. Briefly, they were instructed to follow a low-iodine diet 1 month before, during, and 1 month after ^{131}I therapy. Patients were taken off levothyroxine 2 to 4 weeks before starting ^{131}I therapy. [131]I was taken orally. With respect to the dose, 3700 MBq was recommended for patients receiving it as remnant ablative therapy, 3700 to 5550 MBq for patients with cervical lymph node metastasis (LNM) and/or extra-thyroid extension (adjuvant therapy), and 5550 to 7400 MBq generally was recommended for distant metastasis (therapeutic therapy). Diagnostic ^{131}I whole-body scintigraphy (Dx-WBS) was performed 2 to 7 days later with a dual-detector single-photon emission computed tomography/computed tomography (SPECT/CT) machine with high-energy collimators. Otherwise, neck and chest CT or ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) was used to evaluate the patients' physical condition and detect potential metastases. Whole-body radioactivity after ^{131}I therapy was monitored once daily during hospitalization. Patients were advised to limit close contact with relatives for at least 7 days after hospital discharge. A therapeutic and follow-up recommendation was given to each patient. According to the 2015 American Thyroid Association (ATA) [13], based on the results of serological examination (sTg and stimulated thyroglobulin antibodies [sTgAb]) and imaging such as neck ultrasound, Dx-WBS, chest CT, and PET/CT, treatment responses were divided by efficacy into 4 categories: excellent response (ER), indeterminate response (IDR), biochemical incomplete response, and structural incomplete response. Approximately 4 to 6 months after each ^{131}I treatment, the patients returned to the outpatient department for evaluation. If their treatment response was not ER or IDR and their lesions had adequately absorbed the ^{131}I, continued ^{131}I therapy for 4 to 6 months was considered, following Chinese guidelines [14], after the initial course. The cumulative dose was the sum of each ^{131}I dose. The charts for all patients were reviewed and analyzed retrospectively.

An automated CBC was obtained within 3 days before ^{131}I therapy and retesting was delayed for 4 to 6 months after each treatment so that the results would not reflect the transient influence of ^{131}I on bone marrow. All serum blood tests were performed in the hematology laboratory of Tianjin Medical University General Hospital using an automated CBC analyzer (Sysmex xn-2000, Sysmex Corporation, Kobe, Japan).

The normal ranges for hemoglobin (Hb) are 130 to 175 g/dL and 115 to 150 g/L in men and women, respectively. The normal ranges for red blood cells (RBCs) are 4.3 to 5.8×10^{12} cells/L and 3.8 to 5.1×10^{12} cells/L in men and women, respectively. For both sexes, the normal ranges for white blood cells (WBCs), platelets (PLTs), neutrophils, lymphocytes, and monocytes are 3.5 to

Table 1. Patient groupings.

	Gender		Age (years)		
	Male	Female	<45	45-54	≥55
Treatment cycles					
One	113 (20.8%)	303 (55.9%)	165 (30.4%)	123 (22.7%)	128 (23.6%)
Two	26 (4.8%)	57 (10.5%)	38 (7.0%)	28 (5.2%)	17 (3.1%)
Three	7 (1.3%)	16 (3.0%)	12 (2.2%)	2 (0.4%)	9 (1.7%)
Four	6 (1.1%)	14 (2.6%)	6 (1.1%)	2 (0.4%)	12 (2.2%)
Cumulative dose, MBq					
≤5550	117 (21.6%)	300 (55.3%)	170 (31.4%)	119 (22.0%)	128 (23.6%)
5551-11100	26 (4.8%)	66 (12.2%)	38 (7.0%)	26 (4.8%)	28 (5.2%)
>11100	9 (1.7%)	24 (4.4%)	13 (2.4%)	10 (1.8%)	10 (1.8%)

9.5×10^9 cells/L, 125 to 350×10^9 cells/L, 1.8 to 6.3×10^9 cells/L, 1.1 to 3.2×10^9 cells/L, and 0.12 to 0.80×10^9 cells/L, respectively.

Ethics Approval

The ethical, methodological, and protocol aspects of this investigation were approved by the Institutional Review Board and Ethics Committee of Tianjin Medical University General Hospital. All methods used in the current study were carried out in accordance with the relevant guidelines and regulations. (Ethical. No. IRB2020-WZ-165).

Statistical Analysis

Quantitative data are expressed as means±standard deviations (SDs). Normal distribution of quantitative data was tested with a Q-Q plot. Quantitative data with normal distribution were analyzed with a paired *t* test, independent sample *t* test, and analysis of variance, which were followed by least significant difference post-hoc testing when appropriate. Quantitative data that were not normally distributed were analyzed with a Wilcoxon signed rank test. All data and statistical tests were performed using SPSS Statistics for Windows software, version 19.0 (IBM Corp., Armonk, New York, United States). Descriptive statistics were used to summarize the data. *P*<0.05 was considered statistically significant.

Results

Patient Groups

The present study enrolled 542 patients with a mean age of 46.64±12.77 (range: 14 to 78) years. The patients included 152 men with a mean age of 45.98±13.12 years (range: 19 to 78 years) and 390 women with a mean age of 46.91±12.63 years (range: 14 to 76 years). The patients were divided into 4 groups according to treatment cycles (1; n=416, 2; n=83, 3; n=23, and 4; n=20) and 3 groups according to cumulative dose (low-dose; ≤5550 MBq, n=417) (medium-dose; 5551 to 11 100 MBq, n=92) (high-dose; >11 100 MBq, n=33). The patient groups were then subdivided into subgroups according to sex (male and female) and age (<45 years, 45 to 54 years, and ≥55 years).

Baseline Patient Characteristics

Baseline characteristics for and groupings of the patients are summarized in **Table 1**. Univariate analysis showed that thyroid stimulating hormone (TSH) status did not influence CBC (*P*>0.05). Before ^{131}I therapy, there were no significant differences in CBC among the different treatment cycle groups or the different cumulative dose groups.

Effects of Treatment Cycles and Cumulative Dose of ^{131}I Therapy on CBC

CBC data before and after ^{131}I therapy are shown in **Table 2**. The mean CBC remained within the normal reference range during treatment. There were significant fluctuations in the mean levels of WBCs, RBCs, Hb, PLTs, lymphocytes, and monocytes.

There were significant decreases in WBC and PLT counts after the first (*P*<0.001 and *P*=0.043, respectively) and second cycles (*P*=0.003 and *P*=0.032, respectively). There were significant decreases in lymphocyte counts after each cycle (*P*=0.002, *P*<0.001, *P*<0.001, and *P*=0.030, respectively) and in monocyte counts after the fourth cycle (*P*=0.025). In contrast, RBC counts were significantly increased following each cycle (*P*<0.001, *P*<0.001, *P*=0.018, and *P*<0.001, respectively), as was Hb (*P*=0.040, *P*<0.001, *P*=0.001, and *P*<0.001, respectively).

Table 2. CBC data before and after ^{131}I therapy according to the number of treatment cycles and cumulative dose.

Mean±SD	Before	After (treatment cycles)				After (cumulative dose)		
		One cycle	Two cycles	Three cycles	Four cycles	≤5550	5551–11100	>11100
WBCs, 10^9/L	6.24± 1.63	5.89± 1.55*b	5.87± 1.42*b	6.14± 1.75	6.13± 1.06	5.90± 1.55*b	5.95± 1.47*b	5.99± 1.41
RBCs, 10^{12}/L	4.63± 0.46	4.78± 0.50*a	4.72± 0.49*a	4.71± 0.48*a	4.95± 0.49*a	4.78± 0.50*a	4.72± 0.50*a	4.85± 0.49*a
Hb, g/L	137.07± 17.53	141.86± 54.64*a	139.56± 16.72*a	138.84± 16.25*a	143.06± 16.85*a	139.68± 19.17*a	147.78± 101.71	141.33± 17.06*a
PLTs, 10^9/L	255.03± 65.88	251.63± 67.17*b	249.24± 74.63*b	260.81± 77.18	254.16± 66.18	251.58± 67.25	254.70± 74.84	246.70± 71.72*b
Neutrophils, 10^9/L	4.03± 3.78	3.93± 3.73	3.79± 1.18	4.06± 1.48	3.91± 0.71	3.93± 3.73	3.83± 1.20	3.97± 1.17
Lymphocytes, 10^9/L	2.04± 1.40	1.82± 1.16*b	1.66± 0.58*b	1.63± 0.63*b	1.73± 0.57*b	1.82± 1.16*b	1.69± 0.61*b	1.57± 0.52*b
Monocytes, 10^9/L	0.33± 0.43	0.33± 0.47	0.27± 0.09	0.30± 0.11	0.32± 0.09*b	0.33± 0.47	0.28± 0.10	0.29± 0.10*b

Hb – hemoglobin; PLT – platelet; RBC – red blood cell; SD – standard deviation; WBC – white blood cell. * $P<0.05$ indicates a statistically significant difference. [a] Indicates an increase and [b] a decrease.

WBC counts were significantly decreased in the low- and medium-dose groups ($P<0.001$, 0.001, respectively), PLT counts were decreased in the high-dose group ($P<0.001$), lymphocytes were decreased in all 3 groups ($P=0.002$, $P<0.001$, and $P<0.001$, respectively), and monocytes were decreased in the high-dose group ($P=0.019$). In contrast, RBC counts were significantly increased in all 3 groups (all $P<0.001$), and Hb was increased in the low- and high-dose groups (both $P<0.001$).

CBC Data for Different Sexes Before and After [131]I Therapy

Table 3 shows the influence of the number of treatment cycles and cumulative ^{131}I dose on CBC in different sex.

Men had significantly decreased WBC counts after the second cycle ($P=0.002$) and significantly decreased lymphocyte counts after the first 3 cycles (all $P<0.001$). They also had significantly increased RBC counts after each cycle ($P<0.001$, $P=0.001$, $P<0.001$, and $P=0.001$, respectively), as well as increased Hb after the first, third, and fourth cycles ($P=0.005$, $P=0.000$, and $P=0.001$, respectively). In women, WBC counts were significantly decreased after each of the first 3 cycles ($P<0.001$, $P<0.001$, and $P=0.003$, respectively), PLT counts were decreased after the second and the third cycles ($P=0.036$ and $P=0.007$, respectively), lymphocyte counts were decreased after the first, third, and fourth cycles ($P=0.015$, $P<0.001$, and $P=0.001$, respectively), and monocyte counts were decreased after the fourth cycle ($P=0.003$). There were significant increases in RBC counts after the first, second, and fourth cycles ($P<0.001$, $P<0.001$, and $P=0.010$, respectively) as well as in Hb after the final 3 cycles ($P<0.001$, $P=0.012$, and $P=0.007$, respectively). On

further observation, the influence of ^{131}I therapy on WBC counts in women was apparent from the first cycle to the third cycle, meaning it persisted longer than in men. [131]I therapy influenced PLT and monocyte counts only in women. The increase in Hb was more significant in men than in women ($P=0.003$).

In men, there were significant decreases in lymphocyte counts in the low- and medium-dose groups (all $P<0.001$). There were also significant increases in all 3 dose groups in RBC counts (all $P<0.001$) and Hb ($P=0.005$, $P<0.001$, and $P<0.001$, respectively) as well as in neutrophil counts in the medium-dose group ($P=0.034$). In women, WBC counts were significantly decreased in the low- and medium-dose groups (all $P<0.001$) and PLT counts were decreased in the high-dose group ($P=0.002$), as were lymphocyte counts in all 3 groups ($P=0.016$, $P<0.001$, and $P<0.001$, respectively). RBC counts were significantly increased in the low- and medium-dose groups ($P<0.001$ and $P=0.004$, respectively). There were significant differences in Hb, which were significantly decreased in the high-dose group ($P=0.002$) and significantly increased in the low-dose group ($P=0.034$). We also found that cumulative ^{131}I dosage had an influence on WBC and PLT counts only in women. In addition, the increases in RBC counts in the medium-dose group ($p=0.021$) and of Hb in the low- and high-dose groups were more significant in men than in women ($P=0.007$ and $P=0.001$, respectively).

Age and CBC Before and After [131]I Therapy

Table 4 shows the influence of the number of treatment cycles and cumulative ^{131}I dosage on CBC in patients of different ages.

Table 3. CBC data before and after ^{131}I therapy by gender and according to the number of treatment cycles and cumulative dose.

Mean ±SD	Before	After (treatment cycles)				After (cumulative dose)		
		One cycle	Two cycles	Three cycles	Four cycles	≤5550	5551–11100	>11100
WBCs, 10^9/L								
Male	6.31± 1.45	6.14± 1.51	6.28± 1.46*b	6.81± 1.68	5.86± 0.82	6.14± 1.50	6.52± 1.55	5.84± 1.10
Female	6.21± 1.69	5.80± 1.55*b	5.69± 1.37*b	5.85± 1.72*b	6.10± 1.21	5.80± 1.56*b	5.70± 1.38*b	6.06± 1.56
RBCs, 10^{12}/L								
Male	4.99± 0.48	5.18± 0.48*a	5.05± 0.55*a	5.18± 0.43*a	5.42± 0.45*a	5.18± 0.48*a	5.07± 0.53*a	5.29± 0.45*a
Female	4.49± 0.37	4.63± 0.41*a	4.57± 0.39*a	4.52± 0.34	4.72± 0.43*a	4.63± 0.41*a	4.56± 0.39*a	4.63± 0.35
Hb, g/L								
Male	149.13± 21.41	154.76± 17.34*a	154.33± 14.20	156.46± 9.83*a	160.83± 10.50*a	154.73± 17.29*a	154.30± 13.92*a	159.74± 8.85*a
Female	132.37± 13.05	136.84± 62.82	132.93± 13.19*a	131.20± 11.95*a	133.57± 12.49*a	133.76± 16.47*a	144.92± 121.74	132.13± 11.89*b
PLTs, 10^9/L								
Male	239.11± 64.65	236.39± 63.84	232.87± 67.35	264.69± 82.35	224.67± 60.92	236.58± 63.68	244.02± 74.46	222.89± 59.70
Female	261.23± 65.39	257.58± 67.57	256.57± 76.90*b	259.13± 76.23*b	274.29± 76.38	257.48± 67.78	259.38± 74.90	258.61± 74.93*b
Neutrophils, 10^9/L								
Male	4.30± 4.81	4.34± 4.61	4.16± 1.30	4.71± 1.59	3.74± 0.85	4.34± 4.59	4.32± 1.38*a	4.00± 1.17
Female	3.92± 3.30	3.77± 3.31	3.62± 1.08	3.78± 1.36	3.92± 0.69	3.77± 3.32	3.62± 1.04	3.95± 1.19
Lymphocytes, 10^9/L								
Male	1.91± 0.60	1.73± 0.59*b	1.67± 0.56*b	1.58± 0.81*b	1.66± 0.60	1.73± 0.58*b	1.73± 0.65*b	1.38± 0.43
Female	2.09± 1.61	1.85± 1.32*b	1.66± 0.59	1.65± 0.55*b	1.70± 0.48*b	1.85± 1.32*b	1.67± 0.60*b	1.67± 0.53*b
Monocytes, 10^9/L								
Male	0.37± 0.53	0.34± 0.39	0.29± 0.11	0.36± 0.11	0.32± 0.05	0.34± 0.39	0.30± 0.12	0.32± 0.08
Female	0.31± 0.39	0.32± 0.50	0.26± 0.08	0.27± 0.10	0.31± 0.11*b	0.32± 0.50	0.27± 0.08	0.28± 0.10

Hb – hemoglobin; PLT – platelet; RBC – red blood cell; SD – standard deviation; WBC – white blood cell. * $P<0.05$ indicates a statistically significant difference. [a] Indicates an increase and [b] a decrease.

In patients younger than age 45 years, WBC counts were significantly decreased after the first 2 cycles ($P<0.001$ and $P=0.001$, respectively) and lymphocyte counts were significantly decreased after the third cycle ($P<0.001$). RBC counts were significantly increased after each cycle ($P<0.001$, $P<0.001$, $P=0.030$, and $P=0.023$, respectively) and Hb was significantly increased after the second and the third cycles ($P=0.002$ and $P=0.037$, respectively). In patients aged 45 to 54 years, WBC counts were significantly decreased after the second cycle ($P=0.003$) and lymphocyte counts were decreased after the first and the third cycles ($P<0.001$ and $P=0.029$, respectively). RBC counts were significantly increased after the first cycle ($P<0.001$) and

Table 4. CBC data before and after ^{131}I therapy by age group and according to the number of treatment cycles and cumulative dose.

Mean ±SD	Before	After (treatment cycles)				After (cumulative dose)		
		One cycle	Two cycles	Three cycles	Four cycles	≤5550	5551-11100	>11100
WBCs, 10^9/L								
<45	6.43± 1.71	6.08± 1.60*b	5.96± 1.31*b	6.07± 1.78	6.58± 1.44	6.09± 1.60*b	5.94± 1.49*b	6.26± 1.83
45-54	6.06± 1.64	5.79± 1.60	5.39± 1.49*b	5.59± 1.21	5.59± 0.57	5.79± 1.60	5.71± 1.61	5.43± 0.99
≥55	6.33± 1.60	5.81± 1.45*b	5.95± 1.51*b	5.95± 1.71	5.92± 0.82	5.81± 1.44*b	6.20± 1.48	5.88± 1.10
RBCs, 10^{12}/L								
<45	4.67± 0.50	4.83± 0.51*a	4.83± 0.52*a	4.75± 0.51*a	5.12± 0.52*a	4.84± 0.51*a	4.75± 0.52*a	4.87± 0.54*a
45-54	4.67± 0.40	4.84± 0.43*a	4.75± 0.43	4.93± 0.41	5.01± 0.47	4.84± 0.43*a	4.75± 0.48	4.83± 0.47
≥55	4.62± 0.46	4.75± 0.53*a	4.72± 0.50*a	4.73± 0.45	4.86± 0.50*a	4.75± 0.53*a	4.66± 0.50	4.84± 0.49*a
Hb, g/L								
<45	135.69± 19.74	144.13± 88.43	140.97± 18.31*a	140.26± 19.30*a	144.60± 21.93	138.01± 22.91	160.35± 158.93	139.27± 20.16*a
45-54	139.04± 15.05	142.41± 15.96*a	140.62± 14.68	140.75± 20.99*a	142.33± 7.57	142.40± 15.96*a	139.64± 15.10	133.50± 14.11
≥55	138.49± 17.38	140.21± 17.60	138.68± 22.08	142.50± 14.87*a	142.81± 16.34*a	140.28± 17.56	138.83± 16.21	144.50± 14.92*a
PLTs, 10^9/L								
<45	266.69± 68.06	266.77± 69.39	268.99± 70.10	274.96± 82.36	274.30± 76.09	266.98± 69.51	274.02± 82.54	273.95± 84.97
45-54	260.02± 58.10	253.88± 57.08	261.84± 67.12	229.00± 54.40	276.67± 43.82	253.38± 57.51	258.79± 67.73	257.50± 64.51
≥55	246.33± 67.96	242.10± 71.81	239.87± 69.98*b	231.75± 60.32	234.63± 64.63*b	242.26± 71.59	242.23± 69.46	222.57± 55.17*b
Neutrophils, 10^9/L								
<45	4.56± 6.05	4.23± 4.53	4.45± 5.89	3.96± 1.49	4.32± 0.91	4.23± 4.54	3.78± 1.12	4.21± 1.43
45-54	3.71± 1.39	3.61± 1.35	4.36± 6.77	3.92± 1.12	3.66± 0.34	3.60± 1.36	3.67± 1.42	3.7917± 0.95
≥55	3.85± 1.21	3.97± 4.65	8.71± 37.25	3.93± 1.48	3.79± 0.52	3.97± 4.64	4.03± 1.24	3.82± 1.00
Lymphocytes, 10^9/L								
<45	2.18± 2.13	1.91± 1.76	2.09± 3.63	1.66± 0.62*b	1.72± 0.59	1.91± 1.76	1.73± 0.60*b	1.58± 0.53*b
45-54	1.91± 0.60	1.73± 0.48*b	2.21± 5.05	1.29± 0.38*b	1.53± 0.32	1.74± 0.48*b	1.58± 0.44*b	1.31± 0.33*b
≥55	2.01± 0.81	1.80± 0.73*b	1.76± 0.59*b	1.55± 0.63*b	1.68± 0.57	1.79± 0.73*b	1.71± 0.75*b	1.61± 0.54*b

Table 4 continued. CBC data before and after ^{131}I therapy by age group and according to the number of treatment cycles and cumulative dose.

Mean ±SD	Before	After (treatment cycles)				After (cumulative dose)		
		One cycle	Two cycles	Three cycles	Four cycles	≤5550	5551–11100	>11100
Monocytes, 10⁹/L								
<45	0.41± 0.70	0.37± 0.57	0.35± 0.48	0.29± 0.09	0.38± 0.12	0.37± 0.57	0.29± 0.09	0.32± 0.11
45–54	0.29± 0.08	0.29± 0.08	0.39± 0.79	0.27± 0.05	0.28± 0.05	0.29± 0.08	0.29± 0.07	0.25± 0.05
≥55	0.30± 0.11	0.35± 0.62	0.32± 0.24	0.30± 0.13*a	0.28± 0.06*b	0.35± 0.62	0.28± 0.11	0.28± 0.09*b

Hb – hemoglobin; PLT – platelet; RBC – red blood cell; SD – standard deviation; WBC – white blood cell. * $P<0.05$ indicates a statistically significant difference. [a] Indicates an increase and [b] a decrease.

Hb was significantly increased after the first and the third cycles ($P<0.001$ and $P=0.031$, respectively). In patients aged 55 years and older, WBC counts were significantly decreased after the first and the second cycles ($P<0.001$ and $P=0.002$, respectively), PLT counts were decreased after the second and the fourth cycles ($P=0.016$ and $P=0.008$, respectively), and lymphocyte counts were decreased after the first 3 cycles ($P<0.001$, $P<0.001$, and $P=0.006$, respectively). RBC counts were significantly increased after the first, second, and fourth cycles ($P<0.001$, $P=0.012$, and $P=0.003$, respectively) and Hb was increased after the final 2 cycles ($P=0.008$ and $P=0.001$, respectively). There were significant differences in monocyte counts, which were significantly increased after the third cycle ($P=0.031$) and significantly decreased after the fourth cycle ($P=0.003$). Through further observation, we found that in patients aged 45 to 54 years, the duration of influence on RBC counts was short. On reevaluation, none of the patients suffered severe hematologic complications.

In patients younger than age 45 years, WBC counts were significantly decreased in the low- and medium-dose groups ($P<0.001$ and $P=0.032$, respectively), as were lymphocyte counts in the medium- and high-dose groups ($P<0.001$ and $P=0.043$, respectively). RBC counts were significantly increased in all 3 dose groups ($P<0.001$, $P<0.001$, and $P=0.048$, respectively), as was Hb in the high-dose group ($P=0.045$). In patients aged 45 to 54 years, lymphocyte counts were significantly decreased in all 3 groups ($P<0.001$, $P<0.001$, and $P=0.007$, respectively), whereas RBC counts and Hb were significantly increased in the low-dose group (both $P<0.001$). In patients aged 55 years or older, WBC counts were significantly decreased in the low-dose group ($P<0.001$), PLT counts were decreased in the high-dose group ($P=0.001$), lymphocyte counts were decreased in all 3 groups ($P<0.001$, $P=0.002$, and $P=0.003$, respectively), and monocyte counts were decreased in the high-dose group ($P=0.001$). In contrast, RBC counts were significantly increased in the low- and
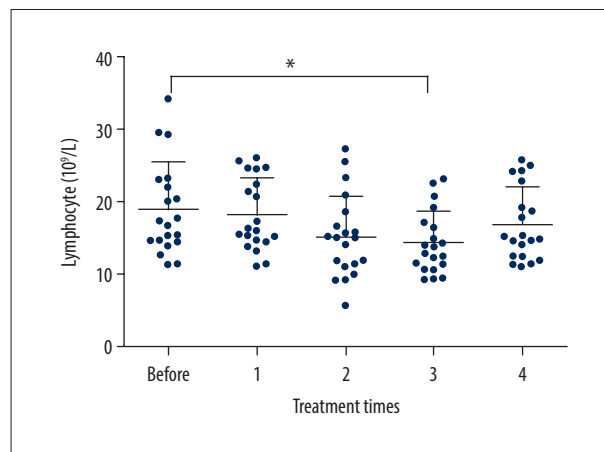

Figure 1. Changes in lymphocyte counts after ^{131}I treatment cycles. The counts consistently declined from the first to the third ^{131}I cycles and then increased after the fourth ^{131}I therapy. The decrease that was statistically significant compared with the baseline lymphocyte count occurred after the third ^{131}I cycle (1.44±0.43 vs 1.90±0.63, $P=0.001$).

high-dose groups ($P<0.001$ and $P=0.001$, respectively), as was Hb in the high-dose group ($P<0.001$). Further analysis showed no significant influence of ^{131}I on WBC counts in patients aged 45 to 54 years. An effect of cumulative ^{131}I dose on PLT count was seen only in patients aged 55 years and older.

Patients treated with 4 cycles of ^{131}I were analyzed independently. In this group, there were significant fluctuations in lymphocyte and monocyte counts ($P=0.032$ and $P=0.002$, respectively). Lymphocyte counts consistently declined from the first to the third ^{131}I cycle and then increased after the fourth cycle (**Figure 1**). The only statistically significant decrease compared with the baseline lymphocyte value occurred after the third ^{131}I cycle (1.44±0.43 vs 1.90±0.63, $P=0.001$). Monocyte
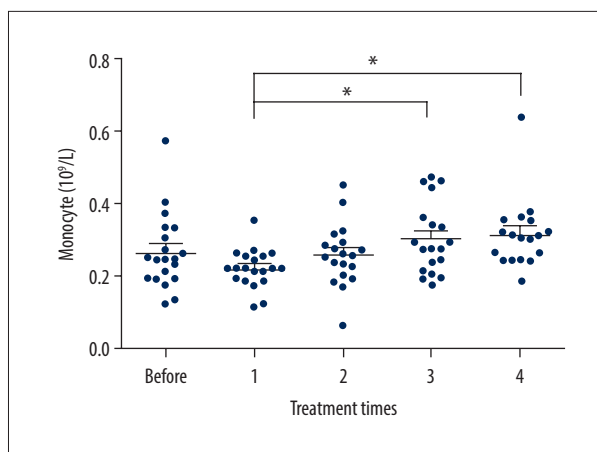
Figure 2. Changes in monocyte counts after ^{131}I treatment cycles. The number of monocytes decreased after the first treatment and then gradually increased after the last 3 treatments. While the differences between post-treatment and baseline values were not significant, the last 2 post-treatment values were higher than the value after the first treatment (0.30±0.10 and 0.31±0.09 vs 0.22±0.05, both P=0.001).
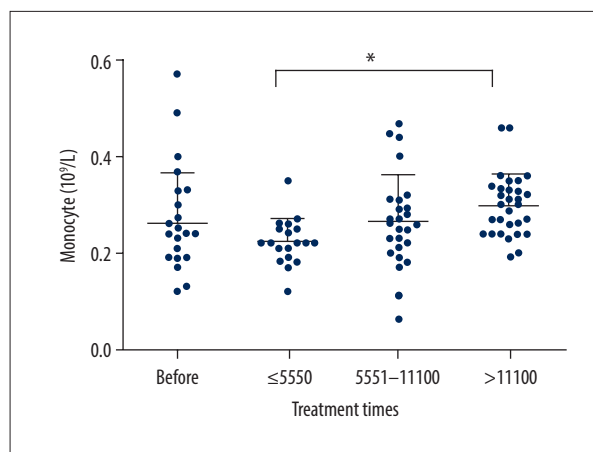

Figure 3. Changes in monocyte counts after cumulative doses of ^{131}I therapy. The number of monocytes decreased when patients had received ≤5550 MBq of ^{131}I and then gradually increased after patients had received >5550 MBq of [131]I. While there were no statistically significant differences between post-treatment and baseline values, patients who received >11 100 MBq of ^{131}I had higher monocyte counts than those who received ≤5550 MBq of [131]I (0.30±0.09 vs 0.22±0.05, P=0.003).

counts decreased after the first cycle and then gradually increased after the third cycle (**Figure 2**). There were no statistically significant differences between any post-treatment and baseline values. However, the final 2 post-treatment values were higher than the value after the first cycle (0.30±0.10 and 0.31±0.09 vs 0.22±0.05, all P=0.001). Data from patients who received >11 000 MBq of ^{131}I were analyzed independently and they revealed a significant fluctuation only in monocyte counts (P=0.027). As shown in **Figure 3**, monocyte counts decreased after patients had received ≤5550 MBq of ^{131}I and then gradually increased after >5550 MBq had been received. However, there were no statistically significant differences between the post-treatment and baseline values. Finally, it was noteworthy that monocyte counts were higher in patients who received >11 100 MBq of ^{131}I than in those who received ≤5550 MBq (0.30±0.09 vs 0.22±0.05, P=0.003) (**Figure 3**).

Discussion

Thyroid cancer is becoming prevalent worldwide. Most patients with DTC have an excellent prognosis; 5- and 10-year relative survival rates are between 90% and 95% [15]. However, recurrence occurs in 5% to 20% of patients [16]. [131]I therapy is standard for ablation of remnant thyroid tissue and iodine-avid metastases after surgery in patients with intermediate- and high-risk DTC [5]. Thereafter, appropriate TSH suppression therapy should be given routinely. As a systemic treatment, ^{131}I has the major advantage of reducing the risk of local recurrence as well as distant metastasis [17]. It can also serve

as a diagnostic tool, enabling visualization of normal and carcinomatous thyroid tissue by means of whole-body scintigraphy [6]. However, ^{131}I therapy can cause long-term or temporary adverse effects such as pulmonary fibrosis and myelosuppression [7,10,18,19]. Hematological toxicity is a common adverse effect of ^{131}I therapy [7]. A study [20] showed that the kinetics of ^{131}I incorporation induced DNA double-strand breaks in blood lymphocytes during radioiodine therapy as a function of the dose absorbed by the blood. However, a study by Zhang et al [21] showed that ^{131}I therapy can contribute to the recovery of patients with DTC by restoring the balance of T helper 17, T cytotoxic 17, and regulatory T cells. In the present study, we documented the effects of ^{131}I therapy on CBC in patients with DTC. We were able to make this clinical observation because of the relatively large number of patients with DTC treated at our institution who undergo regular hematologic monitoring.

A study by Molinaro et al [22] showed a statistically significant decline in total WBC and PLT counts 1 year after treatment compared with baseline CBC before ^{131}I therapy. A study by Padovani et al [23] showed a statistically significant decrease in Hb and PLT count 1 year after treatment in 50 patients who received ≥9250 MBq of [131]I. A clinical study by Hu et al [11] also showed that administration of approximately 3700 MBq of ^{131}I was associated with significant declines in WBC, PLT, and lymphocyte counts that persisted for at least 6 months after ablation. Tofani et al [24] showed that 10 patients (group A) who underwent whole-body scintigraphy with 185 MBq of ^{131}I only had a reduction in natural killer cells on Days 7 and 15. Meanwhile, another 10 patients (group B) received 3700

MBq of ^{131}I and showed a delayed reduction in total lymphocyte counts on Days 15, 30, and 60. Our study had a similar conclusion, in that the mean levels of WBCs, PLTs, lymphocytes, and monocytes declined over the course of ^{131}I treatment. In contrast, we found significant increases in RBC counts and Hb. However, the studies by the other investigators that were discussed previously only assessed the effect of a single ^{131}I cycle on CBC. Prinsen et al [10] showed that PLT and WBC counts were transiently decreased after repeated ^{131}I therapy in a population with DTC that had abnormal CBCs. Keldse et al [12] showed, in 24 patients, that compared with pretreatment levels, the median WBC count declined to 78% and the median PLT count declined to 69% after 4 treatment cycles. The study by Prinsen et al [10] demonstrated that post-treatment PLT and WBC counts were transiently decreased compared with pretreatment values in the general population with DTC and that cumulative ^{131}I dose was independently associated with thrombocytopenia. Probst et al [25] reported on a case of severe myelosuppression requiring hospitalization and transfusion support in an otherwise well young woman who had received 6475 MBq of ^{131}I for low-volume micronodular lung disease 1 month before and had a cumulative lifetime dosage of 21 275 MBq. Our study showed that the number of treatment cycles and cumulative doses were associated with significant declines in WBC, PLT, lymphocyte, and monocyte counts as well as significant increases in RBC counts and Hb. However, none of the patients required hospitalization because of myelosuppression.

In the present study, the post-treatment data showed slightly increased RBC counts and Hb levels compared with the pre-treatment data. A possible explanation for this phenomenon could be that thyroid hormones have important effects on RBCs in humans [26]. Meanwhile, some studies have reported that low-dose radiation can have a hermetic effect on the hematopoietic system. Total-body low-dose radiation can modulate the capacity of bone marrow cells to differentiate into dendritic cells [27]. Vrndic et al [28] concluded that ^{131}I led to a reduction in all peripheral blood cells (PBCs) and that the decrease in B cells was directly correlated with PBC apoptosis. Radiation damage to B cells also has been shown to lead to elimination of the cells by apoptosis.

In the present study, significant sex-based differences were found in WBC counts, PLT counts, Hb, and monocyte counts in patients who underwent different numbers of treatment cycles. We found that the influences of the number of treatment cycles on WBC counts persisted longer in women than in men. Furthermore, the number of treatment cycles had an effect only on PLT and monocyte counts only in women. In men, the increase in Hb was more significant. Significant sex-based differences were found in WBC, PLT, and RBC counts, and Hb in the groups that received different cumulative doses. The influence

of cumulative dose on WBC and PLT counts was only seen in women. In men, the increases in RBC counts in the medium-dose group and in Hb in the low- and high-dose groups were more significant in men than in women. However, our findings were different than those from the study by Prinsen et al [10]. This may be because the patients were from different regions or because the follow-up times in the studies differed. Further research will be needed to understand the influence of sex on hematological characteristics in patients who receive [131]I. Therefore, during the course of ^{131}I therapy, clinicians should anticipate decreased levels of WBCs, PLTs, and monocytes in women and increased levels of RBCs and Hb in men.

Because it represents the median age of most large cohorts upon which staging systems are based, an age cutoff of 45 years for DTC has been used in most major thyroid cancer staging systems for many years. The TNM (tumor, node, metastasis) staging system for thyroid cancer, for example, has been in existence for 55 years (AJCC 8th Edition). In our study, we divided patients with DTC into 3 subgroups according to age (<45, 45 to 54, and ≥55 years). After not only accounting for different numbers of treatment cycles but also different cumulative doses, we found that the duration of increased RBC counts was minimal in patients aged 45 to 54 years, decreases in PLT and monocyte counts were seen only in patients older than age 55 years, and the decrease in lymphocyte counts was minimal in patients younger than age 45 years. These findings were similar to those of Prinsen et al [10]. It is possible that slower metabolism associated with increased age allows the radiopharmaceutical to remain in the body longer. Therefore, during the course of ^{131}I therapy, clinicians should pay more attention to elderly patients who receive ≥11 100 MBq of [131]I.

A previous study showed that TSH administration increased the expression of the proatherogenic monocyte gene [29]. Van der Weerd et al [30] showed that TSH acts as a previously unrecognized growth factor for developing T cells, with potential clinical use for enhancing thymic output, and thereby, the functional T-cell repertoire in the periphery. Our univariate analysis showed that TSH status had no influence on CBC. Further research is needed to clarify these data, perhaps by simply increasing the sample size.

This analysis has some limitations. First, the present study was cross-sectional. Second, because of the short follow-up time, the cohort of patients who received ≥11 100 MBq of ^{131}I was small. Thus, future prospective studies are needed with larger cohorts and longer follow-up.

Conclusions

The number of treatment cycles and the cumulative dose of ^{131}I therapy influenced CBC but the indictors were still within the normal range. Different numbers of treatment cycles and the cumulative dose of ^{131}I therapy had differential impacts on CBC depending upon patient sex and age. During treatment, clinicians should pay attention to different CBC indicators in patients with DTC according to their sex and age. Because the benefits of ^{131}I therapy in intermediate- and high-risk patients with DTC outweigh the potential hematological risks, there is no need to reduce the number of treatment cycles or the cumulative dosage of [131]I. The results from the present study could help alleviate the concerns that a large proportion of patients with DTC and their families have about the effects of ^{131}I therapy on CBC. [131]I therapy also can lead to a downward trend in counts of some cells. Therefore, in patients who have decreased counts before ^{131}I therapy, we suggest that the treatment be delayed until the counts have returned to normal.

Acknowledgments

Conflicts of Interest

None.

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