How I treat monoclonal gammopathy of renal significance (MGRS)

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Recently, the term monoclonal gammopathy of renal significance (MGRS) was introduced to distinguish monoclonal gammopathies that result in the development of kidney disease from those that are benign. By definition, patients with MGRS have B-cell clones that do not meet the definition of multiple myeloma or lymphoma. Nevertheless, these clones produce monoclonal proteins that are capable of injuring the kidney resulting in permanent damage. Except for immunoglobulin light chain amyloidosis with heart involvement in which death can be rapid, treatment of MGRS is often indicated more to preserve kidney function and prevent recurrence after kidney transplantation rather than the prolongation of life. Clinical trials are rare for MGRS-related kidney diseases, except in immunoglobulin light chain amyloidosis. Treatment recommendations are therefore based on the clinical data obtained from treatment of the clonal disorder in its malignant state. The establishment of these treatment recommendations is important until data can be obtained by clinical trials of MGRS-related kidney diseases. (*Blood*. 2013;122(22):3583-3590)

Introduction

Monoclonal gammopathy of renal significance (MGRS) is defined by the causal relationship between a small B-cell clone and renal disease, usually through deposition of the secreted monoclonal immunoglobulin (MIg) or a fragment thereof.[1] The spectrum of MGRS is evolving, with the recent description of novel entities. With the exception of immunoglobulin light chain (AL) amyloidosis, few studies have focused on therapeutic issues. The International Kidney and Monoclonal Gammopathy Research Group initiated a collaborative effort aimed at delineating treatment strategies.

What is MGRS?

The B-cell clone corresponds to the definition of a dangerous small B-cell clone, suggesting that its deleterious consequences are not directly related to cellular proliferation but to other mechanisms, such as MIg deposition.[2] Accordingly, myeloma cast nephropathy, which almost invariably complicates high tumor mass myeloma, should not be included in MGRS. Most MGRS are due to deposition of the MIg fragment with distinct localization and pattern of ultrastructural organization. This results in glomerulopathies with organized deposits, either fibrillar (AL, immunoglobulin heavy chain [AH] and immunoglobulin light and heavy chain [ALH] amyloidosis), microtubular (type I and type II cryoglobulinemias, immunotactoid glomerulopathy [ITG]), or nonorganized deposits (Randall type monoclonal immunoglobulin deposition disease [MIDD] and non-Randall type proliferative glomerulonephritis with monoclonal immunoglobulin deposits [PGNMID]). MGRS also includes tubular disorders such as Fanconi syndrome (FS).[3,4] Nonamyloid fibrillary glomerulonephritis should not be considered as MGRS because it is nearly always characterized by polyclonal IgG deposits without a detectable clonal B-cell disorder.[5,6] In MGRS, deposits of different ultrastructural patterns derived from the same MIg can occur. For instance, fibrillar AL and amorphous Randall-type deposits can coexist in the same patient.[7] In most cases, the overall survival of patients with MGRS is significantly better than that of multiple myeloma, but the renal outcomes are not.[1] The exception is patients with AL amyloidosis, particularly those with cardiac involvement in which death can occur rapidly.[8] Many patients who develop end-stage renal disease (ESRD) are often not considered for kidney transplantation due to their high rate of recurrence.

In a patient in whom MGRS is suspected, it is essential to assess the characteristics of monoclonal gammopathy, particularly its isotype and whether it corresponds to an overt lymphoid and/or plasmacytic disorder, and to assess the type of nephropathy and its impact on renal function. In addition, it is mandatory to carefully search for extrarenal manifestations. To accurately characterize the renal disease, a kidney biopsy with detailed immunofluorescence (IF) and electron microscopic (EM) studies to identify deposit composition and pattern of organization is needed in most cases. The one exception is AL amyloidosis, which can be diagnosed if AL deposits can be demonstrated in other tissues such as fat.

Which therapeutic options?

Treatment of the B-cell clone

To date, no strategy is available to inhibit MIg tissue deposition or to directly clear the already deposited material. Innovative strategies

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that are currently in early clinical testing include small molecule weight inhibitors of serum amyloid P protein and monoclonal antibody against neoepitope on ALs.[9] Thus, targeting the underlying B-cell clone with chemotherapy, although it is not an evidently malignant clone per se, is the only available therapeutic option for MGRS.

The choice of chemotherapeutic agents should take into account their renal metabolism and potential renal and extrarenal toxicity. For alkylating agents, cyclophosphamide is preferred to melphalan due to its lower toxicity in patients with reduced kidney function.[10] Similarly, within the immunomodulatory drug class, thalidomide may be more appropriate than lenalidomide because the latter is, in part, cleared renally and may also sometimes worsen renal function in certain disease states notably in AL amyloidosis.[11,12] In contrast, bortezomib can be used without dose adjustment with a good tolerance profile, including in the setting of ESRD.[13-15] The risk of peripheral neuropathy remains a concern, but has been shown to be reduced by weekly administration and the use of the subcutaneous route of administration in patients with myeloma.[16] Bendamustine, which has been proposed for the treatment of various lymphoid disorders, has also a predominantly nonrenal metabolism and can be given to patients with ESRD.[17,18] Among nucleoside analogs, fludarabine requires dose adaptation and should be avoided in patients with renal failure.[19] The use of rituximab and other anti-CD20 monoclonal antibodies raises no concerns in patients with renal impairment, including ESRD.[20,21]

High-dose melphalan (HDM) supported by autologous peripheral blood stem cell transplantation (ASCT) may be a therapeutic option in some patients. It is essential to collect stem cells early in the course of the treatment, avoiding excessive prior use of drugs with potential stem cell damage, such as melphalan and lenalidomide. HDM/ASCT is feasible in multiple myeloma (MM) patients with renal failure, even requiring dialysis.[22-24] However, mortality and morbidity, including the risk of worsening renal function, increases with the severity of renal impairment.[25-27] Melphalan dose should be adjusted in patients with chronic kidney disease (CKD) stage 3 or above, and risk/benefit ratio should be carefully evaluated in each case.

The underlying plasma cell clone responsible for MGRS may manifest as a solitary plasmacytoma. Although this situation is rare, it has key therapeutic implications. Local radiotherapy may result in a complete and sustained control of the MIg production and, consequently, of its renal consequences.[28] The initial work-up of MGRS should include a complete skeletal survey using conventional radiographs, and magnetic resonance imaging or positron emission tomography scan may be required for imaging suspected mass lesions or a solitary plasmacytoma.

In MGRS, assessment of hematological response is crucial. It depends on the evaluation of the MIg component that is responsible for renal lesions. In AL amyloidosis, measurement of serum free light chain (FLC) provides an essential tool. Current response criteria in AL amyloidosis distinguishes complete response (normal FLC ratio and negative serum and urine immunofixation), very good partial response (difference between involved and uninvolved FLCs <40 mg/L), partial response (difference between involved and uninvolved FLCs decrease $>50\%$), and no response.[29] The use of the same criteria in all types of MGRS due to the deposition of monoclonal light chain (LC), particularly light chain deposition disease (LCDD) and FS is logical. In MGRS involving an intact MIg, the criteria recommended in MM should be applied.[30] When the causal MIg is not detectable or difficult to measure, evaluating the cellular response, usually by repeated bone marrow examination, is the only way to assess the hematologic efficacy of treatment. In all cases, renal (and extrarenal, if present) response should be regularly monitored, bearing in mind that it is usually delayed and depends on the quality of the hematologic response.[31] Whether new molecular or cytometric techniques are useful to detect residual disease and impact outcomes deserves further investigation.[32]

In all MGRS subtypes, evidence for relapse of the underlying clonal disease should prompt the clinician to reinitiate therapy based on criteria similar to the ones applied for the initiation of primary therapy. Treatment choice should take into account characteristics of the first response, toxicity of prior therapies, general status, and renal function.

Treatment of renal disease

MGRS should be monitored according to usual best practices including, for example, thrombotic and infectious risk prevention in case of nephrotic syndrome. Except in AL amyloidosis, hypertension and proteinuria should be controlled, preferably using blockers of the renin-angiotensin system. In patients with FS, bicarbonate, phosphate, and vitamin D supplementation should be given to prevent osteomalacia.[33] For AL amyloidosis, introduction of an angiotensin-converting enzyme inhibitor and angiotensin receptor blocker should only be considered in patients who are hypertensive given these patients' tendency toward orthostatic hypotension.

MGRS should not be considered as a contraindication to renal transplantation because the risk of patients dying from their clone is low. However, there are no data to suggest that small B-cell clones are truly curable, thus the risk of disease recurrence does expose the graft to risk of failure. This can occur after a variable delay depending on each type of renal disease. Recurrence of AL amyloidosis usually slowly impacts graft function, whereas graft loss rapidly occurs in most patients with PGNMID.[34-39] Reducing the level of the MIg by obtaining the best hematologic response is a critical issue in allograft survival. Although this ideally means stringent complete response, a renal transplant may be considered in patients who are not in hematologic complete response and have no cardiac involvement.[30,40] This must be discussed in each individual case, particularly taking into account the estimated time before the expected deterioration of renal function that could likely be irreversible. During posttransplant follow-up, careful surveillance of MIg parameters is mandatory. Reintroduction of therapy should be considered upon progression of the clonal disorder. Thus, the decision for renal transplantation should be taken considering the underlying MGRS characteristics, initial therapeutic response, presence of extrarenal manifestations, and the patient's status.[38] The risk of graft loss, its link with the B-cell clone and the potential need for reintroduction of chemotherapy should be clearly explained to the recipient (and to the donor, if a living donor transplantation is considered).

AL (AH and ALH) amyloidosis

AL (AH and ALH) amyloidosis is usually associated with a low-grade plasma cell clone, most often secreting λ LC. The amyloid in AL is composed of monoclonal ALs, whereas it is composed of monoclonal AHs in AH, and ALH contains the entire immunoglobulin. Renal involvement is present in approximately 70% to 80% of patients and extrarenal manifestations are frequent.[41-43] Approximately 75% of all AL patients present with proteinuria and 36% are in the nephrotic range. Elevated creatinine is noted in more

than half the patients. Because the kidney is not an important contributor to early mortality in these patients, the type of treatment used is guided by the degree of cardiac involvement, as assessed by cardiac biomarkers. At the start of the 21st century, patients were now classified according to Mayo Clinic criteria as stage I, II, or III, depending on whether the N-terminal prohormone of brain natriuretic peptide and troponin T levels are both low (<332 ng/L and 0.035 μg/L), are high for only 1 level, or are both high, respectively.[29,44] More recently, the level of immunoglobulin FLC was added to the criteria with minor modifications of cut-points and inclusion of FLC burden.[45] Achieving the best and most durable hematologic response is the goal of therapy and must be adapted to patients who are often very fragile. The more severe the cardiac disease, the quicker response should be obtained. Because direct myocardial toxicity of amyloidogenic LC has been documented, rapid suppression of involved FLC is an important prognostic factor, particularly in patients with stage III cardiac disease.[29,44,46-48]

Current recommendations can be summarized as follows:

- In patients with stage I and II disease, first line treatment should be based on melphalan + dexamethasone (M-Dex). It is likely that reinforcing this regimen with bortezomib increases hematologic and organ response rate.[49-52] This is currently under investigation through an international phase III trial comparing M-Dex with M-Dex plus bortezomib (clinical trial #NCT01277016). Until the results of this study are available, the current approach is to rapidly introduce bortezomib, after 1 or 2 courses of M-Dex in the absence of a clonal response. In patients with advanced CKD, cyclophosphamide is preferred to melphalan, and regimens such as cyclophosphamide-bortezomib-dexamethasone (CBD, also referred to as CyBorD or VCD) have demonstrated their efficacy.[53,54] Another option is to use thalidomide instead of bortezomib (CTD regimen).[55]
- Patients with stage III cardiac involvement represent a therapeutic challenge because their median survival remains poor. Preliminary encouraging results have been obtained using the CBD regimen, which seems to significantly reduce the early death rate based on small case series.[53,54] In young selected patients, cardiac transplantation can be considered, preferably after hematologic remission has been achieved.[34,36]
- In selected patients (mainly stage I and II disease), HDM/ASCT should be considered, in the absence of overt renal insufficiency and the absence of other advanced organ failure.[56,57]

Randall-type MIDD

In MIDD, as with AL, the monoclonal gammopathy may occasionally be an overt myeloma (>10% bone marrow plasma cells with at least 1 myeloma-defining event); however, in MIDD, the clone more often secretes κ LC. Renal involvement is nearly constant and usually manifests with high-grade proteinuria, hematuria, hypertension, and renal insufficiency. Extrarenal manifestations, particularly cardiac and hepatic, are not uncommon, but are rarely symptomatic. The most frequent form of MIDD is LCDD. IF study of the kidney biopsy is mandatory for the diagnosis, showing typical linear amorphous LC deposits along the tubular basement membranes. Glomerular and vascular deposits are usually associated with a pattern of nodular glomerulosclerosis in two-thirds of patients with LCDD.[58-61] Heavy chain deposition disease and light and heavy chain deposition disease are rare and should be managed similarly as LCDD.[62,63]

As MIDD is rare, controlled studies are lacking and the therapeutic approach is based on consensus opinion. Achieving the best hematologic response appears to be as important as in AL. It may result in regression of MIg tissue deposits, providing that complete and sustained remission has been obtained.[64,65]

Small retrospective series suggested that HDM/ASCT is a good therapeutic option, with high hematologic response rates and low treatment-related mortality. This contrasts with AL amyloidosis in which patients are much more fragile with frequent systemic complications that increase treatment-related mortality.[64-71] Data regarding HDM/ASCT have been published before the era of novel antimyeloma agents. Preliminary results suggest that bortezomib-based regimens could produce hematologic response rates similar to those obtained with HDM/ASCT, as is the case in MM.[72-77]

Taking into account these points, therapeutic recommendations should be based on the degree of renal impairment:

- In patients with CKD stages 1 to 3, the main goal of treatment is preserving kidney function. The panel recommends the use of a bortezomib-based regimen, such as CBD, as front line. HDM/ASCT should then be considered in selected patients with good performance status and no significant extrarenal manifestations, particularly when they have achieved only partial hematological response to the initial treatment.
- In patients with CKD stages 4 and 5, the probability of renal recovery is low. In patients not eligible for renal transplantation, the main goal of the treatment is preserving extrarenal organs, particularly the heart. The panel recommends a bortezomib-based regimen, such as CBD. If a renal transplantation is planned, the therapeutic goal is the preservation of long-term allograft function, which requires an optimal clonal response.[59,78] Accordingly, HDM/ASCT should be considered after a 3 to 4 cycles of a CBD-like regimen.

Type I cryoglobulinemia

Monoclonal immunoglobulin may precipitate under cold exposure, thus defining cryoglobulinemia. Type I cryoglobulins are composed of a single MIg.[79] A serum rheumatoid factor (RF) is typically not detected and complement abnormalities are not constant. Type I cryoglobulinemia may be asymptomatic or cause cold-triggered ischemic symptoms, predominantly cutaneous (Raynaud's phenomenon).[80] Articular manifestations are mostly observed when the cryoglobulin (usually an IgG3) precipitates as crystals (crystal-cryoglobulinemia).[81,82] Renal manifestations are more common with IgG type I cryoglobulin and less frequent with IgM.[82,83] Cryoglobulinemia typically manifests as chronic glomerular disease with flares characterized by nephritic syndrome, acute renal insufficiency, and severe hypertension. Histologically, the hallmark of the disease is membranoproliferative glomerulonephritis with glomerular thrombi and microtubular deposits made up of the monoclonal cryoglobulin.[82,83]

Type I cryoglobulinemia may be observed in patients who would otherwise be classified as monoclonal gammopathy of undetermined significance (MGUS) based on level of clonal burden, MM, Waldenström's macroglobulinemia (WM) or any other type of B-cell lymphoid disorder secreting an entire MIg.[82-84] Patients should carefully avoid cold exposure and take appropriate protective measures. As data regarding management of this rare condition are scarce, the following recommendations are only guided by the panel experience:

- In patients with few systemic symptoms and a low-grade underlying B-cell proliferation, observation alone is recommended, including

serial assessment of renal parameters, because renal manifestations may occur secondarily.

- In patients with symptomatic and/or progressive systemic disease, particularly in the presence of renal complications, therapy is indicated and should be selected based on the underlying clone:
  1. If it is plasmacytic, usually secreting a monoclonal IgG (or IgA), treatment should rely on antimyeloma agents. In patients with renal failure, bortezomib, cyclophosphamide, and/or thalidomide-based regimens should be used. Rituximab is not indicated. In selected patients, HDM/ASCT may be considered.
  2. If it is lymphoplasmacytic, usually associated with a monoclonal IgM, the treatment should be that of WM, currently based on Rituximab-containing regimens.
  3. If the underlying disease is chronic lymphocytic leukemia (CLL) or a B-cell lymphoma of any type, then the treatment should be adapted accordingly.

In all cases, bendamustine, which is not eliminated by the kidney, is likely to be a good alternative. In patients with acute severe systemic symptoms, complete plasma exchange is indicated in addition to chemotherapy.[82-84]

Type II cryoglobulinemia

Type II mixed cryoglobulins are composed of an MIg, usually an IgM κ with a RF activity, associated with polyclonal immunoglobulin. A serum RF is always detectable and serum complement levels are constantly decreased. Type II cryoglobulinemia is often a silent condition. When symptomatic, vascular purpuric lesions are nearly always present. Other manifestations are usually related to small vessel vasculitis, including arthralgias and/or peripheral neuropathy. Disease flares are common and more often triggered by activity and orthostatism than by cold exposure.[78,79,84] Clinical and pathological renal manifestations are close to that observed in type I cryoglobulinemia. However, IF studies show that glomerular deposits contain both the monoclonal IgM and polyclonal IgG along with complement components.[81]

Most cases are associated with chronic hepatitis C virus (HCV) infection.[85] Other conditions include hepatitis B virus infection and autoimmune disorders, particularly Sjögren's syndrome. In all cases, type II cryoglobulinemia implicates the presence of an underlying B-cell clone most typically a very small clone with less than 10% bone marrow involvement. An overt lymphoid proliferation, usually a WM or a low-grade lymphoma, can be detected initially or may develop during follow-up.[79,86]

The knowledge of whether or not type II cryoglobulinemia is associated with HCV infection is imperative to guide treatment. Accordingly, HCV testing infection should be systematic, including serum HCV RNA detection, and genotyping if present.[85,87]

In the absence of prospective studies, treatment strategy may be summarized as follows:

- Antiviral therapy, usually combining pegylated α interferon and ribavirin should be given to all patients with symptomatic type II cryoglobulinemia associated with chronic HCV infection. Antiviral therapy may be given alone in patients who have only a few symptoms (ie, episodic flares of vasculitic purpura). In those with more symptomatic vasculitis, antiviral therapy should be combined with rituximab. In addition, in patients with rapidly progressive renal disease and/or other severe organ involvement, total plasma exchange should be considered. Importantly because of their remarkable symptomatic efficacy, high-dose steroids should be added in all cases with overt vasculitis. Due to the risk of their side effects, one should avoid long-term administration of steroids if possible.[88,89]
- In those patients with no detectable viral replication, who present with episodic purpuric flares, surveillance only is recommended. In case of recurrent symptoms or of renal involvement, rituximab is the treatment of choice.[90]
- In all patients with overt WM or B-cell lymphoma, chemotherapy should be considered in patients with symptoms more significant than occasional purpura, regardless of their HCV status. The regimen should be defined by taking into account the type of the underlying B-cell clone and the level of renal function (see previously). Rituximab-containing regimens and bendamustine can be used in all levels of renal function.[91]

ITG

ITG, also referred to as glomerulonephritis with organized microtubular monoclonal immunoglobulin deposits is a rare glomerular disease with proteinuria, frequent nephrotic syndrome, hematuria, CKD, and hypertension. Extrarenal manifestations are uncommon. Glomerular lesions are usually characterized by atypical membranous and MPGN patterns. By IF, glomerular deposits are composed of monotypic IgG and complement components. EM, which is required for the diagnosis, shows a typical organization of deposits into microtubules of 10 to 60 nm in diameter, arranged in parallel bundles.[3,5,6,92] Similar microtubular inclusions may be observed in the cytoplasm of the circulating and medullary clonal B-cell population.[3,5]

Importantly, the underlying B-cell lymphoid disorder is a CLL or a small lymphocytic lymphoma in more than half of the cases. A low-grade plasma cell clone is less frequent.[5,92] Accordingly, the initial workup should include a careful search for a clonal B-cell population among peripheral blood and bone marrow lymphocytes, including phenotypic and immunoglobulin gene rearrangement studies.

Although therapeutic choice relies on a few, small case series, a CLL-adapted treatment may be proposed in most patients. In case of severe CKD, cyclophosphamide and/or bendamustine-based regimens, including corticosteroids, may be recommended. The addition of rituximab should be considered in patients with overt CLL. In patients with gammopathy only, the role of rituximab is questionable and bortezomib-based therapy may be considered.[5,92]

PGNMID

PGNMID is a recently described entity that should be distinguished from Randall-type MIDD. Both diseases are featured by glomerular nonorganized MIg deposits. However, in PGNMID, deposits usually consist of an entire MIg (most commonly IgG3κ), with a granular nonlinear appearance by IF and EM, without detectable deposits along tubular basement membranes and around vascular myocytes. Various patterns can be observed, including mesangial, atypical membranous, and membranoproliferative glomerulonephritis. Globally, PGNMID resembles an immune complex-like glomerulonephritis, but with monotypic immunoglobulin deposits, a feature that should draw the pathologist's attention.[93-96]

Extrarenal manifestations are rare and PGNMID appears as a renal limited disorder with prominent glomerular symptoms and frequent CKD. Importantly, sensitive techniques including nephelometric tests for FLCs can detect a serum and urine MIg in approximately one-third of patients only. A monoclonal proliferation of plasma cells in the bone marrow is found in less than 10% of patients.[93-96]

Some authors are reluctant to recommend chemotherapy in PGNMID with no detectable MIg. However, monotypic glomerular deposits are the result of a circulating MIg, which indicates the presence of an underlying B-cell disorder. Consequently, PGNMID almost always recurs after renal transplantation.[37,97]

The panel recommends adapting the therapeutic approach to the severity of renal disease:

- In patients with stages 1 and 2 CKD, proteinuria of less than 1 g/day and no evidence of progressive disease, symptomatic measures only may be advised with careful surveillance. In such cases, occasional spontaneous renal remissions may occur.
- In patients with stages 1 and 2 CKD and high-grade proteinuria (>1 g/day) or progressive disease, and in patients with stages 3 and 4 CKD, chemotherapy is indicated. Cyclophosphamide and bortezomib are the drugs of choice, and a CBD-like regimen is a good option. In some patients aged <65 years, HDM/ASCT may be performed. Preliminary reports suggest a beneficial effect of rituximab, including the effect in patients without a detectable B-cell clone.[90] However, it seems reasonable to propose rituximab only to patients in whom an associated CD-20 positive B-cell clone can be demonstrated.
- In patients with stage 5 CKD who are candidates for renal transplantation, the achievement of a complete hematologic remission is a key goal for patients with a detectable monoclonal gammopathy.[37,97] Thus, HDM/ ASCT should be strongly considered. For those who never had a detectable monoclonal gammopathy or plasma cell clone, there is no consensus regarding their treatment prior to kidney transplant. In contrast, in patients ineligible for renal transplantation, the benefit of chemotherapy is highly questionable and conservative treatment should be recommended.

Acquired FS

Acquired FS is characterized by proximal tubular dysfunction secondary to accumulation of monoclonal κ LCs crystalline inclusions within the endolysosomal compartment of proximal tubular cells. Similar LC inclusions can be detected in the cytoplasm of associated clonal plasma cells. FS typically complicates MGUS or a low-grade MM, which is almost always of the κ class.[4,33,98,99] Few cases have been described in WM.[100] Most patients present with moderate CKD, with unusual hypophosphatemia and hypouricemia, which should prompt the search for other signs of proximal tubule dysfunction, particularly generalized aminoaciduria. Of note, the urine phosphate leak frequently causes osteomalacia and subsequent bone pain that should not be misinterpreted as secondary to myeloma.

Other extrarenal manifestations are absent in typical FS. However, FS may be part of the so-called crystal-storing histiocytosis (CSH), which is characterized by the accumulation of LC crystals, not only in proximal tubular cells, but also in lysosomes of histiocytes of bone marrow. In addition, CSH can involve various tissues, including spleen and lymph nodes, sometimes in the context of systemic symptoms with macrophage activation.[101-102]

Very few series of LC-associated FS have been published, and the efficacy of the so-called novel anti-myeloma agents has not been evaluated. In most cases, FS appears to slowly progress toward ESRD and rarely symptomatic myeloma.[33,98] Accordingly, therapeutic decisions should take into account treatment side effects, particularly the potential risk of secondary myelodysplastic syndrome from alkylating agents.[98]

Symptomatic measures to prevent osteomalacia are mandatory. All patients with an associated overt lymphoid disorder should receive appropriate chemotherapy. For the rare patients with symptomatic CSH, steroids should be considered in addition to chemotherapy.

Otherwise, treatment choices should be adapted to the degree of renal failure:

- In patients with stages 1 to 3 CKD, chemotherapy should be considered to try to slow progression to ESRD. Cyclophosphamide-, bortezomib-, or thalidomide-based regimens are the best options. Bendamustine may also be used. HDM/ASCT may be performed in selected nonresponding patients, although the benefit of this strategy remains to be proven.
- In patients with stages 4 to 5 CKD who are eligible for renal allograft, chemotherapy, including HDM/ASCT, should be considered either prior to and/or after transplantation. In patients who will not be candidates for renal transplantation, there is no benefit to introduce chemotherapy.

Miscellaneous

In addition to kidney deposition of a MIg, other mechanisms may induce renal lesions in MGRS. They may involve the secretion of various biological factors and/or autoantibody activity of the MIg.

The so-called POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, and Skin abnormalities) syndrome can include renal manifestations, usually featured by vascular and glomerular thrombotic microangiopathy including mesangiolysis. These are considered to be due to the secretion of vascular endothelial growth factor by the clonal cells or their environment, which is a hallmark of this syndrome. Whether the causal plasmacytic proliferation is localized or not is the key point for therapeutic decisions.[103]

A novel MGRS entity characterized by glomerulonephritis with isolated glomerular C3 deposits has been recently described. It is associated with a circulating monoclonal IgG, most often with MGUS or indolent MM. Hypocomplementemia secondary to activation of the complement alternative pathway is usual, in the absence of detectable anti-C3 convertase activity (nephritic factor). Autoantibody activity of the MIg against a complement alternative pathway regulatory protein is the main current hypothesis. Because the disease course is rapid, with a high risk of recurrence after renal transplantation, chemotherapy should be given early.[104-105]

Conclusions

Current treatment of MGRS is based on therapies targeting the causal B-cell clone with treatment choices based on extrapolation of treatments used for the equivalent overt malignancy. Therapeutic choices should take into account the renal characteristics of the disease, particularly the risk of CKD progression, the presence and severity of extrarenal manifestations, and the safety profile of antineoplastic drugs in renal impairment. Early diagnosis, when renal function is still preserved, usually facilitates treatment management

and results in better long-term outcome. Because MGRS is a heterogeneous and relatively rare entity, a common effort of both nephrologists and hematologists inside well-designed prospective collaborative studies is required to improve management.

Authorship

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