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Akinori Uruha, MD, PhD

Université Pierre et Marie Curie, Paris VI (UPMC), Institut National de la Santé et de la Recherche Médicale (INSERM), Unité Mixte de Recherche (UMR) 974, Centre de Recherche en Myologie, Institut de Myologie, Groupe Hospitalier Pitié-Salpêtrière (GHPS), Paris, France

Olivier Benveniste, MD, PhD

Département de Médecine Interne et Immunologie Clinique, UPMC, Assistance Publique - Hôpitaux de Paris, GHPS, INSERM UMR974, DHU I2B, and Centre de Référence des Pathologies Neuromusculaires Paris Est, Institut de Myologie, Paris, France

Correspondence to Akinori Uruha. 105, boulevard de l'Hôpital, 75013 Paris Cedex 13, France.

Tel : +33 140779684; Fax : +33 140778129; E-mail: a.uruha@gmail.com

Abstract

Purpose of review Sporadic late-onset nemaline myopathy (SLONM) with monoclonal gammopathy of undetermined significance (MGUS) is a rare subacute progressive muscle disease. The prognosis is poor due to severe respiratory insufficiency. Recently, however, autologous stem cell transplantation following high-dose melphalan (HDM-SCT) has been shown to be effective unless there is delay before the treatment. Therefore, early recognition of the disease is important. This review gives an overview of recent advances in SLONM-MGUS, which could help to understand clinical and pathological features and treatment.

Recent findings Efficacy of HDM-SCT has been demonstrated in a long-term observation study. Subsequently, reports from other groups also have supported it. Furthermore, efficacy of chemotherapy toward plasma cell dyscrasia without SCT have been reported as well. A few case reports have suggested the presence of cardiac involvement related to SLONM-MGUS.

Summary SLONM-MGUS is now considered as a treatable disease. Anti-plasma cell dyscrasia therapy is a promising therapeutic option. Meanwhile, the pathomechanic link between muscle degeneration and monoclonal gammopathy remains unclear, and further investigations are warranted.

Keywords

Head drop

Nemaline body

Monoclonal gammopathy of undetermined significance (MGUS)

Autologous stem cell transplantation following high-dose melphalan

Key points

- Sporadic late-onset nemaline myopathy (SLONM) with monoclonal gammopathy of undetermined significance (MGUS) shows subacute progressive muscle weakness with severe respiratory insufficiency.
- Head drop, MGUS and nemaline body are typical signs of SLONM-MGUS.
- Heart failure possibly appears as an extramuscular involvement.
- Anti-plasma cell dyscrasia therapy including autologous stem cell transplantation following high-dose melphalan is effective.

Introduction

In 1963, Shy, et al. originally reported a form of congenital myopathy characterized by the unique cytoplasmic aggregates, which looked like coils of thread or rods, in muscle cells [1]. The aggregate was called as nemaline body (NB) after “nema” meaning thread in Greek, and the disease was named as nemaline myopathy. Currently, nemaline myopathy is regarded as a heterogeneous disease entity. Most of the cases show child-onset and usually chronic progressive course with autosomal recessive or dominant inheritance pattern, and now at least 11 causative genes are identified: *TPM3*, *NEB*, *ACTA1*, *TPM2*, *TNNT1*, *KBTBD13*, *CFN2*, *KLHL40*, *KLHL41*, *LMOD3*, and *MYPN* [2]. Meanwhile, adult-onset form is also occasionally seen. Some of such patients have actually congenital nemaline myopathy, the symptom of which develops insidiously and manifests obviously in the adulthood. Other patients show literally adult-onset and subacute progression without any evidence of inheritance. This form is called as sporadic late-onset nemaline myopathy (SLONM), which was first described by Engel in 1966 [3]. However, yet, SLONM is multifactorial. Concomitant monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma, and human immunodeficiency virus (HIV) infection have been reported in SLONM patients [4-30]. SLONM with HIV infection and that with neither MGUS or HIV appear to be heterogeneous, although SLONM with HIV infection is usually responsive to corticosteroid, intravenous immunoglobulin (IVIg), and plasmapheresis [24, 25, 27, 30]. On the other hand, SLONM with MGUS (SLONM-MGUS) patients show a particular phenotype: severe weakness and atrophy in axial, limb-girdle, and occasionally distal muscles, dysphagia, and respiratory insufficiency, which are often refractory to immunotherapy [4-22]. Of note, respiratory involvement is lethal, and the majority of the patients died within 1 to 5 years from the onset [8]. Because of this poor prognosis, our group has shown that autologous stem cell transplantation following high-dose melphalan (HDM-SCT) can lead to dramatical improvement in the SLONM-MGUS patients [10, 11, 16]. Subsequently, the efficacy of HDM-SCT or chemotherapy to the plasma cell dyscrasia has been demonstrated by other groups as well [13, 15, 17-19]. Hence, today,

regardless of rarity of the disease, the significance of early recognition of SLONM-MGUS is increasing since the disease is lethal but now can be considered treatable. This review gives an overview of clinical and pathological features, treatments, and recent advances of SLONM-MGUS with some discussion of the etiology.

Clinical features

Through our literature search in PubMed until April 2017, we identified 31 SLONM-MGUS patients in 19 articles [4-22]. On review of the cases, the disease usually appears in their late 30s or older (the median of onset age is 47 years old [range: 27 - 78]). Elderly onset (65 years of age or older) is reported in 2 patients [8]. Sex ratio is 1.6 : 1 (19 males versus 12 females). Muscle weakness and atrophy are observed mainly in axial and limb-girdle muscles. Distal and facial muscle weakness, dysphagia, dysarthria, and muscle pain can also be seen in some patients. Head drop is characteristically seen. Head drop or neck muscle weakness is described in more than half of the patients during their clinical course (head drop: 12 patients; neck muscle weakness: 6 patients). Symptoms in neck muscles, including back neck muscle pain, are recorded as an initial manifestation in 9 patients. Head drop or severe neck extensor muscle weakness appearing in the early (ambulant) stage of disease is well known in amyotrophic lateral sclerosis, myasthenia gravis, and several other neuromuscular diseases, but it is infrequent even in those diseases. The relatively frequent occurrence of head drop in SLONM-MGUS may show that it is a clinical feature suggestive of SLONM-MGUS, as Lomen-Hoerth, et al. also advocated [31]. Severe respiratory involvement is also characteristic in SLONM-MGUS. In the report of Chahin, et al., 5 out of 7 patients with MGUS died of respiratory failure within 1 to 5 years if they had no treatment or ineffective therapy [8].

A recent series of case reports have suggested a possibility of cardiac muscle involvement in SLONM-MGUS [19, 20, 22]. In the report of Belhomme, et al., one SLONM-MGUS patient was admitted to the intensive care unit due to acute heart failure after 2 years from the onset of muscle weakness at the age of 55 years [22]. The left ventricular ejection fraction (LVEF) was reduced to 30%, but it recovered to 60% after chemotherapy of bortezomib, cyclophosphamide and dexamethasone, together with selective beta-blockers. In another report, a 37-year-old patient was pointed out to have left ventricular systolic dysfunction due to diffuse hypokinesia within 2 years after the onset of muscle weakness [20]. Subsequently, severe congestive heart failure with

20% of LVEF appeared, and three cardiac arrests due to ventricular tachycardia and fibrillation occurred, requiring intensive care and an implantable cardioverter defibrillator. Although response to anti-plasma cell dyscrasia therapy is not mentioned, the report has described that his heart condition was controlled by ivabradine, a sinus node I_f channel inhibitor, with the rehabilitation program. In the other article, an asymptomatic left ventricular systolic dysfunction with a moderate reduction of LVEF to 42% was detected in a 44-year-old patient 5 years after the onset of muscle weakness, although response to the HDM-SCT is not mentioned [19]. These 3 cases showing cardiac abnormality developed 2-5 years after the onset of SLONM-MGUS may imply the presence of cardiomyopathy as an extramuscular manifestation. The case with improvement after anti-plasma cell dyscrasia therapy is especially suggestive. However, only anecdotal evidence from a limited number of patients is available at present. Also, there has been no pathological evidence, such as NB in cardiac muscle cells, yet. Further investigation is necessary to solidly demonstrate cardiac muscle involvement in SLONM-MGUS.

As a concurrent autoimmune disorder, vitiligo that developed 2-year prior to the onset was reported in one patient, although the actual association remains unknown [14]. The patient showed significant improvement in muscle strength by monthly IVIg, although the response of immunotherapy toward the skin lesions was not mentioned.

Serum creatine kinase levels are within, or occasionally lower than, normal range in almost all patients. About MGUS, both types of free light chain predominance (κ and λ) are described (17 : 12. Two different M proteins, IgG-κ and -λ, were simultaneously present in one patient [biclonal gammopathy] [12]. Not available in one patient). Correlation of the predominant light chain type and serum M protein levels with clinical course and severity is not well known. However, the re-increase of the serum M protein levels after HDM-SCT appears to be associated with the relapse [16]. One patient was described as having multiple myeloma, not MGUS, as her bone marrow aspiration showed clonal plasma cells occupied 20% of the cells [18].

Screening for monoclonal immunoglobulin had been performed conventionally by means of protein electrophoresis and immunofixation. However, in the early 2000s, the serum free light chain (FLC) assay was developed [32, 33]. This technology is based on immunonephelometry using specific antibodies that react with the epitopes which are hidden when bound to a heavy chain but exposed when not associated with it [32, 33]. Some studies demonstrated that serum FLC assay in combination with serum protein electrophoresis and immunofixation could detect light chains more sensitively than the respective assay alone. Therefore, currently, the combination of the assays is recommended for screening of monoclonal gammopathy [33, 34]. When a patient is suspected to have SLONM, measurement with the combination of the assays may lead to avoid overlooking MGUS.

In muscle magnetic resonance images, patchy high intensity on T2-weighted images or short-tau inversion recovery images, which can reflect edematous change and is often observed in inflammatory myopathies, was reported, although only few reports described the images precisely [14, 21].

Electromyography shows myopathic changes with abnormal spontaneous activity at rest in almost all cases when the results of the test were described. This pattern is observed commonly in inflammatory myopathies, albeit not disease-specific [35].

Muscle pathology

The main pathologic feature is NB in myofibers [**Figure 1a**]. The size of NB is smaller than 1 μm [8] and than NB seen in congenital nemaline myopathy; NB in SLONM-MGUS looks like “sand” rather than nema (thread) on light microscopy. NB often occupy the whole sections of atrophic fibers. When NB are seen in myofibers with larger diameter, they are accumulated in the central portion. Proportion of myofibers bearing NB is variable among patients and among different muscle samples of the same patient in whom more than one muscles were biopsied [8]. Repeated muscle biopsy or re-assessment is sometimes required to detect NB [12, 14-16, 21, 22]. To observe NB, modified Gomori trichrome stain is useful. NB are visualized as fine cytoplasmic aggregates with dark to reddish purple color on the staining. On hematoxylin and eosin stain, NB seem mere basophilic areas and will be difficult to detect [8, 11, 12, 15, 22]. Observation of trichromatically stained frozen sections with higher magnification is recommended. NB are positively stained on immunohistochemistry for Z-band proteins such as alpha-actinin and myotilin because NB are derived from degenerated Z bands. On electron microscopy, NB are morphologically confirmed by the high electron density similar to Z bands and the presence of internal lattice-like structure [**Figure 1b, c**]. The ultrastructural observation contributes to distinguish from other cytoplasmic aggregates such as cytoplasmic body and spheroid body. Intranuclear rods, which are known to be associated with severe-infantile form of nemaline myopathy with *ACTA1* mutation and relatively mild form with *MYPN* mutation, has been rarely reported [2, 4, 8, 36]. It should be noted that NB per se is not specific although its presence is a mandatory finding of nemaline myopathies. NB can be observed also in idiopathic inflammatory myopathies, alcoholic myopathy, advanced stage of muscular dystrophies, hypothyroidism, cancer invasion, and chronic neuropathy like spinal muscular atrophy [37-42]. Empirically, a small number of fibers with NB can be seen physiologically if the muscle is biopsied near tendon.

In congenital nemaline myopathy, bimodal distribution of fiber size, type 1 fiber predominance and atrophy, and type 2B fiber deficiency are observed. Also in SLONM-MGUS,

type 1 fiber predominance and / or atrophy was reported in some cases, requiring attention in terms of differential diagnosis from adult-onset congenital nemaline myopathy [5-8, 20, 21]. Although there is limited data on type 2B fiber deficiency, lack of type 2B fiber deficiency may be a pathologic differential point to distinguish both conditions [21].

Necrotic or regenerating fibers are not seen, or rare if present, unlike muscular dystrophy and immune-mediated necrotizing myopathy. There is no significant endomysial lymphocyte infiltration as seen in polymyositis and inclusion body myositis. Expression of major histocompatibility complex (MHC) class I is not observed, or detected only on sarcolemma, immunohistochemically. Chahin, et al. mentioned that, in their experience, the biopsy findings of SLONM-MGUS were similar to HIV-associated nemaline myopathy [8].

Immunoreactivity for light chains on muscle tissues, mainly sarcolemma, was reported in 4 patients, while amyloid deposition was not observed [6, 7, 15, 16] Based on the facts, Doppler, et al. inferred that SLONM-MGUS was a continuum of light-chain deposition disease (LCDD). LCDD is a rare disease characterized by deposition of monoclonal immunoglobulin light chains (commonly κ type) on multiple organs (mainly kidney, liver, and heart) [43-46]. The deposits are not stained with Congo-red stain and do not exhibit a fibrillar structure like amyloid but a fine granular appearance on electron microscopy [47, 48]. Their thought is consistent with the fact that light chain deposition was observed on skeletal muscles. However, the difference of affected organs / tissues between LCDD and SLONM-MGUS will have to be considered; LCDD is a multiple organ disease, but, in contrast, SLONM-MGUS affects exclusively muscles (skeletal and possibly cardiac). This selectivity may rather imply the implication of autoimmunity in the pathogenesis.

Treatment

During the decade, our group has shown the efficacy of HDM-SCT in SLONM-MGUS [**Figure 2**] [10, 11, 16]. HDM-SCT has been established as the treatment for plasma cell dyscrasia including amyloid light chain (AL) amyloidosis and POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy / edema, M protein, Skin abnormalities; Crow-Fukase syndrome). Considering the similarity to the etiology of SLONM-MGUS and its severity and rapid progression, HDM-SCT was tried [10, 11]. Since the initial reports in 2008, there have been reports of 11 patients receiving HDM-SCT from several different groups [10, 11, 13, 15-17, 19]. Favorable response is observed in 10 out of the 11 patients. Long-standing improvement in muscle strength were observed in most of the patients, although second HDM-SCT and additional anti-plasma cell chemotherapy (lenalidomide, bortezomib, cyclophosphamide, and dexamethasone) were added in 5 patients [15, 16]. The increase of the serum M protein levels preceded clinical deterioration in the 2 patients who required second HDM-SCT [16]. Monitoring of M protein levels may be helpful for follow-up of patients. Disappearance of NB were confirmed when muscle biopsy was performed after the treatment [10, 11]. Age at onset of muscle weakness, severity of muscle weakness before HDM-SCT, the level and type of M protein, and results of bone marrow aspiration before the transplantation did not correlate with the clinical response [16]. One patient died of *Salmonella typhi* septicemia 5 months after the treatment, despite significant improvement in muscle strength [19]. The only one patient who showed neither a clinical nor hematologic response to the HDM-SCT received additional chemotherapy, but later she died [16]. The factors of unfavorable outcome in the patient were considered as a long disease course before HDM-SCT (11 years) and a poor hematologic response to the treatments.

The mortality rates within 100 days after HDM-SCT were reported to be 1.9% in multiple myeloma and 13 - 24% in AL amyloidosis [49, 50]. The mortality might be influenced by involved organs. A large population study, enrolling 701 consecutive patients with AL amyloidosis, revealed that the survival of the participants treated by HDM-SCT was adversely affected by the presence

of cardiac involvement [50]. The same study also reported that there was no difference in the survival of the participants aged over 65 years compared to younger participants (eligible patients up to age 80 years were treated in the study) [50], although a prior study of another group had suggested that patients 65 years of age or older should not be considered for the treatment [51]. In SLONM-MGUS, as described early, cardiac muscle involvement is possible, and elderly patients can also be encountered [8, 19, 20, 22]. In such cases, indication of HDM-SCT should be considered more carefully. Recently, some chemotherapies without SCT for multiple myeloma have been developed [52]. In patients with risk, such therapies might be an option. Belhomme, et al. reported that a patient with cardiac failure possibly related to MGUS received a chemotherapy without SCT (four cycle of the bortezomib-cyclophosphamide-dexamethasone) and showed a significant improvement in motricity and cardiac function [22]. Montagnese, et al. also described a patient with one cycle of lenalidomide-dexamethasone therapy showed a significant improvement [18]. Furthermore, in the report of Doppler, et al., bortezomib with dexamethasone ± cyclophosphamide was effective toward relapse after HDM-SCT [15]. These cases suggest a possible efficacy of anti-plasma cell dyscrasia therapy without SCT in SLONM-MGUS.

Immunotherapy and plasmapheresis without or before any anti-plasma cell dyscrasia therapy were done in 17 patients [4-8, 11, 12, 14, 16, 17, 21, 22]. The outcomes are summarized in **Table**. Among immunotherapies, IVIg alone or in a combination with other immunotherapies seems relatively hopeful; it showed favorable responses in 6 out of 9 patients (significant improvement in 3 [14, 21], modest improvement in 1 [12], and inhibition of progression in 2 [8, 21]). There is one report showing a patient whose muscle strength improved and remained stable with methylprednisolone and azathioprine [7], but, collectively, corticosteroid alone or with immunosuppressants would not be promising [4-6, 8, 11, 12, 21].

Considering the increase of serum M protein levels preceding the relapse after HDM-SCT, SLONM-MGUS may be classified as a disease associated with toxic M proteins, like POEMS syndrome [16]. In POEMS syndrome, not the deposition of the monoclonal

immunoglobulins in affected tissues but the antibody activity toward autoantigens, which is possibly augmented by other humoral mediators such as VEGF, is considered causative [53]. POEMS syndrome and other related disorders show a similar response to HDM-SCT as observed in the SLONM-MGUS patients. Yet, the exact role of the M proteins in SLONM-MGUS remains unknown. Albeit lack of consistency of efficacy, the presence of patients showing favorable responses to immunotherapies including IVIg may provide indirect evidence that SLONM-MGUS has a dysimmune etiology.

Conclusion

SLONM-MGUS is a severe, lethal disease, but today it is considered as a treatable disease. There are 3 typical features of SLONM-MGUS in clinical, serological, and pathological aspects: head drop, MGUS, and NB. Although each of them is not a specific finding, their combination is a hallmark of the disease. Anti-plasma cell dyscrasia therapy such as HDM-SCT is beneficial for SLONM-MGUS patients.

At present, the pathomechanic link between muscle degeneration and monoclonal gammopathy remains unclear. Further investigation is necessary and the better understanding of the pathogenesis will lead to development of more effective and safer therapy.

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Conflicts of interest A. Uruha reports grants from The Uehara Memorial Foundation and from Japan Foundation for Neuroscience and Mental Health.

Figure Legend

Figure 1 (a) Nemaline bodies are observed as fine and reddish purple aggregates in cytoplasm on modified Gomori trichrome stain. Frozen biopsied skeletal muscle of a SLONM-MGUS patient. (b) On electron microscopy, nemaline bodies show high electron density. (c) The structure is lattice-like. Longitudinal section.

Figure 2 (a, b) The SLONM-MGUS patient could not raise her arms above her shoulders or walk without assistance before treatment of HDM-SCT. (c, d) After the treatment, the patient could raise her arms above her arms and walk independently.

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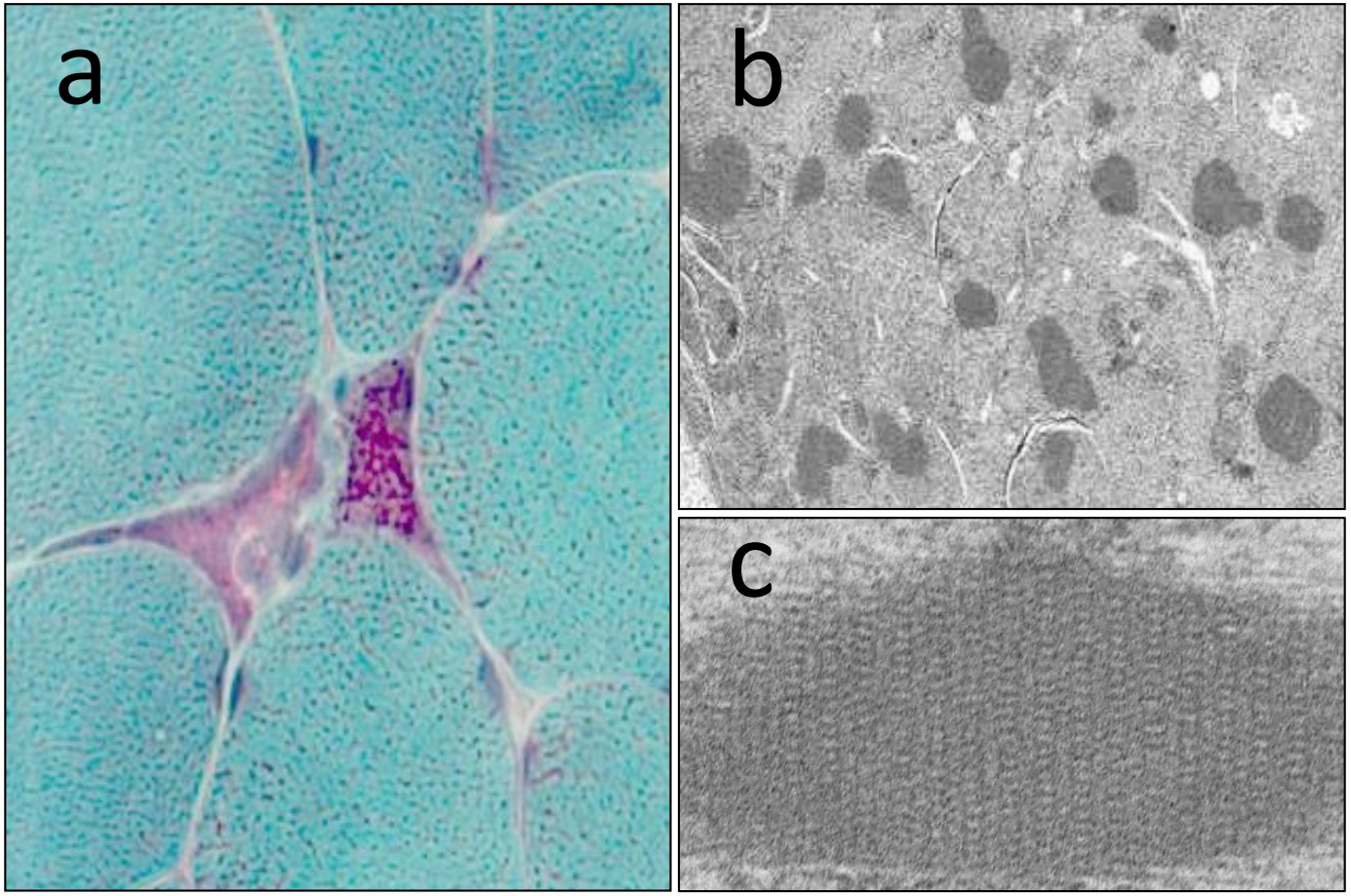
Table. Outcome of therapy.

		Effective	Partially effective	Poor	Total	Reference
HDM-SCT ± additional chemotherapy		10	-	1	11	10, 11, 13, 15-17, 19
Without / before HDM-SCT	Chemotherapy	2	-	-	2	18, 22
	IVIg ± CS / IS	3	2	2	7	8, 12, 14, 17, 21, 22
	IVIg + PP + CS + IS	-	1	1	2	16, 21
	PP ± CS	-	1	3	4	6, 7, 16, 21
	CS ± IS	1	2	7	10	4-8, 11, 12, 21

Effective: significant clinical improvement in muscle strength. Partially effective: slight improvement in muscle strength or no improvement but inhibition of disease progression. Poor: neither improvement nor inhibition of disease progression. HDM-SCT: autologous stem cell transplantation following high-dose melphalan. Chemotherapy: anti-plasma cell dyscrasia agents including lenalidomide and bortezomib, with dexamethasone and cyclophosphamide. IVIg: intravenous immunoglobulin. CS: corticosteroid. IS: immunosuppressant agents. PP:plasmapheresis.


a
b
c


a
b
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d