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Thyroid dysfunction in patients with diffuse large B-cell lymphoma receiving lenalidomide is mediated by TNF-α

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Abstract

As the use of lenalidomide expands, the poorly understood phenomenon of lenalidomide-induced thyroid abnormalities will increase. In this study we compared rates of therapy-induced hypothyroidism in 329 patients with DLBCL treated with conventional chemotherapy (DLBCL-c) or conventional chemotherapy plus lenalidomide (DLBCL-len). We measured serum levels of tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin-6 (IL-6), interleukin-12 (IL-12), and interleukin-15 (IL-15) before and after treatment. We found a significantly higher rate of therapy-induced hypothyroidism in the DLBCL-len group (25.8% vs 1.3%), and we found a statistically significant increase in serum TNF-α in patients with lenalidomide-induced hypothyroidism.

Keywords

Thyroid dysfunction; lenalidomide

I. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of Non-Hodgkin Lymphoma (NHL). Up to one-third of patients with DLBCL treated with standard chemotherapy exhibit refractory disease or suffer disease relapse. The use of lenalidomide monotherapy and lenalidomide in combination with rituximab is being investigated in phase

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II and phase III clinical trials in patients with refractory or relapsed DLBCL[1–5]. Our institution has conducted a randomized phase II trial of lenalidomide with or without rituximab to treat patients with high-intermediate or high-risk DLBCL (NCT #00765245).

Rituximab is a chimeric monoclonal antibody directed against the cluster of differentiation 20 (CD20) antigen on B lymphocytes, and it has not been associated with clinical or subclinical hypothyroidism. Lenalidomide is a thalidomide-analogue immunomodulatory drug (IMiD). IMiDs exert their antineoplastic effect through a multitude of mechanisms affecting not only malignant cells but also immune effector and stromal cells. IMiDs promote T cell proliferation, induce endogenous cytokine release, inhibit angiogenesis, and increase natural killer (NK) cell numbers and function[6–9].

In contrast to thalidomide, lenalidomide is more potent and has fewer associated adverse reactions. While thalidomide use is associated with clinical or subclinical hypothyroidism in up to 20% of patients[6,10], the association between lenalidomide and hypothyroidism is less commonly observed and is thought to occur in 5–10% of patients[6,11]. In the largest retrospective review to date (n=170), ten patients (6%) with multiple myeloma (MM) developed thyroid abnormalities attributable to lenalidomide[11]. The mechanism of lenalidomide-induced hypothyroidism is unknown. Proposed mechanisms include initiation of autoimmune thyroid destruction through pro-inflammatory cytokine deregulation, inhibition of iodine uptake[12], direct thyroid cell injury, and decreased thyroid secretory capacity[6,10,13].

In order to determine the role of inflammatory cytokines in lenalidomide-induced hypothyroidism, we measured pre- and post-treatment levels of TNF-α, IFN-γ, IL-6, IL-12, and IL-15 in patients with DLBCL treated with lenalidomide with or without rituximab. We also compared the rates of hypothyroidism between patients treated with standard chemotherapy alone for DLBCL and those who received lenalidomide in addition to standard therapy.

2. Materials and Methods

2.1 Patient selection

Three hundred and twenty nine consecutive patients older than 18 years diagnosed with DLBCL diagnosed between 2000 and 2013 who received treatment at Vanderbilt University Medical Center were included in our study. No patients were excluded for any reason. Corresponding medical records were reviewed and data detailing patient age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, Ann Arbor stage, extranodal disease involvement, International Prognostic Index (IPI), therapy received, and the development of hypothyroidism was extracted. The Institutional Review Board of Vanderbilt University Medical Center approved this retrospective chart review and corresponding serum analysis.

2.2 Lenalidomide schedule and dosing

The doses of lenalidomide varied between 10 mg and 25 mg administered on a 21 day schedule for 12 cycles. For patients receiving combination therapy, rituximab (375 mg/m^2)

was administered on day eight of odd numbered cycles. Rituximab was administered as part of a prospective study as maintenance therapy following chemotherapy for high-risk DLBCL (clinical trials.gov # NCT00765245). Three patients who received lenalidomide off study for disease relapse were also included in this analysis.

2.3 Hypothyroidism diagnosis, grading, and treatment

The primary outcome of the study was the development of hypothyroidism. Hypothyroidism was diagnosed by elevated thyroid stimulating hormone (TSH) level accompanied by decreased thyroxine (T4) level. Grading of hypothyroidism was symptom-based as defined by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Table 1). Abnormal thyroid function tests were defined as TSH above or below the normal reference range (0.3–5.0 mU/ml) and correlated with Free T4 levels. Patients who were on the clinical trial had TSH checked routinely every four months per protocol. All patients who developed hypothyroidism were treated with levothyroxine, and all patients achieved normalization of their thyroid function tests within 4.0 months ± 1.6 months. Dose adjustments in lenalidomide occurred for grade 3 non-hematological toxicity, including hypothyroidism.

2.4 Cytokine analysis

Peripheral blood samples were collected in EDTA tubes from 31 patients on day 0, prior to the initiation of lenalidomide, and day 28, following completion of 21 days of therapy with lenalidomide as described above. Mononuclear cells and red cells were isolated from serum and stored at −80. Analysis was performed at the completion of the study. Serum levels of TNF- α, IFN-γ, IL-6, IL-12, and IL-15 were analyzed in duplicate with a high sensitivity human cytokine kit using luminex technology. Cytokine levels were detectable in 27 patients, and these patients were included in the statistical analysis.

3. Statistical analysis

Non-parametric analysis was performed. Baseline patient characteristics and disease-related variables were described with median and range for continuous variables and percent of total for categorical variables. Student's t test (for paired samples) was used for the statistical analysis. The Mann-Whitney U rank sum test was used to compare continuous variables. For ratio comparisons, the X^2-test or Fisher's exact test was used. All statistical tests were two-sided, and an α of 0.05 was used to determine statistical significance. Statistical analyses were performed using SPSS software (v.21) (IBM-SPSS, Chicago, IL, USA).

4. Results

4.1 Patient characteristics

Patient and disease-related characteristics are presented in Table 2.

A total of 329 patients with DLBCL were included in this study. Of these, 31 patients were treated with lenalidomide (n=15) or lenalidomide and rituximab (n=16). The median age of all patients with DLBCL was 60 years (range 17 years - 97 years), and the median age of the

patients who received lenalidomide as part of their treatment was 56 years (range 29 years – 85 years).

4.2 Treatment regimens and development of hypothyroidism

Of the 329 patients with DLBCL, 298 (90.6%) patients were treated with conventional chemotherapy (c) with or without stem cell transplantation (DLBCL-c). Thirty one (9.4%) patients received conventional chemotherapy and lenalidomide as either maintenance therapy or salvage treatment (DLBCL-len). Complete data was missing on a total of 34 patients in DLBCL-c, but these patients were included since they had documentation of thyroid function testing. Data was complete on all patients in the DLBCL-len arm. Fourteen patients (4.7%) received radiation therapy to the neck or mediastinum. None of the patients receiving lenalidomide had radiation as part of their treatment regimen. In the DLBCL-c arm 30 patients (10%) had pre-existing thyroid abnormalities, while in the DLBCL-len arm two patients (6.4%) had pre-existing thyroid dysfunction. Of these two patients, one had hypothyroidism and the other had hyperthyroidism. In the DLBCL-c arm, four patients (1.3%) were diagnosed with hypothyroidism after starting conventional therapy, while in the DLBCL-len arm eight patients (25.8%) were diagnosed with hypothyroidism after initiating lenalidomide ($p<0.0001$). The median onset of thyroid abnormalities after initiation of lenalidomide was 5.2 months. All patients in the DLBCL-c arm had grade 2 hypothyroidism by CTCAE criteria (Table 1). Five patients in the DLBCL-len arm had grade 2 and three had grade 3 hypothyroidism. Two patients who developed thyroid abnormalities in the DLBCL-c group had received prior radiation to the mediastinum.

4.3 Cytokine abnormalities in patients treated with lenalidomide

Serum levels of TNF-α, IFN-γ, IL-6, IL-12, and IL-15 were measured at pre-specified time intervals. There was a non-significant increase in the levels of these cytokines in the twenty-seven patient cohort receiving lenalidomide. There was no quantitative difference in cytokine levels when comparing patients who received lenalidomide with or without rituximab (Figure 1a–1c). At baseline in all twenty-seven patients treated with lenalidomide, the mean serum levels of TNF-α, IFN-γ, IL-6, IL-12, and IL-15 were 14.1pg/ml, 5.82pg/ml, 4.19pg/ml, 3.58pg/ml, and 2.89pg/ml, respectively. After 21 days of treatment with lenalidomide, the mean levels of TNF-α, IFN-γ, IL-6, IL-12, and IL-15 were 17.6pg/ml, 7.73pg/ml, 6.89pg/ml, 4.61pg/ml, and 3.28 pg/ml, respectively. None of these differences reached statistical significance (P= 0.09, 0.56, 0.13, 0.54 and 0.65 respectively).

5. Discussion

Serum cytokine levels pre and post lenalidomide therapy in patients who developed new or worsening thyroid function test abnormalities were available in all ten patients. Eight patients developed new onset hypothyroidism; two had hypothyroidism at baseline that worsened. In the 10 patients who developed new or worsening hypothyroidism after treatment with lenalidomide, TNF-α levels significant increased from a mean of 16.2pg/ml pre-treatment to 22.9pg/ml post-treatment ($p=0.002$, 95% CI 4.21–9.03) (Figure 2a–c). In these patients who developed worsening hypothyroidism with lenalidomide, there was no significant increase in mean IFN-γ, IL-6, IL-12, and IL-15 levels pre- and post-treatment

[pre-treatment 13.8pg/ml, 5.65pg/ml, 6.5 pg/ml, 5.25pg/ml and post-treatment 16.7pg/ml, 9.16pg/ml, 8.25pg/ml, 6.46pg/ml, respectively (p=NS)].

Lenalidomide-induced hypothyroidism is a poorly understood phenomenon that affects 5–10% of patients receiving this anti-neoplastic agent[6,11,14,15]. In our study cohort of DLBCL, we found higher rates of lenalidomide-related hypothyroidism than previously reported (1.3% in patients treated with conventional chemotherapy alone versus 25.8% in patients treated with conventional chemotherapy and lenalidomide. The addition of rituximab did not appear to increase the risk of thyroid abnormalities. A potential explanation is that the patients in this study are a unique group with DLBCL, who received lenalidomide maintenance with in 8–10 weeks of completing systemic immunochemotherapy. Lenalidomide could have potentiated or altered the immune reconstitution following administration of chemotherapy that may have been abrogated by a longer wash-out period. The mechanism of lenalidomide-induced hypothyroidism is poorly understood, and potential mechanisms include inhibition of iodine uptake[12], direct thyroid cell injury, decreased thyroid secretory capacity, and initiation of autoimmune thyroid destruction through pro-inflammatory cytokine deregulation[6,10,13].

The potential mechanisms of IMiD-induced hypothyroidism have been studied in a rat model[13] and through assessments of radioiodine uptake amongst thalidomide-treated patients[12]. Despite pro-inflammatory cytokine deregulation being postulated as a mechanism of lenalidomide-induced hypothyroidism, pre- and post-treatment serum inflammatory cytokine levels following lenalidomide administration have only been published in one small case series and have not been assessed in relation to the development of hypothyroidism. In a group of six patients with MM and a significant elevation (over 1 mg/dL increase) in C-reactive protein (CRP) after lenalidomide treatment, Harada et al. found no significant increase in serum tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin-2 (IL-2), or interleukin-6 (IL-6) after therapy[7]

In murine models it has been shown that normal thyroid tissue has TNF-α receptors, and that elevated TNF-α levels inhibit thyroid function[16,17]. This finding was further confirmed by Diez et al. when they evaluated serum TNF α levels in 20 patients with hypothyroidism, 20 patients with hyperthyroidism, and 20 healthy control patients. This group found that in both patients with hypothyroidism and hyperthyroidism, serum levels of TNF-α were significantly elevated compared with control patients[18]. Interestingly, case reports have shown both that TNF-α administration for cutaneous T cell lymphoma can exacerbate hypothyroidism[19], and that infliximab administration, a monoclonal antibody against TNF-α, can reduce thyroid hormone replacement needs in a patient with hypothyroidism[20].

While the current study is small and cannot assert causation, the finding of increased serum TNFα levels in patients with lenalidomide-induced hypothyroidism has a viable pathophysiologic mechanism and has been previously observed in other clinical situations. These findings warrant validation studies in larger patient populations. A limitation to our study is that the serum cytokine levels were not measured at the time of thyroid function abnormalities. Based on the available data, serum TNFα may have been much higher at the

actual time of occurrence of thyroid dysfunction. Another limitation is that patients who received lenalidomide on the clinical trial had routine thyroid tests performed per protocol. It is however; notable that these patients were symptomatic that may have otherwise prompted an evaluation.

6. Conclusions

Lenalidomide-induced hypothyroidism is a poorly-understood adverse event which warrants further investigation as its treatment indication expands to treat patients with NHL. We found higher rates of hypothyroidism when patients with DLBCL are treated with lenalidomide in addition to standard chemotherapy that is likely mediated by TNF-α. We recommend close monitoring of thyroid function tests in patients treated with lenalidomide for NHL.

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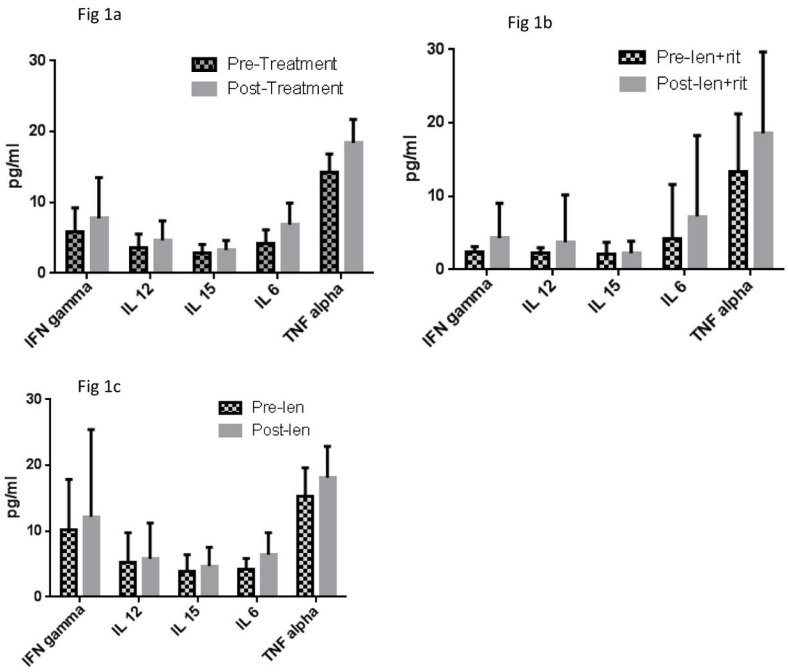

Figure 1.

a–c: 1a- serum cytokine levels pre and post lenalidomide based therapy (n=27). 1bserum cytokine levels pre and post lenalidomide alone (n=27). 1c-serum cytokine levels pre and post lenalidomide with rituximab (n=27).

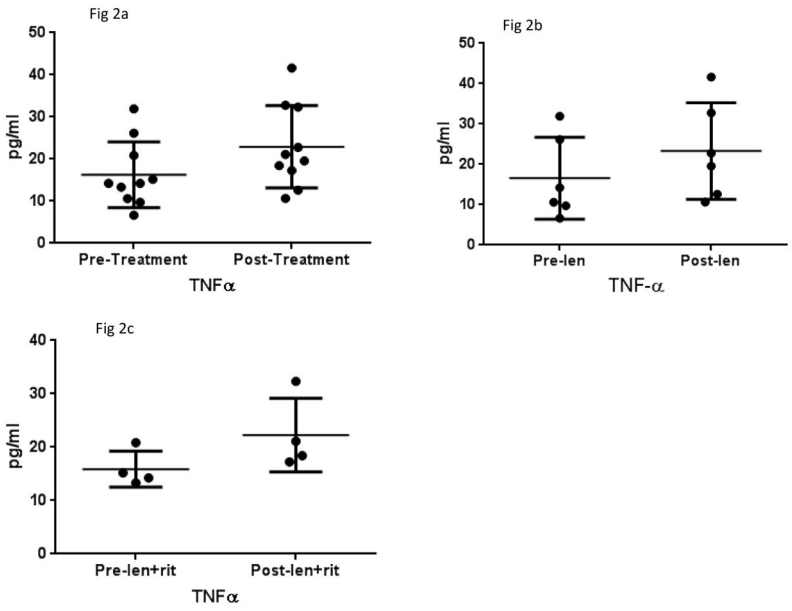

Figure 2.

a–c: 2a- TNFα levels of all patients pre and post lenalidomide based treatment who developed worsening hypothyroidism (n=10), P=0.002 (95% CI 4.21–9.03). 2b-TNFα levels pre and post lenalidomide who developed worsening hypothyroidism (n=6), P=0.0053 (95% CI 3.07–10.48). 2c- TNFα of patients treated with lenalidomide and rituximab who developed worsening hypothyroidism (n=4),

Table 1

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.0) used to grade hypothyroidism

Grade of Hypothyroidism	CTCAE Definition
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2	Symptomatic; thyroid replacement indicated; limiting instrumental ADL
Grade 3	Severe symptoms; limiting self-care ADL; hospitalization indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Table 2

Baseline characteristics.

	DLBCL-No Lenalidomide (N = 298)	DLBCL- Treated with Lenalidomide (N = 31)
Gender		
Male	181 (61%)	15 (48%)
Median age (range)	60 (17–97)	56 (29–85)
Pre-existing thyroid abnormalities	30 (10%)	2 (6%)
IPI		
0–1	102 (34.2%)	-
2	62 (20.8%)	6 (19.3%)
3	61 (20.4%)	18 (58%)
4–5	39 (13%)	7 (22.5%)
N/A	34 (11.4%)	
Radiation to mediastinum/neck	14 (5%)	0 (0%)
Thyroid abnormalities diagnosed after lymphoma therapy	4 (1%)	8 (26%)

N/A: not available