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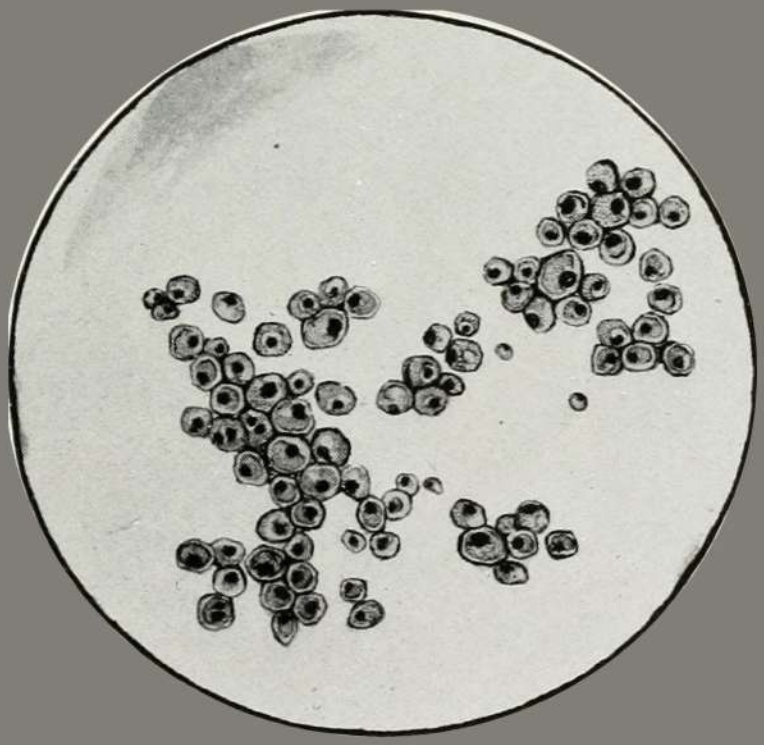

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CONTENTS

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Case Report

Early Onset, But Late Diagnosis of a Rare Disease

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ABSTRACT

One of the most common sphingolipidosis, Gaucher disease (GD) remains rare till date. A case report of a 56-year-old patient diagnosed with GD is presented herein. Her sister was known to have Gaucher disease. Her personal medical record consisted of splenectomy, anemia, recurrent infections, and bone lesions at a young age. Taking into consideration her personal and familial history, the clinical and paraclinical examinations, she was diagnosed with Gaucher disease which was confirmed with enzyme and gene testing. Upon introduction of specific enzyme replacement treatment for Gaucher patients,much evidence demonstrated the substantial improvement of hematological and visceral parameters. However, it has been observed that the bone tissue does not respond equally to the treatment.

Learning Points

• The physician should always investigate the splenomegaly of unknown etiology before deciding to do a splenectomy
• Bone lesions in Gaucher disease are sometimes irreversible, hence the importance of early diagnosis of this rare disease

Keywords
Gaucher disease; Bone lesion; Splenomeagly.

Acronyms
GD: Gaucher disease; Hb: Hemoglobin; MRI: Magnetic resonance imaging; ERT: Enzyme replacement therapy.

INTRODUCTION

Lysosomal diseases are a group of rare afflictions linked to innate errors of metabolism. Lysosomes are subcellular organelles limited by a membrane and contain many digestive enzymes involved in the catabolism of complex molecules, such as glycolipids, glycoproteins and mucopolysaccharides. The deficiency of a lysosomal enzyme obstructs the degradation of these molecules, causes their accumulation in lysosomes and creates metabolic abnormalities disrupting cell function. There are about fifty lysosomal diseases. Gaucher disease (GD) is one of the most frequent lysosomal diseases,[1] with an incidence of around 1/40,000 to 1/60,000 births in the general population. The disease was first described by Philippe Gaucher in 1882 in a patient with massive splenomegaly without leukemia. Gaucher is a genetic disease caused by mutations in the *GBA1* gene, located on chromosome 1 (1q21). More than 300 GBA mutations have been described in the *GBA1* gene, and the most common ones are *N370S, L444P*, *84GG*, *IVS2*.[2] The clinical aspects of the disease are caused by a deficiency of the lysosomal enzyme, glucocerebrosidase that leads to the accumulation of its substrate (glucosylceramide) in lysosomal macrophages in the bone marrow, liver, spleen, lungs, and other organs, which contributes to pancytopenia, massive hepatosplenomegaly, and, at times, diffuse infiltrative pulmonary disease. Progressive infiltration of Gaucher cells in the bone marrow may lead to thinning of the cortex, pathologic fractures, bone pain, bony infarcts, and osteopenia. These bony features may also be related to macrophage-produced cytokines. Gaucher disease has traditionally been divided

into the following 3 clinical subtypes:

Type 1–Non neuronopathic form, which is the most common type
Type 2–Acute neuronopathic form
Type 3–Chronic neuronopathic form

However, these distinctions are not absolute, and GD represents a phenotypic continuum.[2]

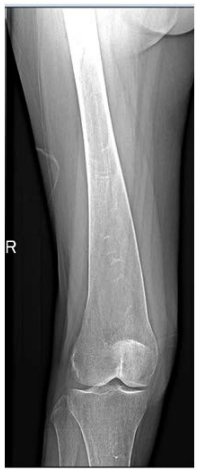
A case report of a 56-year-old patient diagnosed with GD is presented herein.

CASE DESCRIPTION

The patient was born from non Jewish consanguineous parents in 1962. She presented to the emergency department in August 2018, for extreme pain on her right hip. The pain was local without specific irradiation, increased on mobilization and improved upon taking rest. It had started one month ago, without trauma or other identified cause, and was not relieved with analgesics.

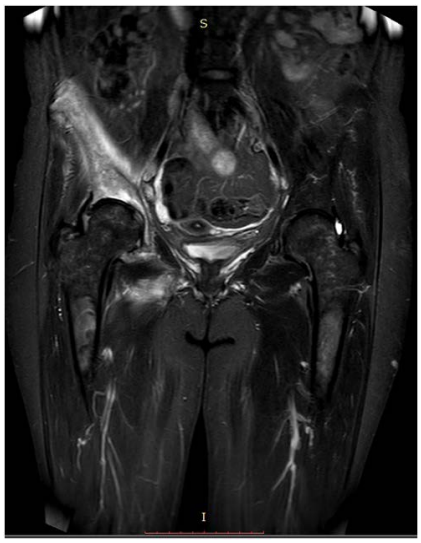
Her medical record consisted of splenectomy at the age of 9-years-old. Secondary to splenomegaly, recurrent infections in the upper respiratory system, recurrent tonsillitis, anemia that attributed to gynecological loss, fracture at L2 treated with percutaneous cimentoplasty in 2014 and an aggressive spinal hemangioma prior to that. Her sister was diagnosed with Gaucher disease at the age of 10-years-old, and she died from the disease's complications at the age of 45.

Figure 1. *Erlenmeyer Flask Sign of the Femur*



Upon admission, the blood test reports revealed the following results: Hb 11.5 g/dL, MCV 95 fl, white blood cells 8200/mm^3, platelets 261000/mm^3, ferritin 2654 ng/mL, normal liver function tests, and normal creatinine clearance. Right femoral X-ray revealed an Erlenmeyer flask sign (Figure 1). The magnetic resonance imaging (MRI) of the right hip revealed diffused significant heterogeneity in the signal of the trabecular bone of pelvic bones, femur and the visualized part of the lumbar spine, with individualization in particular of a much more diffuse and more intense signal abnormality in the spongy bone of the right iliac bone involving the acetabulum and the ilio and ischio-pubic branches, with cortical thinning visible at the height of the iliac crest, and a very important edema of the adjacent soft parts, involving the muscles iliopsoas, glutes, adductors and external obturators on the right side (Figure 2). The MRI concluded no osteonecrosis of the iliac bone, acetabulum and the femoral head.

Figure 2. *Diffuse Significant Heterogeneity in the Signal of the Trabecular Bone of Pelvic Bones, Femur*



Taking into consideration the clinical presentation of the patient (splenomegaly, hepatomegaly confirmed by abdominal ultrasound, anemia, high ferritinemia, bone lesions) and the family history, the patient was suspected to have Gaucher disease.

In order to confirm the diagnosis, the dosage of the lysosomal enzymes from dried blood, and the molecular genetic testing were performed. The first test revealed that the activity of beta-glucosidase was below its reference range (24.06 pmol/spot*20 h), with an elevated concentration of glucosylsphingosine, and the later tests showed a homozygous mutation of p.V414G which is similar to the known missense mutation p.V414.

The patient was operated in January 2019 with a total right hip replacement and was treated, since November 2018, with intra-venous Imiglucerase (60 UI per kilogram) once every 2-weeks. Moreover, she presented two fractures on D11 and D12, confirmed with lumbar MRI, in March 2019.

DISCUSSION AND CONCLUSION

Although it is the most common all the lysosomal storage diseases, Gaucher disease still remains rare and most cases present a gradual onset phenotype, which explains its delayed diagnosis. The spectrum of the disease is wide, and its clinical manifestation varies from being asymptomatic to presented with all complica-

tions. This patient had presented splenomegaly at infancy, which led to splenectomy at the age of nine, without any diagnosis. It is important to include Gaucher disease in the diagnostic decision tree in cases of splenomegaly and/or thrombocytopenia, in order to avoid potentially harmful splenectomy. Before the advent of enzyme replacement therapy (ERT), total or partial splenectomy was the standard of care for massive splenomegaly or severe pancytopenia.[3]

Another common manifestation of GD is a bone disease. The bone lesions in Gaucher disease are caused mainly due to alterations in its metabolism (turnover, remodeling, and mineralization), leading to various skeletal complications such as osteoporosis, marrow infiltration, avascular necrosis or osteolysis.[4] Patients with preexistent skeletal complications tend to suffer episodes during ERT, such as medullary infarctions, avascular necrosis, or fractures, but the frequency of these occurings is reduced.[3] In our case, the patient had aseptic necrosis of the right femoral head and iliac bone that was treated surgically with total hip replacement shortly after being started on ERT.

The efficacy of ERT on hematological and visceral parameters, such as anemia, thrombocytopenia and splenomegaly, is well established in the literature.[5] However, enzyme therapy cannot reverse established osseous injury; pathological damage such as osteonecrosis, bone infarcts and fracture, once it has occurred, is irreversible. Thereby, despite the low risk of early failure due to aseptic loosening, total hip replacement in patients with Gaucher's disease with symptomatic osteonecrosis of the femoral head is advised.[4]

On an additional matter, patients with GD suffer from early osteopenia. The bone mineral density tends to increase during ERT but with a slow rate, hence early diagnosis and treatment becomes important, in order to avoid severe complications. Furthermore, the use of bisphosphonates can be an effective and safe mean to increase bone density.

CONSENT

The authors have received written informed consent from the patient.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Original Research

Efficacy and Safety of Clarithromycin, Lenalidomide and Dexamethasone (Bird) Therapy for Japanese Patients with Relapsed or Refractory Multiple Myeloma

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ABSTRACT

Object
It is difficult for the elderly, those with complications, and those who live in remote areas to visit the hospital, and as a result, there are limits on the drugs they are able to use. It is therefore effective to prescribe such patients oral medications that have few adverse effects and in regimens that require few hospital visits. Clarithromycin can induce cell death by autophagy and it has a direct antitumor effect. There have been reports of the outcomes of Lenalidomide and Dexamethasone therapy with Clarithromycin which is administered orally and is safe on multiple myeloma. However, in Japan, there have been few studies. Here, we report on Clarithromycin, Lenalidomide and Dexamethasone therapy in our hospital.

Method
We analyzed 7 patients with relapsed refractory or refractory multiple myeloma who were treated at this hospital between January 2012 and December 2014. The Clarithromycin, Lenalidomide and Dexamethasone therapy were administered in a 28-day cycle as follows: Clarithromycin 400 mg/day for 28-days, Lenalidomide 15 mg/day for 21-days, and Dexamethasone was administered in a dose of 20 mg once per week. The response criteria used were standard International Myeloma Working Group (IMWG) Uniform Response Criteria. and adverse events were graded according to the national cancer institute-common terminology criteria for adverse events (NCI-CTCAE) Ver. 4. Statistical analysis was performed using Easy R (EZR).

Result
The response to Clarithromycin, Lenalidomide and Dexamethasone therapy were selective catalytic reduction (sCR) in 2 patients, CR in 1 patient, per rectum (PR) in 3 patients, and standard deviation (SD) in 1 patient. Response rates of PR or better were observed in 86% of the patients. Duration of response was median 316-days (range, 160-522-days). Median oculus sinister (OS) period was 1,907 days. Median OS following discontinuation of the study was 1,385 days. Hematological adverse events were G1-2 anemia in 3 patients and G3-4 anemia in 1 patient. G1-2 thrombocytopenia was observed in 1 patient and G3-4 thrombocytopenia was observed in 1 patient. Leukopenia of G1-2 was observed in 6 patients but G3 was not observed. Non-hematological adverse events were G1-2 liver disorder in 6 patients, G1-2 skin rash in 3 patients, and G1-2 constipation in 2 patients. G4 adverse events were fainting and duodenal ulcer in 1 patient each.

Conclusion
Clarithromycin, Lenalidomide and Dexamethasone can be safely and effectively administered in the relapsed refractory multiple myeloma

Keywords
Multiple myeloma; Bird; Clarithromycin, lethal dose (Ld).

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INTRODUCTION

Multiple myelomas are a hematologic malignancy that originates in the plasma cells. In recent years, the appearance of novel drugs has led to improvements in therapeutic outcomes, but these outcomes remain insufficient in the case of elderly and patients with complications. However, novel drugs such as Bortezomib (Bor) and Lenalidomide (Len) may represent new therapeutic strategies and their appearance means that their single and combined use provides a wider range of drug options. In particular, the immunomodulatory drug (Imid), Len, is an oral drug that is highly beneficial to elderly patients and patients who live in remote areas with poor access to the hospital, and for this reason, it has become a key drug.

Dimopoulos and Weber have reported that the efficacy of Len, when used in combination with Dexamethasone (Dex), is an improvement over Dex monotherapy when used on new multiple myeloma.[1,2] In addition, the FIRST study, which conducted a comparison of melphalan, prednisolone and thalidomide (MPT) and Ld (Lenalidomide and Dex), verified the efficacy of Ld.[3] VRd therapy, which combines Ld with Bor, is also thought to be an effective therapy.[4] In recent years regimens that combine Ld with Darazalex, Carfilzomib, Ixazomib, Elotuzumab, and other drugs have been attempted. Thus, the issue of which drug to combine with Lenalidomide is important. Currently, there are cases – such as the elderly or those with particular circumstances – who are unable to utilize novel drugs.

Clarithromycin (CAM) is an oral drug that is already available and as a result, it is easy to use. When CAM is used in combination with corticosteroids it is thought to have an optimizing action on the pharmacological effect of the corticosteroid by increasing the area under the curve (AUC) and the maximum blood concentration of the steroid. It also has the characteristics of an immunomodulator and suppresses inflammatory cytokines such as IL-6 in particular. CAM may also induce cell death by autophagy, and it has been shown to have a direct antitumor effect.[5-8] Rossi reported on Clarithromycin, Lenalidomide and Dexamethasone (Bird) therapy, in which CAM is used in combination with Ld therapy, for newly diagnosed multiple myeloma patients.[9] They indicated that it is highly effective, with a total response rate of 90% and CR of 39%. However, there are few data on its efficacy and safety in Japanese patients. Niesvizky used a CAM initial dose of 1,000 mg/day with Bird therapy in a Phase II trial, CAM dose is mostly used at 400 mg/day.[10] Therefore, in the present study we assessed the efficacy and safety of Bird therapy with CAM 400 mg/day when used on the Japanese elderly, those with complications, and those who live in remote areas to visit the hospital.

SUBJECTS AND METHODS

We analyzed 7 patients with relapsed refractory or new refractory multiple myeloma who were visited at this hospital between January 2012 and December 2014. We obtained informed consent from all patients in writing. Treatment was performed a 28-day cycle, with CAM 400 mg/day for 28-days and Len 15 mg/day for 21-days, with a drug rest of 7-days. Dex was administered in a dose of 20 mg/dose once per week. The Len and Dex doses were increased or decreased on the determination of the attending physician. All patients were registered in Rev-Mate and the required safety management guidelines were followed. Low dose aspirin is recommended to prevent thrombosis. The use of granulocyte-colony stimulating factor (G-CSF) was administered at the physician's discretion for adverse events of neutropenia. The response criteria used were standard International Myeloma Working Group (IMWG) uniform response criteria. and adverse events were graded according to the national cancer institute-common terminology criteria for adverse events (NCI-CTCAE) Ver. 4. Statistical analysis was performed using Easy R (EZR).[11]

The primary outcome measures were response rate and safety, and the secondary outcome measure was overall survival rate.

The exclusion criteria were: patients with uncontrollable disease complications and patients with a history of allergy to macrolide antibiotics.

RESULTS

Patient background characteristics are shown in Table 1. The enrolled patients consisted of 4 with relapsed refractory disease and

Figure 1. *The Change of M Protein After One Cycle.The Average was 3711 mg/dl in Before and 1305 in After*

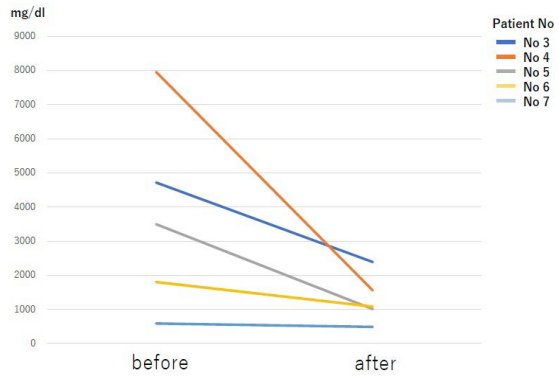

Figure 2. *OS. Panel A Shows OS of Bird Therapy. Panel B Shows OS After Discontinue Bird Therapy*

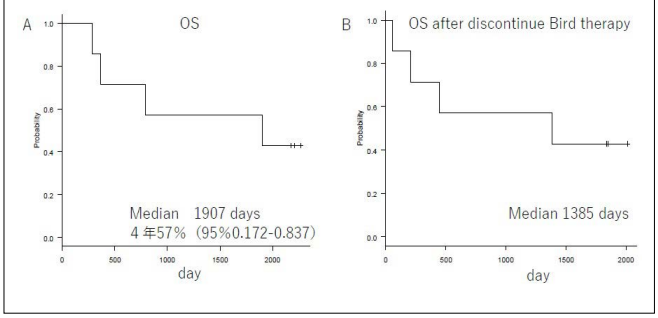

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Table 1. *Patient Characteristics*

N	7
Age, median (range)	65.3(43-76)
Sex	
Male	3(43%)
Famale	4(57%)
Satge(ISS)	
I	3(43%)
II	1(14%)
III	1(14%)
ND	2(29%)
Class	
IgG	4(57%)
IgA	1(14%)
B-J	2(29%)
Creatine level	
>2	0(0%)
<2	7(100%)
previous therapy	
Bor regimen	4(57%)
Imids regimen	2(29%)
3>	2(29%)
ABMT	1(14%)
only dex	3(43%)
induction time	
Diagnosis(day)	552(11-2295)
NDMM (day) n=3	16(11-26)
RRMM (day) n=4	954(158-2295)
reason for change	
PD	4(57%)
AE	0(13%)
BEST response to prior therap	
CR	1(14%)
VPPR	1(14%)
PR	2(29%)
ND	3(43%)

In parentheses indicates Account for a percentage ISS: international staging system, Bor: bortezomib, ABMT: Autologous bone marrow transplantation, PD: progressive disease, AE: adverse event, Imids: immunomodulator agent, NDDM: newly diagnosed multiple myeloma, RRMM: relapse and refractory multiple myeloma

Table 2. *Beat Response, Duration of Response and Survival*

No	Age	ISS	Time form Diagnosis	Duration Response	Cycles	Prior Therpy	Best Response	Survival
1	56	1	2295	522	18	4	CR	death
2	43	1	1193	231	8	3	SD	death
3	69	3	26	420	13	1	PR	alive
4	70	ND	11	368	12	1	SCR	alive
5	73	ND	12	160	4	1	PR	death
6	70	1	173	344	12	2	PR	death
7	76	2	158	167	6	2	SCR	alive

SCR: Stringent complete response; CR: Complete response; VGPR: Very good partial response; PR: Partial response; SD: Stable disease

Table 3. *Adverse Events*

Adverse Events (Number)		
Hematological adverse events	G1-2	G3-4
Anemia	3	1
Trombocytopenia	1	1
Leukopenia	6	0
Non-Hematological adverse events		
liver disorder	6	0
Skin rash	3	0
constipation	2	0
syncope	0	1
Duodenal ulcer	0	1

G1-2: Grade 1 to 2, G3-4: Grade 3 to 4

3 with new refractory disease. Bone lesions were observed in all patients. Patients with the new refractory disease were started on Bird therapy after administration of Dex monotherapy (20 mg for 4-days). Patients who already underwent a regimen that included Bor/Imids as the prior therapy were 4/2 patients respectively. Two patients underwent at least 3 regimens, and 1 patient underwent autologous transplantation. None of the patients had kidney dysfunction of creatinine 2 mg/dL or above. The reason for drug switching in the relapsed group was progression disease. No drug switching was done as a result of adverse effects (AE). The M protein decreased rapidly from 3711 mg/dL to 1305 mg/dL on average after one cycle (Figure 1). For the relapsed patients, the best effects of the prior therapy were CR/VGPR/PR in 1/1/2 patients respectively. The best response is shown in Table 2. The results were sCR/CR/PR /SD in 2/1/3/1 patients respectively. Response rates of per rectum (PR) or better was observed in 86% of the patients, indicating sufficient therapeutic efficacy. The mean duration of response was 316-days (range, 160-522-days). The median oculus sinister (OS) during the follow-up period of April 30, 2019 was 1,907-days. The median OS after the conclusion of the Bird therapy was 1,385-days (Figure 2). Currently, 3 patients are still alive. The mean number of treatment cycles was 10 cycles. Prior therapy consisted of 2 regimens.

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Safety

Adverse events are shown in Table 3. Hematological adverse events were as follows: Anemia of Grade (G) 1-2 was observed in 3 patients and anemia of G3-4 was observed in 1 patient. Thrombocytopenia of G1-2 was observed in 1 patient and thrombocytopenia of G3-4 was observed in 1 patient. Leukopenia of G1-2 was observed in 6 patients and leukopenia of G3 was not observed. Investigation of non-hematological adverse events indicated that 6 patients had G1-2 liver dysfunction, 3 patients had a G1-2 skin rash, and 2 patients had G1-2 constipation, G-4 adverse events were fainting and duodenal ulcer in 1 patient each.

DISCUSSION

In the FIRST trial for newly diagnosed multiple myeloma, the 4-year OS of Ld continues group was 59%. (3) Asher A et al. reported that the response rates of PR or better for Ld therapy on relapsed refractory multiple myeloma patients were 60.9%, 54.2%, and 69.8% for age groups 64-years and younger, 65-74-years, and 75-years and older respectively. The median survival rates were 43.9-months, 33.3-months, and 34.3-months respectively.[12] The results of our study indicate that the 4-year OS was 57% (Figure 2). This is the same as the 4-year OS reported by the FIRST trial, and it indicates sufficient efficacy since it includes relapsed refractory patients. The overall response rate was 86%, indicating a satisfactory result. In addition, the median survival rate for patients who were able to undergo at least 10 cycles tended to be satisfactory, at 4202-days (p-0.319) (Figure 3). The best therapeutic effect in patients with CR or above did not reach the median value (Figure 4). The duration of response was 316-days (range, 160-522), but the survival rate was satisfactory. These findings are related to the fact that the OS after discontinuation of Bird therapy was satisfactory, at 1,385-days. Recently, survival post-progression (SPP) has been gaining attention.[13] This indicates that even when the PFS for the prior therapy was satisfactory if the subsequent treatment following relapse is poor, the overall survival rate is also poor. This is because, in contrast, even when the PFS for the prior therapy was not satisfactory if the subsequent treatment following relapse is good, the overall survival rate will improve. Thus, it is difficult to extend OS when the subsequent treatment is poor, even in cases when the prior therapy is good. Therefore, it is necessary to select a prior therapy that does not have a negative effect on the subsequent treatment, and therefore particular care is required when treating elderly patients. We think that the results of Bird therapy were further extended OS by the effect of subsequent treatment in this study. Novel drugs for use following Bird therapy have been developed, and their use as a subsequent treatment that is not negatively affected by Bird therapy probably led to the good outcomes. In particular, patients that achieved CR or better as a result of Bird therapy had better survival rates after cessation of Bird therapy than patients who did not achieve CR. Combination therapy with Clarithromycin and Imids was first reported in 2002 by Coleman who also reported on combination therapy with Clarithromycin, Thalidomide, and Decadron (BLT-D). These drugs achieved an overall response rate of 92%, including 13% of CR, in cases of newly and relapsed multiple myeloma.[14] Subsequently, Gay reported on their comparison of Bird therapy and Ld therapy on cases of newly diagnosed multiple myeloma. They reported the following results indicating that CR was superior to Ld; 45.8%:13.9% of CR; 73.6%:33.3% of VGPR; 89.7%:73% of 3-year OS.[15] Rossialso reported a 5-year survival rate of 75.2%[9] and in an even more intriguing study, Ghosh reported that in patients with resistance to Ld who were administered Clarithromycin, 41.7% attained at least PR and the median survival period was 25-months. Thus, it is considered that even in Ld-resistant patients the additional administration of Clarithromycin may be effective.[16] With regard to CAM, even in the report of Niesvizky, the average dose was 400 mg/day, and it is considered that even when CAM was 400 mg/day in the study, the effect was recognized from OS.[10]

Figure 3. *Subgroup Analysis of OS in 10 Cycles or More and Less than 10 Cycles*

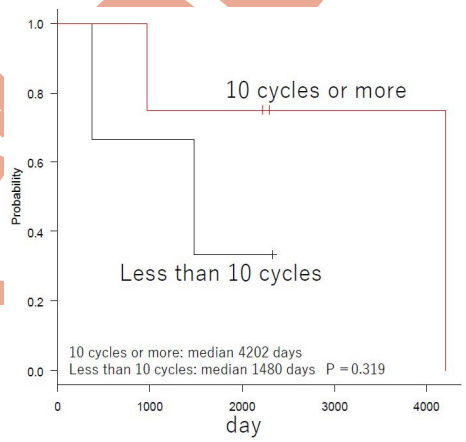
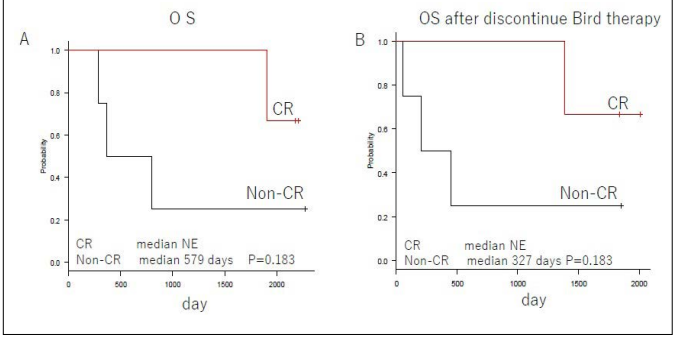


Figure 4. *Subgroup Analysis of OS in 1CR and Non-CR. Panel A Shows OS of Bird Therapy. Panel B Shows OS After Discontinue Bird Therapy. NE Denotes Could Not be Estimated*



In terms of safety, as the mean dose of Len was low, at 16 mg, hematological adverse events were no problems with G1-2. Non-hematological adverse events were within the tolerable range. Although all patients who were administered Clarithromycin experienced liver dysfunction, it was of G1-2 and therefore could be controlled. Syncope was temporary and did not present problems with treatment. The patient with duodenal ulcer required fasting and pharmacotherapy, but this resulted in improvement, and Bird

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therapy could be resumed.

"In Japan, the starting dose is often reduced in the practice because of intolerable problems. We, therefore, reduced the starting dose in this protocol." in the discussion part.

CONCLUSION

Bird therapy, which consists of additional Clarithromycin administration to patients whose Ld therapy does not have a satisfactory effect improves the response rate of Ld therapy. In addition, Bird therapy had few adverse effects and had little effect on post-relapse therapy. Therefore, after Bird therapy, sufficient treatment can be performed, and post-relapse therapy can obtain a good response and the duration of response to Post-relapse therapy becomes longer. For those reasons, we think that Bird therapy can improve overall survival. Bird therapy is considered to be effective from the antitumor effects of CAM and the concept of SPP. However, as this study included only a small number of patients, further study is required.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Retrospective Study

Morbidity and Mortality Associated with Development of Hypogammaglobulinemia after Rituximab

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ABSTRACT

Objective

Low-levels of gamma globulin are associated with a risk of infection, and complications of hypogammaglobulinemia are often observed in hematologic malignancies. In chronic lymphocytic leukemia (CLL), IgG≤600 mg/dL is reportedly associated with higher risks of infection. The objective was to determine the risks of hypogammaglobulinemia and infection in malignant lymphomas for which rituximab that targets B-cells is used.

Methods

A retrospective analysis of data from medical records of patients with malignant lymphomas treated with rituximab-containing therapy at our hospital between April 2014 and March 2016 was performed to assess the risks of infections through an evaluation of IgG levels and hospitalizations for and deaths due to infections in patients hospitalized with infections during this period.

Results

From April 2014 to March 2016, 128 patients with malignant lymphomas received rituximab-containing therapy at our hospital, and 94 (61%) of these patients had IgG levels measured. These 94 patients were included in the analysis. The histological types were as follows: 30 had follicular lymphoma (FL), 17 had indolent non-Hodgkin's lymphoma (iNHL), 42 had diffuse large B-cell lymphoma (DLBCL), and 5 had mantle cell lymphoma (MCL). The mean minimum immunoglobulin G (IgG) level in patients hospitalized for infection was 546 mg/dL and was 628 mg/dL in those not hospitalized (p=0.6). Although a significant difference was not observed, IgG levels tended to be low in hospitalized patients with infection. In addition, there were 4 patients with mean IgG levels that were 600 mg/dL or less in the 6-months immediately prior to hospitalization. Among these 2 died of infection.

Conclusion

Low-levels of gamma globulin are associated with a risk of mortality due to infections in malignant lymphomas.

Keywords

Hypogammaglobulinemia; Malignant lymphoma; Rituximab.

Abbreviations

CLL: Chronic lymphocytic leukemia; FL: Follicular lymphoma; iNHL: Indolent non-Hodgkin's lymphoma; DLBCL: Diffuse large B-cell lymphoma; MCL: Mantle cell lymphoma; FN: Febrile neutropenia.

INTRODUCTION

Secondary hypogammaglobulinemia (IgG<600 mg/dL) occurs for a variety of reasons, including due to disease, drugs, or treatment. In particular, in hematological malignancies (chronic lymphocytic leukemia, multiple myeloma, malignant lymphoma, etc.), the frequency of onset of secondary hypogammaglobulinemia is also high, and this is important for the onset of infections. Specifi-

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cally, malignant lymphoma is a representative hematologic malignancy that is associated with secondary hypogammaglobulinemia due to chemotherapy, including rituximab. Although not abundant, there have been a few reports on malignant lymphomas and hypogammaglobulinemia. Filanovsky et al reported that 49% and 11% of 182 malignant lymphoma patients treated with chemotherapy developed hypogammaglobulinemia with immunoglobulin G (IgG) 600 mg/dL or less and with IgG 400 mg/dL or less (severe), respectively. Particular attention was paid to the finding of higher mortality rates due to infections in the low gamma globulin group (32%) than in the normal group (3.6%), and the mortality rate was higher in patients with hypogammaglobulinemia that continued for 6-months or longer than in patients with hypogammaglobulinemia continuing for 6-months or less.[1] In addition, Memorial Sloan-Kettering Cancer Center (MSKCC) also reported on hypogammaglobulinemia in patients with malignant lymphomas. The association between the use of rituximab and hypogammaglobulinemia (IgG<600 mg/dL) in malignant lymphomas treated with rituximab between December 1998 and September 2009 was investigated. The study included 211 patients with malignant lymphomas. Although 15% of patients presented with hypogammaglobulinemia prior to treatment, 38.5% of patients who had normal IgG prior to treatment presented with hypogammaglobulinemia after treatment and 72% of patients with IgG within or below normal limits prior to treatment presented with hypogammaglobulinemia after treatment, meaning overall 43% experienced onset.[2] Hypogammaglobulinemia in malignant lymphoma increases the risk of complications of infections and is associated with increased mortality from infections and interruption of chemotherapy. In order to improve treatment outcomes for malignant lymphomas, there is a necessity to pay attention to hypogammaglobulinemia. We therefore, investigated the risk of hypogammaglobulinemia and infection in patients with malignant lymphomas at our hospital.

PATIENTS AND METHODS

A retrospectively analysis of data from medical records of patients with malignant lymphomas whose IgG levels were measured and who received rituximab-containing therapy at our hospital between April 2014 and March 2016 was performed. Hypogammaglobulinemia was defined as an IgG value of 600 mg/dL or less, and an IgG value of 400 mg/dL or less was defined as severe hypogammaglobulinemia. To assess the risk of infection, IgG levels and hospitalization for and deaths due to infection were studied in patients hospitalized for infection during this period.

RESULTS

From April 2014 to March 2016, 128 patients with malignant lymphomas received rituximab-containing therapy at our hospital, and 94 (61%) of these patients had IgG levels measured (Figure 1). The 94 patients shown in Table 1 were included in analyses. The histological types were as follows: 30 had follicular lymphoma (FL), 17 had indolent non-Hodgkin's lymphoma (iNHL), 42 had diffuse large B-cell lymphoma (DLBCL), and 5 had mantle cell lymphoma (MCL). There were 60 patients with primary, 16 with recurrent, and 18 with refractory disease. Eighteen patients used purine analogues. Eight patients (8%) presented with hypogammaglobulinemia prior to treatment. Four of these patients (4%) had severe hypogammaglobulinemia. After treatment, 42 patients (44%) presented with hypogammaglobulinemia and 18 (19%) had severe hypogammaglobulinemia. Nine patients (10%) were hospitalized for infection. Relationships between rituximab monotherapy/combination therapy, use/non-use of purine analogues, 1/2/3 prior regimens, completion/non-completion of 8 or more administrations of rituximab and minimum IgG levels were investigated. The mean values of each item were shown in Figure 2. The risk of infection was assessed based on the relationship between hospitalization for infection and minimum IgG levels. The mean minimum IgG level in patients hospitalized for infection was 546 mg/dL and 628 mg/dL in those not hospitalized (p=0.6) (Figure 2). There was

Table 1. *Patient Characteristics*

N	**94**
Age, Median(range)	70(46-87)
Sex	
Male	53(56%)
Female	41(44%)
Lymphoma type	
FL	30(32%)
iNHL	17(18%)
DLBCL	42(45)
Mantle	5(5%)
Pre-Treatment	
low IgG	8(8%)
Fludarabine-base chemo	17(18%)
Rituximab cycle>8	36(38%)
Prior Therapy	
1	16(17%)
2	18(19%)
Stage	
Newly	60(64%)
Relapsed	16(17%)
Refractomy	18(19%)

In parentheses indicates Account for a percentage

Figure 1. *The Monitoring Ratio of IgG Level*

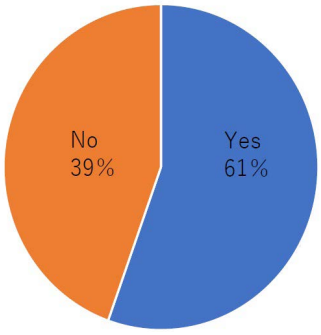

Figure 2. *IgG Levels in Each Item*

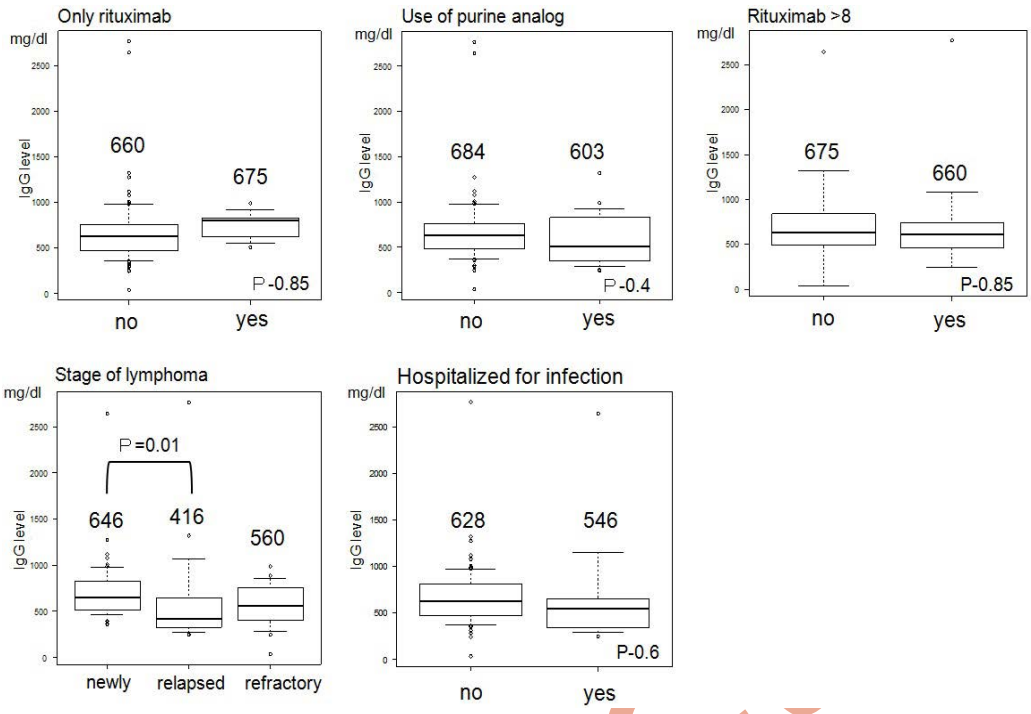

Table 2. *Type of Infection and IgG Average*

ID	Age	Type	Sex	Infection	Survival	Infection-Related Death	IgG Average
1	74	SLL	F	Pneumonia	Alive		413
2	63	DLBCL	F	Herpes encephalitis	Death	No	288
3	55	FL	M	CMV pneumonia	Death	Yes	411
4	75	DLBCL+RA	F	Sepsis	Alive		3248
5	79	DLBCL	F	CMV pneumonia	Death	Yes	353
6	79	FL	M	Febrile Neutopenia	Alive		1202
7	70	DLBCL	M	peritonitis/Febrile Neutopenia	Alive		1014*
8	73	DLBCL	F	Cholecystitis	Death	No	1902*
9	53	DLBCL	M	Pneumocystis pneumonia	Alive		799

**is less than 6-months close to the first visit and hospitalization*

no significant difference in the relationship between hospitalization for infection and hypogammaglobulinemia and severe hypogammaglobulinemia (p=0.383/0.059). And there was a significant difference in the relationship between death from infection and severe hypogammaglobulinemia, but not hypogammaglobulinemia (p=0.00264/0.133). The types of infections were as follows: pneumonia in 5, enteritis in 1, peritonitis in 1, herpes zoster in 1, and infection of unknown etiology in 2 patients. Four patients died, two of whom died from infections, while the other 2 died from underlying malignant disease. In addition, there were 4 patients with mean IgG levels that were 600 mg/dL or less in the 6-months immediately prior to hospitalization (Table 2). Among these 2 (50%) died of infection. Moreover, in terms of minimum IgG levels, a lower IgG value prior to treatment was significantly associated (p<0.05) with a low IgG post-treatment value (Figure 3).

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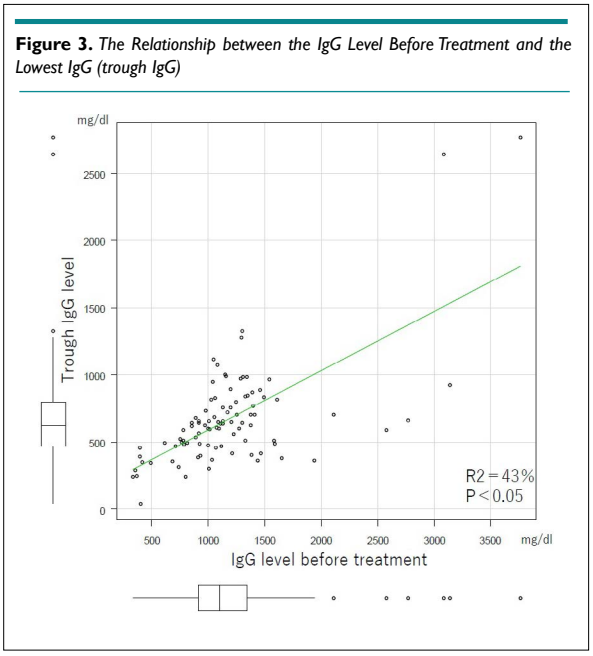
Figure 3. *The Relationship between the IgG Level Before Treatment and the Lowest IgG (trough IgG)*



DISCUSSION

Rituximab is an antibody that targets CD20 and reduces B-cells. As a consequence, IgG values also decrease. In our study, the rate of hypogammaglobulinemia increased from 8% prior to treatment to 44% after rituximab administration. Monitoring of IgG levels during rituximab administration may be necessary; however, only 61% of the patients had IgG measured at our hospital. Since hypogammaglobulinemia is associated with a risk of infection, monitoring of IgG levels is considered important. In terms of the association between hematologic malignancies and hypogammaglobulinemia, Furst reported the onset of infections in association with chronic lymphocytic leukemia (CLL) and serum IgG levels. The onset of infection reportedly increases in CLL when IgG values are 600 mg/dL or less, and that the onset of severe infections increase with lower IgG values.[3] Makatsori also reported on the risks of hypogammaglobulinemia following the administration of rituximab. Twenty-seven percent of patients reportedly developed hypogammaglobulinemia after treatment. Forty-one events of infections were observed, with 10 events of bronchitis/pneumonia and frequent onset of respiratory tract infections.[4] Vacca also reported on hypogammaglobulinemia in multiple myeloma. In this report, there was also a frequent onset of upper respiratory tract infection observed.[5] These findings suggest that hypogammaglobulinemia is associated with a high risk of respiratory tract infections and that IgG levels should be checked when there are complications of upper respiratory inflammation during chemotherapy. In addition, Filanovsky reported that low gamma globulin levels influenced death from infections in malignant lymphomas.[1] In this report, 182 malignant lymphoma patients were analyzed, and the onset of hypogammaglobulinemia was observed in 38%. The mortality rate with infections was 3.6% *versus* 28.5% in patients with normal versus decreased IgG levels (IgG≤600 mg/dL) and was significantly higher in patients with decreased IgG levels than in those with normal IgG levels. In addition, patients whose hypogammaglobulinemia persisted for 6-months or longer had a higher mortality rate of 19% compared to 6% in those whose hypogammaglobulinemia did not persist, suggesting that the long-term persistence of hypogammaglobulinemia was associated with a higher mortality rate. We investigated infections and deaths in patients hospitalized for infections during this period in this study (Table 2). The types of infection were as follows: 4 patients with pneumonia, 2 patients with febrile neutropenia (FN), and 1 patient each with cholecystitis, encephalitis, septicemia, and peritonitis. Similar to previous reports, there were many patients with pneumonia and other respiratory infections. Severe hypogammaglobulinemia had a dominant difference and increases mortality from infection, but the risk of death from infection is related not only to IgG levels but also to duration. There were 4 (44%) deaths, but 2 (22%) were due to infections in this report. In these 2 patients, the mean IgG level was 382, low level, during 6-months prior to hospitalization. In patients with mean IgG values of 600 mg/dL or less, 2 (50%) out of 4 died from infections. Caution should be exercised because persistent hypogammaglobulinemia may increase the risk of death from infections. In addition, post-treatment hypogammaglobulinemia increased from 8% to 44%, and thus caution should be exercised and IgG levels monitored after treatment.

CONCLUSION

In this study, rituximab-containing chemotherapy was found to increase the risk of post-treatment hypogammaglobulinemia in patients with malignant lymphomas. Several authors have made similar observations as our study, on the basis of which the Rituximab Consensus Expert Committee recommends pretreatment screening for hypogammaglobulinemia so appropriate caution may be exercised.[6] In addition, the persistence of hypogammaglobulinemia was associated with an increased risk of developing infections, and high rates of mortality. The risks associated with hypogammaglobulinemia in malignant lymphomas should be understood and treatment should be administered. There is also a need to consider the indications for prevention, such as with substitution therapy of gamma globulin in the future, and further evaluations are necessary.

IRB APPROVAL

This study has been approved by the Institutional Review Board (IRB).

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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