Multiple myeloma: Overview of management

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INTRODUCTION

Multiple myeloma (MM) is characterized by the neoplastic proliferation of clonal plasma cells producing a monoclonal immunoglobulin. These clonal plasma cells proliferate in the bone marrow and often result in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. Additional disease-related complications include hypercalcemia, renal insufficiency, anemia, and infections.

This topic reviews the overall treatment strategy for patients with MM. Further details regarding the selection of initial therapy, the treatment of relapsed and/or refractory disease, the use of hematopoietic cell transplantation, and the management of complications of MM are discussed separately.

- (See "Multiple myeloma: Selection of initial chemotherapy for symptomatic disease".)
- (See "Multiple myeloma: Use of autologous hematopoietic cell transplantation".)
- (See "Multiple myeloma: Treatment of relapsed or refractory disease".)
- (See "Multiple myeloma: Management in resource-poor settings".)
- (See "Multiple myeloma: Treatment of complications".)
- (See "Multiple myeloma: The use of osteoclast inhibitors".)
- (See "Treatment and prognosis of kidney disease in multiple myeloma and other monoclonal gammopathies".)

VERIFY THE DIAGNOSIS

The first step in evaluating a new patient with MM is to verify the diagnosis since the premalignant stages of myeloma, namely monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM), may be easily misdiagnosed as MM if one is not careful (table 1 and algorithm 1). As an example, patients with MGUS may have renal failure due to diabetes or hypertension, or have bone lesions from other cancers. Such patients may be misdiagnosed with MM if these findings are incorrectly attributed to the plasma cell dyscrasia. Therefore, every effort should be made to determine whether the observed "end-organ damage" is truly secondary to the underlying plasma cell disorder or to an unrelated process. (See "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Diagnosis'.)

Unlike persons with MGUS and SMM, all patients with a confirmed diagnosis of MM require treatment. Without effective therapy, symptomatic patients die within a median of six months [1]. In contrast, patients with SMM may remain stable for prolonged periods. As such, if there is doubt about whether the patient has SMM or MM, a reasonable approach is to re-evaluate the patient in two or three months and to delay therapy until the correct diagnosis is evident. The patient should be instructed to monitor for symptoms related to MM and contact the provider immediately should there be a change in his or her condition.

PRETREATMENT EVALUATION

The initial evaluation of patients with MM must establish the extent and sites of disease, the patient's performance status (table 2), and comorbid conditions that could complicate overall management. In addition, specific tests are performed for risk stratification and to determine eligibility for autologous hematopoietic cell transplantation (HCT). Particular attention should be paid in the history and physical examination to constitutional symptoms, bone pain, neurologic findings, and infections.

Our pretreatment evaluation also includes the following studies, some of which are performed as part of the diagnostic evaluation (see "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Evaluation'):

- A complete blood count and differential with examination of the peripheral blood smear.
- A chemistry screen plus measurements of serum calcium, albumin, lactate dehydrogenase, and beta-2 microglobulin. (See "Multiple myeloma: Staging and prognostic studies".)

- Serum creatinine and an estimation of glomerular filtration rate [2]. The assessment of GFR and evaluation to determine the cause of renal dysfunction is discussed separately. (See "Assessment of kidney function", section on 'Assessment of GFR' and "Clinical features, evaluation, and diagnosis of kidney disease in multiple myeloma and other monoclonal gammopathies".)
- Serum free light chain (FLC) assay.
- A serum protein electrophoresis (SPEP) with immunofixation and quantitation of immunoglobulins. A routine urinalysis and a 24-hour urine collection for protein electrophoresis (UPEP) and immunofixation. (See "Laboratory methods for analyzing monoclonal proteins".)
- Bone marrow aspiration and biopsy with immunophenotyping and fluorescence in situ hybridization (FISH). FISH should include probes that identify t(11;14), t(4;14), t(6;14), t(14;16), t(14;20), del17p13, gain 1q, and trisomies of odd numbered chromosomes. FISH for del1p32 can provide additional prognostic information, if available. (See "Multiple myeloma: Staging and prognostic studies", section on 'Other cytogenetic lesions and prognosis'.)
- Cross sectional imaging (eg, CT, PET/CT, or MRI) for the detection of bone involvement. The choice of imaging modality is discussed separately. (See "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Choice of modality'.)

A comprehensive geriatric assessment may be useful in assessing comorbidity and functional status in the older patient with MM, thus permitting the formulation of an appropriate, individualized treatment plan [3]. (See "Comprehensive geriatric assessment for patients with cancer".)

RISK STRATIFICATION

We risk stratify individual cases based on the results of fluorescence in situ hybridization (FISH) for specific translocations and certain other tests (table 3). This risk stratification helps to determine prognosis and impacts treatment choice (algorithm 2):

- **High-risk myeloma –** We consider patients with at least one of the following clinical or pathologic criteria to have high-risk MM:
  - t(4;14), t(14;16), t(14;20), del17p13, or gain 1q by FISH
  - Lactate dehydrogenase (LDH) levels ≥2 times the institutional upper limit of normal
  - Features of primary plasma cell leukemia (defined by either ≥2000 plasma cells/microL of peripheral blood or ≥20 percent on a manual differential count) (see "Plasma cell leukemia")

  While patients with a high-risk signature on gene expression profiling (GEP) are considered to have high-risk myeloma, this test is not recommended on a routine basis.
- **Standard-risk myeloma** – We consider patients who lack all of the high-risk abnormalities described above to have standard-risk MM. This includes patients with trisomies, t(11;14), and t(6;14).

Our risk stratification has evolved over time and will continue to change as our understanding regarding the prognostic value of specific cytogenetic findings in MM improves. While we test for all of the FISH markers described above, some are not available in some regions of the world. The Revised International Staging System, which takes into account the international availability of specific FISH probes, considers patients with any of the following as having high-risk MM: t(4;14), t(14;16), and del17p [4].

Support for our risk stratification comes from the following (see "Multiple myeloma: Staging and prognostic studies"):

- Patients with t(4;14), t(14;16), t(14;20), del17p13, or gain 1q by FISH account for approximately 25 percent of MM and have a shortened median survival with standard treatment [5].
- While deletion 13 and hypodiploidy have been considered adverse prognostic factors when detected by conventional cytogenetics, these are not independent predictors of poor outcome when FISH results are taken into account.
- There are conflicting data on whether the presence of trisomies can ameliorate some of the adverse prognostic effects of high-risk cytogenetic abnormalities. We do not downgrade our risk assignment for those with trisomies.
- Elevated LDH is a marker of adverse prognosis in myeloma. Elevated LDH is included in the calculation of the revised International Staging System (R-ISS) and is used as an inclusion criterion for trials investigating novel therapies for patients with high-risk MM.
- Patients with a high-risk signature on GEP are also considered to have high-risk MM, but this test is not recommended on a routine basis.

The underlying genetic abnormalities in the myeloma clone dictates disease biology and are a major predictor of outcome. Prognosis also depends on host factors (age, performance status, comorbidities), stage, and response to therapy. Staging and prognosis is discussed in more detail separately as is the impact of specific cytogenetic findings. (See "Multiple myeloma: Staging and prognostic studies".)

DETERMINING TRANSPLANT ELIGIBILITY

Following diagnosis and risk stratification, all patients are assessed to determine eligibility for autologous hematopoietic cell transplantation (HCT). When compared with chemotherapy alone, autologous HCT appears to prolong both event-free and overall survival. Stem cell collection should occur early in the treatment course for all eligible patients regardless of whether the plan is for HCT to be incorporated into the initial treatment or postponed until the time of first relapse. The initial chemotherapy given to patients who are candidates for HCT should limit agents that may impair stem cell collection or damage stem cells. Eligibility criteria are discussed in the following section. Practical issues regarding the use of autologous HCT in myeloma are presented separately. (See "Multiple myeloma: Use of autologous hematopoietic cell transplantation".)

A minority of patients will be eligible for allogeneic HCT, but the role of allogeneic approaches in MM remains investigational and controversial. (See "Multiple myeloma: Use of allogeneic hematopoietic cell transplantation" and "Determining eligibility for allogeneic hematopoietic cell transplantation".)

General eligibility requirements — Eligibility for autologous HCT in MM varies across countries and institutions. In most European countries, transplantation for MM is offered primarily to patients younger than 65 years of age. In the United States (US), a strict age limit is not used. Instead, decisions are made on a case-by-case basis based on "physiologic age" and vary across institutions. (See "Determining eligibility for autologous hematopoietic cell transplantation".)

In most centers in the US, patients with one or more of the following factors are **not** usually considered eligible for autologous HCT in myeloma:

- Age >77 years
- Frank cirrhosis of the liver
- Eastern Cooperative Oncology Group (ECOG) performance status 3 or 4 unless due to bone pain (table 4)
- New York Heart Association functional status Class III or IV (table 5)

These are guidelines and the decision on transplant eligibility should be made based on a risk-benefit assessment and the needs and wishes of the patient. There is insufficient evidence at this time that the newer chemotherapeutic programs (eg, bortezomib, lenalidomide) will result in a reduced need for HCT.

In the US, the Centers for Medicare and Medicaid Services approves reimbursement for high-dose therapy with autologous HCT in newly diagnosed patients with myeloma who are less than 78 years old and have Durie-Salmon stage II or III disease, and for selected patients who have been previously treated. Additional details are available on the Centers for Medicare and Medicaid Services website at www.cms.gov. Studies that have evaluated the impact of age on transplant efficacy are described in more detail separately. (See "Determining eligibility for autologous hematopoietic cell transplantation", section on 'Age'.)

Dose adjustment of the conditioning regimen is often necessary for older adults undergoing HCT. This is discussed in more detail separately. (See "Multiple myeloma: Use of autologous hematopoietic cell transplantation", section on 'Older adults'.)

Renal function — Autologous HCT may be safely performed among patients with all stages of kidney disease, even among patients on dialysis. Renal impairment appears to have no adverse effect on either the quality of stem cell collection or engraftment following autologous HCT [6].

The randomized trials that have shown benefit with HCT compared with chemotherapy have mainly studied patients with serum creatinine <2 mg/dL (177 micromol/L). Patients with higher creatinine levels can have a more complicated transplant course and must be approached with care. The conditioning regimen should use a reduced dose of melphalan since toxicity is increased with standard doses in this population. (See "Multiple myeloma: Use of autologous hematopoietic cell transplantation", section on 'Patients with renal insufficiency'.)

Retrospective series suggest that HCT in patients with MM and dialysis-dependent renal failure is associated with a relatively high transplant-related mortality (15 percent) and greater toxicity than in those without renal dysfunction [7]. Studies evaluating autologous HCT in patients with MM and renal impairment are presented separately. (See "Determining eligibility for autologous hematopoietic cell transplantation", section on 'Renal dysfunction'.)

Renal function can also be used to determine eligibility for an outpatient HCT. In our experience and that of others, more than one-half of patients with a serum creatinine <2 mg/dL (177 micromol/L) (or <3 mg/dL [265 µmol/liter]) can undergo HCT as an outpatient [8].

INITIAL THERAPY

Induction therapy — The initial therapy of patients with symptomatic MM depends on risk stratification, eligibility for autologous hematopoietic cell transplantation (HCT), and resources available (algorithm 2). There is no general agreement as to the preferred induction regimen and different experts use different regimens. Our preferred approach and data supporting this approach are discussed in more detail separately, as are alternatives for resource-poor settings. (See "Multiple myeloma: Selection of initial chemotherapy for symptomatic disease" and "Multiple myeloma: Management in resource-poor settings".)

The duration of induction therapy depends on the regimen used and whether the patient will proceed with HCT:

- Patients **eligible** for HCT receive induction therapy with a triplet regimen for three to four months prior to stem cell collection in order to reduce the number of tumor cells in the bone marrow and peripheral blood, lessen symptoms, and mitigate end-organ damage. During this time, specific

arrangements for the subsequent HCT can be made to ease the transition of therapy. Stem cells are collected at this time regardless of whether an early or delayed transplant strategy is used. Those who choose to delay HCT until first relapse complete a total of 8 to 12 cycles of initial therapy followed by maintenance until relapse. (See 'HCT eligible' below.)

- Patients **ineligible** for HCT receive 8 to 12 cycles of initial therapy with a triplet regimen followed with maintenance therapy until progression unless there is significant toxicity. In patients who are frail and are not felt to be candidates for triplet therapy, we offer doublet therapy with lenalidomide and low dose dexamethasone until progression [3]. (See 'HCT ineligible' below.)

Post-induction therapy

HCT eligible — Following induction therapy and stem cell collection, patients who are eligible for HCT must choose among the following approaches:

- Early transplant strategy – Proceed with autologous HCT (single or double) directly after recovery from stem cell collection
- Delayed transplant strategy – Continued therapy, usually with the same regimen used for induction, reserving autologous HCT until first relapse
- Allogeneic HCT

For most patients, the preferred approach is induction chemotherapy followed by early or delayed autologous HCT rather than allogeneic HCT. The incorporation of autologous HCT into the treatment strategy improves progression-free survival (PFS) and overall survival (OS) over that seen with standard doses of chemotherapy alone. Studies evaluating early and delayed transplant strategies have demonstrated similar survival rates so either option is acceptable for most patients. Although allogeneic HCT offers a chance for cure, its use in initial therapy is limited by high early mortality rates and morbidity. (See "Multiple myeloma: Use of allogeneic hematopoietic cell transplantation".)

The choice between early and delayed HCT is individualized. The factors that influence this decision include patient preference, risk stratification (early HCT is preferred for high-risk MM), patient age (as age approaches 70, early HCT is preferred), response and tolerability to the initial chemotherapy regimen, insurance approval (some insurers do not cover stem cell harvest and cryopreservation without immediate transplantation), and whether centers have the facilities and resources for long-term storage of stem cells. Importantly, patients who choose to delay transplant may have an event or complication that makes them ineligible for transplant in the future. This is discussed in more detail separately. (See "Multiple myeloma: Use of autologous hematopoietic cell transplantation", section on 'Timing of HCT'.)

Autologous HCT versus chemotherapy alone — Autologous HCT remains a key component of myeloma therapy in eligible patients and can be incorporated as part of the initial therapy or at the time of first relapse, depending on risk stratification. For eligible patients with MM, we recommend induction therapy followed by early or delayed autologous HCT rather than conventional chemotherapy alone. For standard-risk MM, it is reasonable to consider patient preference and other logistics in deciding between early or delayed HCT. For high-risk MM, we prefer early HCT based on data that such an approach has generally yielded the best long-term survival results [9]. When compared with chemotherapy alone, autologous HCT prolongs survival and is associated with low nonrelapse mortality in the modern era. An analysis of autologous HCT in 1156 patients with MM reported a one-year nonrelapse mortality of 2 percent (95% CI 1-4 percent) [10]. (See "Determining eligibility for autologous hematopoietic cell transplantation".)

In randomized trials comparing autologous HCT versus chemotherapy alone, autologous HCT improved event-free survival (EFS) and OS [11-15]. In these trials, patients in the chemotherapy arm were not eligible for HCT at the time of relapse.

Many of these trials used older induction therapies and none used a triplet regimen. Two incorporated lenalidomide into the induction regimen:

- In one trial, 273 patients received four cycles of lenalidomide plus dexamethasone (Rd) followed by stem cell collection and were then randomly assigned to consolidation with melphalan, prednisone, lenalidomide (MPR) or with high dose melphalan plus autologous HCT [14]. At a median follow-up of 51 months, HCT resulted in longer median PFS (43 versus 22 months; hazard ratio [HR] 0.44; 95% CI 0.32-0.61) and OS (82 versus 65 percent at four years; HR 0.55; 95% CI 0.32-0.93).
- In a second trial, 256 patients underwent induction with Rd followed by stem cell collection and were randomly assigned to consolidation with Rd plus cyclophosphamide or with high dose melphalan plus autologous HCT [15]. After a median follow-up of 52 months, those assigned to chemotherapy without HCT had shorter PFS (median 29 versus 43 months; HR 2.51; 95% CI 1.60-3.94) and OS (73 versus 86 percent at four years; HR 2.40; 95% CI 1.32-4.38).

Several additional randomized trials comparing early HCT versus chemotherapy allowed for HCT at the time of relapse and have not found a survival benefit [16-22]. These studies are more difficult to interpret since they do not directly address the value of HCT as a modality versus chemotherapy alone. However, given the OS benefit seen in a few randomized trials and the marked limitations of the studies that failed to show a benefit, we believe that there is a significant survival benefit to autologous HCT when compared with chemotherapy alone. However, for standard-risk MM, it appears that OS is similar whether HCT is performed as part of initial therapy (early HCT) or at the time of first relapse (delayed HCT) [23].

Autologous versus allogeneic HCT — A minority of patients will be eligible for allogeneic HCT, but the role of allogeneic approaches in MM remains investigational. We offer young patients with high-risk relapsed MM the opportunity to discuss the risks and benefits of allogeneic HCT with a transplant specialist. A decision to perform HCT in this population is largely driven by patient values, preferences, and risk aversion. Such transplants should ideally be conducted in the context of a clinical trial. (See "Multiple myeloma: Use of allogeneic hematopoietic cell transplantation".)

Although allogeneic HCT may be a potentially curative treatment for MM, initial treatment with high dose chemotherapy followed by allogeneic HCT is not commonly employed. This is due to many factors including the fact that a majority of patients are ineligible due to older age or comorbidities and because it is associated with high rates of overall mortality and symptoms of graft-versus-host disease. Moreover the higher probability of cure compared with autologous transplantation remains unproven. We do not recommend **myeloablative** allogeneic HCT for standard-risk MM at this time due to the excessively high mortality rate and toxicity and lack of proven benefit compared with autologous HCT [16,24]. It may be considered, ideally in the context of a clinical trial, in selected young patients with high-risk relapsed MM.

Both prospective and retrospective studies have evaluated the use of **nonmyeloablative** HCT in MM. Nonmyeloablative HCT relies primarily on a graft-versus-myeloma effect, which is unfortunately often accompanied by the detrimental effects of graft-versus-host disease. Outcomes with this therapeutic approach have been mixed. Due to conflicting results, high treatment-related mortality, and toxicity [25], nonmyeloablative allogeneic HCT is not advised for patients with newly diagnosed myeloma outside of a clinical trial setting, except in selected young patients with high-risk relapsed MM. This is discussed in more detail separately. (See "Multiple myeloma: Use of allogeneic hematopoietic cell transplantation".)

Maintenance after HCT — Since virtually all patients who receive autologous HCT for MM eventually develop relapsed disease, trials have investigated the use of chemotherapeutic and biologic agents in an attempt to eliminate residual malignant cells after HCT. Our preferred treatment approach uses lenalidomide maintenance for standard-risk patients, and proteasome-inhibitor-based maintenance for high-risk patients (algorithm 2). The use of maintenance therapy after HCT is discussed in more detail separately. (See "Multiple myeloma: Use of autologous hematopoietic cell transplantation", section on 'Maintenance'.)

HCT ineligible

Maintenance therapy — There is ongoing debate regarding the role of maintenance therapy in patients with MM who are not candidates for autologous HCT and experts differ in their approach. We suggest maintenance therapy for most patients; this preference places a high value on delaying progression and the potential for an as yet unproven survival benefit, and places a lower value on the risks associated with continued therapy. The type of maintenance depends on risk stratification and comorbidities (algorithm 2). The risk of second cancers must be discussed with all patients who are treated with lenalidomide maintenance [26].

- High-risk MM – Following 8 to 12 cycles of triplet therapy, we offer patients with high-risk MM proteasome-inhibitor-based maintenance until progression.
- Standard-risk MM – Following 8 to 12 cycles of triplet therapy, we offer patients with standard-risk MM lenalidomide-based maintenance until progression.
- Frail patients – The doublet regimen of lenalidomide plus dexamethasone used for frail patients with standard-risk MM should generally be continued until progression unless there is significant toxicity.

The rationale for maintenance therapy in MM includes the incurability of MM and recognition that relapse may present acutely with life-threatening complications. So far, prospective trials suggest that maintenance therapy prolongs PFS, but data are limited to determine if there is meaningful improvement in OS.

Most studies of lenalidomide maintenance were performed in patients who underwent HCT. These are discussed in more detail separately. (See "Multiple myeloma: Use of autologous hematopoietic cell transplantation", section on 'Maintenance'.)

The few studies that have examined the role of maintenance in patients who have not undergone HCT are described below.

- In a double-blind, multicenter, phase III trial, 459 older adults with previously untreated MM who were not candidates for HCT were randomly assigned to one of three treatment combinations: melphalan and prednisone plus lenalidomide induction followed by lenalidomide maintenance (MPR-R); melphalan and prednisone plus lenalidomide induction followed by placebo (MPR); or melphalan and prednisone induction followed by placebo (MP) [27]. At a median follow-up of 30 months, MPR-R resulted in a longer median PFS when compared with MPR and MP (31 versus 14 and 13 months, respectively). However, there was no difference in rates of OS at three years (70, 62, and 66 percent, respectively). Lenalidomide maintenance was discontinued in 8 percent due to adverse events.
- Results from this trial were combined with those from two others in a 2015 meta-analysis comparing continuous therapy versus fixed duration therapy in patients with newly diagnosed MM [28]. This analysis was restricted to the 1218 patients who were progression-free and alive at one year after random assignment (ie, those eligible for continuous therapy). Two trials used lenalidomide maintenance while one used maintenance with bortezomib and thalidomide. After a median follow-up of 52 months, maintenance therapy resulted in improved PFS (median 32 versus 16 months, HR 0.47; 95% CI 0.40-0.56), second PFS (median 55 versus 40 months, HR 0.61; 95% CI 0.50-0.75), and OS (69 versus 60 percent alive at four years, HR 0.69; 95% CI 0.54-0.88). The improved second PFS suggests that the administration of maintenance therapy did not adversely impact the ability to respond to subsequent therapy. However, it is not clear whether all patients in the control arms had access to lenalidomide and bortezomib at the time of relapse. Toxicity and impact on quality of life were not examined.
- Lenalidomide maintenance was incorporated into both arms of the SWOG S0777 trial, which demonstrated superior results with VRd versus Rd in previously untreated MM, including those ineligible for transplant [29]. However, the impact of maintenance on the outcomes seen in this trial cannot be assessed given the lack of a maintenance-free control arm.

EVALUATING RESPONSE TO TREATMENT

Response criteria and monitoring for relapse — Patients should be evaluated before each treatment cycle to determine how the disease is responding to therapy (ie, tumor burden) and to assess for potential treatment-related and disease-related complications. Details of this evaluation are presented separately. (See "Multiple myeloma: Evaluating response to treatment" and 'Prevention and management of complications' below.)

Briefly, the preferred method for assessing tumor burden in a given patient depends on the results of baseline studies and on the suspected degree of response (table 6). The International Myeloma Working Group (IMWG) uniform response criteria are the preferred criteria to determine the patient's best response to treatment and to define when a relapse has occurred (table 7).

The rationale for monitoring disease response is to modify therapy if needed, adjust doses based on response and toxicity, and to identify transplant candidates with resistant disease. In such patients, early hematopoietic cell transplantation (HCT) may be preferred. (See "Multiple myeloma: Use of autologous hematopoietic cell transplantation".)

Approximately 7 percent of patients will develop a secondary monoclonal gammopathy of undetermined significance (MGUS) defined as a new monoclonal protein that has an isotype (heavy and/or light chain) distinct from the original clone (eg, IgM MGUS in a patient with IgG MM). This is discussed in more detail separately. (See "Diagnosis of monoclonal gammopathy of undetermined significance", section on 'Secondary MGUS'.)

Significance of response to chemotherapy — The depth of response has prognostic value in myeloma. Patients who achieve a minimal residual disease (MRD)-negative state have superior progression-free and overall survival compared to those in whom MRD testing shows residual disease [30]. However, there are no data from randomized trials evaluating whether outcomes can be improved by administering additional therapy to patients with MRD-positive disease. Thus, although the depth of response has prognostic value, we need more data on whether better outcomes can be achieved by altering therapy based on the extent of response. Randomized trials are being conducted to address this question. MRD assessment is discussed in more detail separately. (See "Multiple myeloma: Evaluating response to treatment", section on 'Minimal residual disease assessment'.)

RELAPSED DISEASE

Almost all patients with MM who survive initial treatment will eventually relapse and require further therapy. Relapsed or refractory MM is usually identified on routine surveillance.

Therapy for relapsed disease is indicated if there is a clinical relapse or a rapid rise in paraproteins [31,32]. Clinical relapse occurs when the patient develops CRAB symptoms (hypercalcemia, renal insufficiency, anemia, or new bone lesions). Relapsed disease can also be documented when there is a doubling of the monoclonal protein over two months, with an increase in the absolute levels of monoclonal protein of ≥1 g/dL in the serum or of ≥500 mg per 24 hours in the urine, confirmed by two consecutive measurements. (See "Multiple myeloma: Treatment of relapsed or refractory disease".)

Treatment options for patients with relapsed or refractory MM include hematopoietic cell transplantation (HCT), a rechallenge of the previous chemotherapy regimen, or a trial of a new regimen. Factors used to determine the choice of therapy include a risk stratification of myeloma (ie, high- or standard-risk disease), prior treatments used, and the duration of response to these treatments. The treatment of relapsed or refractory MM is presented separately. (See "Multiple myeloma: Treatment of relapsed or refractory disease".)

PREVENTION AND MANAGEMENT OF COMPLICATIONS

In addition to therapy directed at the malignant clone, the management of most patients with MM includes preventative measures to reduce the incidence of skeletal events, renal damage, infections, and thrombosis.

- Skeletal lesions and bone health – Osteoclast inhibitors (eg, bisphosphonate therapy) are administered to prevent skeletal events in patients with one or more lesions on skeletal imaging and those with osteopenia. (See "Multiple myeloma: The use of osteoclast inhibitors".)

  Skeletal lesions can result in bone pain, pathologic fractures, and spinal cord compression.

  - Pathologic fractures or impending fractures of long bones require stabilization. Vertebral fractures may benefit from kyphoplasty or vertebroplasty. Most pain related to lytic lesions can be controlled with the combination of analgesics and active myeloma chemotherapy. (See "Multiple myeloma: Treatment of complications", section on 'Skeletal lesions'.)

  - Spinal cord compression is a clinical emergency and should be suspected in patients with severe back pain, weakness, or paresthesias of the lower extremities, or bladder or bowel dysfunction or incontinence. (See "Treatment and prognosis of neoplastic epidural spinal cord compression".)

- Renal insufficiency – All patients with MM should take measures to minimize renal damage (eg, avoid nephrotoxins such as aminoglycosides and NSAIDs and maintain adequate hydration). Many medications used for myeloma require dose adjustment for renal insufficiency (eg, lenalidomide, zoledronic acid). Treatment of renal insufficiency is directed at the underlying cause. (See "Multiple myeloma: Treatment of

complications", section on 'Renal insufficiency' and "Treatment and prognosis of kidney disease in multiple myeloma and other monoclonal gammopathies".)

- Infection – Prophylactic measures that may minimize infection in patients with MM include yearly influenza vaccines, pneumococcal vaccine at the time of diagnosis, prophylactic antibiotics during the first months of induction chemotherapy, and intravenous immune globulin for selected patients who have recurrent, serious infections. Patients suspected of having an infection should be treated promptly with empiric antibiotics covering encapsulated bacteria and gram-negative micro-organisms. (See "Multiple myeloma: Treatment of complications", section on 'Infection' and "Immunizations in adults with cancer" and "Treatment and prevention of neutropenic fever syndromes in adult cancer patients at low risk for complications".)

- Thromboprophylaxis – Patients with MM are at increased risk of having comorbidities known to be risk factors for the development of venous thromboembolism (VTE) in the general population. In addition, treatment with immunomodulatory drugs (eg, lenalidomide, pomalidomide, thalidomide) has been associated with high rates of VTE. All patients with MM should have an assessment of their VTE risk so that appropriate prophylaxis may be employed. (See "Multiple myeloma: Prevention of venous thromboembolism in patients receiving immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide)".)

Patients with MM may also require specific interventions for the management of hypercalcemia, anemia, and neuropathy.

- Hypercalcemia – Patients with hypercalcemia may be asymptomatic or present with anorexia, nausea, vomiting, polyuria, polydipsia, constipation, weakness, confusion, or stupor. The treatment of hypercalcemia depends on the calcium level, the rapidity with which it developed, and the patient's symptoms. Emergent treatment with hydration, glucocorticoids, bisphosphonates, and/or hemodialysis/calcitonin is indicated for symptomatic patients. (See "Multiple myeloma: Treatment of complications", section on 'Hypercalcemia' and "Treatment of hypercalcemia".)

- Anemia – The treatment of anemia associated with myeloma depends on the severity of the anemia, the presence or absence of symptoms related to anemia, and whether the patient is undergoing active chemotherapy. Patients with significant symptoms should be considered for red blood cell transfusion. Erythropoiesis-stimulating agents are generally reserved for patients receiving chemotherapy with a hemoglobin level of 10 g/dL or less. (See "Multiple myeloma: Treatment of complications", section on 'Anemia' and "Role of erythropoiesis-stimulating agents in the treatment of anemia in patients with cancer".)

- Neuropathy – Patients with MM can develop peripheral neuropathy related to the disease itself or as a toxicity of treatment (eg, bortezomib, thalidomide). When it occurs, the painful sensory neuropathy can interfere with quality of life and with performance of activities of daily living, and it may require dose modification and/or treatment discontinuation. (See "Overview of neurologic complications of non-platinum cancer chemotherapy", section on 'Bortezomib' and "Overview of neurologic complications of non-platinum cancer chemotherapy", section on 'Thalidomide and related agents'.)

CLINICAL TRIALS

Often there is no better therapy to offer a patient than enrollment onto a well-designed, scientifically valid, peer-reviewed clinical trial. Additional information and instructions for referring a patient to an appropriate research center can be obtained from the United States National Institutes of Health (www.clinicaltrials.gov).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Multiple myeloma".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Multiple myeloma (The Basics)")

- Beyond the Basics topics (see "Patient education: Multiple myeloma symptoms, diagnosis, and staging (Beyond the Basics)" and "Patient education: Multiple myeloma treatment (Beyond the Basics)" and "Patient education: Hematopoietic cell transplantation (bone marrow transplantation) (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Verification of the diagnosis** – The first step in evaluating a new patient with MM is to verify the diagnosis since the premalignant stages of myeloma, namely monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM), may be easily misdiagnosed as MM if one is not careful (table 1 and algorithm 1). (See 'Verify the diagnosis' above and "Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis", section on 'Diagnosis'.)
  - Among patients with SMM, we recommend deferral of chemotherapy until disease progression (**Grade 1B**). (See "Smoldering multiple myeloma".)
  - Patients who have end-organ damage attributable to the underlying plasma cell disorder or other myeloma-defining biomarker require therapy.
  - For all patients with MM, we recommend prompt initiation of treatment (**Grade 1B**). Without effective therapy, symptomatic patients have a life expectancy less than one year.
- **Risk stratification** – We risk stratify individual cases based on the results of fluorescence in situ hybridization (FISH) for specific translocations and certain other tests (table 3). This risk stratification has considerable prognostic value and also helps guide the selection of initial therapy (algorithm 2). (See 'Risk stratification' above.)
  - High-risk myeloma: Includes patients with t(4;14), t(14;16), t(14;20), del17p13, or gain1q by FISH, those with lactate dehydrogenase (LDH) ≥2 times the institutional upper limit of normal, and those with features of primary plasma cell leukemia.
  - Standard-risk myeloma: Includes patients without any of the high-risk cytogenetic abnormalities or features. This includes patients with trisomies, t(11;14) and t(6;14).
- **Determining transplant eligibility** – All patients are assessed to determine eligibility for autologous hematopoietic cell transplantation (HCT), which appears to prolong both event-free and overall survival when compared with non-transplant strategies. Eligibility for HCT varies across institutions. Although guidelines are provided, eligibility should consider the risk-benefit assessment and the needs and wishes of the patient. (See 'Determining transplant eligibility' above.)

  Patients **eligible** for HCT receive induction therapy for three to four months prior to stem cell collection in order to reduce the number of tumor cells in the bone marrow and peripheral blood, lessen symptoms, and mitigate end-organ damage. Following recovery from stem cell collection, patients may proceed directly to autologous HCT (early transplant strategy) or continue therapy, usually with the same regimen used for induction, reserving autologous HCT until first relapse (delayed transplant strategy). (See 'HCT eligible' above.)
- **Approach to therapy in standard-risk myeloma** – Treatment of standard-risk MM depends on HCT eligibility and comorbidities (algorithm 2):
  - Patients with standard-risk MM who are **eligible** for HCT are treated with a triplet regimen for three to four months prior to stem cell collection. The choice of triplet regimen is discussed in more detail separately. (See "Multiple myeloma: Selection of initial chemotherapy for symptomatic disease".)
  - Following stem cell collection, we recommend early or delayed autologous HCT rather than either chemotherapy alone or allogeneic HCT (**Grade 1B**). (See 'Autologous HCT versus chemotherapy alone' above.)
  - Studies evaluating early and delayed transplant strategies have demonstrated similar survival rates so either option is acceptable for most patients. The decision is individualized taking into account patient preference, age, response to and tolerability of initial chemotherapy, and logistic factors. Importantly, patients who choose to delay transplant may have an event or complication that makes them ineligible for transplant in the future. (See "Multiple myeloma: Use of autologous hematopoietic cell transplantation", section on 'Timing of HCT'.)
  - Those who proceed with early transplant are offered at least two years of maintenance therapy post-transplant. Those who choose to delay HCT until first relapse complete a total of 8 to 12 cycles of triplet therapy followed by lenalidomide-based maintenance until relapse.
  - For most patients **ineligible** for HCT, we offer a bortezomib-based triplet regimen for 8 to 12 cycles followed by lenalidomide-based maintenance therapy. In patients who are frail and are not felt to be candidates for triplet therapy, we offer doublet therapy with lenalidomide and low dose dexamethasone until progression. (See 'HCT ineligible' above.)
- **High-risk myeloma** – Patients with high-risk MM should be encouraged to enroll in a clinical trial investigating novel therapeutic strategies, since they do poorly with all conventional treatment options. Outside of a clinical trial, data are limited and experts differ in their approach. For transplant-eligible patients, we suggest triplet-based induction therapy followed by early autologous HCT and proteasome-inhibitor-based maintenance (**Grade 2C**). Transplant-ineligible patients are offered 8 to 12 cycles of triplet-based induction therapy followed by proteasome-inhibitor-based maintenance. (See "Multiple myeloma: Selection of initial chemotherapy for symptomatic disease", section on 'High-risk myeloma'.)
- **Complementary therapy** – In addition to therapy directed at the malignant clone, the management of most patients with MM includes preventative measures to reduce the incidence of skeletal events, renal damage, infections, and thrombosis. Patients with MM may also require

specific interventions for the management of hypercalcemia, anemia, and neuropathy. (See 'Prevention and management of complications' above.)

- **Evaluating response** – Patients should be evaluated before each treatment cycle to determine how their disease is responding to therapy (table 7). Details on how to determine response to therapy are presented separately. (See "Multiple myeloma: Evaluating response to treatment".)

- **Relapsed disease** – Almost all patients with MM will relapse and require further therapy. Relapsed or refractory MM is usually identified on routine surveillance. Treatment options for patients with relapsed or refractory MM include HCT, a rechallenge of the previous chemotherapy regimen, or a trial of a new regimen. (See 'Relapsed disease' above.)

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Topic 6643 Version 43.0

GRAPHICS

Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smoldering multiple myeloma

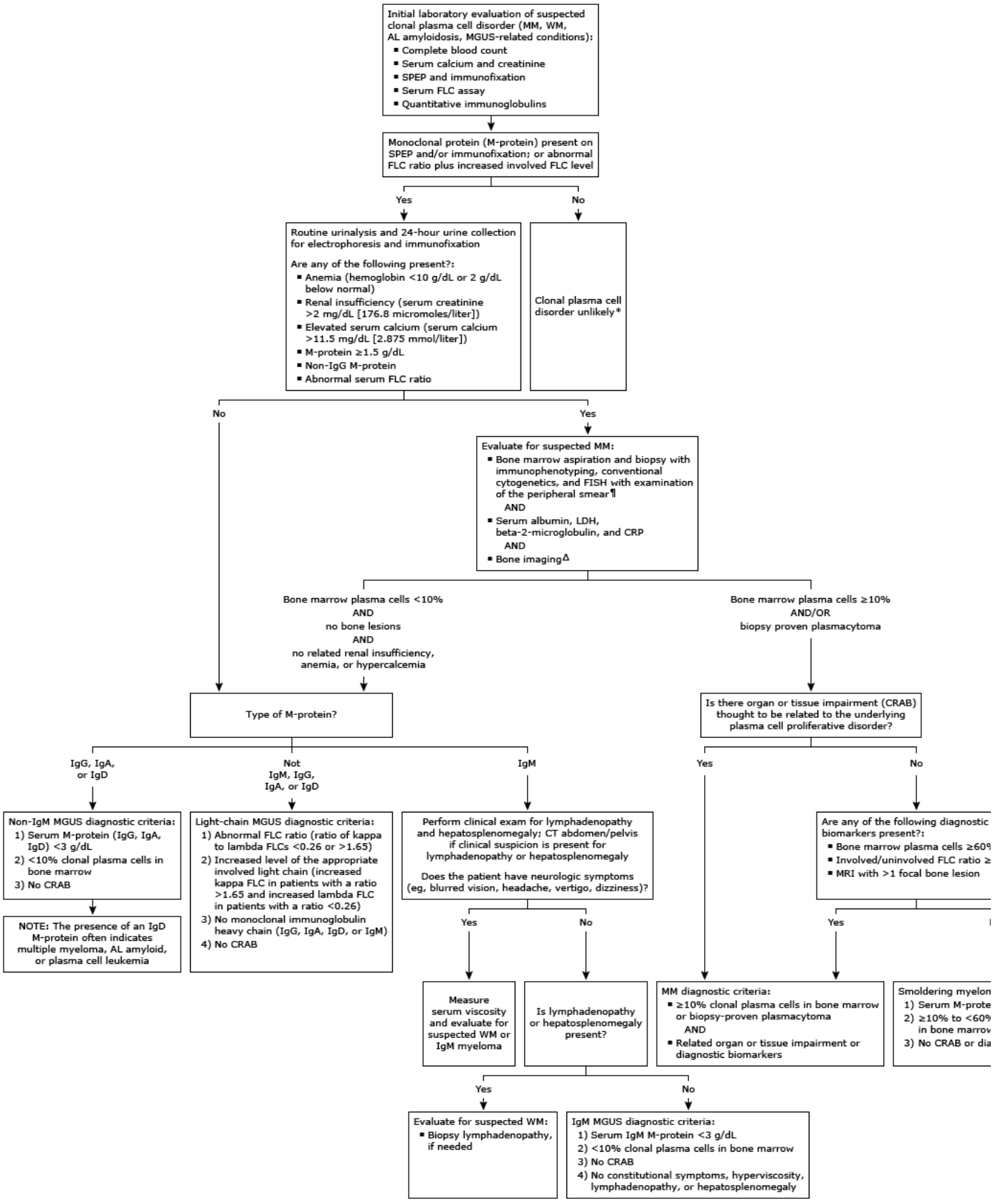
Definition of multiple myeloma
Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma-defining events:
▪ Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: • Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL) • Renal insufficiency: creatinine clearance <40 mL per min¶ or serum creatinine >177 µmol/L (>2 mg/dL) • Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L • Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CTΔ
▪ Any one or more of the following biomarkers of malignancy: • Clonal bone marrow plasma cell percentage* ≥60% • Involved:uninvolved serum free light chain ratio◇ ≥100 • >1 focal lesions on MRI studies§
Definition of smoldering multiple myeloma
Both criteria must be met:
▪ Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 hours and/or clonal bone marrow plasma cells 10 to 60% ▪ Absence of myeloma defining events or amyloidosis
Definition of monoclonal gammopathy of undetermined significance
All three criteria must be met:
▪ Serum monoclonal protein <30 g/L ▪ Bone marrow plasma cells <10% ▪ Absence of myeloma defining events or amyloidosis (or Waldenström macroglobulinemia in the case of IgM MGUS)

PET-CT: ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography.
* Clonality should be established by showing kappa/lambda-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
¶ Measured or estimated by validated equations.
Δ If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
◇ These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.
§ Each focal lesion must be 5 mm or more in size.

Original figure modified for this publication. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014; 15:e538. Table used with the permission of Elsevier Inc. All rights reserved.

Graphic 57627 Version 14.0

Algorithm for the evaluation of suspected clonal plasma cell disorder



MM: multiple myeloma; WM: Waldenström macroglobulinemia; AL: amyloid light-chain; MGUS: monoclonal gammopathy of undetermined significance; SPEP: serum protein electrophoresis; FLC immunoglobulin G; FISH: fluorescence in situ hybridization; LDH: lactate dehydrogenase; CRP: C-reactive protein; CRAB: hyper**c**alcemia, **r**enal insufficiency, **a**nemia, **b**one lesions; IgA: immunoglobulin D; IgM: immunoglobulin M; CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography.

* Patients with solitary plasmacytoma, non-secretory multiple myeloma, and rare cases of AL amyloidosis may not have detectable M-protein or abnormal serum FLC assay.

¶ Bone marrow evaluation can be omitted in patients with normal SPEP and immunofixation who have involved over uninvolved FLC ratio <8, and in patients with IgM M-protein <1.5 g/dL. Such risk of MM or WM needing therapy.

△ Imaging should be performed using whole body low dose CT, whole body PET/CT, whole body MRI, or MRI of the spine and pelvis (depending upon availability and institutional preference). Bo omitted for patients with IgM M-protein and no clinical concern for bone lesions or myeloma, in light chain MGUS with serum FLC ratio <8, and for those with both a IgG M-protein <1.5 g/dL an ratio. Biopsy of the bone lesion should be performed if a solitary lesion is detected or if the cause of the lesion is unclear.

Graphic 94388 Version 9.0

Karnofsky and Eastern Cooperative Oncology Group (ECOG) performance status measures

Karnofsky		ECOG	
Score	**Definition**	**Score**	**Definition**
100	Normal, no complaints, no evidence of disease	0	Fully active; no performance restrictions
90	Able to carry on normal activity, minor signs or symptoms of disease	1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
80	Normal activity with effort, some signs or symptoms of disease	2	Capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
70	Cares for self, unable to carry on normal activity or to do active work	3	Capable of only limited self-care; confined to bed or chair >50% of waking hours
60	Requires occasional assistance but is able to care for most needs	4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair
50	Requires considerable assistance and frequent medical care	5	Dead
40	Disabled, requires special care and assistance		
30	Severely disabled, hospitalization is indicated, although death is not imminent		
20	Hospitalization is necessary, very sick, active supportive treatment necessary		
10	Moribund, fatal processes progressing rapidly		
0	Dead		

Graphic 57945 Version 7.0

Risk stratification of myeloma

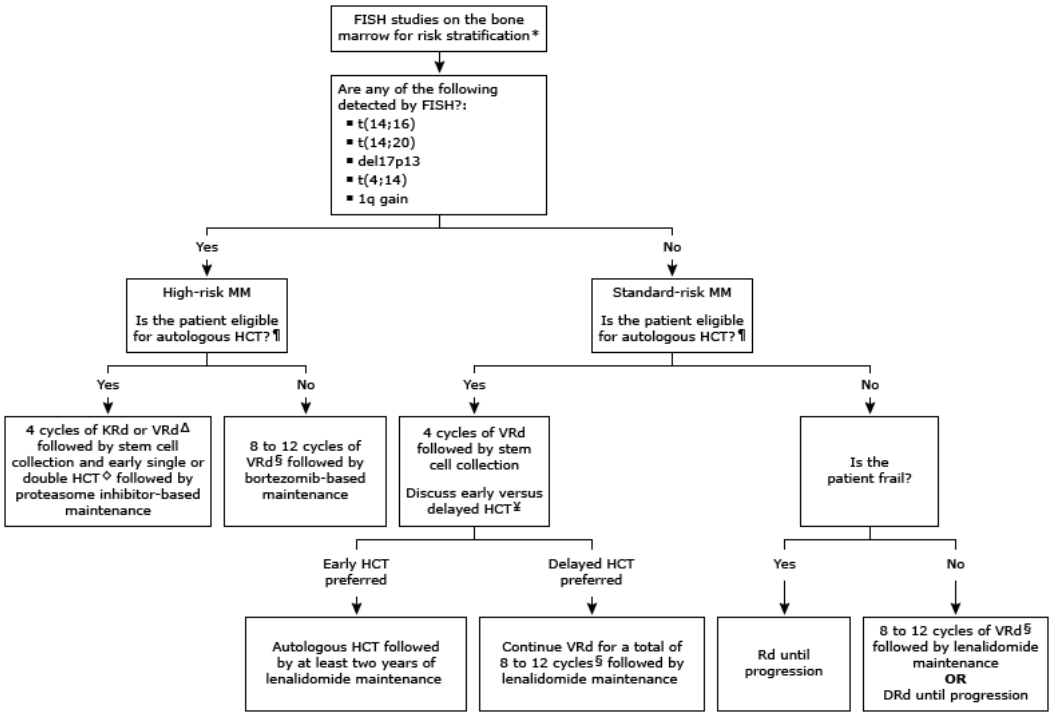
High risk	Standard risk
▪ 17p13 deletion ▪ t(4;14) ▪ t(14;16) ▪ t(14;20) ▪ Gain 1q ▪ LDH ≥2 times institutional upper limit of normal ▪ Features of primary plasma cell leukemia* ▪ High-risk gene expression profiling signature¶	▪ All others including those with: • Trisomies (hyperdiploidy) • t(11;14) • t(6;14)

The definition of high-risk disease continues to evolve based on available evidence. To risk-stratify myeloma patients at initial diagnosis we perform fluorescence in situ hybridization (FISH) studies on the bone marrow for t(11;14), t(4;14), t(6;14), t(14;16), t(14;20), del17p13, gain 1q, and trisomies of odd numbered chromosomes.

LDH: lactate dehydrogenase.
* Defined by either ≥2000 plasma cells/microL of peripheral blood, or ≥20% on a manual differential count.
¶ While patients with a high-risk signature on gene expression profiling are considered to have high-risk myeloma, this test is not recommended on a routine basis.

Graphic 78344 Version 14.0

Initial treatment of multiple myeloma



This algorithm illustrates our general approach to the treatment of a patient with newly diagnosed multiple myeloma. The clinician is expected to use his or her independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

FISH: fluorescence in situ hybridization; MM: multiple myeloma; HCT: hematopoietic cell transplantation; KRd: carfilzomib, lenalidomide, low-dose dexamethasone; VRd: bortezomib, lenalidomide, low-dose dexamethasone; Rd: lenalidomide plus low-dose dexamethasone; DRd: daratumumab, lenalidomide, low-dose dexamethasone; ECOG: Eastern Cooperative Oncology Group; NYHA: New York Heart Association.

* Risk stratification is based on results of FISH on the bone marrow for detection of t(11;14), t(4;14), t(6;14), t(14;16), t(14;20), and del17p13. FISH for 1q gain is included, if available.

¶ Eligibility for autologous HCT in MM varies across countries and institutions. In most centers in the United States, patients with one or more of the following are not considered eligible for autologous HCT in myeloma: Age >77 years, direct bilirubin >2 mg/dL, ECOG performance status 3 or 4 unless due to bone pain, and NYHA functional status class III or IV.

Δ KRd preferred for patients with t(4;14), t(14;16), t(14;20), and those with ≥2 high-risk abnormalities.

◇ Single HCT is preferred for most patients. We offer double (tandem) HCT to some patients with del17p13. With this approach, a second autologous HCT is performed within six months after the completion of the first.

§ The number of cycles used for an individual patient depends on how well he/she tolerates the regimen and the response to treatment. If the disease continues to respond and the patient is tolerating therapy, we will offer up to 12 cycles of initial therapy.

¥ An "early" HCT approach incorporates HCT into the initial treatment while a "delayed" HCT approach reserves HCT until first relapse. For patients with standard-risk MM, early and delayed transplant strategies have been associated with similar survival rates. The choice between early and delayed HCT is influenced by patient preference and age, response and tolerability to the initial chemotherapy regimen, insurance approval, and institutional limitations. Refer to related UpToDate content for more details.

Graphic 97453 Version 8.0

Eastern Cooperative Oncology Group (ECOG, Zubrod, World Health Organization) performance scale

Performance status	Definition
0	Fully active; no performance restrictions.
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
2	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair >50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Adapted from: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649.

Graphic 72901 Version 10.0

NYHA and other classifications of cardiovascular disability

Class	NYHA functional classification[1]	Canadian Cardiovascular Society functional classification[2]	Specific activity scale[3]
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous or rapid prolonged exertion at work or recreation.	Patients can perform to completion any activity requiring ≥7 metabolic equivalents (ie, can carry 24 lb up 8 steps; do outdoor work [shovel snow, spade soil]; do recreational activities [skiing, basketball, squash, handball, jog/walk 5 mph]).
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair-climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions.	Patients can perform to completion any activity requiring ≥5 metabolic equivalents (eg, have sexual intercourse without stopping, garden, rake, weed, roller skate, dance fox trot, walk at 4 mph on level ground), but cannot and do not perform to completion activities requiring ≥7 metabolic equivalents.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less-than-ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	Marked limitation of ordinary physical activity. Walking 1 to 2 blocks on the level and climbing 1 flight in normal conditions.	Patients can perform to completion any activity requiring ≥2 metabolic equivalents (eg, shower without stopping, strip and make bed, clean windows, walk 2.5 mph, bowl, play golf, dress without stopping) but cannot and do not perform to completion any activities requiring >5 metabolic equivalents.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.	Patients cannot or do not perform to completion activities requiring >2 metabolic equivalents. Cannot carry out activities listed above (specific activity scale III).

NYHA: New York Heart Association.

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Graphic 52683 Version 17.0

Baseline and follow-up tests for response assessment in multiple myeloma using IMWG consensus criteria

	Every response assessment timepoint (every cycle)	If electrophoresis shows no measurable protein	At suspected CR	At suspected progression (clinical or biochemical)
SPEP (serum M-spike ≥1 g/dL[1])*	X	◇◇	X	X
Serum immunofixation (any)	◇◇	X	X	X
UPEP (urine M-spike ≥200 mg/24 hours)	X	◇◇	X	X
Urine immunofixation (any)	◇◇	X	X	◇◇
Serum FLC				
Serum M-spike <1 g/dL, urine M-spike <200 mg/24 hours, but involved immunoglobulin FLC is ≥10 mg/dL	X	◇◇	X	X
Any	◇◇	◇◇	X	X
Bone marrow aspirate/biopsy				
Serum M-spike, urine M-spike, or involved immunoglobulin FLC not meeting above criteria but bone marrow plasma cell percentage ≥30%	X (to be done every three or four cycles till a plateau or complete response, or as clinically indicated and then at suspected progression)	◇◇	X	◇◇
Any	◇◇	◇◇	X	◇◇
Plasmacytoma (PET imaging)				
Serum M-spike, urine M-spike, involved Ig FLC or bone marrow not meeting above criteria, but at least one lesion that has a single diameter of ≥2 cm	X (to be done every three or four cycles till a plateau or complete response, or as clinically indicated, and then at suspected progression)	◇◇	X	◇◇
Any	◇◇	◇◇	X	◇◇
Hemoglobin, serum calcium, creatinine (any)	X	◇◇	◇◇	X

IMWG: International Myeloma Working Group; CR: complete response; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis; FLC: free light chain; X: test performed; ◇◇: test not performed.
* A baseline M-spike of ≥0.5 g/dL is acceptable if very good partial response or higher is the response endpoint to be measured and in situations where progression-free survival or time to progression are the endpoints of interest.

Reference:

1. *Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 2013; 28: 1122-08.*

Graphic 111430 Version 1.0

2016 International Myeloma Working Group uniform response criteria for multiple myeloma

	Response criteria*
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years).¶
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGFΔ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells◇ or higher.
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less than the mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue.§
Standard IMWG response criteria¥	
Stringent complete response	Complete response as defined below plus normal FLC ratio‡ and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells).†
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates.
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours.
Partial response	≥50% reduction of serum M-protein plus reduction in 24 hour urinary M-protein by ≥90% or to <200 mg per 24 hours. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)** of soft tissue plasmacytomas is also required.
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50 to 89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)** of soft tissue plasmacytomas is also required.
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease.
Progressive disease¶¶,ΔΔ	Any one or more of the following criteria: ▪ Increase of 25% from lowest confirmed response value in one or more of the following criteria: • Serum M-protein (absolute increase must be ≥0.5 g/dL); • Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; • Urine M-protein (absolute increase must be ≥200 mg/24 hours); • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); ▪ Appearance of a new lesion(s), ≥50% increase from nadir in SPD** of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ▪ ≥50% increase in circulating plasma cells (minimum of 200 cells per microL) if this is the only measure of disease.
Clinical relapse	Clinical relapse requires one or more of the following criteria: ▪ Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; ▪ Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); ▪ Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD** of the measurable lesion; ▪ Hypercalcemia (>11 mg/dL); ▪ Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; ▪ Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; ▪ Hyperviscosity related to serum paraprotein.
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: ▪ Reappearance of serum or urine M-protein by immunofixation or electrophoresis; ▪ Development of ≥5% plasma cells in the bone marrow; ▪ Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia [refer to 'clinical relapse' above]).
Relapse from MRD negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: ▪ Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); ▪ Reappearance of serum or urine M-protein by immunofixation or electrophoresis; ▪ Development of ≥5% clonal plasma cells in the bone marrow; ▪ Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia).

For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4 to 5 mL to avoid hemodilution. Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

IMWG: International Myeloma Working Group; MRD: minimal residual disease; NGF: next-generation flow; NGS: next-generation sequencing; PET: positron emission tomography; CT: computed tomography; SUV: standardized uptake value; FLC: free light chain; M-protein: myeloma protein; SPD: sum of the products of the maximal perpendicular diameters of measured lesions; CRAB features: calcium elevation, renal failure, anemia, lytic bone lesions; FCM: flow cytometry; SUV_{max}: maximum standardized uptake value; MFC: multiparameter flow cytometry; ^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose PET; ASCT: autologous stem cell transplantation.

* All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

¶ Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

Δ Bone marrow MFC should follow NGF guidelines.[1] The reference NGF method is an eight-color two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-color technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-color method is most efficient using a lyophilized mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

◇ DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequenta).

§ Criteria used by Zamagni and colleagues,[2] and expert panel (Italian Myeloma criteria for PET Use [IMPetUs]).[3,4] Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUV_{max} = 2.5 within osteolytic CT areas >1 cm in size, or SUV_{max} = 1.5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.
¥ Derived from international uniform response criteria for multiple myeloma.[5] Minor response definition and clarifications derived from Rajkumar and colleagues.[6] When the only method to measure disease is by serum FLC levels: Complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.
‡ All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).
† Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.
** Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.
¶¶ Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.
ΔΔ In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

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Graphic 55362 Version 4.0

Contributor Disclosures

S Vincent Rajkumar, MD Nothing to disclose **Robert A Kyle, MD** Consultant/Advisory Boards: Celgene Disease Monitoring Committee [Dysproteinemias (lenalidomide, pomalidomide)]; Bristol-Myers Squibb Independent Monitoring Committee [Dysproteinemias (elotuzumab)]; Onyx Pharma (Amgen) Data Monitoring Committee [Dysproteinemias (carfilzomib)]; Pharmacyclics Data Safety Monitoring Board [Dysproteinemias (ibrutinib)]. Other Financial Interest: Pfizer [Lecture on therapy of multiple myeloma, made comments concerning a new Pfizer product and received an honorarium]. **Rebecca F Connor, MD** Nothing to disclose

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