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REVIEW ARTICLE

Multiple myeloma, gammopathies

European myeloma network recommendations on diagnosis and management of patients with rare plasma cell dyscrasias

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Abstract

The introduction of novel agents in the management of multiple myeloma and related plasma cell dyscrasias has changed our treatment approaches and subsequently the outcome of patients. Due to current advances, the European Myeloma Network updated the diagnostic and therapeutic recommendations for patients with Waldenström's macroglobulinemia (WM), AL-amyloidosis, monoclonal immunoglobulin deposition disease (MIDD), POEMS syndrome, and primary plasma cell leukemia. For patients with WM, the combination of rituximab with chemotherapy remains the treatment cornerstone, while the Bruton-tyrosine kinase inhibitor ibrutinib has been introduced and approved for relapsed/refractory disease. The management of light chain amyloidosis depends on the presence and severity of heart disfunction. If present, intensification with an autologous stem cell transplantation (ASCT) is not recommended. Further aggregation of misfolded light chains could be prevented by doxycycline or monoclonal antibodies targeting amyloid deposits. Initial treatment generally consists of melphalan/dexamethasone or bortezomib-based regimens. For relapsing patients, one can consider proteasome inhibitors, immunomodulatory agents, melphalan or daratumumab. Because intact or light-chain immunoglobulins are also the culprits for MIDD, the small monoclonal plasma cells' clones should be treated and generally respond well to bortezomib-based treatment. POEMS syndrome is a well-defined clinical entity that can present as solitary bone lesions or disseminated disease. Radiation therapy is used for patients with localized disease and result in long-lasting response. Systemic treatment should be proposed to patients with disseminated disease, but regimens that can worsen a pre-existing polyneuropathy should be avoided. PPCL is located at the other end of the spectrum of plasma cell disorders and is associated with an aggressive disease course and poor prognosis. It requires an imminent, multi-phase and novel agents-based therapy, including induction, ASCT, consolidation and maintenance, with short treatment-free intervals. Patients not eligible for transplant procedures require personalized, intensive therapeutic approach. Allogeneic stem cell transplantation can be used in selected patients.

Introduction

Plasma cell dyscrasias (PCD) other than multiple myeloma (MM) can present in different clinical forms, ranging from indolent disease with small clones of monoclonal cells that produce a monoclonal protein which can either be innocent or causes devastating complications to highly aggressive forms characterized by malignant plasma cells that evade the bone marrow (BM) resulting in overt plasma cell leukemia. Waldenström's macroglobulinemia (WM), primary systemic AL-amyloidosis, monoclonal immunoglobulin deposition disease (MIDD), POEMS-syndrome, and primary plasma cell leukemia (PPCL) all belong to the

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spectrum of PCD. Due to the rarity of these disorders most available results regarding potential therapeutic strategies are based on phase 2 studies, case series, and registry data. The aim of this paper of the European Myeloma Network (EMN) is to provide useful recommendations on diagnosis and management of these entities.

Methodology

An interdisciplinary panel of PCD experts on behalf of the EMN reviewed all published randomized and phase II clinical trials, guidelines, meta-analyses, systematic reviews, observational studies, case series, case reports and published registry data on diagnosis and management of these disorders. The research was performed in PubMed and ISI until 28th February 2018. The Grading of Recommendations Assessment Development and Evaluation (GRADE) system was used for the grading of the recommendations (Supplementary Table 1). In the case of limited sufficient data an expert consensus was used to develop recommendations. The paper was circulated among the panel members, initial discussion took place at the 9th EMN Trialist meeting (Baveno, Italy, 25–26 September 2016) and the recommendations were approved by the panel members and the participants of the subsequent Baveno meeting (24–25 September 2017). Subsequently, the manuscript underwent two-round revisions between the panel members.

Waldenstrom's macroglobulinemia

Diagnosis

WM is characterized by clonal lymphoplasmacytic cell BM infiltration and the presence of monoclonal IgM paraprotein [1]. According to the Second International Workshop for WM, diagnostic clinic-pathologic criteria have been established for WM diagnosis based on BM results combined with immunophenotyping studies [2]. Especially immunophenotyping is of great value; the profile for lymphoplasmacytic cells should include the expression of B-cells antigens CD19, CD20, CD22, CD25, CD79, and CD112. Approximately 15% of the patients express CD5 as well, while quite common is the expression of CD10 and CD23. Immunophenotype should also include plasma cell component and expression of CD38, CD138 and light chain restriction needs to be encountered. Expression needs to be encountered [3]. Patients with ≥10% lymphoplasmacytic cell infiltration are considered as WM, otherwise as IgM-MGUS. Criteria for treatment initiation include cytopenias, constitutional symptoms, organomegaly, hyperviscosity, cryoglobulinemia, amyloidosis, hemolytic anemia, cold agglutinin disease, and peripheral neuropathy (Table 1) [2, 4].

Recommendations

To diagnose patients with WM perform BM biopsy and immunophenotyping studies. To evaluate tumor burden and treatment response perform serum immunoelectrophoresis, immunoglobulins measurement, CT scans involving pelvis, abdomen, chest and cervical area, cold agglutin, and cryoglobulins measurements.

Treatment

WM is a rare disease; therefore, treatment options have been adopted mainly from phase 2 studies. Rituximab is an anti-CD20 monoclonal antibody which remains standard of care for most patients and is used alone or in combinations. When used as monotherapy duration of response is 8–11 months in both untreated and relapsed/refractory patients [5, 6]. Although it is well tolerated, approximately 50% of patients may experience an IgM flare (defined as ≥25% increase above baseline serum IgM level), therefore in patients with high IgM levels (greater than 5000 mg/dl), it should either be combined with plasma exchange or avoided until the IgM monoclonal protein has decreased [7]. Ofatumumab is a fully human anti-CD20 antibody targeting another CD20 epitope. As monotherapy, overall response rates (ORRs) reach 59%, therefore in rituximab-intolerant patients, this may represent a potentially therapeutic option [8]. Monoclonal antibodies are active and non-myelosuppressive, thus can be combined with chemotherapy when

Table 1 Indication for treatment initiation in patients with symptomatic WM

Clinical indications for treatment initiation
Recurrent fever, night sweats, weight loss, fatigue
Lymphadenopathy which is either symptomatic or bulky (≥5 cm in maximum diameter)
Hyperviscosity
Symptomatic hepatomegaly and/or splenomegaly
Symptomatic organomegaly and/or organ or tissue infiltration
Peripheral neuropathy due to WM
Laboratory indications for treatment initiation
Symptomatic cryoglobulinemia
Cold agglutinin anemia
Immune hemolytic anemia and/or thrombocytopenia
Amyloidosis related to WM
Nephropathy related to WM
Hemoglobin ≤ 10 g/Dl
Platelet count $< 100 \times 10^9$/L

rapid control is required. The combination of dexamethasone, rituximab, and cyclophosphamide (DRC) was evaluated in a prospective study of 72 untreated WM patients with 83% ORR. The 2-year progression-free survival (PFS) was 67%. Median time to response was 4.1 months, suggesting that the combination is not appropriate for rapid disease control [9]. The combination of rituximab with fludarabine, with or without cyclophosphamide (FCR), is very effective with a median PFS exceeding 50 months [10–12]; however, due to the increased risk of long-lasting cytopenias and secondary primary malignancies (high grade lymphoma, MDS, AML), it is not recommended as first-line treatment except for high-risk patients. Rituximab combined with bendamustine showed 95% ORR with 69.5 months PFS and safer toxicity profile when compared to R-CHOP in a phase 3 trial of indolent non-Hodgkin lymphoma (NHL), including WM [13]. Similar ORR (83%), with median PFS of 13 months, were achieved when administered in 30 WM relapsed/refractory patients [14]. Efficacy and toxicity of bortezomib, dexamethasone, and rituximab (VDR) was evaluated in 59 newly diagnosed patients [15]. The results of this study have been recently updated and the median PFS after 6 years of follow-up was 43 months and the overall survival rate was 68%. Carfilzomib is associated with lower neurotoxicity in MM patients and was recently evaluated in combination with rituximab and dexamethasone, mainly in untreated WM patients [16]. The ORR was 87%, MYD88 or CXCR4 mutation status had no impact, and no grade ≥ 3 neuropathy was observed. However, carfilzomib is currently available only in the United States (US) as an off-label indication for WM.

The role of maintenance still remains unclear. Limited data are available; although rituximab seemed to improve PFS and OS, it resulted in pronounced immunosuppression, therefore it is not recommended in everyday clinical practice [17].

Autologous stem cell transplantation (ASCT) remains an option as salvage therapy in WM, particularly for younger patients with multiple relapses or primary refractory disease; however, data on the role of ASCT in the primary refractory setting and on allogeneic transplantation for these patients are very limited [18].

In a phase 1/2 study with 17 previously untreated patients, lenalidomide maximum tolerated dose was defined as 15 mg and provided 29% ORR, with median time to progression of 16 months and 5-year OS of 91% [19]. The toxicity was mainly hematologic. The combination of pomalidomide, dexamethasone, and rituximab was also explored in treatment-naive WM patients in a dose-escalating phase 1 study [20]: among seven enrolled patients, three (43%) achieved major response. The long-term results of a phase 2 trial with everolimus in 60 relapsed/refractory patients showed 50% PR and median PFS 21 months [21]. Toxicity was quite pronounced including cytopenias and pulmonary toxicity. In a phase 1/2 study of everolimus combined with rituximab, with or without bortezomib, in 46 patients showed a response rate of 89% and median PFS of 21 months [21]. Everolimus is currently available only in the US as an off-label indication.

Ibrutinib, a BTK inhibitor, is very effective in high-risk patients with chronic lymphocytic leukemia (CLL) and mantle-cell lymphoma. The results of a prospective study of ibrutinib in 63 patients with WM who had received at least 1 previous line of treatment were recently reported [22]. Median time to at least minor response was 4 weeks. After a median follow-up of 47.5 months the ORR was 91%, the median PFS has not yet been reached and the 2-year OS was 95%. The main adverse events were neutropenia, thrombocytopenia, post-procedural bleeding, and atrial fibrillation [22, 23]. Most patients were able to continue ibrutinib after cardiologic intervention and/or dose reduction [24]. In patients with preexisting atrial fibrillation that require anticoagulants, alternative treatment options should be considered. MYD88 and CXCR4 mutations might have an impact on ORRs and major responses to ibrutinib: WM patients with wild-type MYD88 had lower ORR rates and shorter duration of response [25]. CXCR4 mutations are related to lower ORRs as well as delayed responses [25]. Testing for MYD88 is recommended for ibrutinib candidates. The EMN-panel agreed that MYD88 and CXCR4 mutation status should be further investigated in order to clarify its impact on treatment outcome and whether any therapeutic decisions can be based on the mutational status. Ibrutinib was also assessed in heavily pretreated and refractory to rituximab patients with an ORR of 90%, an estimated 18-month PFS of 86% and estimated 18-month OS of 97%. Although the number of patients included in this study was quite small (31) it seems that ibrutinib is extremely effective even in this heavily pretreated population [26]. Novel BTK inhibitors (CC-292, ONO-4059, ACP-196, and BGB-3111) are in clinical development and may offer potential future options.

The aim of first-line treatment is therefore to achieve high response rates with prolonged PFS (Tables 2A and 2B). The EMN-panel also agreed that clinical trials with chemotherapy-free combinations, with new compounds alone and/or with anti-CD20 antibodies should be performed. Especially trials in the frontline setting including ibrutinib and BCR inhibitors are needed to assess the efficacy and tolerability. Furthermore, the panel agreed that the role of BCR inhibitors with other compounds as well as with proteasome inhibitors to overcome drug-resistance involved in the two key pathways affected by MYD88 should be further explored in the relapsed/refractory setting. Obinutuzumab, a novel anti-CD20 monoclonal

Table 2A Therapeutic algorithm for patients with newly diagnosed (ND), symptomatic WM

Clinical condition	Treatment recommendation
Cytopenias and/or organomegaly	DRC, Bendamustine-Rituximab (R) or Bortezomib-R
Comorbidities and cytopenias	Rituximab, DRC
High M-protein, transplant candidate	DRC, Bortezomib-R or Bendamustine-R
High M-protein, non-transplant candidate	DRC, Bendamustine-R, Bortezomib-R
Older age, slow progression, poor PS, candidate for oral therapy	DRC, Oral fludarabine
Symptomatic hyperviscosity, cryoglobulinemia or cold agglutinemia	Bortezomib followed by Bortezomib-R, Bendamustine-R, FCR
Paraprotein-related neuropathy	R alone, DRC, FR, Bendamustine-R

DRC dexamethasone, rituximab, cyclophosphamide, *FCR* fludarabine, cyclophosphamide, rituximab, *R* rituximab Bortezomib is not recommended for patients with neuropathy

Table 2B Recommendations on management of ND, symptomatic WM patients

Rituximab monotherapy	Consider for WM patients with immunologic disorders related to WM, or for frail patients unlikely to tolerate chemotherapy. Avoid in patients with high IgM levels
DRC	Active, safe combination, even for elderly patients
Bortezomib-based regimens	Consider for patients with high IgM levels, symptomatic hyperviscosity, cryoglobulinemia or cold agglutinemia, amyloidosis, and renal impairment or in young patients to avoid myelotoxic agents. Consider subcutaneous use and weekly administration to reduce neurotoxicity.
Bendamustine-Rituximab	Well tolerated even in elderly patients. In elderly patients and those with renal impairment, consider dose adjustment of bendamustine. Four cycles seem to be adequate to achieve response.
Carfilzomib-based regimens	Neuropathy-sparing option for proteasome-inhibitor based therapy. Consider possible cardiotoxicity. The optimal dose and schedule of carfilzomib are under investigation. Currently limited data
Ibrutinib	Consider as primary for symptomatic patients not candidates for chemoimmunotherapy. Serum IgM might increase and hemoglobin might decrease, if ibrutinib is stopped and should not be considered as treatment failure
Plasmapheresis	Consider immediately for patients with symptomatic hyperviscosity or prevent flare in patients with high IgM level (typically >4000 mg/dL) before rituximab administration. Always combine with chemoimmunotherapy or targeted therapy

antibody which has shown efficacy in CLL and follicular lymphoma, could be a potential therapeutic agent. CXCR4 antagonists such as plerixafor or ulocuplumab are currently under development and may offer options to extend the activity affected by the CXCR4 mutation.

Recommendations

Rituximab monotherapy can be considered for WM patients with immunologic disorders secondary to WM or for frail patients who are less likely to tolerate chemotherapy (1B). Rituximab should be avoided or withheld, or preemptive plasma exchange should be performed in patients with high IgM levels due to risk of IgM flare.

Chemoimmunotherapy combinations with rituximab, cyclophosphamide, and dexamethasone (1B), benda-R (1B), or bortezomib, rituximab, and dexamethasone (1B) provide durable responses with tolerable toxicity and are recommended in most patients. For high-risk patients or patients with hyperviscosity where rapid control of the disease is required bortezomib, nucleoside analogues-based regimens or bendamustin-based regimens should be preferred, while bortezomib should be avoided in patients with paraprotein-related neuropathy (1B).

For elderly patients, DRC or oral fludarabine should be treatments of choice (1A). Ibrutinib represents an effective option for both treatment-naive and relapsing patients (1B) but is not recommended for patients with $MYD88^{WT}$ disease (1A). In the relapsed/refractory setting and in patients intolerant to rituximab ofatumumab can be considered (1B).

ASCT remains an option for high-risk patients, however the data available are very limited (1B). Everolimus should be considered only for non-responders after multiple lines of therapy (1B). Treatment with any of the available therapeutic agents listed for untreated patients can be considered for previously treated patients requiring therapy (Table 2C).

IMiDs and allogeneic SCT should be used only in the context of clinical trials (1C). Enrollment in clinical trials is highly recommended for patients with WM.

Table 2C Recommendation on management of previously treated WM patients

Ofatumumab	Consider for patients intolerant to rituximab
Nucleoside analogues	For fit WM patients where other less toxic treatments have failed. For ASCT candidates: collect stem cells before fludarabine administration.
Ibrutinib	Approved for symptomatic patients. Active. Should not be interrupted because this leads to hemoglobin decrease and IgM increase. Primary choice for rituximab-refractory patients
Everolimus	Considered for non-responders after multiple lines of other better-tolerated therapies. BM biopsies help to clarify disease response or progression given the IgM discordance observed with this agent.
Immunomodulatory agents	Consider only in the context of clinical trials
Autologous/allo-stem cell transplantation	In selected WM cases, for high-risk WM patients. Not beneficial for patients exposed to more than 3 lines of therapy or with chemotherapy refractory disease. Allo-SCT should be preferably done in clinical trials.
Retreatment	Treatment with any of the available therapeutic agents listed for symptomatic, untreated patients can be considered for previously treated patients requiring therapy. May be considered if a response was achieved for 2 or more years with the prior regimen. Patients progressing on first-line ibrutinib should not be retreated with ibrutinib.

AL amyloidosis

Diagnosis

Light chain (AL)-amyloidosis is caused by a usually small plasma cell clone producing a misfolded light chain protein that forms fibrillar deposits in tissues. Although several organs might be involved survival is mainly determined by the extent of heart involvement [27]. Although survival has increased in the past decade, only minor improvement is observed in early mortality as a result of advanced cardiac involvement and approximately 30% of the patients die within the first year from diagnosis [28]. Diagnosis requires proven amyloid deposits in a tissue biopsy. Abdominal fat aspirate is very sensitive and represents a less invasive technique [29]. Salivary gland biopsy is also easy to perform and identifies approximately 60% of the patients with negative abdominal fat [30]. However, to ensure diagnosis, biopsy of the involved organ is recommended if feasible. Imaging techniques are of important value in identifying heart involvement. The echocardiographic features are distinctive, with thickening of the ventricular walls and interventricular and interatrial septa. Furthermore, amyloid deposits give the characteristic "granular sparkling" to the myocardial texture. Cardiac magnetic resonance imaging shows global subendocardial late gadolinium enhancement. The specific amyloid type needs to be identified in amyloid deposits samples. Light microscopy immunohistochemistry can classify almost 95% of the patients, but only in very experienced centers [31]. Immunoelectron microscopy achieves 100% specificity and can classify more than 99% of patients [29]. Mass spectrometry-based proteomics overcome the limitations of the above-mentioned techniques and improve the diagnostic accuracy [32]. Gene sequencing is necessary in order to rule out or confirm hereditary amyloidosis. Cardiac scintigraphy with bone tracers distinguishes AL from transthyretin amyloidosis. The identification of the amyloidogenic light chains requires immunofixation of both serum and urine and FLCs measurement [33].

Recommendations

The diagnosis requires proven amyloid deposits on tissue biopsy. Abdominal fat aspirate is very sensitive; however, when negative, salivary glands biopsy should be performed, otherwise biopsy of the involved organ. Light microscopy, immunohistochemistry, immunoelectron microscopy or mass spectrometry is needed to type the amyloid. Imaging techniques and cardiac biomarkers to evaluate cardiac involvement are crucial. For renal involvement perform 24 h urine collection and urine immunofixation. Perform an abdomen CT scan or ultrasound if alkaline phosphatase is elevated to evaluate liver involvement. The assessment of the plasma cell clone and of the amyloidogenic light chain requires BM biopsy or aspirate, serum immunofixation and FLCs measurement.

Treatment

ASCT represents an important treatment option in the treatment of AL amyloidosis [34]. Cardiac biomarkers play a significant role in the assessment of eligibility for ASCT. Troponin T levels > 0.06 ng/mL or NT-proBNP levels > 5000 ng/L are associated with high transplant-related mortality [34]. Hematologic response rates exceed 70% [35, 36]. Updated results from Boston showed an OS of 7.6 years and approximately 55% of CR patients are projected to be alive at 14 years, suggesting that a proportion of patients achieving CR might be cured [36]. For patients who fail to achieve CR, bortezomib can increase CR rate to almost 60% [37]. Although ASCT is very

effective, the majority of the patients are not eligible (Table 3).

For intermediate-risk patients standard treatment has been oral melphalan/dexamethasone (MDex), BMDex or VCD [38]. In recent updated data after a median follow-up of 6 years, in patients receiving full-dose dexamethasone, the OS was 7.3 years. Hematologic response rate was 76% [38]. 80% of the patients who achieved CR with MDex are expected to be alive at 7 years [38]. These results are similar to those after ASCT. One of the few randomized trials indeed compared ASCT and MDex [39]: unfortunately, treatment related mortality was substantial (24%) due to suboptimal eligibility criteria. However, a landmark analysis excluding early deaths demonstrated no survival advantage for one arm over the other [39]. Further studies are required to define for which group of patients ASCT demonstrates the most significant benefit.

The availability of novel agents, especially bortezomib, have created great expectations [40]: both large retrospective series and prospective trials have proven efficacy and safety of bortezomib in AL-amyloidosis [41, 42]. Recently, two retrospective series showed significant hematologic responses (up to 90%) in newly diagnosed patients receiving VCD [43, 44]. Following these results, two retrospective matched case-control studies compared bortezomib, dexamethasone, and alkylating agents (BMDex and VCD) with MDex or cyclophosphamide/thalidomide/dexamethasone (CTD). The response rates were higher for the bortezomib combinations-although not as high as previously reported; however, with no OS benefit [45, 46]. A randomized phase 3 study comparing MDex and BMDex has completed recruitment (NCT01277016). The first interim analysis showed higher hematologic response rates with BMDex however, further follow-up is needed to determine a potential survival benefit [47]. Patients who fail to achieve deep responses rapidly should be considered for second-line treatment. Immunomodulatory drugs (IMiDs) are mainly used in relapsed/refractory patients. Moreover, lenalidomide and pomalidomide seem to overcome resistance to bortezomib and alkylating agents with hematologic response from 40 to 60% [48, 49]. IMiD combinations especially with alkylating agents can achieve higher response rates, but toxicity and myelosuppression are of concern in these patients [50–52]. Lenalidomide dosing is according to eGFR and relevant dose adjustments should be performed in patients with proteinuria or renal impairment [53]. Ixazomib has been investigated in a phase 1/2 trial in relapsed/refractory patients with AL-amyloidosis, showing efficacy particularly in bortezomib-naïve subjects [54]. A randomized phase 3 trial comparing ixazomib with physician's best choice is still ongoing (NCT01659658). An alternative option for relapsed/refractory patients is bendamustine. A prospective trial showed 40–50% hematologic response [55]. Bendamustine is effective especially in WM-related AL. Daratumumab is well tolerated and effective in heavily pretreated patients, with an overall hematologic response rate of 76%, including CR in 36% and very good partial response in 24%. Median time to response was one month [56]. Carfilzomib showed good efficacy in a phase I/II study, with a 63% response rate, but also important grade 3/4 cardiopulmonary toxicities in 36% of patients [57]. Doxycycline was also shown to promote amyloid fibrils disruption in vitro and managed to reduce the amyloid load in a transgenic mouse model [58]. In a case/control study, the combination of doxycycline with chemotherapy improved survival of patients with stage II/IIIa [59].

CPHPC is a competitive inhibitor of serum amyloid P component binding to amyloid fibrils [60]. The first results of combined CPHPC and anti-serum amyloid P component antibodies in humans were encouraging [61]. The first phase 1/2 study of NEOD001, a monoclonal antibody targeting amyloid deposits, showed a cardiac response rate of 50%, and renal responses of 43% [62]. Therefore, a randomized, placebo-controlled phase 3 trial comparing VCD with or without NEOD001 in patients with AL-amyloidosis and heart involvement was designed and completed accrual (NCT02312206); however, the results showed no benefit in terms of cardiac response and it was very recently discontinued. The anti-LC monoclonal antibody 11-1F4 with specificity for an amyloid-related epitope showed promising results in a phase 1 study inducing cardiac and renal responses [63].

Table 3 Recommended supportives in patients with primary systemic AL-amyloidosis

- Salt restriction and weight monitoring
- Diuretics-do not reduce the intravascular volume
- ACE inhibitors should be used at the lowest dose with caution due to hypotension
- Elastic leotards for hypotension
- Midodrine for hypotension
- Pacemaker for patients with recurrent syncope due to arrhythmia/ICD use remains controversial
- Amiodarone as antiarrhythmic-avoid digoxin
- Nutritional support
- Octreotide for diarrhea
- Gabapentin or pregabalin for neuropathic pain
- Organ transplant for patients with end-organ damage who achieve CR.
- Left ventricular assist devices might be used as a bridge for candidates for heart transplantation

Table 4 Recommended treatment approaches for patients with AL-amyloidosis according to risk-adapted stratification

Risk status	FRONTLINE treatment	**Relapsed/refractory patients**
Low risk, transplant eligible (Mayo stage 1 and 2, PS 0-2, age < 65 years, eGFR > 50 ml/min/1.74 m^2, NYHA < 3, EF > 45%, sBP > 90 mm Hg (standing), DLCO > 50%)	• MEL 200 mg/m^2 • Consider induction with cyclophosphamide/dexamethasone/bortezomib if bone marrow infiltration is > 10% • Consider bortezomib post ASCT if the response is not CR	Repeat frontline treatment *PI naïve*: bortezomib, ixazomib *PI refractory*: Lenalidomide, pomalidomide, daratumumab, bendamustine *Alkylator naïve*: MDex, ASCT if eligible
Intermediate risk (ineligible for ASCT, stages 1-3a)	• For patients with t(11;14) MDex or BMDex • For patients with neuropathy MDex • For patients with 1q21 or renal failure VCD	Repeat frontline treatment *PI naïve*: bortezomib, ixazomib *PI refractory*: Lenalidomide, pomalidomide, daratumumab, bendamustine *Alkylator naïve*: MDex, ASCT if eligible
High risk (stage 3b, NYHA ≥ 3)	• Dose and schedule adjustments at lower doses • Bortezomib-based combinations	Repeat frontline treatment *PI naïve*: bortezomib, ixazomib *PI refractory*: Lenalidomide, pomalidomide, daratumumab, bendamustine *Alkylator naïve*: MDex, ASCT if eligible

Supportive care is essential, especially for AL patients with cardiac involvement in order to gain valuable time until treatment achieves control of the disease. The main recommendations are listed in Table 4.

The design of the therapeutic approach is based on the staging of organ dysfunction and characterization of the plasma cell clone. The cardiac biomarkers are powerful predictors of survival. Therefore, they are combined in an accurate staging system widely used for management and stratification in clinical trials or in everyday clinic [64]. The difference between involved and uninvolved FLCs (dFLC) is also prognostic and can be integrated in the staging system based on cardiac biomarkers [65]. Another study showed that patients with BM plasma cell infiltration >10% have poor outcomes [66] and seem to benefit most from induction treatment before ASCT [67]. Almost 80% of the patients eligible for transplantation receive induction therapy with VCD, while post ASCT bortezomib increases CR. In another study patients with gain of chromosome 1q21 had poorer outcomes when treated with MDex, whereas t (11;14) was associated with inferior survival in patients receiving VCD [68, 69]. High-risk patients do not tolerate full dosed therapy; therefore, we recommend dose and schedule adjustments. For young patients with isolated heart involvement, heart transplantation followed by ASCT may be considered. Furthermore, organ transplant can be considered in patients who achieve CR but have irreversible end-stage organ damage. The main concern remains, however, disease recurrence. Table 4 summarizes tailored therapeutic approaches and recommended therapeutic algorithms.

Recommendations

Due to the unique disease characteristics, the EMN-panel recommends a risk-adapted approach, with dose adjustments, schedule modifications and close monitoring of hematologic and organ response. For low-risk per Mayo stage, transplant-eligible patients consider induction with VCD if BM infiltration is >10%, followed by ASCT/HDM (1B). If the response achieved is less than CR consider bortezomib after ASCT (1B). For intermediate-risk patients consider MDex for those with neuropathy or t (11;14), while for those with 1q21 or renal failure consider VCD (1B). For patients with high dFLC BMDex seems the most effective option (1B). For high-risk patients bortezomib-based regimens and dose adjustments are highly recommended (1B). In the relapsed/refractory setting for PI-naive patients consider bortezomib and ixazomib, while for PI refractory patients consider IMiDs, daratumumab and bendamustine. For alkylator-naive patients consider MDex or even ASCT if the patient is eligible. Frontline treatment can be repeated if it was beneficial. Unfortunately, most available data are based on retrospective case series. Therefore, the enrollment of AL patients in clinical trials is highly encouraged and patients should be referred to specialized centers.

Monoclonal immunoglobulin deposition disease

Diagnosis

Monoclonal immunoglobulin deposition disease (MIDD) is a rare PCD characterized by the deposition of monotypic immunoglobulin fragments along basement membranes in the kidneys leading to subsequent proteinuria and renal deterioration [69]. MIDD is a multi-systemic disease, with almost always renal involvement [70–73], while cardiac, hepatic, and neural deposits are less common [70, 71, 73, 74]. Diagnosis is based on the typical histological findings of renal biopsy using immunofluorescence (IF) and electron microscopy [73, 75]. In the majority of MIDD patients, small, indolent clones are found in the BM, that are responsible for devastating complications and end-organ damage [75].

Recommendations

Perform a renal biopsy whenever MIDD is highly suspected (patients with monoclonal paraprotein and renal disorder which cannot be explained by other causes). A BM biopsy or aspirate, serum, and urine immunoelectrophoresis and FLCs are needed for both diagnostic and response evaluation purposes.

Treatment

Before the era of novel anti-myeloma agents, the overall and renal prognosis was poor [72]. Data regarding the best therapeutic approach remain limited; however, bortezomib-based regimens are considered as a primary choice leading to deep and rapid responses [76, 77]. Two retrospective studies support the use of bortezomib-containing regimens as first line treatment with achievement of VGPR and improved renal outcomes [71, 78]. Recent data [79] reported that patients with hematologic CR, achieved either with ASCT or PI-based therapies, were more likely to achieve a renal response, while baseline GFR < 20 mL/min/1.73 m2 and renal improvement, were identified as independent predictors of progression to dialysis. Earlier diagnosis and treatment initiation improve OS but not disease evolution to end-stage renal disease (ESRD) [80]. Despite the high rates of hematologic response with the bortezomib-based agents, a significant proportion of patients still progresses to ESRD. The non-reversible renal impairment suggests that other processes are involved in the pathogenesis induced by the deposition of heavy and/or light fragments, and therefore may become independent of the primary insult [76, 81]. The therapeutic goal is to eradicate the monoclonal proteins and stabilization or improvement of renal function; however, the optimal combination, treatment duration, and salvage therapeutic options remain to be further investigated. Triplet combinations or the induction of an IMiD are reasonable, although data regarding the role of IMiD are very limited [71, 82].

Recommendations

Bortezomib-based regimens are considered as gold standard for the treatment of MIDD both in frontline and relapsed/refractory setting (1B). However, prospective randomized trials are required to be performed to confirm the available data. ASCT/HDM should be considered for transplant-eligible patients (1B). Triplet combinations should be considered for relapsed/refractory patients (1C). The therapeutic goal is to achieve at least VGPR and stabilize or improve renal function.

POEMS syndrome

Diagnosis

POEMS is a rare syndrome associated with an underlying PC neoplasm. The acronym refers to the disease characteristics: polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes [83]. The major criteria to establish diagnosis are polyradiculoneuropathy, clonal PC disorder, elevated vascular endothelial growth factor (VEGF), sclerotic bone lesions, and Castleman disease. Minor features include endocrinopathy, organomegaly, characteristic skin changes, papilledema, extravascular volume overload, and thrombocytosis. The diagnosis of POEMS syndrome is made with three major criteria, two of which (polyradiculoneuropathy and clonal PC disorder, almost always λ) are mandatory, and at least one minor criterion (Supplementary Table 2).

Recommendations

Perform iliac crest BM sampling or aspirate, abdomen and pelvis CT scan, whole body X-rays and FDG-PET, pulmonary function tests, heart U/S, endocrinal lab tests, serum VEGF levels, serum and urine immunofixation and FLCs to evaluate the presence of major and minor POEMS criteria.

Treatment

The most effective therapeutic strategies target the underlying disorder rather than VEGF. Patients are distinguished as those with no BM involvement and those with disseminated disease. The approach differs for both groups.

Table 5 Therapeutic choices for POEMS syndrome

Therapeutic regimen	Clinical outcomes
Radiation	Improvement in 50–70% of patients
Corticosteroids	50% with clinical improvement
Melphalan-dexamethasone	81% with hematologic response, 100% with some neurologic improvement
ASCT	100% with clinical improvement
Cyclophosphamide-dexamethasone	50% with clinical improvement
Lenalidomide-dexamethasone	Majority of patients may respond
Thalidomide-dexamethasone	Not recommended as 1rst-line due to induced neuropathy risk
Bortezomib-based regimen	Almost all patients respond, consider neurotoxicity
Bevacizumab	Will reduce VEGF levels, but several death reports

For the first, radiation is the recommended treatment of choice and improves both symptoms and prognosis: 35 patients were treated in a retrospective study only with radiation with 97% 4-year OS and 52% 4-year failure-free survival [84]. In a recent review both PFS and OS were inferior for patients treated only with radiation, mainly because these patients were sicker at the time of treatment [85]. For patients with disseminated disease, radiation is not curative, therefore systemic therapy is recommended. Large bone lesions might require adjuvant radiation usually 6 months after chemotherapy. Unfortunately, there is a significant lag between successful therapy and neurologic response. Maximum response is expected after 2–3 years. Optimal response with FDG-PET may also lag by 6–12 months. No published randomized trials are available, therefore therapeutic approaches are based on case series. The first prospective trial included 31 patients treated with MDex with 81% hematologic response, 100% VEGF response and 100% improvement of some grades in neuropathy [86]. The French group treated 27 patients with lenalidomide/dexamethasone (Rd) for two induction cycles followed by high-dose therapy or radiation or for 9 cycles followed by 12 cycles lenalidomide monotherapy [NCT01639898, primary analysis]. The follow up is short, however several patients responded neurologically and rapidly, one patient however, progressed and one died.

Thalidomide and bortezomib should be used with caution due to increased risk of induced neuropathy [87–90]. High-dose chemotherapy with ASCT is also effective and should be considered for young patients given the excellent long-term results. Case series suggest that 100% of patients achieve some neurologic improvement [85–87]. In a case series of 59 patients, PFS was 98, 94, and 75% at 1, 2, and 5 years, respectively [86]. Other strategies (often used in case reports or in very small patient cohorts) have been proposed in the past, but their results are inferior or controversial. Recommendations on POEMS therapeutic strategies are listed in Table 5.

Recommendations

For patients with negative BM involvement by iliac crest sampling, radiation is treatment of choice. For patients with disseminated disease consider Rd or MDex (1A). Eligible patients should undergo ASCT (1A). Bortezomib- and thalidomide-based regimens should be avoided due to the increased risk to deteriorate preexisting neuropathy (1B). In the relapsed/refractory setting, retreatment with the available frontline agents is an option (1B).

Primary plasma cell leukemia (PPCL)

Diagnosis

PPCL is a rare and aggressive variant of MM, operationally defined by the presence of 20% and/or an absolute number >2 × 10e9/L of clonal PC in the peripheral blood without a previous history of MM [91–94]. PPCL should be considered a specific entity, distinguished from secondary PCL (SPCL), which generally constitutes the leukemic evolution of a pre-existing, end-stage relapsed/refractory MM, and from extra-medullary myeloma that, by definition, excludes peripheral blood dissemination.

PPCL is characterized by a higher prevalence of adverse clinical and laboratory features as compared to MM [95] (Supplementary Table 3) and an elevated genomic instability, witnessed by an increased number of cytogenetic aberrations and other molecular lesions at diagnosis [95–97]. The prognosis of PPCL, though partially improved as compared to previous decades after the introduction of novel agents in clinical practice [98], remains unsatisfactory, with a median OS of 1–2 years in elderly patients, and about 3-years in patients undergoing stem cell transplants [99–107]. Recently it was demonstrated in 482 newly diagnosed patients with MM or plasma cell leukemia that the presence of ≥5% circulating plasma cells in patients with

myeloma at diagnosis has similar adverse prognostic impact as plasma cell leukemia, indicating that probably a lower cut-off for the definition of plasma cell leukemia should be adapted in the future (107).

Recommendations

Diagnostic work-up and staging procedures in PPCL are similar to those applied in MM; however, they have to be implemented by peripheral blood analysis for measuring circulating PC count and PET-CT for detecting possible extra-medullary lesions [97].

Treatment

With some exception [108, 109], available data support the use of bortezomib-based combinations as first-line induction therapy for fit patients [105, 110–112]. Aggressive chemotherapy, combined with bortezomib ± thalidomide/lenalidomide, such as hyper-CVAD-VD or VTD/VRD-PACE may also be considered in younger patients, but there is no clear evidence of their superiority [96].

Despite being less effective than in MM, high-dose melphalan followed by ASCT is currently recommended in all eligible PPCL patients who achieve a significant response after a brief course of induction treatment [95, 96, 99, 106, 113–118]. Of note, the best results have been so far achieved when ASCT was integrated with the use of novel agents [104, 105, 113]. Some data also suggest a possible advantage of tandem-ASCT [111], but this has not been confirmed in a recent retrospective survey of EBMT [118].

Overall, though an allo-SCT with a myeloablative regimen may be potentially curative, the results so far obtained upfront in PPCL do not show any survival advantage when this procedure is compared to ASCT, being allo-SCT associated with a lower relapse rate, but also with a much higher risk of non-relapse-related mortality [118–120]. Pros and cons of front-line allo-SCT should be therefore carefully discussed with eligible patients, who electively are younger individuals with poor prognosis characteristics at baseline, but who have achieved a good response to first-line induction treatment. In this setting, a sequence of ASCT followed by allo-SCT, including reduced-intensity or non-myeloablative regimens, has provided promising preliminary data [118].

Results in patients not eligible for transplant procedures because of age or frailty appear to be disappointing [95, 96, 99, 101, 112]. Likewise, current salvage therapies for relapsed/refractory PPCL are rarely effective [95, 96, 101]. Therefore, patients with PPCL should always be considered for enrolment in clinical trials [103]. Newer approaches under investigation in MM [115], including various combinations of next generation PI/IMIDs and monoclonal antibodies, CAR-T cells and novel target therapies, such as selinexor (an inhibitor of nuclear exportin-1) or venetoclax (a BCL-2 inhibitor, particularly active in presence of t(11;14) [121], may emerge as possible future therapeutic options also for PPCL patients.

Recommendations

There are no precise guidelines for the treatment of PPCL. In particular, no randomized, phase III trials have been performed in PPCL, while only two prospective, phase II studies [104, 105] (Supplementary Table 4) have been published so far.

Overall, current PPCL treatment should be immediate and initially oriented toward a PI and IMID-based triplet as induction, with short treatment-free intervals (1B). Prevention of tumor lysis syndrome, bisphosphonates and anti-infective prophylaxis are recommended in all patients. Intrathecal prophylaxis should be also considered for patients at high risk of CNS infiltration (i.e., those with a high WBC count). Thromboprophylaxis should be given in patients receiving IMIDs.

After induction phase, the treatment should ideally include double ASCT, consolidation, and maintenance in all eligible patients (1B). Frontline allo-SCT should be considered in selected cases (1B). The expert panel suggests that aged, but still fit patients not eligible for transplant procedures, should be planned for continuous therapy, ideally until response is maintained or significant toxicities occur. In very old and/or frail individuals, personalized treatments (i.e. dose and time adjusted combinations of lenalidomide or bortezomib plus dexamethasone) should be given according to efficacy and tolerability, aiming to maintain patients on therapy as long as possible.

In relapsed/refractory PPCL a switch to drugs not used at diagnosis should be considered, favouring combinations of lenalidomide or pomalidomide plus dexamethasone with carfilzomib or monoclonal antibodies (daratumumab or elotuzumab) (expert consensus). Allo-SCT in relapsed and eligible patients with sensitive disease after salvage treatments is recommended (1B) A possible algorithm is illustrated in Fig. 1.

Conclusions

The treatment paradigm for PCDs has evolved over the past few years resulting in substantial improvements in survival. This trend is expected to continue with agents under investigation for both newly diagnosed and relapsed or refractory patients and combinations of them with the existing regimens. The accurate and timely diagnosis along with the emerging therapies expect to control the disease

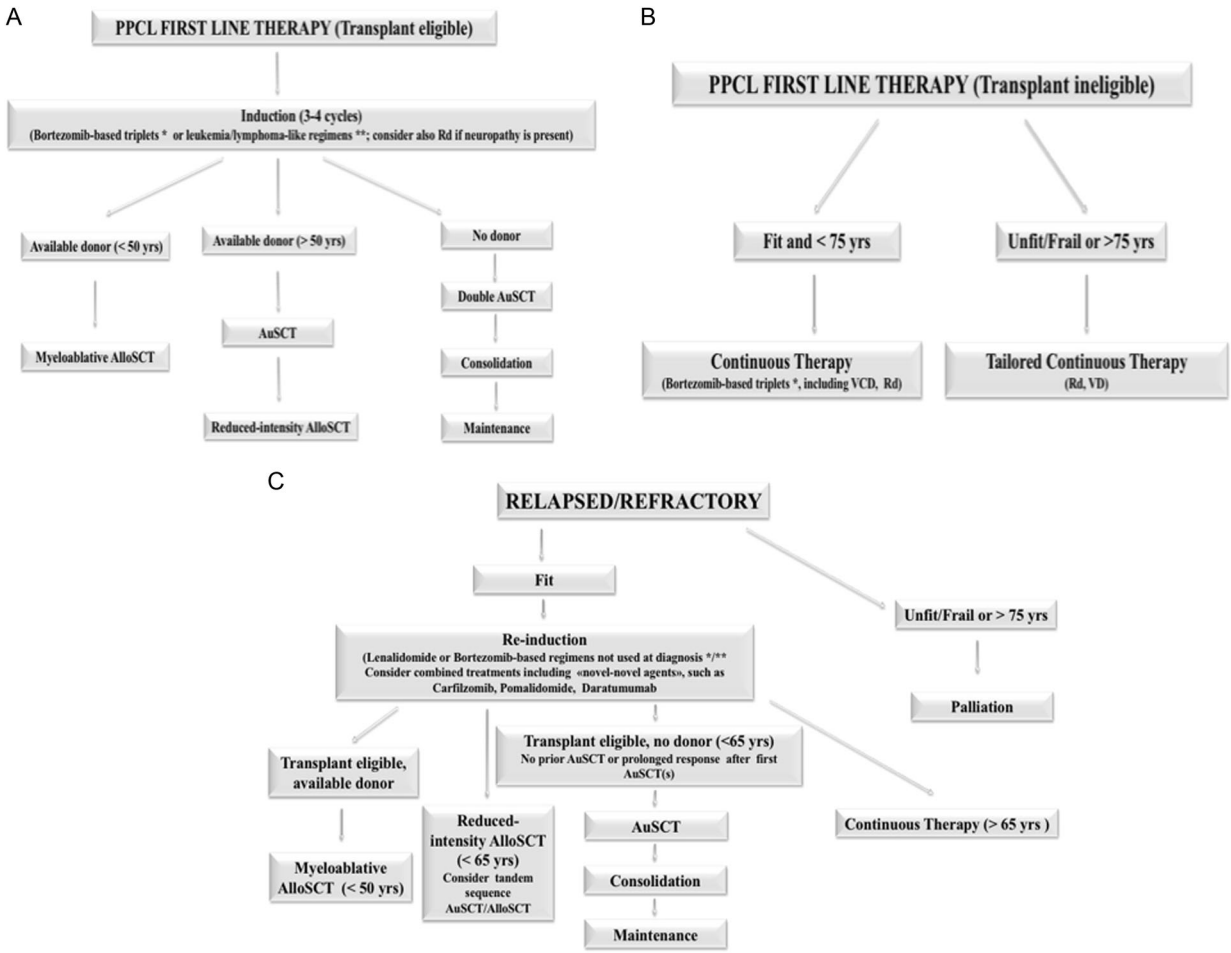

Fig. 1 Proposed therapeutic algorithm for primary plasma cell leukemia (PPCL). **a** First line therapy in transplant eligible patients. **b** First line therapy for patients not eligible to transplantation. **c** Treatment for relapsed/resistant patients. AlloSCT allogeneic stem cell transplantation, ASCT autologous stem cell transplantation, Rd lenalidomide, low-dose dexamethasone, VD bortezomib and dexamethasone, VCD (bortezomib, cyclophosphamide, dexamethasone). * VRD (bortezomib, lenalidomide, dexamethasone); VTD (bortezomib, thalidomide, dexamethasone; PAD (bortezomib, doxorubicin, dexamethasone).** HyperCVAD-VD (hyperfractionated cyclophosphamide, vincristine, continue-infusion doxorubicin, bortezomib, dexamethasone; VTD/VRD-PACE (bortezomib, thalidomide, lenalidomide dexamethasone, continue infusion cisplatin, doxorubicin, cyclophosphamide, etoposide)

burden and improve the clinical outcomes. Despite the rarity of these entities prospective, randomized trials should be designed in order to identify the most beneficial and effective therapeutic approaches for these patients in need, specifically those with AL-amyloidosis and plasma cell leukemia.

Compliance with ethical standards

Conflict of interest Maria Gavriatopoulou has received honoraria for advisory boards and honoraria from Amgen, Takeda, and Janssen. Pellegrino Musto has received honoraria for advisory boards and honoraria from Janssen, Celgene, Takeda, Amgen, and Bristol-Myers Squibb. Efstathios Kastritis has received honoraria for advisory boards and honoraria from Janssen, Celgene, Amgen, Takeda, and Prothena. Niels van de Donk has received research funding and honoraria for participating in advisory boards from Janssen, Celgene, Bristol-Myers Squibb, and Amgen. Francesca Gay has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, and Takeda, and honoraria for participation in advisory boards from Janssen, Amgen, Celgene, Roche, and Takeda. Roman Hájek has received consultancy fees, research funding, and honoraria for participation in advisory boards from Amgen, Takeda, Bristol-Myers Squibb, Celgene, Novartis, and Janssen. Sonja Zweegman has received honoraria for participating in advisory boards and research funding from Janssen, Celgene, Novartis, and Takeda. Meletios A. Dimopoulos has received consultancy fees and honoraria from Celgene, Onyx, Janssen, Novartis, and Amgen, and honoraria for participation in advisory boards from Amgen, Takeda, Celgene, and Janssen. Hermann Einsele has received speakers' honoraria and honoraria for participation in advisory boards for Celgene, Janssen, Amgen, Bristol-Myers Squibb, and Novartis, and consultancy fees or honoraria from Celgene, Janssen, Bristol-Myers Squibb, and Amgen. Pieter Sonneveld has received honoraria for participating in advisory boards and honoraria from Amgen, Bristol-Myers-Squibb, Celgene, Janssen, and Karyopharm and research support from Amgen, Celgene, Janssen, Karyopharm, and SkylineDx. Monika Engelhardt has received educational grants from Celgene, Janssen, Amgen, Takeda and MSD. Evangelos Terpos has received honoraria from Janssen, Amgen, Takeda, Abbvie, Bristol-Myers Squibb, PharmaMar, and Celgene, research funding from Amgen,

Genesis, Janssen, Novartis, and Takeda, honoraria for participation in advisory boards from Takeda, as well as honoraria for participation in the data monitoring committee from Celgene. Jo Caers, Giampaolo Merlini, Ute Hegenbart, Benedetto Bruno, Christian Straka and Mario Boccadoro have no relevant conflicts to disclose.

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