ResearchTJH-2021-0092.R1

doi: 10.4274/tjh.galenos.2021.2020.0092

The Assessment of the Long Term Hematologic Effects in Differentiated Thyroid Cancer Patients Treated with Radioactive Iodine

Sönmez B. et al. Hematologic effects of radioactive iodine therapy

Bircan Sönmez, MD[1], Özlen Bektaş, MD[2], Nergiz Erkut, MD[2], Mehmet Sönmez, MD[2]

[1]Department of Nuclear Medicine, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey
[2]Department of Hematology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey

Özlen Bektaş, MD, Department of Hematology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey
ozlenbektas@hotmail.com
+90-532-5430575

February 2, 2021
March 22, 2021

ABSTRACT

Objective: Radioactive iodine (RAI) therapy may cause hematological abnormalities. The aim of the study is to evaluate long-term hematological changes in differentiated thyroid cancer (DTC) patients after RAI therapy.

Materials and Methods: One thousand three hundred eighty nine patients with DTC who were treated with RAI were retrospectively evaluated. Complete blood cell counts before the RAI therapy and last follow up and hematologic malignancy development were obtained from the electronic records.

Results and Conclusion: In the long term analysis, thrombocytopenia and lymphopenia were observed significantly over 60 years of age. We suggested that, these cytopenias should be surveyed more carefully in this group of age. Thrombocytopenia was observed more frequently in men. Leukopenia, thrombocytopenia and lymphopenia were observed significantly with $\geq$175 mCI doses. Thrombocytopenia and lymphopenia were observed significantly with multiple dose administration. The higher frequency of anemia, thrombocytopenia, leukopenia, neutropenia, and lymphopenia were found in patients with advanced stage disease. However patients with

advanced stage disease had higher doses and multiple doses than patients with early stage disease. The rate of hematological malignancy was found to be higher than the general population.
Key words: Radioactive iodine, thyroid cancer, cytopenia, hematologic malignancy, long term hematologic effects, thrombocytopenia, neutropenia

Introduction

Radioactive iodine (RAI) therapy is a commonly used therapeutic option in patients with differentiated thyroid cancer (DTC) for ablation of residual thyroid tissue after thyroidectomy or for the treatment of recurrent and metastatic disease (1). RAI doses between 30-100 mCI are used for ablation of residual thyroid tissue. Higher and repeated doses (up to 200 mCI for single dose and 600 mCI for cumulative dose) can be applied for locoregional recurrence or the metastatic disease (1-3).

After RAI therapy, side effects such as sialadenitis, nasolacrimal duct obstruction, keratoconjunctivitis, amenorrhea, and hematological abnormalities can be observed in the first few months (4). Most of these early side effects are usually temporary and have little long-term clinical significance. However, several meta-analyzes have reported an increased incidence of second primary malignancies in patients with DTC treated with RAI (5-7).

Temporary anemia, leukopenia, thrombocytopenia may occur within the first month after a single RAI therapy (8). Several studies reported the improvement in complete blood cell (CBC) counts at 6 months to 1 year after treatment (9, 10), while in others, the decrease in leukocytes (11), platelets (8, 11, 12) and lymphocytes (12) was persevered.

In our study, we aimed to evaluate the potential long term effect of RAI on hematologic systems in patients with differentiated thyroid cancer who received RAI therapy.

Methods

One thousand three hundred eighty nine patients who were treated with RAI therapy after total thyroidectomy during 2005-2018 were retrospectively evaluated. Exclusion criteria were i) bone marrow infiltration, ii) receiving external beam radiotherapy and/or chemotherapy at any time, iii) concurrent or pretreatment hematologic malignancies, iv) those who developed solid cancer. Inclusion criteria were i) those who developed hematologic malignancy after RAI therapy. At the time of the initial treatment, all patients were staged according to AJCC TNM classification 8th version. Each patient was categorized according to receiving single or repeated doses of RAI therapy.

Radioiodine therapy were performed with fixed doses, as follows: $\leq$100 mCI (dose I) for remnant ablation, 125-150 mCI (dose II) for those with lymph node metastasis, and $\geq$175 mCI (dose III) for metastatic disease. Levothyroxine (L-T4) was discontinued 4-6 weeks and triiodothyronine (L-T3) was discontinued 2 weeks before RAI therapy. A low-iodine diet for 2 weeks was recommended to all patients before RAI therapy. L-T4 treatment was restarted after 48 hours of RAI therapy. Two or more doses were applied to the patients with locoregional recurrence and/or distant metastasis. CBC results before the RAI therapy and last follow up and the development of hematological malignancy were obtained from the electronic records. The criteria for anemia was Hb as <12 gr/dl in women, and <13.0 gr/dl in men, neutropenia as <1500/μL, leukopenia as <4000/μL, thrombocytopenia as <150x10^9/μL, lymphopenia as <1000/μL.

This study was approved by the local ethics committee of Karadeniz Technical University.

Statistical Analyis

Data analysis was performed using SPSS for Windows 22.0 software. Descriptive statistics were shown as mean ± standard deviation or median (minimum-maximum) for continuous variables

and as number of cases (%) for categorical variables. Significance between the basal and last follow up laboratory values were analyzed with paired samples T test. Significance between the groups were analyzed with Mann-Whitney U test when the number of independent groups were two and analyzed with Kruskal-Wallis test when the group number was more than two and if there was a significant difference in the outcome of Mann-Whitney U test or Kruskal-Wallis tests, Post Hoc tests were used to determine the responsible variables for this significance. Correlation between continuous variables was examined with Spearman's correlation test for non-parametric and Pearson's correlation analysis for parametric variables. Odds ratio was analyzed with binary and multinominal logistic regression. A p value <0.05 was considered statistically significant.

Results

Two hundred and sixty three patients (18.9%) were male and 1126 (81.1%) patients were female. Mean age was 47.44 ± 12.52 (range: 8-82). Mean follow-up period and the last follow up CBC results were 60.47 months ± 36.60 (range: 6.67 - 386.33). Baseline characteristics of patients are summarized in Table 1 and 2.

When compared with the difference between basal and last follow-up hematologic values, a significant decrease was observed in the last follow-up hemoglobin and platelets (p= 0.000, p= 0.012). The change in basal and last follow up lymphocytes were significant when patients with hematological malignancies were excluded (p = 0.002) (Table 3).

A negative correlation was found between age and WBC, neutrophils and platelets (r= -0.094, p= 0.000; r= -0.093, p= 0.001; r= -0.126, p= 0.000, respectively) and a positive correlation was found between age and hemoglobin according to the last follow-up laboratory values of the patients (r= 0.076, p= 0.004).

It was observed that platelets were significantly lower over 60 years of age (p<0.001). All series except platelets and lymphocytes in women were found to be significantly lower than in men. It was observed that the lymphocytes decreased significantly when the dose was increased. The dose 1 with 2 and the dose 1 with 3 made the differences (p= 0.001 and p = 0.008, respectively). It was observed that hemoglobin, platelets and lymphocytes decreased as the stage increased. The stage I and IV for hemoglobin, platelets and lymphocytes (p= 0.041, p= 0.001, p= 0.006, respectively) and the stage II and IV for hemoglobin (p= 0.046) made the differences (Table 4).

Before treatment, there was anemia in 223 patients (16.1%), leukopenia in 33 patients (2.4%), thrombocytopenia in 21 patients (1.5%), neutropenia in 10 patients (0.7%), lymphopenia in 20 patients (1.4%). When the last follow-up cytopenia status of the patients was examined, it was observed that thrombocytopenia and lymphopenia were significantly higher in patients over 60 years of age (p= 0.013, p= 0.018, respectively). Males have more thrombocytopenia than females (p = 0.006). Higher doses were risk factor for leukopenia, thrombocytopenia and lymphopenia and the risk increased with ≥175 mCI RAI. The frequency of thrombocytopenia and lymphopenia was increased with repeated doses (p= 0.003, p= 0.003, respectively). Cytopenias in all 5 series were more frequent in stage >2 (stage IV for this study since there was no stage III patients in the study group) compared to the early stage (Table 5).

Acute myeloid leukemia (AML) developed in 0.2% (n = 3), CLL in 0.3% (n = 4) and myelodysplastic syndrome (MDS) in 0.1% (n = 2) (Table 6). The mean time until the development of hematological malignancy was 38.13 ± 33.82 (5.46 - 104.45) months. When hematological malignancies were evaluated according to their prevalence in the world, the prevalence in our sample was found to be higher than the general population.

Discussion

RAI therapy is the one of the standard treatments for DTC. Orally administered RAI diffuse into the circulation through the gastrointestinal tract. The whole body is exposed to highly energetic β- and γ- radiation (IR) during transport, accumulation to, the destruction of thyroid tissue and the urinary excretion of the RAI (13). Cell renewal, apoptosis and redistributions of the hematopoietic cells are affected by this IR (14).

In this study, we have evaluated the long term hematologic complications of RAI therapy in DTC patients. When the difference between pretreatment and last follow-up laboratory values was examined, it was observed that hemoglobin and platelets were significantly lower than the basal levels, regardless of gender, applied activity and number of applications, which suggested that RAI therapy could decrease blood cell levels regardless of cytopenia. There was no significant change between the basal and the last follow up lymphocytes when patients with hematological malignancies were included. We considered that patients with chronic lymphocytic leukemia (CLL) could increase last follow up mean lymphocyte count and repeated the statistical analysis without patients with hematologic malignancies. It was observed that the lymphocytes were significantly lower when hematological malignancies were excluded ($p= 0.002$). In the literature, one of the most common complications in long-term follow-up after RAI therapy is a decrease of platelets (11, 15). Lymphocytes are the most radiosensitive cells of all hematological cells (14). Granulocytes / monocytes are also more sensitive than erythroid series (13). However, a decrease in the erythroid series is an expected finding. Molinaro et al did not observe a change in hemoglobin during 1-year follow-up (11), while Schober et al showed that, thrombocytopenia and erythrocytopenia were the most common cytopenias in a period of 65 months (15). Sonmez et al showed a significant decrease in hemoglobin during 1-year of follow-up (8).

We observed that hemoglobin was higher in higher ages. As the age increases, the number of women entering menopause also increase. Considering that women constitute a significant part of our cases (81%), this may explain the hemoglobin increase. We found that platelet counts were significantly lower and clinical thrombocytopenia and lypmhopenia were significantly higher in patients with over age of 60 years. A decrease in platelets with age after RAI has been previously reported (16). The decrease in bone marrow reserve with age may explain the thrombocytopenia and lymphopenia.

We have found that, there was a gender specific differences in certain cells. Mean hemoglobin, WBC and neutrophils were lower in women than in men. The reason for the difference of hemoglobin is that the normal range of hemoglobin of women is lower than men. When the presence of anemia was evaluated, it was observed that there was no difference between men and women. However, thrombocytopenia was observed more frequently in men than in women which indicates platelets in men are more sensitive to RAI therapy than women. Prinsen et al reported more frequent thrombocytopenia in men after RAI (16). Hu et al. showed in a study with 385 patients that there was a decrease in WBC and lymphocyte without gender difference and a greater decrease in platelets in women than in man during the 6-month follow-up (12). Fewer cases and shorter follow-up period of the latter study may be the main reason of the difference with our results.

We observed that cytopenias occurred more with higher applied activity of RAI. Leukopenia, thrombocytopenia and lymphopenia occurred more frequently at RAI dose $\geq$175 mCI. Similar result was reported about thrombocytopenia and excessive cumulative dose (16). Padovani et al showed a low hemoglobin and platelets, especially at > 250 mCI activity (17). When we evaluated the effects of multiple doses, we observed that, thrombocytopenia and lymphopenia were more common.

In our study, platelets and lymphocytes were found to be lower in patients with stage IV disease. Since there were no patients with stage III in our study, evaluation could not be made with this stage. Additionally, as the stage increased, an increase in the frequency of cytopenias was detected in all series. However, the point should be noticed was that advanced stage patients received higher dose activity and more multiple-dose therapy. It is known that after RAI treatment, blood RAI concentration shows a diphasic course. In the first 24-48 hours, a rapid decrease in inorganic ^{131}I in the blood is observed due to rapid clearance by the kidneys, functional tumor tissue and remaining thyroid tissue. In the next 2-10 days, protein-bound ^{131}I peak is observed due to release by residual thyroid tissue and / or functional tumor tissue. This can cause RAI to be carried in the body for days (18). Therefore, the higher tumor burden may cause the large amount of RAI releasing into the circulation, long duration of its stay in the circulation and, as a result, the increased bone marrow toxicity may happen. It has been reported that thrombocytopenia is observed more frequently in individuals with large tumor masses (16). The strongest results in our study were obtained from disease stage and cytopenias. We suggested that the clinical effect on cytopenias of the advanced disease stage was due to the combined effect of three factors which are higher applied activity, multiple RAI administration and higher tumor burden.

The incidence of AML is 2.8-1.6 cases per 100.000 in men and 2.2-1.0 cases per 100.000 in women (19) and the incidence of CLL is approximately 4.2 cases per 100.000 people in the world population (20). Acute and chronic leukemias have been reported after RAI therapy (18, 21). The incidence of leukemia increases with > 600mCI activity, > 45y and treatment with short intervals (11, 22). Leukemia has been reported very rare at < 300mCI activity (11). Cumulative dose was reported to be the strongest risk factor for leukemia (22, 23), AA and MDS (23). When hematological malignancies were evaluated according to their incidence in the world, the incidence in our sample was found to be higher than the general population. Regarding hematologic malignancy we have observed that; 1. The incidences of hematologic malignancies were higher tahn general population, 2. No relationship were observed with age, 3. Diagnosis of MDS, AML, and CLL were more frequent in low döşe RAI group including single dose administration and early disease. We did not observe the reported risk factors for hematological malignancies in our patients group. Although RAI is known to be a risk factor for leukemia, second primary malignancy (SPM) cannot be ruled out. Karaköse et al. detected 70 SPM in 1196 patients with thyroid cancer. Thirty two of them was diagnosed with second malignancy after thyroid cancer and 38 of them diagnosed with another malignancy before thyroid cancer. RAI treatment was given to 25 patients in each group. SPM independent from RAI was detected in 45 patients (3.8%) (24). The incidence of the malignancy in Turkey is 0.2%. As expected, it is reported that the prevalence of SPM was increased by 20 times in patients with thyroid cancer (24). Silva-Vieira et al detected 4.8% SPM in patients with thyroid cancer who did not receive RAI treatment (25). The risk of leukemia is higher in patients with thyroid cancer, especially those treated with RAI. The 5-10 year absolute leukemia development risk is 0.23 – 0.26% in patient with thyroid cancer who treated with RAI (26). In our study, our results were similar as AML was 0.22% and CLL was 0.28% in patients receiving RAI.

The strengths of this study are the long follow-up periods and the large number of cases. The main limitation of our study is its retrospective nature. Therefore, we could not evaluate whether the patients were using a drug that affects hematological parameters or if they had a disease other than malignancy affecting hematological parameters during laboratory testing, and menopause status in women. Additionally, patients cytopenia status could not been evaluated with peripheral blood smear.

Conclusion

In conclusion, thrombocytopenia and lymphopenia were observed more frequently over age of 60 years and we suggest that, especially for this age group of patients who received RAI should be surveyed more carefully for these cytopenias. We also observed that the higher dose RAI therapy, multiple dose RAI administration and higher tumor burden may cause CBC abnormalities and cytopenias. The most important risk factors for the lower platelets after RAI therapy is male gender. Clinically, the most important predictor for cytopenias is advanced disease stage which is related to the combined effects of applied high dose activity, multiple doses application and high tumor burden.

Conflict of Interest:

The authors declare that they have no conflict of interest.

References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SH, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM and Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1-133.
2. Andresen NS, Buatti JM, Tewfik HH, Pagedar NA, Anderson CM , Watkins JM. Radioiodine Ablation following Thyroidectomy for Differentiated Thyroid Cancer: Literature Review of Utility, Dose, and Toxicity. Eur Thyroid J. 2017; 6(4): 187–196
3. Silberstein EB, Alavi A, Balon HR, et al. The SNMMI Practice Guideline for Therapy of Thyroid Disease with 131I 3.0. J Nucl Med 2012;53(10):1633–1651
4. Fard-Esfahani A, Emami-Ardekani A, Fallahi B, Fard-Esfahani P, Beiki D, Hassanzadeh-Rad A, Eftekhari M. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. Nucl Med Comm 2014;35(8):808-817
5. Rubino C, de Vathaire F, Dottorini ME, et al. Second primary malignancies in thyroid cancer patients. Br J Cancer 2003; 89:1638–1644.
6. Zhang Y, Liang J, Li H, et al. Risk of second primary breast cancer after radioactive iodine treatment in thyroid cancer: a systematic review and meta-analysis. Nucl Med Commun 2016; 37:110–115
7. Sawka AM, Thabane L, Parlea L, et al: Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: A systematic review and meta-analysis. Thyroid, 2009; 19:451-457.
8. Sonmez B , İ. Doğan, C. Yavruoğlu, G. Can, M. Sönmez, "The Changes of Complete Blood Count in The Thyroid Cancer Patients Treated with The Radioactive Iodine Ablation Therapy", Turk J Hematol, 2010;27: 269-274.
9. Alexander C, Bader JB, Schaefer A, Finke C, Kirsch CM. Intermediate and long term side effects of high-dose radioiodine therapy for thyroid carcinoma. J Nucl Med. 1998 Sep;39(9):1551-4.
10. Yi W, Kim BH, KimM, Ryang SR, Jang MH, Kim JM, Kim EH, Jeon YK, Kim SS, Kim IJ.Short-term bone marrow suppression in differentiated thyroid cancer patients after radioactive iodine treatment. Endocr J. 2020 28. doi: 10.1507/endocrj.EJ20-0242.

11. Molinaro E, Leboeuf R, Shue B, et al. Mild decreases in white blood cell and platelet counts are present one year after radioactive iodine remnant ablation. Thyroid 2009;19:1035–1041.
12. Hu T, Meng Z, Zhang G, Jia Q,Tan J, Zheng W, Wang R, Li X, Liu N, Zhou P, Upadhyaya A. Influence of the first radioactive iodine ablation on peripheral complete blood count in patients with differentiated thyroid cancer. Medicine 2016; 95:35
13. Monzen S, Mariya Y, Wojcik A, Kawamura C, Nakamura A, Chiba M, Hosoda M, Takai Y. Predictive factors of cytotoxic damage in radioactive iodine treatment of differentiated thyroid cancer patients. Mol Clin Oncol. 2015; 3(3): 692–698.
14. Dainiak D. Hematologic consequences of exposure to ionizing radiation Experimental Hematology. 30 (2002) 513–528
15. Schober O, Günter HH, Schwarzrock R, Hundeshagen H. Long-term hematologic changes caused by radioiodine treatment of thyroid cancer. I. Peripheral blood changes. Strahlenther Onkol. 1987;163(7):464-74.
16. Prinsen HT, Hesselink ENK, Brouwers AH, Plukker JTM, Sluiter WJ, van der Horst-Schrivers ANA, van Imhoff GW, Links TP Bone Marrow Function After 131I Therapy in Patients With Differentiated Thyroid Carcinoma. J Clin Endocrinol Metab 100: 3911–3917, 2015
17. Padovani RP, Tuttle RM, Grewal R, Larson SM, Boucai L. Complete blood counts are frequently abnormal 1 year after dosimetry-guided radioactive iodine therapy for metastatic thyroid cancer Endocr Pract. 2014 ;20(3):213-20. doi: 10.4158/EP13172.OR.
18. Keldsen N, Mortensen BT, Hansen HS. Haematological effects from Radioiodine Treatment of Thyroid Carcinoma. Acta Oncol. 1990;29(8):1035-9. doi: 10.3109/02841869009091796.
19. Miranda-Filho A, Pineros M, Ferlay J, Soerjomataram I, Monnereau A, Bray F. Epidemiological patterns of leukaemia in 184 countries: a population-based study. Lancet Haematol. 2018;5(1):e14-e24. doi: 10.1016/S2352-3026(17)30232-6.
20. Combest AJ, Danford RC, Andrews ER, Simmons A, McAtee P, Reitsma DJ. Overview of the Recent Developments in Chronic Lymphocytic Leukemia, Part 1. J Hematol Oncol Pharm. 2016;6(2):54-56
21. Alsaud A, Mohamed S, Yassin MA, Ashour A, Obeidat K, Azrieh B. Acute Myeloi Leukemia after Low-Dose Radioiodine Therapy for Papillary Thyroid Carcinoma. Case Rep Oncol 2020;13:207–211
22. Albano D, Bertagna F, Panarotto MB, Giubbini R. Early and late adverse effects of radioiodine for pediatric differentiated thyroid cancer. Pediatr Blood Cancer. 2017 Nov;64(11). doi: 10.1002/pbc.26595.
23. Probst S, Abikhzer G, Chaussé G, Tamilia M. I-131 Radiation-Induced Myelosuppression in Differentiated Thyroid Cancer Therapy. Mol Imaging Radionucl Ther 2018;27:84-87 DOI:10.4274/mirt.59454
24. Karaköse M, Çordan İ, Can M, Kocabaş M, Kulaksızoğlu M, Karakurt F. Incidence of second primary malignancies in patients with thyroid cancer in the Turkish population. Turk J Med Sci. 2019;49(5):1529-1533. doi: 10.3906/sag-1903-104.
25. Margarida Silva-Vieira , Sofia Carrilho Vaz**,** Susana Esteves, Teresa C Ferreira, Edward Limbert, Lucília Salgado, Valeriano Leite. Second Primary Cancer in Patients with Differentiated Thyroid Cancer: Does Radioiodine Play a Role? Thyroid. 2017;27(8):1068-1076. doi: 10.1089/thy.2016.0655.

26. Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, Straus S, Ezzat S, Goldstein DP. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid. 2009;19(5):451-7. doi: 10.1089/thy.2008.0392.

Table 1. Baseline characteristics of patients	
Patients Characteristics	Mean ± SD, n (%)
Age (Mean ± SD)	47.44 ± 12.5
<60 years	1150 (82.8%)
≥60 years	239 (17.2)
Histology	
Micropapillary	355 (25.6)
Papillary	954 (68.7)
Follicular	59 (4.2)
Hurthle Cell	8 (0.6)
Poorly Differentiated	6 (0.4)
Follicular and Papillary	5 (0.4%)
Hurthle Cell and Papillary	1 (0.1)
Hyalinizing Trabecular Cancer	1 (0.1)
Dose I (≤ 100)	1150 (82.8%)
Dose II (125-150)	173 (12.5%)
Dose III (≥175)	66 (4.8%)
Repeated RAI doses	
1	1329 (95.7%)
2	49 (3.5%)
3	8 (0.6%)
4	3 (0.2%)
Staging	
I	1224 (88.1%)
II	149 (10.7%)
IV	16 (1.2%)
Lymph node involvement	109 (7.8%)
Metastasis	20 (1.4%)

Table 2. Applied doses according to stage						
	Dose I	Dose II	Dose III		1 dose	≥1 doses
Stage I	1041 (85.5%)	145 (11.8%)	38 (3.1%)		1190 (97.2%)	34 (2.8%)
Stage II	109 (73.2%)	27 (18.1%)	13 (8.7%)		135 (90.6%)	14 (9.4%)
Stage III	NA	NA	NA		NA	NA
Stage IV	0 (0%)	1 (6.3%)	15 (93.8%)		4 (25%)	12 (75%)

Table 3. Changes in hematologic parameters with RAI therapy			
	Basal	Last follow-up	Changes between basal and last follow-up values
Hemoglobin (gr/dl)	13.50 ± 1.5 (8.4-19.0)	13.3 ± 1.4 (7.9-18.0)	0.18 ± 1.22
P			**<0.001**
Platelet (10^3/μL)	260.3 ± 64.9 (16-733)	256.9 ± 63.0 (31-710)	3.42 ± 5.66
P			**0.012**
WBC (10^3/μL)	6.89 ± 1.79 (0.43-17.75)	6.98 ± 3.62 (1.97-83.02)	-0.10 ± 3.57
P			0.284
Neutrophil (10^3/μL)	4.0 ± 1.40 (0.2-11.97)	3.942 ± 1.43 (0-17.64)	0.06 ± 1.51
P			0.141

Lymphocyte (10^3/μL)	2.26 ± 0.74 (0.17-14.38)	2.24 ± 1.52(0-45.30)	0.02 ± 1.33
P			0.570 **0.002***
(WBC: White blood cell) (* When the hematological malignancies were excluded, the basal lymphocyte: 2.25/μL, last follow up lymphocyte: 2.18/μL and the differences between basal and last follow up values: 0.63 ± 0.76, p= 0.002).			

Table 4. Analysis of last follow up hematologic parameters					
	Hemoglobin (10^3/μL)	WBC (10^3/μL)	Platelet (10^3/μL)	Neutrophil (10^3/μL)	Lymphocyte (10^3/μL)
Age					
<60 years	13.34 ± 1.45	6.98 ± 3.56	261.46 ± 63.34	3.95 ± 1.39	2.2 ± 0.76
≥60 years	13.28 ± 1.36	7.02 ± 3.9	235.02 ± 57.09	3.9 ± 1.63	2.42 ± 3.36
p	0.537	0.875	**<0.001**	0.636	0.305
Gender					
Female	12.97 ± 1.20	69.04 ± 32.09	262.63 ± 62.34	39.03 ± 14.48	22.46 ± 16.50
Male	14.85 ± 1.35	73.48 ± 50.00	232.38 ± 60.38	41.06 ± 13.52	22.05 ± 0.74
P	**<0.001**	**0.008**	**<0.001**	**0.007**	0.948
Doses					
I	13.36 ± 1.41	69.76 ± 31.45	257.49 ± 60.76	39.23 ± 13.70	2.88 ± 1.63
II	13.19 ± 1.52	71.13 ± 57.74	256.16 ± 74.07	40.44 ± 16.91	2.02 ± 0.62
III	12.89 ± 1.66	65.23 ±23.48	231.10 ± 76.57	40.57 ± 21.10	18.54 ± 0.57
p	0.239	0.188	0.332	0.734	**0.001 [a], 0.008 [b]**
Repeated doses					
1	13.33 ± 1.42	70.03 ± 36.72	257.18 ± 62.41	39.35 ± 14.11	15.45 ± 42.43
>1	13.35 ± 1.81	66.67 ± 21.09	250.83 ± 76.80	40.90 ± 18.42	19.07 ± 06.06
p	0.798	0.181	0.468	0.778	**0.003**
Staging					
I	13.32 ± 1.44	70.36 ± 37.93	258.46 ± 61.71	39.52 ± 14.12	22.62 ± 16.01
II	13.46 ± 1.26	66.77 ± 16.90	249.72 ± 67.86	38.60 ± 14.55	21.02 ± 06.06
III	NA	NA	NA	NA	NA
IV	13.33 ± 1.43	62.67 ± 30.36	205.31 ±	39.39 ± 25.09	16.67± 0.71

			93.25		
p	**0.041[c], 0.046[d]**	0.179	**0.001[c]**	0.389	**0.006[c]**
(a: Significance was in doses between 1 and 2, b: Significance was in doses between 1 and 3, c: Significance was in stages between 1 and IV, d: Significance was in stages between I1 and IV)					

Table 5. Analysis of cytopenias

	Anemia	Leukopenia	Thrombocytopenia	Neutropenia	Lymphopenia
Age					
<60 years	188 (16.3%)	21 (1.8%)	20 (1.7%)	4 (0.3%)	13 (1.1%)
≥60 years	35 (14.6%)	5 (2.1%)	11 (4.6%)	3 (1.3%)	8 (3.3%)
OR (95% CI)	NS	NS	0.43 (0.19 – 0.98)	NS	0.41 (0.15 – 1.12)
p	NS	NS	**0.013**	NS	**0.018**
Gender					
Female	198 (17.6%)	21 (1.9%)	19 (1.7%)	6 (0.5%)	21 (1.9%)
Male	25 (9.5%)	5 (1.9%)	12 (4.6%)	1 (0.4%)	0 (0%)
OR (95% CI)	0.46 (0.32 - 1.72)	NS	2.79 (1.34 – 5.82)	NS	NS
P	**0.002**	NS	**0.006**	NS	NS
Doses					
I	178 (15.5%)	18 (1.6%)	22 (1.9%)	5 (0.4%)	14 (1.2%)
II	40 (23.1%)	4 (2.3%)	4 (2.3%)	1 (0.6%)	3 (1.7%)
III	18 (27.3%)	4 (6.1%)	5 (7.6%)	1 (1.5%)	4 (6.1%)
OR (95% CI) I vs II	NS	NS	NS	NS	NS
P	**NS**	NS	NS	NS	NS
OR (95% CI) I vs III	NS	4.06 (1.33 – 12.35)	4.20 (1.54 – 11.48)	NS	5.23 (1.67 – 16.37)
P	**NS**	**0.014 [a]**	**0.005[a]**	NS	**0.004 [a]**
OR (95% CI) II vs III	NS	NS	NS	NS	NS
P	NS	NS	NS	NS	NS
Repeated doses					

1	220 (16.6%)	23 (1.7%)	26 (2%)	7 (0.5%)	17 (1.3%)
>1	16 (26.7%)	3 (5%)	5 (8.3%)	0 (0%)	4 (6.7%)
OR (95% CI)	NS	NS	0.22 (0.80 – 0.59)	NS	0.18 (0.06 – 0.56)
P	NS	NS	**0.003**	NS	**0.003**
Staging					
I	206 (16.8%)	20 (1.6%)	23 (1.9%)	5 (0.4%)	15 (1.2%)
II	23 (15.4%)	2 (1.3%)	4 (2.7%)	0 (0%)	2 (1.3%)
III	NA	NA	NA	NA	NA
IV	7 (43.8)	4 (25%)	4 (25%)	2 (12.5%)	4 (25%)
OR (95% CI) I vs II	NS	NS	NS	NS	NS
P	NS	NS	NS	NS	NS
OR (95% CI) I vs IV	4.10 (1.51 – 11.15)	20.07 (5.96 – 67.62)	17.41 (5.22 – 58.05)	34.83 (6.22 – 194.96)	26.87 (7.77 – 92.92)
P	**0.006**[b]	**<0.001** [b]	**<0.001** [b]	**<0.001** [b]	**<0.001** [b]
OR (95% CI) II vs IV	4.74 (1.59 – 14.10)	0.41 (0.01 – 0.25)	0.08 (0.02 – 0.37)	NS	0.41 (0.01 – 0.25)
P	**0.005**[c]	**<0.001** [c]	**0.001** [c]	**NS**	**<0.001** [c]
(a: significancy is in dose III, b: significancy is in stage IV, c: significancy is in stage IV, OR: Odds ratio, NS: Not significant)					

Table 6. Distribution of hematologic malignancies			
	AML	CLL	MDS
Age			
<60 years	2	1	2
≥60 years	1	3	0
Gender			
Female	2	3	1
Male	1	1	1
Doses			
I	2	4	1
II	1	0	0
III	0	0	1
Repeated doses			
1	3	4	2
>1	0	0	0

Staging			
I	3	4	1
II	0	0	0
III	NA	NA	NA
IV	0	0	1