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Monoclonal gammopathies and their management in Gaucher disease type 1

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Abstract

Gaucher disease type 1 (GD1) is a rare autosomal recessive genetic disorder characterized by deficiency of the lysosomal enzyme glucocerebrosidase. Among the various clinical manifestations that have been well described for decades, a more recent finding has been the association of GD1 with increased risk of various malignancies, including multiple myeloma. We present a brief review describing the relationship between GD1 and monoclonal gammopathies, as well as the modern standard in the monitoring and management of these conditions. This review aims to increase awareness of a disease that, while rare, is associated with a common malignancy with robust, novel treatment options.

Keywords: Rare disease, Gaucher, multiple myeloma, monoclonal gammopathy

INTRODUCTION

Gaucher disease (GD), which develops due to an inherited deficiency of glucocerebrosidase, is the most common lysosomal storage disease globally[1]. The hallmark pathological finding in Gaucher is the excessive buildup of glucosylceramide (GC) and its bioactive metabolite, glucosylsphingosine, in macrophages. This leads to chronic inflammation in untreated patients, who develop hepatosplenomegaly, anemia, thrombocytopenia, potentially crippling bone involvement, and possible neurological consequences[2]. Of the three known types of Gaucher disease (types 1, 2, and 3), type 1 (GD1) has received the most attention

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from researchers regarding malignancy. It has been repeatedly reported that the incidence of malignancies, especially hematological malignancies, is increased in GD1[3-5]. The purpose of this review is to present information on the incidence of these neoplasms and their treatment. This review was based on literature identified through PubMed and the International Gaucher Registry reports up to August 2025.

INCIDENCE OF MGUS AND MALIGNANCIES IN GAUCHER DISEASE TYPE 1

The tissue microenvironment in GD1 contains a number of factors that contribute to carcinogenesis. These include the accumulation of the growth-promoting metabolite GC, cancer-promoting metabolic shunting (Warburg effect), M2 polarization of GC-saturated macrophages, chronic B-cell stimulation, masked metabolic syndrome with insulin resistance, iron overload, lysosomal dysregulation, and endoplasmic reticulum stress[6,7]. Various studies have reported an overall increased risk of hematological malignancies in GD1 patients, with the risk of multiple myeloma (MM) specifically ranging from 5.9- to 51.1-fold higher[8].

In a recent study from the Gaucher Registry, the risk of MM was ninefold higher than in the wild-type population, and the age of presentation was younger than reported in prior studies[5]. In addition, higher age-adjusted incidence rates of monoclonal gammopathy of unknown significance (MGUS), a known precursor of MM, were also observed. These findings correspond with the increasingly recognized role of Gaucher lipids in driving B-cell proliferation and the generation of anti-lipid antibodies. The number of years between the diagnosis of GD1 and initiation of treatment did not affect the cumulative incidence of MGUS. In patients homozygous for N370S-the most common GD1 genotype-the incidence of MGUS and polyclonal gammopathy was increased compared with previously reported data. This may reflect the higher proportion of patients with N370S homozygosity in this registry study. Furthermore, among patients who developed MM, only about half had an antecedent MGUS phase, a proportion lower than that reported for MM in general[9]. Whereas the incidence of polyclonal gammopathy reached 5% by 50 years of age, the incidence decreased significantly per year in patients treated with enzyme replacement therapy (ERT), but not in those with MGUS[5].

It is notable that patients with MGUS due to lipid-reactive M-spikes showed a reduction of monoclonal protein with substrate reduction therapy (SRT)[10]. Studies have demonstrated an increased risk of B-cell malignancies in murine GD models, which is ameliorated by SRT using a glucosylsphingosine inhibitor, supporting the role of glycosphingolipids in driving carcinogenesis in GD1 models[11,12]. In a study of 63 GD1 patients, none of the 50 receiving ERT developed MGUS, and immunoglobulin levels decreased overall[13]. Similarly, in the murine GD model, SRT reduced disease-associated gammopathy[12]. Eliglustat, an SRT approved for use in humans, has demonstrated efficacy in reducing lyso-GL1 plasma concentrations, a potential stimulatory antigen for the development of monoclonal antibodies[14].

There is evidence that GD patients who develop MGUS do so as a consequence of chronic secretion of proinflammatory cytokines-namely interleukin (IL)-6 and IL-10-by macrophages alternatively activated due to prolonged accumulation of glycosphingolipids. This results in clonal expansion of B-lymphocytes and plasma cells[4]. In addition, some data implicate GC in B-cell stimulation, leading to the formation of anti-GC antibodies and activation of complement, which may contribute to the development of gammopathy. Glucosylsphingosine (lysGb-1) has also been identified as an antigen stimulating antibody formation, and monoclonal immunoglobulins in MGUS of GD patients have shown anti-lysoGb-1 activity in some instances[15,16]. There is very little data in patients with types 2 and 3 GD to draw conclusions about these risks. However, in GD1 patients who are living longer due to treatment with enzyme replacement therapy or substrate reduction therapy, the risk of developing MGUS as a precursor of MM or non-Hodgkin lymphomas (NHL) is a concern and must be carefully monitored[17].

In patients with GD1 who develop solid tumors, there is an increased risk of hepatocellular carcinoma, renal cell carcinoma, breast cancer, and malignant melanoma. Unlike other metabolic disorders that primarily affect a specific organ, these sites of neoplasia do not correspond to organs typically affected by GD1. The increased risk of melanoma may be related to defective T-cell function and impaired immune surveillance in GD1 patients, possibly associated with lyso-GL1[5].

THE MANAGEMENT OF MONOCLONAL GAMMOPATHIES

MGUS

MGUS is a non-malignant plasma cell disorder with the potential to evolve into smoldering MM (SMM) or MM. The incidence of MGUS increases with age, and its prevalence in adults aged 70 and older was 5.3% in a large population study[18]. As reviewed above, the incidence is higher in patients with GD1.

The diagnostic criteria require the detection of a serum monoclonal protein under 3 g/dL or a clonal increase in the serum light chain ratio, fewer than 10% clonal plasma cells on bone marrow examination, and no classic MM clinical features (hypercalcemia, renal impairment, anemia, or lytic bone lesions)[19].

The vast majority of patients diagnosed with MGUS do not progress to MM. The risk of progression is generally described as roughly 1% per year, though specific risk factors can influence an individual patient's risk. Higher-risk features include an abnormal free light chain ratio, a monoclonal protein (M-protein) ≥ 1.5 g/dL, and non-Immunoglobulin G (IgG) MGUS[9].

As MGUS, by definition, does not cause clinical manifestations, its management is focused on periodic monitoring for progression to SMM or MM, rather than treatment. The frequency of monitoring is based on baseline risk assessment. Guideline recommendations for frequency of monitoring range from annually for high-risk MGUS (M-protein ≥ 1.5g/dL, abnormal light chain ratio, or non-IgG type), to every 2-3 years for low-risk MGUS (M-protein < 1.5g/dL, normal light chain ratio, and IgG type)[20]. Potential future improvements in the MGUS management include refinement of tools to risk-stratify patients, which would allow intensified monitoring for some and reduced monitoring for others.

SMOLDERING MULTIPLE MYELOMA

SMM, similar to MGUS, is an asymptomatic premalignant state. It differs from MGUS in that it requires either ≥ 3g/dL of serum monoclonal protein or 10%-59% clonal plasma cells in bone marrow. Several risk stratification models exist to help prognosticate risk of progression to MM, guide monitoring frequency, and inform selection of therapy.

The International Myeloma Working Group (IMWG) uses three readily available risk factors to predict progression to MM: M-protein > 2 g/dL, involved-to-uninvolved free light chain ratio > 20, and bone marrow clonal plasma cells > 20%. A retrospective study of 1,996 patients validated the use of these risk factors. The two-year risk of progression to MM was 6% for patients with no risk factors, 18% for those with one factor, and 44% for those with two to three factors. Further stratification could be achieved by incorporating high-risk cytogenetic abnormalities [t(4;14), t(14;16), +1q, or del13q] as a fourth risk factor[21].

The standard of care for low and intermediate-risk SMM is observation until progression to MM. Lenalidomide, an immunomodulatory drug with regulatory approval in MM, did not demonstrate statistically significant progression-free survival (PFS) benefit compared to observation in the Mayo 2018 intermediate risk subgroup. Lenalidomide did show a significant PFS benefit in the high-risk subgroup, with a 3-year PFS of 91% compared to 66% for the observation arm, though without an improvement in median

overall survival[22].

The phase III AQUILA trial studied high-risk SMM. The protocol randomized patients to three years of the anti-CD38 monoclonal antibody daratumumab or active monitoring. With a median follow-up of 65.2 months, PFS was significantly higher with daratumumab than with active monitoring [hazard ratio (HR) 0.49; 95%confidence interval (CI), 0.36 to 0.67; $P < 0.001$]. Five-year overall survival was 93.0% for the daratumumab arm compared to 86.9% in the control arm, although no *P*-value was reported for Overall Survival (OS). Furthermore, post-protocol first-line therapy in the control arm included anti-CD38 therapy in only 35%, raising the question of whether overall survival would have been similar if a higher proportion of patients in the control arm received an anti-CD38 regimen at the time of future progression[23].

MULTIPLE MYELOMA

MM is a monoclonal gammopathy that typically causes clinical manifestations, classically including osteolytic lesions, renal dysfunction, anemia, and hypercalcemia. The revised IMWG definition requires ≥ 10% clonal plasma cells in bone marrow or a biopsy of a plasmacytoma, in combination with end-organ damage due to the gammopathy, or a biomarker of malignancy including either clonal plasma cell bone marrow percentage ≥ 60%, serum free light chain ratio of ≥ 100, or at least one pathologic bone lesion on magnetic resonance imaging (MRI).

Once a diagnosis of MM is confirmed, patients are risk-stratified, most commonly using cytogenetics, beta-2 microglobulin, lactate dehydrogenase (LDH), and presence of extramedullary disease or plasma cell leukemia. While MM remains incurable, the majority of patients in modern first-line clinical trials achieve overall survival greater than five years. An analysis of 1,000 patients treated in first line with the combination lenalidomide, bortezomib, and dexamethasone between 2007 and 2016 experienced a median overall survival of 126.6 months[24].

The therapeutic landscape of frontline and relapsed and refractory MM has rapidly expanded and evolved over the prior decade, and a detailed discussion of each treatment regimen is beyond the scope of this article. Per mSMART guidelines, a four-drug regimen is recommended for all transplant eligible patients, including an anti-CD38 monoclonal antibody, lenalidomide, bortezomib, and dexamethasone. For transplant ineligible patients, similar four-drug regimens are recommended, except for frail patients, for whom three- or two-drug regimen is advised.

Despite very high overall response rates and durability of response of conventional triplet and quadruplet regimens, these therapies are not considered curative. Goals of therapy are to reverse end-organ damage and to improve symptoms, quality of life, and overall survival. In the United States, the combination of bortezomib, lenalidomide, and dexamethasone served as a standard of care for several years prior to the advent of four-drug regimens. When compared against the doublet regimen of lenalidomide and dexamethasone in a phase III clinical trial, the triplet improved overall survival (median not reached versus 69 months, HR 0.71, 95%CI 0.54-0.93), albeit with higher toxicity including peripheral neuropathy[25]. Most four-drug regimens incorporating the addition of an anti-CD38 monoclonal antibody improve overall response rate, depth of response, and PFS, but have not yet consistently demonstrated improved overall survival.

In the first relapse setting, therapies from the same therapeutic classes as first-line treatment are used, depending on whether a patient is considered refractory to lenalidomide or anti-CD38 monoclonal antibody therapies. Patients who are refractory to lenalidomide or bortezomib may have disease that

responds to pomalidomide or carfilzomib, respectively[26].

There are multiple novel Food and Drug Administration (FDA)-approved regimens in the second- and later-relapse setting. For patients who are refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 monoclonal antibody, the development and approval of B-cell maturation antigen (BCMA) directed therapies have offered improved response rates and median durations of response compared to previous later line regimens. BCMA is selectively and widely expressed on plasma cells.

Idecabtagene vicleucel (Ide-cel) and ciltacabtagene autoleucel (cilta-cel) are chimeric antigen receptor (CAR)-T cell products with regulatory approval in this setting, with data in randomized phase 3 trials demonstrating improved PFS compared to standard approved therapies. Ide-cel demonstrated a median PFS of 13.8 months versus 4.4 months for standard therapy (HR 0.49, 95%CI 0.38-0.65, $P < 0.001$)[27]. Cilta-cel demonstrated a median PFS that was not reached, versus 11.8 months in the standard of care group (HR 0.26, 95%CI 0.18-0.38, $P < 0.001$)[28].

BCMA-directed CAR-T cell therapies are distinguished from other MM therapies by virtue of being administered as a single treatment, rather than on an ongoing, indefinite basis. Further, the toxicity profile is notable for neurologic toxicity and cytokine release syndrome (CRS). CRS is characterized by an inflammatory response, featuring fever, hypotension, and potential for life threatening multiorgan failure. While CRS occurs in most patients, 88% in the KarMMa-3 trial utilizing ide-cel, grade 3 and higher CRS occurred in just 5%[27].

Elranatamab and teclistamab are bispecific monoclonal antibodies specific to both BCMA and CD3 T-cells. Both have regulatory approval in the United States for patients who have received four or more lines of prior therapy including a proteasome inhibitor, immunomodulatory agent, and an anti-CD38 monoclonal antibody. Overall response rates for teclistamab and Elranatamab were 63% and 61%, respectively, in single-arm phase 2 trials. Similar to CAR-T therapy, CRS and neurologic toxicity are common, though grade 3 and higher adverse events of this nature were seen less frequently than described in BCMA-directed CAR-T studies[29,30].

Minimal residual disease (MRD) assessment has emerged as an endpoint in clinical trials and may potentially serve as a future tool in routine clinical practice to help tailor treatment of patients with MM. The revised IMWG response criteria include MRD negativity as a measure of response, in addition to standard response criteria; however, National Comprehensive Cancer Network Guidelines do not yet specifically endorse its use in guiding management[31].

MANAGEMENT IN RELATION TO GD1

While case reports and animal data suggest the possibility of altering the course of a monoclonal gammopathy with GD1 directed therapy, it is not yet known whether any specific GD1 therapy reduces the risk of developing a monoclonal gammopathy[32]. Furthermore, once SMM or MM develops, selection of SMM or MM therapy is generally not altered in a patient with GD1 compared to an unaffected patient. Currently, the only GD1-specific recommendation is screening for monoclonal gammopathy[33]. By contrast, in the general population, screening for gammopathy is not recommended.

CONCLUSION

The spectrum of monoclonal gammopathies, ranging from MGUS to MM, presents several challenges: optimizing risk stratification, deciding when to intervene and with which regimen in SMM, and sequencing

the multitude of novel therapies to maintain quality of life and long-term survival in MM. The proliferation of novel targeted therapies in MM has expanded the boundaries of success in patients refractory to existing therapies, but these therapies carry unique logistical and toxicity challenges. With improvements in GD1 therapy to prevent classic Gaucher manifestations such as splenomegaly and bone disease, more focus will turn to other disorders that patients are at risk for in middle and older age.

DECLARATIONS

Authors' contributions

Abstract, management of monoclonal gammopathies, MGUS, SMM, MM, Management in relation to GD1, conclusion: Lorber J

Gaucher disease and malignancy, incidence of MGUS and malignancies: Rosenbloom BE

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