Current Hematologic Malignancy Reports (2019) 14:187–196
https://doi.org/10.1007/s11899-019-00507-x

MULTIPLE MYELOMA (P KAPOOR, SECTION EDITOR)

Expert Panel Consensus Statement for Proper Evaluation of First Relapse in Multiple Myeloma

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Published online: 10 May 2019

Abstract

Purpose of Review A working group of six expert physicians convened to assess the spectrum of multiple myeloma relapse presentations, discussed the features that can define the disease as aggressive and not aggressive, and established whether this information could help in selecting treatment together with the characteristics of disease and of patients and type of prior therapy.

Recent Findings The working group agreed that relapse should be distinguished between biochemical and clinical according to IMWG. Moreover, the expert panel defined "aggressive disease" as a clinical condition that requires therapy able to induce a rapid and as deep as possible response to release symptoms and to avoid impending danger of new events. According to this definition, relapse was considered aggressive if it presents with at least one of the following features: doubling of M protein rate over 2 months, renal insufficiency, hypercalcemia, extramedullary disease, elevated LDH, high plasma cell proliferative index, presence of plasma cells in peripheral blood, or skeletal-related complications. Moreover, the panel agreed that this classification can be useful to choose therapy in first relapse together with other patient, disease, and prior therapy characteristics. So, this item was included in a new therapeutic algorithm.

Summary The treatment choice in MM at relapse is wider than in the past with the availability of many new therapeutic regimens leading to increased diversity of approaches and relevant risk of inappropriate treatment decisions. A practical classification of relapses into aggressive or non-aggressive, included in a decisional algorithm on MM management at first relapse, could help to make the appropriate treatment decisions.

Keywords Multiple myeloma · Refractory plasma cell malignancy · Aggressive myeloma · Management of relapsed myeloma

This article is part of the Topical Collection on *Multiple Myeloma*

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Introduction

Multiple myeloma (MM) is a hematologic disorder characterized by neoplastic proliferation of a plasma cell clone in the bone marrow and rarely outside (extramedullary disease) [1]. MM is the second most common hematologic malignancy [2] and it primarily presents in elderly patients [3, 4]. Median age at the time of diagnosis is about 65 years in the USA [5] and 72 in Europe [3, 4]. Due to the increased life expectancy in the general population, myeloma cases are predicted to grow up to 60% by 2030, with an increase rate during this period ranking the third among all cancers [6]. Although a significant improvement in the 5-year overall survival (OS) was observed among patients of all age and race/ethnicity groups in the last decades [7], MM remains an incurable disease and most patients eventually relapse, requiring further treatment.

The International Myeloma Working Group (IMWG) defines MM as "relapsed and refractory" if the disease is non-responsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved at least a minimal response (MR) and primary refractory MM as a disease which is non-responsive in patients who have never achieved a MR [8–10].

Several classifications of the types of relapse were proposed, e.g., classical, clinical, insidious, indolent, symptomatic, asymptomatic or aggressive, due to the high heterogeneity of MM presentation at relapse [11–15]. However, these classifications did not carry out recommendations in the clinical practice despite several therapeutic algorithms, taking into account disease- or patient-related features, were proposed [16–21].

Moreover, in a retrospective study from Lopez A et al. [15], three different types of relapses in elderly patients not eligible for HDCT and ASCT were identified: "biological" relapse with asymptomatic increase in the M-component only, "clinical" relapse, presenting with the classical CRAB criteria (calcium elevation, renal insufficiency, anemia, bone lesions), and "aggressive" relapse, characterized by extramedullary plasmacytoma (EMP), plasma cell leukemia (PCL), or severe renal failure requiring hemodialysis. In patients with a more aggressive form of relapse, OS was found to be significantly shorter if compared with that of patients with clinical or biological relapses (7.6 vs 18 vs 28.6 months respectively). However, it should be outlined that patients included in this study were treated with a bortezomib-based regimen at induction and received at relapse a lenalidomide-based regimen (54%), retreatment with bortezomib (17%) or conventional chemotherapy (23.5%), regardless of the type of relapse.

The recent introduction of novel agents, such as proteasome inhibitors and immunomodulatory drugs (IMiDs) and monoclonal antibodies (MoAbs), has extensively changed the management of newly diagnosed [22–26, 27•] and relapsed-refractory MM patients [28–34]. As a consequence, a commonly shared approach for the definition of the criteria of choice of salvage treatments is warranted in order to balance efficacy, toxicity, and costs among the plethora of highly effective novel regimens.

Objective

The objective of the study is to review the current evidence on MM presentation at relapse and its classification, distinguishing between aggressive and non-aggressive forms, with the aim to include this new variable in the development of a practical algorithm and guidance, helping clinicians to make evidence-based decisions for the management of relapsed patients.

Methods

To that end, six expert physicians (expert panel) with long-standing clinical practice in MM management and treatment, convened to assess the spectrum of MM relapse presentations, discussed the features that can define the disease as aggressive and non-aggressive and established whether this classification could be used as a factor affecting the choice of therapy together with the characteristics of disease and of patients and type of prior therapy.

A systematic review of studies published from 2002 to 2018 was conducted on MEDLINE, EMBASE, CINAHL and the proceedings from major conferences on MM were also included. After that, a nominal group technique was adopted to define the key issues in discriminating the type of relapse and its management.

The nominal group technique is a widely used method, which attempts to provide an orderly procedure for obtaining qualitative information from target groups who are most closely associated with a problem area. The first step in the nominal group process is to assemble all participants and individually ask them to list down their own ideas on a specific topic or question with no previous group discussion. Subsequently, each individual presents the most important idea on his or her list in a round-robin fashion. In the next phase, a highly structured discussion of the ideas on the composite list takes place and then, each participant privately writes down his ranking of the idea's worth. As a last step, the group's views are assessed.

The Consensus Meeting

In this meeting the expert panel convened and reviewed current evidence identifying knowledge gaps. In the first step, a decisional tree was built, in order to discriminate aggressive vs non-aggressive relapse according to specific parameters which met the consensus of the expert panel. In the second

step, a decisional algorithm was designed, in order to provide a helpful guide in the management of patients with relapse according to their characteristics and aggressiveness of relapse. The document is the outcome of the consensus reached within the expert panel as supported by the extensive literature review and gap analysis.

Preparation of the Consensus Paper

One of the experts drafted the manuscript. All the participants reviewed it and eventually approved the final draft.

Results

Definition of Relapse in MM

Given the different patterns of relapse in MM patients, the expert panel agreed that accurate diagnostic evaluation and biochemical characterization are recommended.

Firstly, the expert panel found consensus in the work-up to assess relapse. Blood/urine tests include serum paraprotein electrophoresis with immunofixation, 24-h urine collection to measure both total proteinuria and urine paraprotein, serum FLC assay, a complete blood count to detect cytopenias or circulating plasma cells, renal function, calcium concentration, serum β2-microglobulin, LDH, and serum albumin. In MM patients producing a whole immunoglobulin, an increase of free light chain (FLC) without a corresponding increase of the intact monoclonal Ig at relapse is defined as "FLC escape". This phenomenon can be considered a marker of subclonal progression, and it has been observed in a percentage of patients ranging from 3 to 10% [35, 36].

Bone marrow evaluation is usually performed at disease relapse, and it is of value especially in a context of non- or oligo-secretory MM, cytopenias (differential diagnosis between marrow infiltration by myeloma itself or secondary to prior anti-myeloma chemotherapy), or when a secondary bone marrow process is suspected, such as myelodysplasia. Moreover, bone marrow aspirate should be performed to investigate new chromosomal abnormalities, with possible exceptions in cases where high-risk cytogenetic features have already been identified at diagnosis.

Moreover, a skeletal survey by skeletal X-ray, CT scan, MRI, or CT-PET scan is recommended to assess bone lesions. This latter tool is recommended if extramedullary disease is suspected.

MRI is particularly useful in the evaluation of a painful lesion in the axial skeleton and to detect spinal cord compression [37]). Subsequently, the expert panel achieved consensus in the definition of type of relapse as biochemical and clinical according to IMWG criteria as previously published [10].

Biochemical Relapse

According to the IMWG criteria, the following conditions occur in patients with relapsing multiple myeloma [10]:

- increase of at least 25% from nadir in serum paraprotein (absolute increase must be at least ≥ 0.5 g/l)
- increase of at least 25% in urine paraprotein (absolute increase must be at least ≥ 200 mg/24 h)
- increase of > 25% in the difference between involved and uninvolved free light chain (FLC) with an abnormal FLC ratio and absolute increase of at least > 10 mg/dl
- increase in plasma cell infiltration ≥ 10%, in patients affected by non-secretory MM

Clinical Relapse

Clinical relapse was defined as the presence of at least one CRAB criteria namely hypercalcemia, renal insufficiency, anemia, and bone lesions attributable to myeloma [10].

Criteria of Relapse Classification

The expert panel tried to reach a consensus on the criteria for relapse classification, as aggressive or non-aggressive disease according to the statement that "aggressive disease" is a clinical condition, not necessarily prognostic, that requires such a therapy that, with the highest probability, should be able to induce a rapid and as deep as possible response in order to relieve symptoms and to avoid impending danger of new events. According to this definition, the expert panel agreed that relapse in MM should be considered aggressive if it meets at least one of the following criteria, while non-aggressive relapse meets none:

- Presence of renal failure or hypercalcemia
- Presence of extramedullary plasmacytoma (EMP)
- LDH > normal range
- Skeletal-related complications
- Peripheral blood plasma cells
- High increase in M protein rate (doubling in 2 months)
- High plasma cell proliferative index

Renal Failure, Hypercalcemia

Renal insufficiency is defined as creatinine clearance < 40 mL/min or serum creatinine > 177 mmol/L (> 2 mg/dL) [38••]. Renal insufficiency at relapse may be due to either disease progression or coexisting comorbidities, such as hypertension, diabetes, and vascular disease; therefore, they should be

distinguished from cast nephropathy typically leading to rapid progressive renal insufficiency due to light chain excretion. The presence of renal dysfunction usually affects treatment decisions at relapse. Patients with severe renal failure should be treated with proteasome inhibitors and adequate supportive care [39, 40]. Patients with moderate renal insufficiency may be treated with either a proteasome inhibitor or a lenalidomide combination but lenalidomide dosage needs to be reduced according to the severity of the renal insufficiency [39].

The condition of hypercalcemia is defined as serum calcium level increase of > 0.25 mmol/L (> 1 mg/dL) above the upper normal limit or > 2.75 mmol/L (> 11 mg/dL) [38••]. Therefore, a level of serum calcium ≥ 2.875 mmol/L (≥ 11.5 mg/dL) is considered a marker of organ damage and disease progression [17]. These clinical conditions should be promptly treated with the aim to achieve a rapid serum creatinine and calcium normalization avoiding hemodialysis or chronic renal insufficiency and cardiac arrhythmia.

Both renal failure and hypercalcemia belong to the CRAB criteria, and the expert panel agreed that the presence of renal insufficiency or hypercalcemia as a consequence of MM requires rapid and deep response.

Extramedullary Disease

Extramedullary disease can be detected clinically or by computer tomography imaging (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans. At relapse, this is a frequent condition (about 14% of overall cases) and is usually associated with the presence of other unfavorable characteristics [41, 42] such as adverse cytogenetic (52% of the patients), elevated levels of lactate dehydrogenase (LDH), and presence of bone fractures. The outcome is usually poor and associated with a reduction in OS [12]. This event requires an immediate intervention with effective chemotherapy in some cases associated with radiotherapy and/or surgery; therefore, the expert panel agreed that in the presence of this condition, the relapse has to be considered aggressive.

Elevated LDH

Elevated LDH is usually associated with adverse clinical features according to R-ISS staging system in newly diagnosed MM [43••]. In patients who had undergone novel agent-based induction and ASCT, LDH > normal range was found to be an independent prognostic factor for OS [44]. Moreover, in elderly patients, elevated LDH was identified as a marker of early death due to myeloma progression [45]. In this context, indeed, we considered elevated LDH an index of rapid duplication of plasma cells, namely, a rapidly growing disease that must be quickly controlled.

Peripheral Blood Plasma Cells

The presence of circulating plasma cells (CPCs) in patients not fulfilling the criteria of plasma cell leukemia (PCL) (defined by an absolute plasma cell count of $\geq 2 \times 10^9$/L and a burden of > 20% of total leukocyte count) [46], is considered a criteria of aggressive, rapidly evolving disease [47] and, consequently, of a disease requiring to be quickly controlled. Moreover, CPCs represent a prognostic factor as reported by some studies showing that patients with either ≥ 2% or ≥ 5% CPCs have similar outcomes to patients with PCL [48–50], for which studies reported a median OS of 2–7 months [11–13].

Skeletal-Related Complications

The presence of at least one focal bone lesion of ≥ 5 mm in size detected by skeletal radiography, CT, MRI, or PET-CT has been reported as a marker of myeloma requiring treatment [17]. Comparing prior imaging studies with the imaging studies at relapse, it is mandatory to identify new lesions or clear progression of previous skeletal lesions prior to re-initiation of therapy for relapsed-refractory myeloma. Moreover, existing lesions that may or may not show evidence of healing on subsequent radiographic studies are not an indication for treatment. Bone disease is often associated with severe pain or related complication such as fractures, or request for surgery and/or radiotherapy. In this clinical condition, a prompt symptom control and consequently a rapid disease response is required.

Increase in M Protein Rate

Monoclonal (M) proteins are immunoglobulins or light chains produced by clones of malignant cells. The level of M proteins can be measured in blood serum or in the urine. The expert panel agreed that the relapse is considered aggressive in presence of a rapid increase of M protein, and specifically when the level of M protein is doubled over 2 months having reached at least 1 g/dl in the serum and 0.5 g/24 h in the urine, as per IMWG recommendations [17]. This, indeed, could be regarded as an index of rapidly disease growth requiring rapid disease control.

High Plasma Cell Proliferative Index

The plasma cell proliferative index (PCPI), measuring the phase S of the cell cycle, is an indicator of the proliferative rate of the plasma cells and a high index is suggestive of aggressive disease. Recent studies, using flow-cytometric methods to measure the PCPI, showed that elevated PCPI predicts earlier progression of smoldering multiple myeloma (SMM) [51] and represents an independent predictor of PFS and OS in patients failing to achieve CR at 100 days post-transplant [52].

Other Screened Predictors Role

Duration of Response

Despite the highly heterogeneous vocabulary adopted to characterize disease relapse, most studies agree to consider progression-free survival (PFS) duration from front-line treatment as the main variable associated with the outcome of the disease [45, 53–55]. The expert panel agreed that the disease should be considered at worse outcome when relapse occurs early. However, many factors may play a role in determining the duration of PFS in different therapeutic strategies such as transplantation or standard therapy, consolidation and/or maintenance, continuous vs fixed duration of therapy. In addition, it should be noted that, based on selection criteria, studies with similar therapeutic approaches may end up with different PFS durations. Eventually, patient outcomes in real-world practice are generally worse than in clinical trials [56]. Therefore, although an early relapse is known to be a negative prognostic factor, it is not possible to establish a unique cut-off of relapse timing to estimate the outcome of patients with relapsed disease.

In any case, early relapse does not necessarily occur with the aggressive clinical features as those defined above so the expert panel agreed that this parameter should be considered rather a prognostic factor than a marker of aggressiveness in absence of any of the above-mentioned markers of aggressiveness.

Cytogenetics

According to IMWG, patients with del(17p), t(4;14), t(14;16), t(14;20), and amp(1q21) should be considered at high risk of relapse [16]. It should be acknowledged that, as MM is an evolving disease [57, 58], patients with standard-risk disease at diagnosis might acquire new mutations at relapse [59–64]. Stratification based on cytogenetic subgroups is quite controversial at relapse, because of the lack of large clinical trials and prospective studies. The Intergroupe Francophone du Myelome (IFM) [65] showed that lenalidomide-dexamethasone (Rd) combination could never overcome the negative impact of t(4;14) on OS. Reece et al. [66] found that only patients with del(17p), but not those with t(4, 14), faced a dismal outcome (median PFS 2.2 months and OS 4.7 months) when treated with Rd at relapse. With regard to treatment with bortezomib at relapse, only patients with 1q21 gain showed significantly shorter OS (5.3 months vs 24.6 months, $p = 0.0006$) and PFS (2.3 months vs 7.3 months, $p = 0.003$) compared with patients without such abnormality [67]. However, triplet therapies recently approved for the treatment of relapsed-refractory MM treated with 1–3 prior lines of therapy, such as carfilzomib-lenalidomide-dexamethasone (KRd), elotuzumab-lenalidomide-dexamethasone (Elo-Rd), ixazomib-lenalidomide-dexamethasone (IRd), daratumumab-lenalidomide-dexamethasone (DRd), and daratumumab-bortezomib-dexamethasone (DVd) [28, 30, 32–34], seem to be all active in high-risk cytogenetic disease [68, 69]. The expert panel agreed that the cytogenetic profile could be a prognostic marker though not necessarily linked to clinical aggressive relapse according to the above definition; therefore, the expert panel decided not to include high-risk cytogenetics in the criteria of aggressiveness.

Management of First Relapse

The expert panel reached consensus that, in order to decide the proper therapeutic strategy, patients' characteristics (age, performance score, and comorbidities or frailty score), disease history (cytogenetic risk, prior therapy, response, duration of response, toxicity), patient's preference, and other logistic features should be taken into account. Moreover, the expert panel agreed to include type of relapse (biochemical, clinical: aggressive vs non-aggressive) as above defined in the decisional algorithm for the management of first MM relapse.

Patient Characteristics

Although age, performance score (PS) and comorbidities are well-known factors affecting therapy-induced toxicities and outcome [70–72, 73•], in order to assign each patient to the appropriate treatment, avoiding the application of less effective therapies or side effects due to overtreatment, the IMWG frailty score [73•] seems to be the best tool to predict toxicity, therapy discontinuation, and outcome. Although it has been built and validated in newly diagnosed MM, the expert panel recommended its use also in relapsed patients. Regarding comorbidities, a great care should be taken over cardiovascular diseases since these imply caution in the carfilzomib administration [28, 29].

Disease History

Cytogenetics

Based on the results of phase III clinical trials such as ASPIRE, ELOQUENT-2, POLLUX, CASTOR, and TOURMALINE MM-1 [28, 30, 32–34], the expert panel agreed that cytogenetic is not a discriminant for therapy choice at first relapse since all triplet therapies included in the above trials are likewise effective in high-risk disease. On the contrary, in relapse, duplet therapies such as lenalidomide-dexamethasone (Rd), bortezomib-dexamethasone (Vd), and carfilzomib-dexamethasone (Kd) are less effective in high-risk disease.

Prior Therapy, Response, and Duration of Response

As reported by the IMWG, depth and duration of the response to prior treatment should be evaluated for a suitable choice of subsequent therapy. They recommended that relapse can be treated with the same regimen or adding drug to the same regimen when the duration of the response reaches 24 months with standard therapy, 18–24 months with autologous stem cell transplantation (ASCT) without maintenance, and 36–48 months with ASCT followed by maintenance [16]. Moreover, in patients eligible for transplantation, ASCT salvage therapy can be considered when the first remission duration lasted at least 24 months. However, the expert panel agreed that re-treatment is not just the best therapeutic option, in light of the recently available results obtained with the triplet therapies. Patients who were treated with bortezomib-based regimens in first line should receive lenalidomide-based triplets (KRd, EloRd, DRd, IRd) or Kd whereas in those treated with lenalidomide-based regimens as induction DVd, EloVD, or Kd should be used. Patient refractory to lenalidomide should receive DVd or Kd whereas those refractory to bortezomib should receive EloRd or DRd or even KRd.

Toxicity of Prior Therapy

Among the side effects occurred during induction therapy, the most discriminating to choose therapy at relapse is the bortezomib-induced peripheral neuropathy. In patients with these side effects, bortezomib-based regimens are not recommended but the other proteasome inhibitors should be used cautiously whereas IMiD-based regimens can be administered safely. In patients with a prior thromboembolic event, adequate thromboprophylaxis should be administered if a IMiD-based regimen is chosen.

Type of Relapse

First relapse should be recognized as biochemical or clinical according to the above definitions. Biochemical relapse not fulfilling the criteria of treatment should be observed with examination and ambulatory visit every 2 months or less. Biochemical relapse needing therapy should be treated as non-aggressive clinical relapse. Clinical relapse should be distinguished between aggressive and non-aggressive as per expert panel definition and treated accordingly (Fig. 1).

Quality of Life/Patient Choice/Caregiver Availability/Traveling

Quality of life and patient choice and caregiver availability and travel possibility should be carefully taken into account in the choice of therapy at first relapse. Indeed, the success of the treatment is strictly connected with adherence to therapy, and discontinuation might be the major cause of a poor outcome. Finding a balance between treatment strategy and quality of life is strictly recommended in all patients with relapsed MM.

MM Patient Management: The Proposed Decisional Algorithm (Fig. 2)

With the development of new therapeutic regimens, the treatment choice at relapse is wider than in the past. As of today, in order to

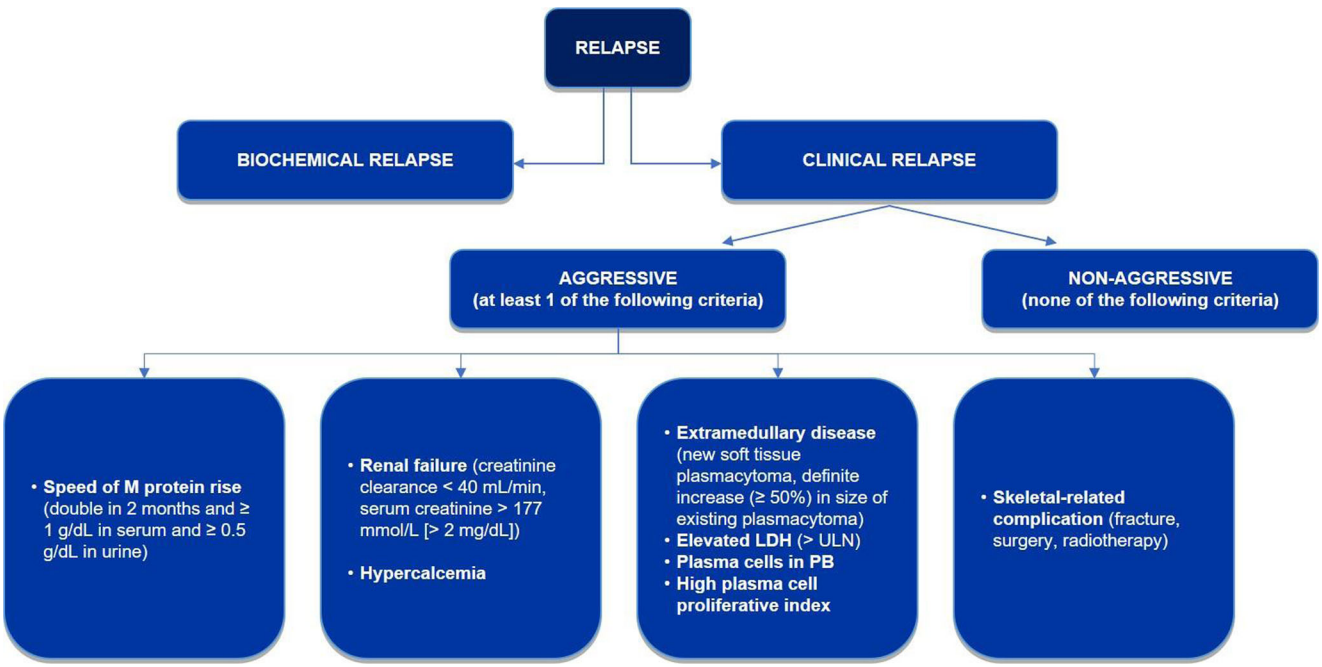

Fig. 1 Decisional tree in the evaluation of aggressive vs non-aggressive relapse. PB peripheral blood, ULN upper limit normal

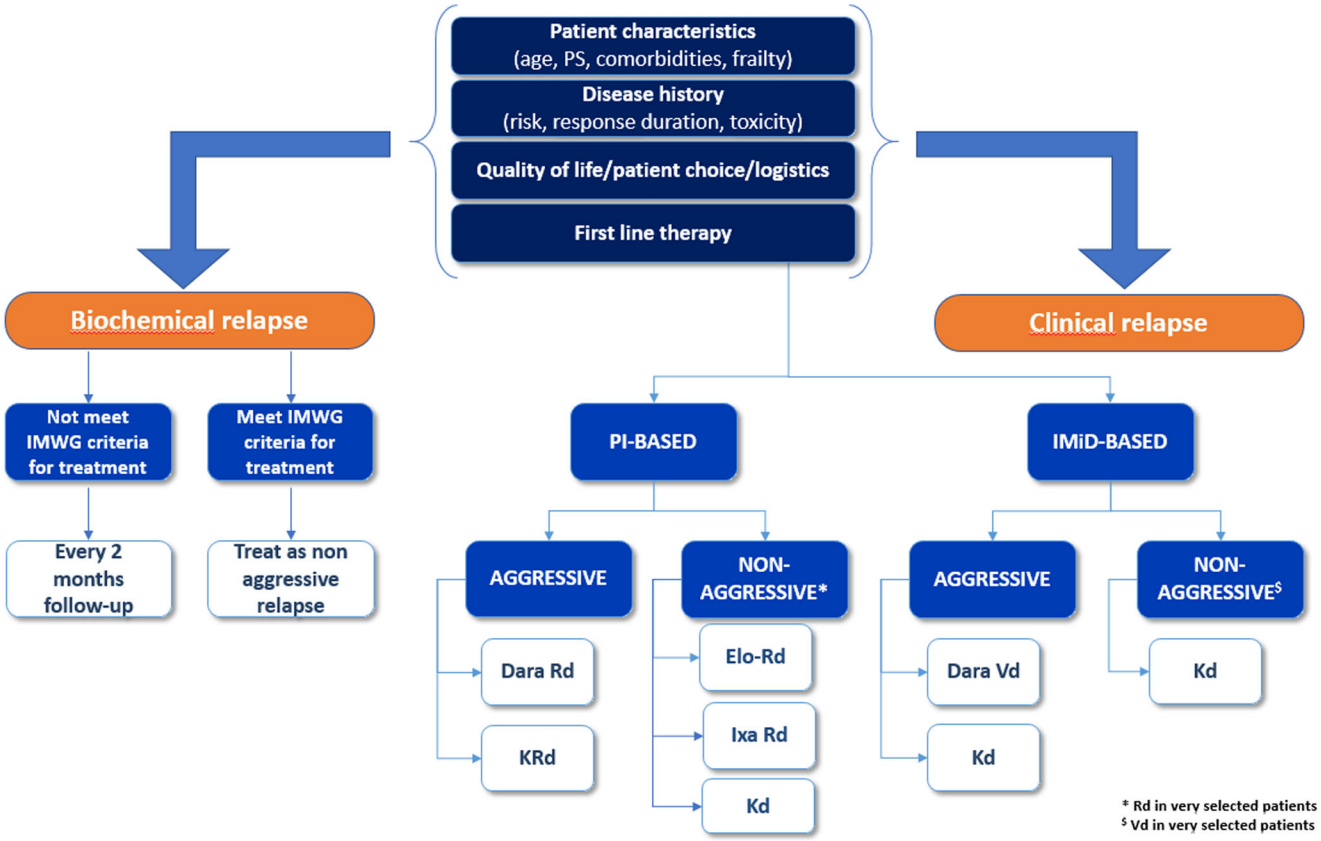

Fig. 2 Decisional tree in the management of relapsed MM. IMWG International Myeloma Working Group, PS performance score, D daratumumab, Elo elotuzumab, IMiD immunomodulatory drug, I ixazomib, K carfilzomib, d dexamethasone, R lenalidomide, PI proteasome inhibitor, V bortezomib

make appropriate decisions, it is really important to take into account the characteristics of the disease, the profile of the individual patient, and the components of the initial therapy.

A salvage ASCT can be proposed in young patients at first relapse if stem cells are available and an 18–24 months least duration of time from the first ASCT has been reached. The same approach is also feasible in patients with durable and high-quality response to the first-line treatment using the same agents for re-treatment, but the currently broader choice of treatment options suggests switching to a different drug class as being a better approach at first relapse. After the evaluation of patient characteristics, disease history, prior therapy toxicity, and quality of life/patient choice, the expert panel agreed that the aggressiveness of relapse becomes the main driver of treatment choice. The expert panel agreed that relapse should be considered aggressive if the M protein rate doubles over 2 months (and reaches at least 1 g in the serum and 0.5 g in the urine) or in the presence of one of the following conditions: renal insufficiency, hypercalcemia, extramedullary disease, elevated LDH, high plasma cell proliferative index, presence of plasma cells in peripheral blood, or skeletal-related complications. For patients with aggressive relapse, as defined above, the treatment might include daratumumab in combination with bortezomib and dexamethasone (DVd) or lenalidomide and dexamethasone (DRd) or carfilzomib in combination with lenalidomide and dexamethasone (KRd). The agreement reached in this regard by the expert panel is based on the fact that these regimens might have the highest probability to reach a deep and fast response as needed in the aggressive relapse setting.

For patients with non-aggressive relapse, as defined above, the treatment could include elotuzumab in combination with lenalidomide and dexamethasone (Elo-Rd) or ixazomib in combination with lenalidomide and dexamethasone (IRd) or carfilzomib and dexamethasone (Kd). The agreement reached by the expert panel is based on the fact that in the non-aggressive relapse setting, long-term control, maximizing safety, is the main goal of therapy.

Conclusions and Future Directions

In the last few years, several new agents have been approved by the European Medicines Agency (EMA) for the treatment of MM, with particular regard to the treatment of relapsed disease. If not yet marketed, these agents will be available soon in clinical practice. MM is a highly relapsing and still incurable malignancy. Based on the increase in OS observed in the last decade [7], novel therapies are welcome with great

expectations in terms of further improvements in the management of this disease. However, the increased number of therapeutic options will also increase the complexity of treatment selection. Furthermore, in addition to novel agents, new combinations are also going to be evaluated in the management of MM, leading to increased diversity of approach and relevant risk of inappropriate treatment decisions. In such a context, a unique classification of relapse might help clinicians to choose the proper treatment, reducing complexity and heterogeneity. Relapse aggressiveness, together with patient characteristics, should guide clinical decisions made with the aim of managing each patient with the most appropriate therapeutic option.

For this purpose, the expert panel has proposed an easy and practical classification of relapse into aggressive or non-aggressive to be included in a decisional algorithm on MM management at first relapse. The purpose of this new algorithm will help to make the appropriate treatment decisions, although the therapeutic choice should ultimately be a clinical decision based on a case by case evaluation, awaiting molecular markers for precision medicine.

Compliance with Ethical Standards

Conflict of Interest M. Boccadoro, M. Cavo, F. Di Raimondo, M. Offidani, M.T. Petrucci, and P. Tosi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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