Cytogenetics and Genetic Screening
Rafael Fonseca, MD

Background
Much progress has been made in the understanding of multiple myeloma (MM) biology through the use of classic genetic techniques and more recent genomic tools. It is now understood that MM comprises various genetic subtypes, each with unique clinicopathological features and outcomes. Since myeloma is heterogeneous with regard to prognosis and clinical course, it is now accepted that the majority of these differences can be attributed to the genetic makeup of the disease. Indeed, several MM subtypes are associated with a more aggressive clinical course and shorter survival. In particular, chromosomal translocations such as t(4;14) and t(14;16) and deletions of 17p13 have been associated with shortened durations of remission. This monograph reviews the current understanding of MM biology, mainly as it pertains to the clinical aspects of MM, and how this information has become transformative in the management of MM.

Genetic classification
At the highest level, MM is classified into two major subtypes: hyperdiploid and nonhyperdiploid disease.1 Hyperdiploid myeloma (H-MM) is characterized by the presence of multiple trisomies. Patients who have H-MM have a median number of 53 chromosomes. H-MM is associated with a more favorable outcome and longer survival, and is more common with advancing age. Nonhyperdiploid MM is a heterogeneous group mainly characterized by the presence of unique translocations that are believed to be founder effects in the disease. Chromosome translocations involving chromosome 14 are common and are seen in about 50% of myeloma cases.1 These translocations are derived from errors that occur during the process of class switching. Since these translocations arise from errors during normal B-cell development, it can be argued that they are random events that occur during immune responses. One unresolved observation in myeloma is that some patients who have trisomies also have evidence of IgH translocations; however, this overlapping group has not been thoroughly characterized.2

Gene expression profiling
Gene expression profiling (GEP) has been used by multiple groups to stratify patients into various risk categories. The pioneering work was done by investigators at the University of Arkansas who identified genetic signatures capable of selecting patients with the most aggressive disease.3 Their observations have been validated in several subsequent studies and the test is now commercially available (http://www.carislifesciences.com).4 Other investigators, including our group at the Mayo Clinic, have subsequently used GEP as a mechanism to unravel myeloma biology and also to establish prognosis. A Dutch group developed another such signature.5 We were able to establish various prognostic categories within the hyperdiploid variant employing these ribonucleic acid (RNA) microarrays.6

Other genomic tools
Other genomic tools also have been used to classify subgroups and establish prognoses in myeloma. These include single nucleotide polymorphism arrays, array-based comparative genomic hybridization, and high-throughput sequencing. In particular, the availability of next-generation sequencing holds the promise of delivering not only a more accurate description of the disease and its prognosis, but also identifying “druggable” targets.7 However, this technique remains in development and as of yet no concerted clinical laboratories offer it routinely.

Why do risk stratification?
The quest to establish risk stratification needs to be justified by utilitarian value and not merely represent an academic exercise. Understanding risk statistics is of paramount importance for patient counseling and to properly execute a long-term treatment plan.

Patient counseling based on risk is essential. While much progress has been made in the treatment of myeloma, which has resulted in improved overall survival, the situation is still suboptimal for patients at high-risk of developing the disease. The potential for myeloma becoming a chronic disease is a reality for patients who lack the markers of aggressive disease, such as del17p13, t(4;14), and t(14;16). This is of particular importance in younger individuals with MM who have the greatest projection of loss of years of their lives. Unfortunately, younger individuals also harbor some of the higher-risk variants in greater proportions and are less likely to have the hyperdiploid variant of the disease.8

The second aspect for which risk becomes of paramount importance is in the process of treatment planning. Initially, risk was considered important for the selection of induction therapy. Because increasing numbers of patients are now being treated with combinations that contain proteasome inhibitors as front-line therapy, the application of risk stratification for induction selection is of less importance; however, patients with standard-risk disease who otherwise would be candidates for lenalidomide-based induction can still do so safely. Nevertheless, most patients in the United States now receive induction with either the combination of lenalidomide, bortezomib and dexamethasone (VRD) or the combination of cyclophosphamide, dexamethasone, and bortezomib (CyBORD).9 Knowing the risk remains critical in the setting of maintenance therapy post-induction and stem cell transplant.

Several studies point to the benefits of therapy in the post-transplant maintenance setting. Two large randomized studies have shown that the administration of lenalidomide in this setting is associated with improvements in progression-free survival and, in
one study, overall survival.\textsuperscript{10} Previous studies using thalidomide, an agent that has a higher level of toxicity, showed similar results but the effects on overall survival have not been clear.\textsuperscript{10} However, data suggest that for patients with high-risk disease, treatment post-stem cell transplant with bortezomib is important to maintain remission. In one study, Cavo and colleagues studied the effects of risk stratification according to post-stem cell transplant consolidation.\textsuperscript{11} The outcomes of patients who received treatment with thalidomide and dexamethasone were dictated by the presence of t(4;14) and del17p13. However, for patients treated with bortezomib, thalidomide, and dexamethasone as consolidation, the long-term outcomes were similar. If further large studies confirm these observations, post-stem cell transplant administration of bortezomib will become mandatory for this patient population. Likewise, Neben and colleagues addressed the same question with regard to patients with del17 who were treated with bortezomib or thalidomide.\textsuperscript{12} Patients who received bortezomib showed similar long-term outcomes irrespective of risk classification.

**How to risk stratify**

While several methods exist for risk classification, at least one should be routinely used in the clinic.\textsuperscript{13} If fluorescence in situ hybridization (FISH) is used, the assay needs to be done on cells that are either selected/ enriched via flow cytometry or magnetic bead separation, or FISH should be coupled with other methods of detecting plasma cells (e.g., cytoplasmic immunoglobulin FISH [cIg-FISH]).\textsuperscript{14} Performing FISH in unselected cell populations is inappropriate given the high risk of the results being falsely negative. When bone marrow cells are sent to the cytogenetics lab for analysis, it is not unusual for this to be the last tube of the aspirate. At this point, the sample can be greatly diluted by peripheral blood and not be representative of the real plasma cell population. A patient with 50% plasmacytosis may have a third aspirate tube containing only 5% plasma cells. Even if this patient has a 17p deletion, the test will come back as normal because 5% is within the range of normal for a FISH assay. The patient and the physician will then be falsely reassured that the patient does not have high-risk MM. While multiple methods exist for classifying patients by risk stratification, one scheme proposed by the Mayo Clinic is the Stratification for Myeloma and Risk-Adapted Therapy (mSMART; see msmart.org, 2014).\textsuperscript{15} At the very least, one must test for deletion 17p, t(4;14), and t(14;16). The presence of any one of these markers will be indicative of high-risk myeloma.

An alternative method is gene expression profiling. This method has the advantage that it can detect more accurately those patients with very high-risk disease.\textsuperscript{16} The assay analysis can be conducted at reference laboratories and involves the purification of plasma cells prior to executing the RNA analysis. The assay also can provide information regarding the biologic subtype of the disease and can be used to derive one of many gene expression profiling prognostic signatures.

**The subclones**

Recent studies have shown the presence of subclones in myeloma.\textsuperscript{17-20} When one uses sophisticated genetic methods such as next-generation sequencing and single-cell FISH, it is clear that subclones exist within a given tumor subpopulation. All of the cells share a common genetic ancestry but they vary slightly due to genomic instability. Subclonal markers have been used to show that individual treatments may have therapeutic effects only in some of the subclones, while others show resistance.\textsuperscript{18} The importance of this is mostly conceptual and not necessarily practical at this time. It is unlikely we will be testing for subclones in the clinic, given that the possible number of them is very large; however, understanding that MM is a subclonal disease has been used as an argument to propose that a combinatorial and protracted treatment strategy is important.

**Predictive versus prognostic**

While many markers exist and have been proposed as prognostic in MM, very few are of a predictive nature. The exception to this is cereblon (CRBN) gene, which has been demonstrated to be a prerequisite for the antitumor activity of the immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide.\textsuperscript{21} While the pathway is still being explored and the mechanism of action is not fully elucidated, it is clear that in the absence of CRBN, these drugs do not work. Development of tests that have predictive ability for other specific agents is currently being explored.

**Future implications in the clinic**

It is likely that in the future we will test all myelomas with novel tools such as next-generation sequencing, and that such effort will allow more tailored treatment approaches. While many research efforts conclude that knowing the genetics can help us predict who will not respond (a negative assertion), it is far more important to use this information to find ways to make all patients respond for long periods of time or cured (a positive assertion). Detailed study of genomic complexity holds the potential to provide a blueprint for personalized treatment.\textsuperscript{22} While much progress has been made in the treatment of multiple myeloma, the coupling of genomics and biology to these treatments is still lagging.
References


Current Therapies for Multiple Myeloma
Kenneth Anderson, MD

Practicing clinicians are faced with the challenge of identifying patients who meet International Myeloma Working Group (IMWG) criteria for treatment, choosing the optimal induction therapy, identifying transplant eligibility, assessing the need for a maintenance regimen, and selecting novel agents and regimens for managing relapsed/refractory multiple myeloma (MM). The challenge for physicians managing patients with MM is to rationally apply evidence-based strategies in such a way that disease control can be maintained with minimal burden on patients. Unfortunately, hematologists and oncologists often are not up-to-date on the latest clinical data and guidelines on the large variety of agents and regimens now available for the treatment of MM.

Who needs treatment for MM?

The criteria for therapy for MM has been defined as ≥10% clonal bone marrow plasma cells, presence of serum or urine monoclonal protein, and evidence of underlying end organ damage including hypercalcemia, renal dysfunction, anemia, and bone disease.2 Smoldering MM (SMM) has traditionally been defined as ≥3 g/dL monoclonal protein and/or ≥10% monoclonal bone marrow plasma cells in the absence of end-organ damage, or both.2 Traditionally, patients with SMM have therefore not been treated; however, redefinition of criteria patients must meet in order to benefit from therapy was precipitated by a Spanish study demonstrating that lenalidomide/dexamethasone therapy can prolong progression-free and overall survival in patients with SMM at high risk for progression.3 Consequently, the IMWG has recently defined a group of patients with MM at high risk of progression to active MM within 2 years of diagnosis who are now considered eligible for treatment.2 These include patients with >60% bone marrow plasma cells, involved/uninvolved serum free light chain ratio ≥100, and >1 focal lesions on magnetic resonance imaging studies. Thus the group of SMM patients not requiring therapy is smaller, and the subset of patients with active MM requiring therapy is now larger. This is made possible by identifying biomarkers on the one hand, and the availability of well-tolerated and novel efficacious therapies on the other. Ongoing clinical trials of novel agents, monoclonal antibodies, vaccines, and other strategies aim to delay the progression of disease to active MM requiring therapy.

What is the best therapeutic option?

A confirmed diagnosis of myeloma requiring therapy leads to two major considerations. First is whether the patient is a transplant candidate or not. Patients eligible for high-dose therapy and autologous stem cell transplantation include those less than a physiologic age of 70 years, with adequate hepatic, renal, pulmonary, and cardiac status. The performance status of the patient also is pertinent when making treatment considerations, in particular whether the patient is fit or frail. The second major consideration is whether the patient has standard- or high-risk myeloma. For example, fluorescence in situ hybridization (FISH) studies can define risk4:

- high risk: t(14;16), t(14;20), del 17p;
- intermediate risk: t(4:14), cytogenetic del 13, hypodiploidy;
- standard risk: t(11;14), hyperdiploidy.

Should complete (or stringent) remission be an important consideration in selection of initial therapy?

Complete response (CR) stringency has evolved, as has our ability to achieve increased extent of response with novel therapies. Complete response is absence of monoclonal protein in blood or urine by immunofixation and normal bone marrow. Stringent CR also requires a normal kappa/lambda free light chain ratio, and molecular CR has incorporated polymerase chain reaction negativity for immunoglobulin gene rearrangement. Most recently, multicolor flow cytometry and gene sequencing have been used to detect minimal residual disease (MRD); absence of MRD using these measures defines a new level of immunophenotypic or molecular CR.5 In addition, magnetic resonance imaging and positron emission tomography–computed tomography scanning can detect occult medullary or extramedullary residual disease and are now incorporated into both staging and response criteria.6

What is optimal induction, consolidation, and maintenance therapy for transplant candidates?

In newly diagnosed transplant candidates, thalidomide, lenalidomide, and bortezomib have been incorporated into initial therapies. Studies combining thalidomide with dexamethasone (thalidomide/dexamethasone) as initial therapy for MM have achieved rapid responses in two-thirds of patients, allowing for successful harvesting of peripheral blood stem cells (PBSCs) for transplantation.7 Thalidomide/dexamethasone has been compared with vincristine/doxorubicin/dexamethasone (VAD) and with dexamethasone as initial therapy for patients prior to collection of autologous stem cells and transplantation.8,9 In a case-control analysis, thalidomide/dexamethasone achieved higher overall response rates, whereas randomized phase III trials also demonstrated statistically significantly higher response rates for thalidomide/dexamethasone than dexamethasone-treated patient cohorts, providing the rationale for FDA approval of thalidomide for initial treatment of MM.10 Remarkably, phase II studies demonstrated 91% responses, including 6% complete and 32% near complete response (nCR)/very good partial response (VGPR) to lenalidomide combined with dexamethasone, preserving the ability to collect stem cells for transplantation.11 Importantly, a phase III trial compared lenalidomide with high-dose dexamethasone versus lenalidomide with low-dose dexamethasone to treat newly diagnosed
Although response rates were higher in the high-dose cohort, complications including clots and infections contributed to decreased survival in this cohort. Prophylaxis against clotting with aspirin, warfarin, or subcutaneous heparin is required when patients are treated with lenalidomide therapy. Ability to collect autologous stem cells may be suppressed in individuals receiving lenalidomide therapy, which can be overcome with cyclophosphamide or plerixafor (or both) and granulocyte colony-stimulating factor mobilization. With continued lenalidomide and low-dose dexamethasone treatment, frequency of response and very good/complete response rates approach 90% and 50%, respectively.

Richardson and colleagues examined single-agent bortezomib, and Jaggi et al. tested bortezomib combined with dexamethasone as initial therapy. In both cases, high frequency of response, extent of response, and ability to collect stem cells were observed. Studies have similarly shown that thalidomide/bortezomib/dexamethasone is superior to bortezomib/dexamethasone when used before or as consolidation after autologous stem cell transplantation. Two other three-drug regimens that have achieved high extent and frequency of response include bortezomib/dexamethasone/lenalidomide and cyclophosphamide/bortezomib/dexamethasone. Given the success of these three-drug regimens, randomized studies have compared three- and four-drug combinations of novel and conventional therapies as initial therapy. In the EVOLUTION trial, for example, cyclophosphamide/bortezomib/dexamethasone and lenalidomide/bortezomib/dexamethasone were both active, but no substantial advantage was derived by adding a fourth drug.

Recently, the use of carfilzomib/lenalidomide/dexamethasone has achieved high CR/nCR rates, including molecular CRs.

Therefore, the standard of practice at present is a three-drug regimen (lenalidomide/bortezomib/dexamethasone, thalidomide/bortezomib/dexamethasone, or cyclophosphamide/bortezomib/dexamethasone) as induction therapy, due to the high overall rate and extent of response, including molecular CR assessed by multicolor flow cytometry. After high-dose melphalan and autologous stem cell transplantation (ASCT), two to four cycles of consolidation therapy is administered, often with the same three-drug regimen used for induction. Consolidation can increase the extent and prolong the duration of response, and markedly enhance the frequency of molecular CR.

Thereafter, lenalidomide maintenance therapy can prolong progression-free survival (PFS) and overall survival (OS), with most studies showing prolongation even of OS when administered until progression of disease. A two- to three-fold increased risk of secondary malignancies occurs when lenalidomide maintenance is administered post-high-dose melphalan and ASCT; however, the benefit far outweighs the risk. In patients with high-risk MM, the induction and consolidation therapy post-transplant is similar: the maintenance therapy incorporates bortezomib, either alone or with lenalidomide. Early reports indicate prolonged PFS can be achieved with combined lenalidomide/bortezomib maintenance post-transplant even in the high-risk setting. Therefore, integration of novel therapies into the transplant paradigm as induction, consolidation, and maintenance has markedly improved outcomes.

What is the role of allogeneic transplantation?

Although ablative therapy followed by HLA-matched allogeneic transplantation has achieved prolonged PFS and OS in a minority of patients, it is rarely performed at present due to its high attendant morbidity and mortality. Nonmyeloablative allotransplantation, often preceded by high-dose therapy and ASCT, also has been reported to achieve prolonged PFS and OS in a minority of patients. Nonetheless, allogeneic transplantation in MM is now recommended primarily in the context of a clinical trial due to 10% to 20% attendant mortality and morbidity of chronic graft-versus-host disease.

What is the optimal therapy for patients who are not candidates for transplantation?

In patients newly diagnosed with MM who do not meet the criteria for transplantation, thalidomide, lenalidomide, and bortezomib have each been incorporated into initial therapies. To date, multiple clinical trials have compared melphalan/prednisone/thalidomide (MPT) to melphalan/prednisone (MP); in aggregate, better response rates and increased PFS and OS were observed with MPT versus MP alone. A meta-analysis of randomized trials of melphalan/prednisone with or without thalidomide concluded that
thalidomide extended median survival by 20%. The VISTA trial compared bortezomib/melphalan/prednisone (VMP) versus MP and demonstrated increased extent and frequency of response and prolonged PFS and OS, providing the basis for the FDA approval of bortezomib therapy for newly diagnosed MM. Achievement of VGPR or CR portended for superior outcome, neuropathy was reversible in most cases, and increased bone healing was noted in responders. At 5 years median follow-up, patients treated with VMP had a prolonged survival of 13.3 months compared to the MP cohort. Similarly, the addition of thalidomide to bortezomib/melphalan/prednisone with bortezomib/thalidomide maintenance was compared to bortezomib/melphalan/prednisone, and the four-drug combination was superior only in patients with no or moderate renal insufficiency. Palumbo et al noted increased overall and extent of response, and prolonged PFS but not OS, in patients treated with MP/lenalidomide followed by lenalidomide maintenance compared to MP alone, supporting the use of lenalidomide both during induction and as maintenance treatment. In the lenalidomide maintenance-treated patients, the benefit in terms of reduced risk of progression and death from MM far outweighs the low risk of secondary malignancies. A major advance in MM is the recent completion of the FIRST trial comparing lenalidomide dexamethasone until progression in nontransplant patients, who are not candidates for transplantation. Importantly, however, patients who are not candidates for transplantation can benefit from combination novel therapies and from continuous maintenance therapy. As noted above, the FIRST trial compared melphalan/prednisone/thalidomide for 18 months, lenalidomide/dexamethasone for 18 months, and lenalidomide/dexamethasone until progression in nontransplant patients with newly diagnosed MM. The overall and extent of response, and prolonged PFS and OS, were superior in the lenalidomide/dexamethasone-until-progression cohort. Moreover, fewer secondary malignancies occurred in the absence of alkylating agents in the patients treated continuously with lenalidomide/dexamethasone. This study establishes the use of novel therapies continuously until progression in patients newly diagnosed with MM who are not candidates for transplantation. Importantly, patients who are fit but do not meet the criteria for transplantation are eligible for therapy combining this lenalidomide/dexamethasone platform with triplet therapy such as lenalidomide/bortezomib/dexamethasone or cyclophosphamide/bortezomib/dexamethasone, albeit at reduced doses.

**What is optimal therapy for relapsed disease?**

When addressing relapse of disease, it is important to distinguish biochemical relapse and clinical relapse that requires treatment. In patients who are asymptomatic, monoclonal protein can be observed to determine the rate of rise and nature of the relapse. Hypercalcemia, renal dysfunction, anemia, and bone disease are again indications for treatment, although we often do not wait for complications to occur in patients with a progressive rise in monoclonal protein. Considerations in terms of choice of therapy for relapsed/refractory MM include prior therapy, resistance to prior therapy, age, performance geriatric status, cytogenetic abnormalities, increased β2 microglobulin, decreased serum albumin, low platelet count, renal dysfunction, extramedullary disease, and extensive bone disease.

Drug regimens that are currently FDA approved for treatment of relapsed or refractory MM (or both) include bortezomib, lenalidomide/dexamethasone, bortezomib and pegylated doxorubicin, pomalidomide/dexamethasone, carfilzomib, and panobinostat. The phase II SUMMIT trial demonstrated responses, including CR, prolongation of time-to-progression (TTP) and OS, and associated clinical benefit, forming the basis for accelerated FDA approval. The APEX trial evaluated dexamethasone versus bortezomib for relapsed MM and was unblinded due to a statistically significant prolongation in TTP in the bortezomib-treated cohort, forming the basis for its FDA approval. Two large phase III trials comparing lenalidomide/dexamethasone with dexamethasone/placebo were unblinded because of statistically significantly higher response rates, and an prolongation in TTP and OS in the lenalidomide/dexamethasone-treated cohort, leading to its FDA approval to treat relapsed MM after one prior therapy. Predicated upon preclinical data that bortezomib can inhibit DNA damage repair, bortezomib/pegylated doxorubicin was compared to bortezomib in relapsed MM; the combination achieved increased extent and frequency of response, and prolonged PFS and OS, forming the basis for its FDA approval. Studies now suggest equivalent efficacy and marked reduction in neuropathy with the use of weekly instead of twice-weekly bortezomib. Moreover, subcutaneous bortezomib is equivalent in anti-MM activity to intravenous bortezomib, and the incidence of neuropathy is markedly reduced with the former. Finally, bortezomib retreatment and combination therapies incorporating novel therapies including bortezomib/thalidomide/dexamethasone and lenalidomide/dexamethasone with bendamustine have been utilized to effectively treat relapsed MM.

Pomalidomide is a new more potent immunomodulatory
drug that has been evaluated in multiple phase II clinical trials and in one large phase III trial comparing it to high-dose dexamethasone in relapsed/refractory MM.\textsuperscript{40,41} It received accelerated approval from the FDA based on a 34% response rate lasting 8 months and favorable tolerability; it also received approval in Europe, as response and survival were improved with pomalidomide/low-dose dexamethasone. The benefit extended to high-risk MM, including patients with t(4:14) and del 17p MM. Ongoing phase III trials are comparing pomalidomide/low-dose dexamethasone with or without bortezomib.

Carfilzomib is an irreversible inhibitor of the chymotryptic activity, with increased extent and duration of inhibition and less neuropathy compared to bortezomib. In the context of a phase II single-arm trial in MM resistant to bortezomib and exposed to immunomodulatory drugs, it achieved a 20% response rate lasting a median of 8 months, with 15 months survival, and received accelerated FDA approval in summer 2012.\textsuperscript{42} Moreover, higher response rates (40%-50%) are observed in patients with relapsed MM who have not yet received bortezomib. The ASPIRE trial comparing carfilzomib/lenalidomide/dexamethasone with lenalidomide/dexamethasone in patients with 1 to 3 prior therapies showed an 8-month PFS advantage for combination therapy, and this combination upfront has achieved 80% CR/nCR, including molecular CRs.\textsuperscript{43} Already, pomalidomide/low-dose dexamethasone and carfilzomib have been combined to achieve 70% response rates in relapsed and refractory MM.\textsuperscript{44}

Most recently the histone deacetylase inhibitor (HDACi) panobinostat/bortezomib/dexamethasone received accelerated FDA approval for treatment of MM exposed to bortezomib and an IMiD based on a randomized trial showing a 4-month PFS advantage for the triplet therapy.\textsuperscript{40,41,45} About one third of patients discontinued therapy due to side effects including diarrhea, fatigue, and thrombocytopenia. Isoform selective HDACi are now under clinical evaluation to enhance anti-MM activity while avoiding attendant toxicity.\textsuperscript{46}

**Summary**

Laboratory and animal models of MM in the bone marrow have allowed for the identification of novel targets promoting tumor growth, survival, and drug resistance, and have led to the development of novel targeted therapies. These studies have translated to clinical trials, leading to nine FDA-approved treatments and a threefold prolongation of median survival. Already in 2015, lenalidomide as initial and maintenance therapy and panobinostat for relapsed MM have been FDA approved. Novel immune therapies include monoclonal antibodies against SLAMF7 and CD\textsuperscript{38} with lenalidomide to augment antibody-dependent cellular cytotoxicity\textsuperscript{47,48}, immunotoxins directed against CD138 and B-cell maturation antigen\textsuperscript{49,50}, MM-dendritic cell fusion vaccines to treat residual disease post-transplant\textsuperscript{51}; and CD138, CS1, and XBP-1 peptide vaccines to delay progression from smoldering to active MM.\textsuperscript{52} Clinical trials also are targeting IL-3R and TLR-7 on plasmacytoid dendritic cells and PD-1/PD-L1 checkpoint inhibitors to inhibit MM growth and restore immunity.\textsuperscript{53,54} Next-generation proteasome inhibitors such as ixazomib\textsuperscript{16} and marizomib,\textsuperscript{55} and deubiquitylating inhibitors targeting USP14/UCHL5 to block the ubiquitin proteasome system upstream of the proteasome\textsuperscript{50} also are being tested.

In epigenetic studies, the role of histone deacetylase (HDAC) 6 in aggresomal protein degradation has been validated and the selective HDAC6 inhibitor ricolinostat has entered clinical trials in combination with bortezomib.\textsuperscript{46} Ricolinostat combined with lenalidomide and bromodomain inhibitors, which downregulate cMyc transcription, are promising in early-phase trials,\textsuperscript{55} and HDAC3-selective inhibitors also are active in preclinical models.\textsuperscript{56} Ongoing genomic studies are delineating MM heterogeneity, defining mechanisms of sensitivity or resistance to targeted therapies, identifying novel targets, and allowing for individualized treatments in MM. For example, low expression of yes-associated protein 1 (YAP1) in MM cells permits their survival despite constitutive DNA damage; conversely, knockdown of serine-threonine protein kinase 4 (STK4) upregulates YAP1 and related P73-mediated apoptosis, providing the rationale for the first kinase inhibitor trial targeting STK4 in MM.\textsuperscript{57} Although progress to date has been remarkable, participation in clinical trials of these new agents will assure that in most patients, MM is a chronic disease with curative potential.

**References**


Investigational Therapies for Multiple Myeloma
Jonathan Kaufman, MD

Multiple myeloma (MM) remains an incurable disease, with an estimated 26,850 new cases expected and an estimated 11,240 deaths in 2015.1 Recent developments in treatment options have contributed to improved survival and novel agents in clinical trials raise new hope for continued improvement. This monograph describes ongoing clinical research for MM with a focus on emerging treatment agents and multimodal regimens.

Proteasome inhibitors
The proteasome is required for protein turnover and maintaining cellular homeostasis.2-3 Inhibition of proteasome function has shown to inhibit growth and promote apoptosis of cancer cells. Current agents in this class include bortezomib and carfilzomib. Novel proteasome inhibitors under investigation include ixazomib (MLN9708), marizomib (NPI-0052), and oprozomib (ONX-0912). Of these, ixazomib, the first oral proteasome inhibitor, is furthest in development. A phase II study combining ixazomib with lenalidomide and dexamethasone resulted in 92% overall response rate (ORR), including 27% of patients achieving a complete response (CR).4 The most common adverse events (AEs) were rash (40%), nausea (5%), and vomiting (5%).

Immunomodulatory (IMiD) agents
The IMiD agents target MM in the bone marrow microenvironment. They exert an anti-MM effect via multiple mechanisms, including activating caspase 8-mediated apoptosis, diminishing adhesion of MM cells to bone marrow, prohibiting angiogenesis and cytokine excretion, and promoting autologous natural killer (NK) cell and T-cell immunity.5 The IMiDs exert these effects via interaction with cereblon (CRBN) and low expression of CRBN is correlated with decreased IMiD efficacy.6 Current IMiD agents include thalidomide, lenalidomide, and the next-generation IMiD pomalidomide. Although structured similarly, these agents qualitatively and quantitatively function differently.

Pomalidomide received FDA approval in 2013 and is indicated for relapsed or refractory MM previously treated with at least two therapies. Trials in this setting demonstrated an overall response rate of 33% with a median progression-free survival (PFS) of 4.2 months when used in combination with dexamethasone, compared to an ORR of 18% and PFS of 2.7 months when used alone.7 Reported adverse events of pomalidomide/dexamethasone included neutropenia (41%), anemia (22%), thrombocytopenia (19%), pneumonia (22%), and fatigue (14%). When used as monotherapy, AEs included neutropenia (48%), thrombocytopenia (22%), anemia (24%), and pneumonia (15%).7

Genetic mutations such as del17p and t(4;14) are hallmarks of an aggressive MM.8 A multicenter trial of the combination of pomalidomide and dexamethasone in patients with these mutations and who had known intolerance to thalidomide and lenalidomide was conducted by Leleu et al.9 The data demonstrated that the combination of pomalidomide and dexamethasone is safe and provides responses in patients with adverse cytogenetics. The combination appears to rescue patients characterized with deletion 17p in malignant plasma cells; however, the survival endpoints were shorter in patients with t(4;14).9 Triplet pomalidomide-based regimens were suggested for future studies in patients with adverse cytogenetics, particularly with t(4;14).9 The safety and efficacy of pomalidomide in combination with other agents (e.g., bortezomib, carfilzomib, and pegylated liposomal doxorubicin) is the focus of ongoing studies.

Histone deacetylase inhibitors
Histone deacetylases (HDACs) control the acetylation status of proteins and affect a broad array of physiologic processes (e.g., cell cycle, apoptosis, and protein folding) involved in cell growth and survival.10 Histone deacetylase inhibitors inhibit cell growth and induce apoptosis in myeloma cells. Recent trials of these agents in combination with protease inhibitors demonstrate a synergistic effect that blocks an alternate pathway for misfolded protein degradation in the myeloma cell.11

Ricolinostat (ACY1215) is a highly potent, oral, selective inhibitor of HDAC 6 synthesized in the fall of 2009. It is synergistic with bortezomib in vitro and in vivo, and has a favorable toxicity profile.12 Interim results from phase Ia/ib/II clinical trials of ricoliniostat with bortezomib demonstrated an ORR of 25% in heavily pretreated patients, with 6 of 10 patients refractory to bortezomib achieving stable disease (SD) or better (1 very good partial response [VGPR], 1 minimal response [MR], 4 SD).13 Trials with lenalidomide plus dexamethasone found that 69% of patients had a partial response (PR) or better while 100% demonstrated a clinical benefit (MR and SD).14 Grade 3/4 adverse events included thrombocytopenia and elevated amylase levels. Trials of ricolinostat combined with pomalidomide and carfilzomib are in early stages of development.

In February 2015, panobinostat was approved for use in the United States for patients with relapsed disease who have previously been exposed to bortezomib and an IMiD. The approval was based on a phase III trial comparing bortezomib plus dexamethasone versus a combination of panobinostat with bortezomib and dexamethasone.15 Patients treated with the panobinostat combination had a nearly 12-month PFS compared to approximately 8 months with the bortezomib/dexamethasone combination alone. The key toxicities of this regimen were diarrhea (26% grade 3), thrombocytopenia (67% grade 3), and fatigue (24% grade 3).
Monoclonal antibodies

Monoclonal antibodies (moAbs) are a promising new therapeutic option for the treatment of relapsed and refractory MM. Monoclonal antibody therapy involves a range of mechanisms, including complement-dependent cytotoxicity, interference with receptor-ligand interactions, and conjugation to radioisotopes or toxins. Numerous moAbs are under investigation, such as elotuzumab, daratumumab, and SAR 65094.

Elotuzumab is a humanized IgG1 moAb targeting human SLAMF7, a cell surface glycoprotein. It is believed to work primarily through NK cell-mediated antibody dependent cellular cytotoxicity against myeloma cells. In a MM xenograft mouse model, the combination of elotuzumab plus lenalidomide significantly reduced tumor volume compared with either agent alone. In trials across dosages, most treatment-emergent AEs occurred within 18 months of therapy and included neutropenia, thrombocytopenia, anemia, and diarrhea. Elotuzumab also has been studied in combination with bortezomib in relapsed and refractory MM. In this study, the primary AEs included lymphopenia, neutropenia, fatigue, neutropenia, hyperglycemia, and pneumonia. Among the 27 patients completing the trial, 48% achieved at least a partial response. Current elotuzumab trials include the ELOQUENT trials in patients with newly diagnosed MM who are not candidates for transplantation, and in patients with refractory or relapsed disease who are receiving treatment with lenalidomide and dexamethasone with or without elotuzumab. The first report of the trial involving relapsed disease is expected in 2015.

Daratumumab is an anti-CD38 human monoclonal antibody currently under investigation for the treatment of relapsed and refractory MM. CD38 has a role in cell-to-cell signaling, cellular adhesion, and intracellular cation mobilization and is highly expressed on myeloma cells. Daratumumab causes antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, which differentiates it from other monoclonal antibodies. Phase I/II trials with daratumumab have examined its safety and efficacy as monotherapy or in combination with lenalidomide and dexamethasone. Infusion reactions were common in early trials, prompting the requirement for premedication with steroids, acetaminophen, and diphenhydramine. Trials are ongoing and preliminary data are anticipated in 2015.

SAR650984, like daratumumab, is a humanized antibody that also targets CD38. It is the focus of Phase I trials that are currently in progress investigating its use as monotherapy and in combination with lenalidomide in patients who were heavily pretreated. Early results also revealed infusion reactions that warranted the addition of premedication with steroids and antihistamines.

Improved therapeutic options offer new hope for patients with MM. Novel agents in development include proteasome inhibitors, immunomodulatory agents, HDACs, and monoclonal antibodies. Preliminary data from ongoing clinical trials of these agents indicate promise in broadening the treatment options for this chronic disease.

References


Management of Painful Chemotherapy-Induced Peripheral Neuropathy
Beth Faiman, PhD, RN, APRN, BC, AOCN

Background
Peripheral neuropathy is commonly cited as a major side effect of multiple myeloma (MM) therapy that negatively affects patients’ quality of life. Symptoms may occur in as many as 75% of individuals as a result of disease progression (e.g., from nerve-root compression of tumors), prolonged exposure to neurotoxic therapies (e.g., bortezomib and thalidomide), and the disease itself. Patients with MM and peripheral neuropathy experience a variety of sensations that range from mild discomfort and loss of sensation, to painful burning and muscle cramping, to paralysis in the most severe cases. These deleterious effects are cumulative over time and can cause significant morbidity, limit a patient’s ability to receive the appropriate doses of anticancer medication, and lead to decreased treatment compliance.

Preserving nerve function is critical, as even mild peripheral neuropathy can prevent the patient from benefitting from existing and emerging agents. Drugs used to treat MM that may cause chemotherapy-induced peripheral neuropathy (CIPN) include vinca alkaloids, platinum-containing agents, the immune modulator thalidomide, and the proteosome inhibitor bortezomib. No standardized method for evaluating CIPN exists, and detection of CIPN mainly relies on patient-reported symptoms. No evidence-based interventions have been validated to prevent CIPN, nor is a standardized approach to analgesic selection available. Dose reduction or discontinuation of the offending agent(s) are the two most effective strategies to manage CIPN in MM. Medications to treat CIPN include opioids, antiepileptics, antidepressants, and local anesthetics. Baseline and early CIPN detection via comprehensive and routine monitoring practices are recommended to construct a more accurate and timely profile of the toxicity. This monograph highlights the current state of knowledge with regard to peripheral neuropathy in patients with MM.

Overview of chemotherapy-induced peripheral neuropathy in MM
To understand the pathology of peripheral neuropathy, the normal neurophysiologic function of the nervous system must be reviewed. Each peripheral nerve (neuron) fiber consists of an axon surrounded by Schwann cells that form a myelin sheath, a cell body, and dendrites that synapse with other nerves. The cell bodies of sensory neurons are bundled together within the dorsal root ganglia. Motor nerve cell bodies are located in the ventral spinal cord. Motor and sensory neurons are responsible for different actions. Large, myelinated neurons are responsible for vibration, proprioception, and light touch, while small, myelinated sensory neurons transmit impulses for temperature. Pain impulses can be transmitted by either small myelinated or unmyelinated nerve fibers.

Bortezomib, thalidomide, and other agents can induce sensory and motor neuropathy through mechanisms that may include damage to Schwann cells or axons, or through cell-mediated injury. Damage to the nerves can lead to loss of touch, cramping, pain, and even motor dysfunction.

Clinician and patient barriers to identification and reporting of CIPN
Despite having adequate knowledge of the importance of CIPN monitoring, clinicians do not routinely assess CIPN in clinical practice for several reasons. Often, clinicians fail to perform a baseline assessment of CIPN, making it difficult to distinguish the presence of a prior comorbidity (e.g., diabetes) from treatment-emergent neuropathy. Additionally, clinicians may lack the requisite knowledge and confidence to conduct a thorough symptom and clinical neurologic assessment for CIPN. Functional assessment of simple skills or tasks and questions about the patient’s ability to perform activities of daily living are needed but often neglected during office visits. Chemotherapy-induced peripheral neuropathy may be underreported due to patient reluctance to report symptoms because they fear cessation of cancer treatment. Given these clinician and patient-related barriers, novel strategies are needed to facilitate feasible but comprehensive assessments of CIPN in the clinical setting.

Measurement of CIPN
There is no gold standard for objective measurement of peripheral neuropathy. Electromyography (EMG) and nerve conduction studies (NCS) are two techniques that are available but not widely used. Electromyography involves the placement of a needle into various muscles to record stages of muscle activity, including rest and contraction. This technique can be useful to detect abnormal motor neuropathy but uses needles, which can be painful. Nerve conduction studies measure the amount of electrical charge delivered to a nerve. The velocity and action potential of the charge can measure the myelination of the nerve and amplitude of muscle contraction. This procedure can aid in categorizing the pathophysiology of the peripheral neuropathy as demyelinating, axonal, or mixed.

Because sophisticated EMG and NCS techniques are not always readily available, most clinical studies have relied on patient self-report of the symptom to detect and measure CIPN. One of the most common subjective self-report measures for symptoms that has been validated is the Gynecologic Oncology Group–Neurotoxicity (GOG-Ntx) neuropathy subscale. This 11-item questionnaire addresses patient-reported concerns presumed to be associated with CIPN and has been used in several bortezomib studies.

The National Comprehensive Cancer Network (NCCN) Task Force and International Myeloma Working Group (IMWG) recommend that, prior to the administering...
each dose of neurotoxic therapy, health providers inquire about patient symptoms of CIPN, conduct baseline evaluations of functional performance, and objectively assess clinical neurologic findings. Close monitoring and prompt intervention to treat CIPN may reduce the risk of chemotherapy dose reductions or discontinuation, severe disability, injury due to falls, chronic pain, and diminished quality of life.

Prevention of CIPN
Currently, no evidence-based interventions exist for effective prevention of CIPN; however, bortezomib-related neuropathy can be lessened by changing the route of administration. A randomized, noninferiority trial demonstrated a statistically significant decrease in the onset and severity of CIPN symptoms when bortezomib was administered subcutaneously (SC) versus intravenously (IV): the onset of CIPN was 37% vs. 53%, respectively. Therefore, SC bortezomib is recommended to decrease the risk of severe CIPN. Unfortunately, no over-the-counter or prescription agents have been proven in clinical trials to prevent CIPN in MM.

Management of CIPN
Because standardized practice guidelines have not yet been established, clinical management of painful CIPN varies. To guide practice, the IMWG and the International Myeloma Foundation Nurse Leadership Board have created guidelines and consensus statements for the diagnosis and monitoring of treatment-emergent peripheral CIPN in MM. Although no standardized approach to analgesic selection has emerged, dose reduction or discontinuation of the offending agent (most commonly thalidomide or bortezomib) are the two most effective strategies to manage CIPN.

The CIPN treatment approach is generally one of pain management. Medication classes used for the treatment of painful CIPN include vitamins, opioids, neuroleptics, antidepressants, and local anesthetics that have been studied in other disorders. At this time, recommendations for the treatment of painful CIPN include choosing an agent with a reasonable safety and efficacy profile for the specific patient and titrating the agent to the maximum-tolerated dose. Table 1 outlines the doses and schedules of common nonopioid drugs to treat neuropathy symptoms.

The use of complementary and alternative medicine, including modalities such as supplement use, massage, meditation, and acupuncture, warrants further investigation for the management of CIPN. Evidence for the efficacy of acupuncture in preclinical and animal models and small studies of cancer patients is mixed. Treatments such as neurostimulation may provide some benefits when combined with pharmacologic approaches to pain control. The NCCN Task Force Report panel concluded that for patients who are unable to tolerate pain medications, or for patients in whom pain medications are ineffective, transcutaneous electrical nerve stimulation could be helpful in treating painful CIPN. Additionally, rehabilitation services such as physical and occupational therapy are recommended to address functional deficits secondary to CIPN.

Future directions
Peripheral neuropathy is a devastating side effect of MM and its treatment. More rigorous clinical trials and real-world data are needed to identify preventive strategies and effective treatment in patients with MM. A thorough baseline and ongoing assessment for CIPN should be performed and continue throughout the duration of treatment. The development of a standard evaluation method, including standardized questions based on the chemotherapy classification, warrants further investigation and development.

### Table 1. Drugs used in the management of CIPN in Multiple Myeloma

<table>
<thead>
<tr>
<th>Vitamin/Supplement</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-B complex vitamins (with B1, B6, B12, folic acid, and other)</td>
<td>B6 should be approximately 50 mg daily, not to exceed 100 mg per day; folic acid should be 1 mg per day</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 IU daily</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>400-800 IU daily, up to 2,000 IU daily or 50,000 IU weekly</td>
</tr>
<tr>
<td>Fish oils (Omega-3 fatty acids [from long chain fatty acids EPA and DHA1])</td>
<td>1-2 capsules daily with food (1 capsule is usually 1g)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Suggested doses include 250 mg twice per day, may cause diarrhea in larger doses</td>
</tr>
<tr>
<td>Potassium</td>
<td>Either as provided by the treating physician or foods that are rich in potassium (e.g., bananas, oranges, and potatoes)</td>
</tr>
<tr>
<td>Tonic water</td>
<td>Drink one glass in evening and any other time cramping occurs</td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>500 mg twice per day with food; can take up to 2,000 mg per day</td>
</tr>
<tr>
<td>Alpha-lipoic acid</td>
<td>300-1,000 mg per day with food</td>
</tr>
<tr>
<td>Glutamine</td>
<td>1 g up to three times per day with food</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>50-60 mg daily with food</td>
</tr>
</tbody>
</table>

IU indicates international units; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Adapted from Richardson PG et al, Smith EM et al, Tariman et al.
References


Supportive Care of Patients with Multiple Myeloma: Neutropenia and Anemia
Joseph Tariman, PhD

Neutropenia
Neutropenia is a distressing side effect of chemotherapy characterized by an absolute neutrophil count (ANC) of less than 500 neutrophils/mcL or an ANC of 1,000 neutrophils/mcL. According to Lyman and Kuderer,1 if a predicted decline to less than or equal to 500 neutrophils/mcL occurs over 48 hours, neutropenia should be assessed and monitored. Neutropenia puts a patient at major risk of acquiring potentially fatal infections that could lead to septic shock and death. For this reason, nurses and physicians institute dose delays and dose reductions of chemotherapies; however, these actions may compromise clinical outcomes. To avoid delays and dose reductions, it is critical to prevent neutropenia in order to sustain or increase chemotherapy dose density and improve overall clinical outcomes. Several major international health care organizations have developed clinical guidelines for the prevention of chemotherapy-induced neutropenia, which are continuously updated based on new published data.2-4 These guidelines clearly stipulate the need for febrile neutropenia risk assessment in order to appropriately initiate prophylactic use of colony-stimulating factors (CSF).4,6

One of the professional practice gaps identified among nurses and physicians treating patients with multiple myeloma (MM) is the lack of consistent application of evidence-based guidelines for preventing and treating neutropenia. Although some studies have been conducted utilizing newly developed neutropenia risk assessment tools with promising results, randomized controlled trials are needed to identify an optimal risk assessment method for febrile neutropenia.7-11 Furthermore, routine prophylactic use of antibiotics and the ideal time period for the initial administration of antibiotics for patients with febrile neutropenia remain controversial issues due to a lack of systematic clinical studies.12,13 Despite these limitations, a consensus among experts is that patient- and disease-related factors have to be considered as important components of neutropenia risk assessment tools.4,5 In myeloma patient care, it is important to understand which myeloma therapies can lead to neutropenia, assess which patients are most at risk, and institute evidence-based guidelines that can prevent and treat neutropenia, all of which can lead to improved quality of life and increase a patient’s overall survival.

Specific examples of MM chemotherapy regimens that carry the highest risk for febrile neutropenia (>20%) include treatment protocols comprising dexamethasone, thalidomide, cisplatin, adriamycin, cytoxan, and etoposide (DTPACE)14 and bortezomib plus DTPACE (VDTPACE).15 When using one of these regimens, nurses and physicians must use prophylactic granulocyte colony stimulating factors (G-CSF) to prevent febrile neutropenia, hospitalization, and intravenous antibiotics during the course of therapy.16 One dose of 6 mg pegfilgrastim is recommended on the day after the completion of a 4-day treatment with DTPACE, given that evidence supports the use of pegfilgrastim in regimens administered at least every 3 weeks.17-18 Either DTPACE or VDTPACE is typically administered every 4 to 6 weeks as an induction regimen for newly diagnosed MM or as a salvage regimen for relapsed, refractory MM.

In terms of the two- or three-drug regimens that include novel agents such as thalidomide, lenalidomide, bortezomib, or carfilzomib, no reports cite greater than 20% probability of febrile neutropenia, which would require prophylactic CSF use. However, when combining three or four agents (e.g., bortezomib, lenalidomide and dexamethasone [BLD] or cyclophosphamide, bortezomib, lenalidomide, and dexamethasone [CVRD]), the risk for febrile neutropenia could potentially reach the intermediate-risk level of 10% to 20% or high-risk level (>20%), respectively. In this case, the most recent American Society of Clinical Oncology,3 European Organization for Research and Therapy in Cancer,4 and National Comprehensive Cancer Network (NCCN) guidelines,5 recommend the prophylactic use of CSF based on risk-to-benefit ratio, the consequences of a neutropenic event, and the implications for reduced chemotherapy dose delivery. All of these factors must be discussed between the patient and the clinician, and mutual agreement of the plan of care should be reached. Furthermore, a consensus among myeloma experts states that G-CSF treatment is indicated when patients undergoing low-risk chemotherapy experience grade 3/4 neutropenia. If ANC restores to >1,000 cells/mL, therapy can be resumed with no dose modifications. In case of persistence of severe neutropenia, treatment should be delayed until ANC reaches >1,000 cells/mL, and dose reductions are necessary.19 Table 1 outlines the regimens commonly used for the treatment of MM with their corresponding neutropenia risk category based on NCCN guidelines.

Anemia
Anemia induced by chemotherapy is defined as a hemoglobin level of 10 g/dL or lower.20 Anemia is a prevalent side effect of chemotherapy, occurring in 30% to 90% of patients with cancer.5 For the purpose of this monograph, anemia will be operationally defined as anemia occurring in cancer patients who are receiving concomitant chemotherapy. This type of anemia directly results from chemotherapies that impair the process of red blood cell production in the bone marrow, including the synthesis of red blood cell precursors and the nephrotoxic effects of chemotherapeutic agents causing decreased erythropoietin production by the kidney.21,22 Table 1 identifies the incidence of grade 3 and grade 4 anemia in patients receiving chemotherapies for MM.

The 2015 NCCN guidelines on chemotherapy-induced
anemia outline the latest updates on the NCCN expert panel’s recommendations for the appropriate use of erythropoiesis-stimulating agents (ESAs). The latest update concurs with a new FDA warning on the potential adverse effects of ESAs, including shortened overall survival. The NCCN panel recommendations are as follows:

1. All clinicians must use the Risk Evaluation and Mitigation Strategy (REMS) program for ESAs in patients with cancer. The REMS program provides the clinician with an opportunity to get the patient’s informed consent related to the use of ESAs and to provide patient education and medication guides.

2. Patients who are not receiving concomitant chemotherapy should not receive any ESAs; ESAs should be used only to treat anemia induced by chemotherapy.

3. Erythropoiesis-stimulating agents should not be used when the intent of therapy is cure, which is not an issue in treating patients with MM.

4. Patients undergoing palliative therapy may consider ESA or blood transfusion depending on their personal values and preferences.

5. When it is not clear that the treatment is curative (e.g., Total Therapy Protocols from University of Arkansas for Medical Sciences Myeloma Institute for Research and Therapy), the NCCN panel recommends considering red blood cell transfusion, clinical trial enrollment, or ESAs. If ESA use is considered, the lowest dose of ESA to prevent the need for transfusion is recommended.

6. Patients with chronic kidney disease not on active chemotherapy for a malignancy should avoid ESAs, while patients receiving palliative care should be given carefully dosed ESAs to prevent the need for blood transfusions.

In the MM care setting, the intent of therapy is rarely curative. Thus, the use of ESAs is possible, but the patient’s hemoglobin must be monitored closely and the lowest dose of ESA that can prevent transfusion needs to be considered in order to prevent potential adverse events noted in the FDA warnings.

### Table 1. Neutropenia and anemia risk categories in patients receiving therapies for multiple myeloma

<table>
<thead>
<tr>
<th>Low-risk neutropenia (&lt;10%)</th>
<th>Intermediate-risk neutropenia (10-20%)</th>
<th>High-risk neutropenia (&gt;20%)</th>
<th>Low-risk anemia (&lt;10% grade 3/4 incidence)</th>
<th>Intermediate-risk anemia (&gt;10-20% grade 3/4 incidence)</th>
<th>High-risk anemia (&gt;20% grade 3/4 incidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose dexamethasone</td>
<td>Melphalan/ prednisone/thalidomide</td>
<td>Lenalidomide/ adriamycin/ dexamethasone</td>
<td>High-dose dexamethasone</td>
<td>Bortezomib/melphalan/prednisone</td>
<td>Single-agent carfilzomib</td>
</tr>
<tr>
<td>Thalidomide/ dexamethasone</td>
<td>Cytoxan/thalidomide/dexamethasone</td>
<td>Melphalan/ lenalidomide/ prednisone</td>
<td>Lenalidomide/ lowdose dexamethasone</td>
<td>Cytoxan/bortezomib/lenalidomide/dexamethasone</td>
<td>Melphalan/ lenalidomide/prednisone</td>
</tr>
<tr>
<td>Bortezomib/low-dose dexamethasone</td>
<td>Lenalidomide/ low-dose dexamethasone</td>
<td>Cytoxan/lenalidomide/dexamethasone</td>
<td>Bortezomib/low-dose dexamethasone</td>
<td>Thalidomide/ dexamethasone</td>
<td></td>
</tr>
<tr>
<td>Single-agent carfilzomib</td>
<td>Cytoxan/bortezomib/lenalidomide/dexamethasone</td>
<td>Thalidomide/ dexamethasone</td>
<td>Bortezomib/melphalan/prednisone</td>
<td>Cytosar/lenalidomide/dexamethasone</td>
<td></td>
</tr>
</tbody>
</table>

Data from Caravita et al, Kumar et al, Morgan et al, Palumbo et al, Rajkumar et al, San Miguel et al.
Infection in Patients with Multiple Myeloma
Tiffany Richards, MS, ANP, AOCNP

Infections in patients with multiple myeloma (MM) are common and may lead to significant morbidity and mortality. In one study of 9,253 patients with MM, 22% of deaths were attributed to infections. Investigators found a 7-fold increase in bacterial infections and a 10-fold increase in viral infections in patients with myeloma compared to matched controls. Therefore, patients should be counseled on how to recognize signs and symptoms of infection and the importance of promptly reporting them to his or her physician.

Risk factors
Patients with both newly diagnosed and relapsed or refractory myeloma are at increased risk of infection as a result of disease- or therapy-related immunodeficiency, including hypogammaglobulinemia, lymphocyte dysfunction, and neutropenia. In addition, steroids such as dexamethasone may lead to elevated glucose levels, placing patients at risk for the development of infections. Older age also is a risk factor due to the reduction of phagocytosis, chemotaxis, and intracellular pathogen killing. Older patients may also have reduced antibody responses to vaccinations. Patients with compression fractures or who are receiving opioid therapy may experience diminished lung capacity leading to increased risk of developing pneumonia. Organ dysfunction and comorbid conditions such as renal failure and chronic obstructive pulmonary disorder may increase an individual’s susceptibility to infection. The incidence of grade 3 infection varies between the various antymyeloma regimens, but range between 6% in patients taking thalidomide plus dexamethasone to 21% in patients taking lenalidomide plus high-dose dexamethasone. However, lenalidomide and low-dose dexamethasone reduced the rates of infection to 16%.

Vaccinations
Research data vary with regard to the development of an appropriate antibody response to influenza and pneumococcal vaccines; however, all patients with myeloma should receive the trivalent influenza and pneumococcal vaccines. A tetanus booster every 10 years is recommended. In patients who have undergone a stem cell transplant, revaccination with polio (inactivated), tetanus toxoid, diphtheria toxoid, pneumococcal pneumonia, hepatitis B, and haemophilus influenza type B is recommended starting at approximately 6 to 12 months post-transplant. Patients should be informed that, due to their immunocompromised state, they cannot receive live vaccines such as the herpes zoster, yellow fever, or the intranasal influenza vaccines.

Prevention of Infection
The most important intervention to prevent infection is hand washing, including in patients with neutropenia. When performing hand washing, it is important to use alcohol-based sanitizers both before and after patient contact. When in contact patients with Clostridium difficile, washing hands with soap and water is the preferred method to prevent spread of the bacteria. Family members and close contacts should be instructed to receive both the influenza and pneumococcal vaccines. Patients who have received the influenza vaccine need to be instructed that they may still be at risk for contracting influenza, as it is not possible to determine if an individual has developed an adequate antibody response.

Patients should be instructed to avoid contact with individuals with signs and symptoms of infection, or who have undergone recent vaccination (within 3 to 6 weeks) with a live vaccine. Additionally, patients should be educated to thoroughly cook all foods, avoid contaminated water, and avoid swimming in areas that may place them at risk for infection. All patients traveling outside of the United States should meet with an infectious disease consultant to determine which infectious disease risks are associated with the country they are planning to visit.

In patients with MM who experience recurrent infections, initiating intravenous gammaglobulin may be useful to decrease the frequency of infections in patients. Testing for immunoglobulin G (IgG) subclass to confirm hypogammaglobulinemia may be necessary to obtain insurance approval, particularly if the IgG level is high or within the normal range. Intravenous gammaglobulin is administered via slow infusion and presedication with a combination of acetaminophen and diphenhydramine or hydrocortisone.

Antimicrobial prophylaxis
Patients with MM receiving bortezomib- or carfilzomib-based therapy should be placed on herpes zoster prophylaxis, such as acyclovir or valacyclovir. In patients with impaired renal function, dose adjustments are recommended with valacyclovir. Patients require education on herpes zoster and the importance of prompt reporting of a vesicular rash to their clinical team or on-call physician. In patients receiving intense regimens, such as the combination of bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (VDT-PACE) or the combination of cyclophosphamide, vincristine, doxorubicin, and dexamethasone (modified hyperCVAD), prophylaxis with an antifungal, an antiviral, and a fluoroquinolone is recommended.

Monitoring for infection
Educating patients on the importance of monitoring temperature and other signs and symptoms of infection, and reporting of signs and symptoms to his or her physician, is important. Patients receiving steroids may not develop fever, so patients need to be instructed to monitor and report chills, respiratory symptoms, dysuria, shortness of breath, diarrhea, or other symptoms of infection. In older patients, altered mental status may be the
presenting symptom of an infection; therefore, caregivers and family members should be made aware that they should bring the individual to the emergency center for further evaluation.

Management of fever

In patients with MM presenting with fever, pan culturing is recommended and should include blood cultures x2, urine culture, site-specific cultures such as stool for *Clostridium difficile* or respiratory viral cultures, and a chest radiograph. Older patients presenting with altered mental status should receive not only a neurological workup, but also an infectious workup. In patients who are neutropenic, initiating intravenous broad spectrum antibiotics including pseudomonas coverage is recommended and needs to be started immediately. Selection of antimicrobial therapy is dependent upon the following factors: infection risk, drug allergy, infection site, clinical stability, local resistant strains, and recent antimicrobial therapy.6

In patients who are not neutropenic, antibiotics can be initiated in the outpatient setting as long as the patient is not on a fluoroquinolone prophylaxis. The type of antimicrobial therapy will depend upon the site of infection, allergies, and resistant strains reported locally. Similar to evaluations conducted in the inpatient setting, outpatients should undergo blood and urine cultures, chest radiograph, and any additional site-specific cultures. In patients receiving antimicrobial therapy in the outpatient setting, fever persisting for more than 24 hours may require treatment with intravenous antibiotics. In patients presenting with upper respiratory symptoms, it is essential to test for influenza regardless of vaccine status.6

Pneumonia

In patients presenting with upper respiratory symptoms, obtaining a nasal wash for viral cultures (influenza, respiratory syncytial virus, and other respiratory viral syndromes), sputum culture, and/or chest radiograph is recommended. Additionally, in patients at high risk for aspergillus, serum galactomannan assay screening may be warranted. Treatment of pneumonia should include a fluoroquinolone or azithromycin to ensure coverage of atypical organisms. In patients who test positive for influenza, starting therapy with an antiviral such as oseltamivir is recommended within the first 48 to 72 hours of the onset of symptoms.2,6

Conclusion

Patients with MM are at increased risk of infection as a result of their disease and treatment. Management of infection in these patients includes primary, secondary, and tertiary prevention. Patients require education on strategies for prevention of infection, including hand washing and avoiding contact with individuals who are sick or have respiratory symptoms. In order to manage infection at an early stage, patients must know how to recognize the signs and symptoms of infection and understand the impact of therapy on their ability to fight off infection. Finally, in patients who develop an infection, prompt assessment and treatment is required, particularly in those at risk for neutropenia.

References

Dyspnea
Tiffany Richards, MS, ANP, AOCNP

Dyspnea is defined as a “subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors and may induce secondary physiological and behavioral response.”

Dyspnea may occur in patients with multiple myeloma (MM) as result of drug toxicity, pulmonary embolism, anemia, infections, and other comorbid conditions. Untreated dyspnea may lead to worsening respiratory status resulting in emergency room visits, hospitalizations, and, in severe cases, to mechanical ventilation. Therefore, it is essential to perform a thorough assessment and intervene quickly when a patient with MM reports dyspnea.

Incidence
Dyspnea was reported in approximately 42% of patients in four phase 2 clinical trials of carfilzomib as a single agent; most of these were grade 1 although 4.8% of patients experienced grade 3 dyspnea. In a phase 3 trial of bortezomib versus dexamethasone, rates of dyspnea were similar in both arms (20% vs. 17%) with 6% grade ≥3 in the bortezomib arm. While reports of dyspnea with immunomodulatory agents are rare, case reports of pulmonary toxicity due to thalidomide, lenalidomide, and pomalidomide have been reported. Dyspnea may also be one of the initial presenting symptoms of a pulmonary embolism. The incidence of thromboembolic disease, including pulmonary embolism, ranges from 12% with an immunomodulatory agent combined with low-dose dexamethasone to 15% to 26% when combined with high-dose dexamethasone.

Patients with MM may experience dyspnea as a result of anemia due to bone marrow infiltration or as a result of therapy. In phase 2 and phase 3 clinical trials of lenalidomide, pomalidomide, bortezomib, or carfilzomib, grade 3 and 4 anemia range between 10% and 37%. Patients with MM may present with or develop other comorbid conditions, such as chronic obstructive pulmonary disease (COPD), during their disease trajectory.

In 2011, an estimated 12.7 million people were diagnosed with COPD in the United States. Dyspnea is one of the main symptoms that individuals with COPD experience.

Assessment
Assessment of dyspnea begins with obtaining a thorough history from the patient including descriptors of the shortness of breath and the onset (acute versus chronic). For example, is the dyspnea described as chest tightness, increased work of breathing, air hunger, or inability to take a deep breath. Additionally, patients should rate their dyspnea on a scale of zero to 10 at various times, including at rest, immediately following exercise, or during a specific task such as climbing the stairs. A variety of tools exist to assist clinicians in obtaining descriptors and ratings of dyspnea, including the modified Borg scale, baseline dyspnea index, or the Chronic Respiratory Disease Questionnaire. It is also important for clinicians to assess for nocturnal dyspnea and inquire about the number of pillows the patient uses at night to sleep. Additional questions include the presence of edema, chest pain, snoring, cough, fever, rhinorrhea, and environmental exposures (asbestos, tobacco use, pets, water damage in the home). If the patient is currently receiving carfilzomib-based therapy, it is important to determine the timing of onset of the dyspnea in relation to when they received their dose of carfilzomib; this helps to determine if dyspnea is a result of therapy.

Workup
Workup for dyspnea should include a chest radiograph to evaluate for cardiac size, congestive heart failure (CHF), pneumonia, or pleural effusions. In patients with worsening infiltrates who remain febrile on antibiotic therapy, a computed tomography (CT) chest scan may be useful to differentiate between bacterial or fungal infections and pneumonitis. In patients receiving treatment with an immunomodulatory agent along with dexamethasone, a ventilation–perfusion (VQ) scan or CT chest angiogram is used to determine if a pulmonary embolism is present. Caution should be used in patients with impaired creatinine and CT scans should be avoided in these patients due to the risk of worsening kidney function. Additionally, pulse oximetry, echocardiogram, pulmonary function studies, electrocardiogram, hemoglobin level, and thyroid function studies should be included in the diagnostic work up for dyspnea. An arterial blood gas should be obtained in patients with pulse oximetry less than 90%. In patients with worsening pulmonary infiltrates, bronchoscopy with bronchoalveolar lavage may be performed to obtain cultures and cytology. Additionally, a sleep study is beneficial to determine if the patient has sleep apnea that is contributing to increased pulmonary pressure. If the chest radiograph reveals a moderate to large pleural effusion, a thoracentesis can be obtained and fluid sent to a pathology laboratory to rule out a malignancy process. While myeloma in the pleural fluid is rare, patients can develop a malignant pleural effusion as a result of their disease, particularly patients with pleural-based plasmacytomas.

Management
Management of dyspnea is dependent on its underlying etiology, such as pneumonia, drug toxicity, pulmonary embolism, pulmonary edema, cardiomyopathy, anemia, sleep apnea, or pulmonary disease. In patients who present with pulmonary infiltrates on chest radiograph, broad spectrum antimicrobial therapy may be initiated until culture sensitivities return. If infiltrates worsen or if the fever continues, an antifungal agent may be added to the antimicrobial therapy.

Pulmonary toxicity has been reported with use of immunomodulatory agents and bortezomib; therefore, drug-induced pneumonitis should be considered a
If a CT chest angiogram reveals a pulmonary embolism, full-dose anticoagulation is recommended; patients treated with warfarin require close monitoring of international normalized ratio (INR) levels. If low molecular weight heparin (LMWH) is being considered for anticoagulation, ensure adequate renal function prior to initiation. The use of LMWH in individuals with a creatinine clearance less than 30 mL/min is not optimal as it is excreted by the kidneys and requires dose reductions and close monitoring.

Individuals with pulmonary edema may require emergent hospitalization for diuresis. However, it is important to determine the etiology of pulmonary edema, such as CHF, hypoalbuminemia, dialysis, or fluid imbalance. In patients with CHF, reinforcement of daily weights, sodium restriction, and communication with their cardiologist if their weights increase are important.18

Patients with MM may develop a coexisting diagnosis of amyloid, which may affect the heart, kidneys, and lungs. Individuals with cardiac amyloid require close monitoring, particularly if dexamethasone is administered to treat the fluid retention that can occur in this patient population.

Patients presenting with dyspnea who are found to have anemia may require blood transfusion. Patients with risk factors such as cardiac disease or older age require a higher threshold for transfusions than patients without risk factors. Patients receiving therapy may require more frequent blood count monitoring.

If the chest radiograph reveals hyperinflation, then referral to a pulmonologist is indicated. Pulmonary function studies assist in distinguishing between emphysema and other obstructive diseases (amyloid).7 In patients with pleural effusions, correction of the underlying problem, such as treatment of a malignancy, left ventricular failure, hypoalbuminemia, or mitral valve stenosis, or congestive heart failure, is required in order to prevent reaccumulation of the fluid. Placement of a Denver catheter can be considered in patients who have a malignant pleural effusion and require repeat thoracentesis. In patients with elevated pulmonary pressures or sleep apnea, referral to a cardiologist and a pulmonologist is warranted to determine the etiology.

In all patients with dyspnea, oxygen should be initiated if oxygen saturation drops. Nebulizer treatments can be initiated in patients with COPD, asthma, or pneumonia to reduce airway constriction. For patients who will require oxygen at home, a home oxygen evaluation is required by most insurers. Other nonpharmacologic interventions include cooler room temperatures, relaxation therapy, stress management, and fans.19

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Venous Thromboembolism
Patricia Mangan, APRN-BC

Despite tremendous improvements in the effectiveness of modern treatment for multiple myeloma (MM), patients still experience adverse events both from the therapies and the underlying disease. A serious and potentially life-threatening example is venous thromboembolism (VTE), manifested as deep vein thrombosis (DVT) or pulmonary embolism (PE). In addition to significant morbidity and mortality, VTE can impact quality of life and the cost of treatment.1 Cancer patients have a 7- to 10-fold risk of developing VTE and patients with MM have an even greater risk, especially those receiving oral immunomodulatory agents (IMIDs) in combination with corticosteroids or chemotherapy.2-5 Venous thromboembolism can occur at any time during the course of the disease and treatment, but most commonly during the first cycles of initial therapy (3%–34% of patients) or at the time of relapse (2%–15%).4

Risk factors
Numerous factors increase the risk for VTE in patients with monoclonal gammopathy of undetermined significance (MGUS) or MM (Table 1). The combination of low albumin, higher levels of IL-6 (an inflammatory cytokine), and advanced age have been implicated in the promotion of coagulation.6 Chemotherapy and corticosteroids amplify the prothrombotic effect of cancer cells and may damage blood vessel walls directly.4 In addition, patients with myeloma tend to have pain, bone lesions, fractures, and fatigue leading to decreased ambulation and immobilization, which increases the likelihood of clot formation.5

The International Myeloma Working Group, American Society of Clinical Oncology, and National Comprehensive Cancer Network have recommended management strategies for the prevention and treatment of acute VTE based on factors known to infer a higher risk of VTE in patients with myeloma. These risk factors include (1) patient-specific risks such as age (>65), obesity, history of VTE, central-venous catheter, comorbidities (diabetes, infections, cardiac diseases, renal disease), surgical procedures (including vertebroplasty and kyphoplasty), immobility, and inherited thrombophilia; (2) myeloma-specific risks, including diagnosis of MGUS versus MM or presence of hyperviscosity; and (3) therapy-related risks, including dose, schedule, and type of corticosteroid, combining IMIDs with doxorubicin or other chemotherapy regimens, and the use of erythropoiesis-stimulating agents.

Prophylaxis
Immunomodulatory agents
Patients with MM treated with immunomodulatory agents such as thalidomide or lenalidomide in combination with steroids or chemotherapy have an increased risk of VTE and, therefore, require routine thromboprophylaxis.3,5,7 The use of single-agent thalidomide or lenalidomide carries a low incidence of VTE (<5%), so anticoagulant prophylaxis is not usually required.5 When thalidomide is administered in combination with dexamethasone, however, the risk of VTE is higher but can be reduced when therapeutic-dose warfarin or low molecular weight heparin (LMWH) is used. It is not recommended to use low-fixed-dose warfarin or full-dose aspirin in patients receiving thalidomide plus doxorubicin or multiagent chemotherapies since several studies have shown it to be ineffective.5

Aspirin is an appropriate prophylaxis in patients receiving lenalidomide in combination with low-dose dexamethasone, melphalan, or doxorubicin, reducing the incidence of VTE to less than 10%.4,5 Use of high-dose dexamethasone in combination with lenalidomide increases the risk of VTE despite aspirin prophylaxis; therefore, LMWH or full-dose warfarin is recommended. Aspirin alone is recommended for low-risk patients, with either no patient- or myeloma-specific risk factors or only one. Patients who have at least two patient- or myeloma-specific risk factors or are taking high-risk therapy (high-dose dexamethasone, doxorubicin, or multiagent chemotherapy) should receive LMWH (equivalent to enoxaparin 40 mg once daily) or therapeutic-dose warfarin (international normalized ratio [INR] of 2-3) as thromboprophylaxis. All patients with only therapy-related risks should receive LMWH or therapeutic-dose warfarin.

### Table 1. Risk factors associated with increased risk of VTE in patients with multiple myeloma

<table>
<thead>
<tr>
<th>Patient-related risks</th>
<th>MM-related risks</th>
<th>Therapy-related risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt;65)</td>
<td>Diagnosis of MM</td>
<td>High-dose dexamethasone (&gt;480 mg/month)</td>
</tr>
<tr>
<td>Obesity (body mass index ≥30-35 kg/m)</td>
<td>MGUS</td>
<td>IMIDs + dexamethasone, doxorubicin</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>Hyperviscosity</td>
<td>Multiagent chemotherapy</td>
</tr>
<tr>
<td>Immobility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central venous catheter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacemaker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid conditions: cardiac disease, renal disease, diabetes, infection, clotting disorders, thrombophilia (platelets &gt;350,000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent surgery with anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of erythropoietin</td>
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</tr>
</tbody>
</table>

Immunomodulatory agents also may inhibit the healing of chemotherapy-induced endothelial injury, increasing the risk of VTE.4 In addition, patients with myeloma tend to have pain, bone lesions, fractures, and fatigue leading to decreased ambulation and immobilization, which increases the likelihood of clot formation.5
related risks should receive LMWH or full-dose warfarin. Ongoing randomized trials comparing aspirin, warfarin, and LMWH will inform the optimal prophylaxis strategy. The goal remains to define a strategy that will reduce the risk of VTE below 10% in patients receiving thalidomide or lenalidomide.

Proteasome inhibitors

The proteasome inhibitor bortezomib, when used in various combination therapies for newly diagnosed and relapsed patients with MM, has been shown to protect against the development of VTE. The mechanism of protection is not completely understood but may be related to interference with inflammation and procoagulant abnormalities that may increase thrombus formation. Thromboprophylaxis is still recommended when administered in combination with an IMID and dexamethasone. To date, carfilzomib, a second-generation proteasome inhibitor, has not been associated with an increased risk of thrombosis, potential cardiac toxicity remains under investigation.2,7

Diagnosis of venous thromboembolism

Despite appropriate thromboprophylaxis in patients with MM, 5% to 8% will develop thrombosis.2 Patient education on common signs and symptoms of DVT (redness, pain, or swelling of an extremity, particularly the distal lower extremity) or PE (chest pain, shortness of breath, or rapid heartbeat) and the importance of prompt reporting of these clinical changes to their health care provider, is essential for effective early intervention.

Approximately 25% of untreated distal thromboses propagate quickly and extend into the proximal veins, and approximately 50% of patients with proximal-vein thrombosis develop either symptomatic or asymptomatic PE. When DVT is suspected, the recommended diagnostic test is ultrasonography, which carries a greater than 95% detection rate. To rule out PE, imaging with computed tomography with pulmonary angiography is recommended over less frequently used nuclear medicine techniques such as ventilation–perfusion (VQ) scan. Magnetic resonance angiography can be utilized if iodinate contrast dye is contraindicated.

Treatment of venous thromboembolism

Treatment of VTE aims to avoid remobilization, relieve symptoms, and prevent recurrence. It is recommended that patients who develop VTE while on thalidomide or lenalidomide discontinue these agents until therapeutic anticoagulation is achieved. Low molecular weight heparin is recommended for the initial 5 to 10 days of treatment for patients with established DVT and pulmonary embolism. The agents most commonly used in practice are dalteparin (doses of 100 U/kg every 12 hours or 200 U/kg daily); enoxaparin (doses of 1 mg/kg every 12 hours or 1.5 mg/kg daily), and nadroparin (doses of 86 U/kg every 12 hours or 171 U/kg daily).5,8 In obese patients, optimal dosing should be based on actual body weight since no increase in bleeding risk has been seen in clinical trials. If warfarin is to be used for anticoagulation, it should start on the first day of treatment with LMWH. Heparin should be administered for a minimum of 5 days and not stopped until the patient’s INR has been 2.0 to 3.0 for 2 consecutive days. Optimal duration of treatment once symptoms have resolved is unclear. Since the risk of recurrence after discontinuation of anticoagulation is greater than 10%, extended therapy with LMWH should be considered in cancer patients, keeping in mind cost and need for daily subcutaneous injections.

Bleeding is a significant risk associated with anticoagulation and is highest in patients with renal impairment. Therapeutic doses of LMWH with creatinine clearances < 30mL/min results in a 2-fold higher risk of bleeding than in patients with normal creatinine clearance. Newer oral anticoagulants now clinically available may be an attractive option in the near future since they do not require frequent monitoring and do not have many drug interactions. Studies are needed to evaluate their activity in this patient population; therefore, their use in thromboprophylaxis for patients with MM and VTE is not recommended.4

Recurrent venous thromboembolism

Patients whose VTE recurs despite standard doses of anticoagulant therapy should be assessed for treatment compliance, heparin-induced thrombocytopenia, or any evidence of mechanical compression resulting from their malignancy. Management strategies for recurrent VTE include treatment with an alternate anticoagulant regimen or increasing the dose of LMWH. In patients for whom standard doses of LMWH fail, higher doses (increase of

Table 2. Venous thromboembolism prophylaxes and treatment

<table>
<thead>
<tr>
<th>Recommended VTE prophylaxis</th>
<th>0-1 risk factors</th>
<th>Aspirin 81-325 mg once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 risk factors</td>
<td>LMWH (equivalent to enoxaparin 40 mg once daily)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Therapeutic dose of warfarin (target INR 2-3)</td>
<td></td>
</tr>
</tbody>
</table>

| Recommended VTE treatment   | Acute/new VTE | LMWH is recommended for the initial 5 to 10 days of treatment for patients with established deep vein thrombosis and pulmonary embolism, as well as for long-term (6 months) secondary prophylaxis |
|-----------------------------|---------------|
| Recurrent VTE              | Treatment with an alternate anticoagulant regimen |
|                             | Increasing the dose of LMWH |
|                             | Vena cava filter ± LMWH |

Adapted from Palumbo et al6 and Lyman et al.8
20% to 25%) has been shown to effectively prevent further recurrence. This higher-dose LMWH is well tolerated without an increased risk of bleeding. The role of inferior vena cava (IVC) filters is controversial but may be an option in combination with LMWH or if anticoagulation is contraindicated. Retrievable filters can be utilized for a period of time but their use has been associated with a number of adverse events.

**Summary**

Because of the high incidence and danger of VTE in patients with MM, routine thromboprophylaxis is recommended. The recommendations for thromboprophylaxis and treatment of acute VTE presented here are based on available data and should be utilized along with the health care provider’s clinical judgment and characteristics of the individual patient, balancing the potential benefits and harms of the various thromboprophylaxis regimens. Further investigation is needed to determine the incidence of VTE in patients undergoing treatment with various drug combinations with varying mechanisms of action, including newer agents currently being evaluated in clinical trials.

**References**

Diarrhea in Patients with Multiple Myeloma
Charise Gleason, MSN, RN, NP-BC, AOCNP

Diarrhea is a frequent side effect of cancer treatment with significant clinical consequences. Diarrhea is a common cause of unexpected clinic visits, emergency department visits, and hospitalizations. Numerous therapeutic agents used in the treatment of multiple myeloma (MM) are associated with diarrhea, including bortezomib and lenalidomide, which require treatment modification or discontinuation until resolution of symptoms. Therefore, diarrhea can interfere with cancer treatment and ultimately may have an impact on survival.

Diarrhea is defined as three or more liquid stools over a 24-hour period. Patients with MM may have diarrhea related to treatment, to infection secondary to destruction of normal gut flora by antibiotics, or to primary infection secondary to compromised immunity. Untreated, prolonged diarrhea may lead to dehydration, electrolyte imbalance, weight loss, nutritional deficits, and even cardiovascular compromise and death. The severity of diarrhea is graded using the National Cancer Institute’s Common Terminology Criteria for Adverse Events as depicted in Table 1.

Pathophysiology of diarrhea
Cancer treatment-induced diarrhea (CTID) is a complication experienced by many patients receiving agents that target rapidly dividing cells such as the epithelial lining of the gastrointestinal tract. The prevalence of CTID is unknown, as its cause may be drug-related or organic in nature. Often overlooked causes of diarrhea include malabsorption syndrome, bacterial overgrowth, and inflammatory or infectious enteritis.

The incidence of CTID varies with treatment regimens and patient characteristics. Agents associated with the highest incidence of grade 3/4 diarrhea include fluorouracil, irinotecan, tyrosine kinase inhibitors, and small molecule monoclonal antibodies. In patients with MM, agents such as lenolidomide, thalidomide, bortezomib, and carfilzomib have the highest incidence (Table 2).

Table 2. Incidence of diarrhea in patients with multiple myeloma receiving novel therapies

<table>
<thead>
<tr>
<th>Novel Therapy</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide (+ dexamethasone)</td>
<td>29</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>(two studies, n=346)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalidomide (+ dexamethasone)</td>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(open-label study, n=102)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib (phase III trial, n=331)</td>
<td>57</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Carfilzomib (phase III trial, n=526)</td>
<td>33</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Adapted from Smith et al and Hemdon et al

The cause of diarrhea induced by immunomodulatory agents is poorly understood but it is thought to be secretory in nature caused by an immune reaction involving antigens on the epithelial cells of the gastrointestinal tract. A recent report of 12 patients receiving lenolidomide therapy found that 9 were experiencing bile acid malabsorption. This case report requires further investigation with multicenter studies involving larger numbers of patients. It does, however, highlight a potential treatment for this dose-limiting side effect: 50% of the patients had resolution of diarrhea with bile acid sequestrant therapy plus reducing dietary fat intake.

Treatment recommendations
Both the American Society of Clinical Oncology (ASCO) and the Oncology Nursing Society (ONS) have published strategies to appropriately assess and manage diarrhea. Recommendations include dietary modification (smaller, more frequent, lactose-free meals) and over-the-counter medications (loperamide) for patients experiencing grade 1 or 2 diarrhea. Therapy cessation is required for grade 3 or grade 4 diarrhea, with restart once symptom severity has lessened.

Figure 1 details an algorithm for cancer treatment-induced diarrhea. The National Comprehensive Cancer Network (NCCN) evidence-based guidelines for clinical practice in palliative care also describe initial dietary modification and use of loperamide for grade 1 and grade 2 diarrhea. Antibiotics, anticholinergics, and corticosteroids are employed when diarrhea persists or worsens despite intervention.

Table 1. Diarrhea grading

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>An increase of &lt;4 stools over baseline, per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>An increase of 4-6 stools over baseline, per day</td>
</tr>
<tr>
<td>Grade 3</td>
<td>An increase of 7 or more stools over baseline, per day</td>
</tr>
<tr>
<td></td>
<td>Incontinence</td>
</tr>
<tr>
<td></td>
<td>Hospitalization indicated</td>
</tr>
<tr>
<td></td>
<td>Limits self-care activities of daily living</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences</td>
</tr>
<tr>
<td></td>
<td>Urgent intervention indicated</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death</td>
</tr>
</tbody>
</table>

This monograph reviews the pathophysiology of diarrhea, the drugs used to treat MM that may cause diarrhea, and treatment guidelines, including dietary recommendations, diarrhea medications, and the role of dose adjustment in diarrhea management.
Patient/family education

Patients must be taught to notify their care team when they experience an increase of four or more stools above baseline for more than 24 hours. Successful management of low-grade diarrhea can obviate or reduce the need for therapy reductions or hospitalization. Patients should be knowledgeable about over-the-counter antidiarrheal agents and when and how to use those agents as well as nutritional interventions when symptoms are mild.

Diarrhea is a common yet complex complication of cancer therapy. It is common in patients receiving treatment for multiple myeloma, particularly with agents such as bortezomib, carfilzomib, and lenalidomide. Successful management of CTID can enable patients to continue therapy without dose modification or cessation of therapy. It is critical, therefore, that patients are aware of early detection principles and know how and when to contact their care providers for management. Providers must also be aware of and employ the evidence-based recommendations in the treatment algorithms supported by the NCCN and ONS.

Figure 1. Treatment of cancer treatment-induced diarrhea

References

Fatigue in Multiple Myeloma Survivors
Sandra Kurtin, MSN, CNP

Fatigue is accepted as a major component of health-related quality of life (HRQOL) and symptom burden in cancer survivors. A number of symptoms correlate with fatigue, and fatigue is described as a key component of a variety of cancer symptom clusters. Cancer-related fatigue is defined by the National Comprehensive Cancer Network (NCCN) as: “...a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.”

Fatigue may vary in intensity over the course of the survivor’s life, but may continue for many years after diagnosis regardless of disease or treatment status.

The prevalence of fatigue in specific cancer populations varies widely in the literature. The Eastern Cooperative Oncology Group (ECOG) Symptom Outcomes and Practice Patterns Study (SOAPP) evaluated core cancer-related symptoms in 3,106 patients with a median age of 61 years diagnosed with one of four common solid tumors including breast (n=1,544), colorectal (n=718), prostate (n=320), and lung (n=724) cancers. Patients completed the 19-item MD Anderson Symptom Inventory (MDASI) using an 11-point numeric rating of 0 (“not present”) to 10 (“as bad as you can imagine”) for 13 core symptoms including fatigue/tiredness, disturbed sleep, pain, distress, numbness/tingling, shortness of breath, lack of appetite, sadness, constipation, diarrhea, nausea, vomiting, and drymouth. Moderate-to-severe symptoms were defined as patient-reported scores greater than five. The survey was repeated 28 to 35 days from the initial evaluation. Fatigue was rated as the most severe symptom across diagnostic groups at baseline and in follow-up. Moderate to severe fatigue was more common in patients with lung cancer (46%) and breast cancer (31%) and in those on active treatment compared to those not on active treatment (37% vs. 27%).

Advanced disease and declining ECOG performance status (ECOG-PS) were also associated with increased incidence and severity of fatigue (42% to 53% for advanced disease and 24% for ECOG-PS 0 vs. 68% for ECOG-PS 2-4), although 27% of patients with no current evidence of disease reported moderate to severe fatigue. The incidence and severity of fatigue and sleep disturbance remained stable at the time of the second survey.

A similar study conducted by Wang and colleagues used the MDASI questionnaire to evaluate fatigue in 3,123 patients with breast, colorectal, prostate, and lung cancers. The median time from diagnosis for study participants was 13 months for patients on active therapies and 27 months for patients in remission. Seventy-seven percent of the patients reported some level of fatigue, and 45% of patients on active treatment reported moderate-to-severe fatigue, with lung cancer being the most common diagnostic group (59%). In multivariate regression analysis, opioid use, weight loss greater than 5% of body weight within the previous 6 months, taking 10 or more medications, a history of depression, and a diagnosis of lung cancer were significantly related to fatigue in patients receiving active therapies. Poor ECOG-PS and depression were significantly related to moderate-to-severe fatigue in 29% of patients in remission. Both of these trials acknowledge that they did not evaluate comorbid conditions and nutritional status as contributing factors to fatigue.

Based on these and other studies, fatigue is considered the most common symptom reported by cancer survivors in remission or receiving active treatment for common solid tumors, and the majority of patients will experience moderate-to-severe fatigue over the course of their survivorship.

Common contributing factors to fatigue: Comorbidities and nutrition

Given the older age of the majority of patients with multiple myeloma (MM; mean age at diagnosis equals 70 years), it is not surprising that many patients have comorbid conditions at the time of diagnosis. These conditions may be exacerbated during treatment, or in some cases may develop as a result of treatment. The leading cause of death for patients with MM is infections, in particular pneumonia. The most common comorbidities noted in the literature for patients with MM include cardiovascular disease (coronary artery disease, hyperlipidemia, and hypertension), chronic lung disease, endocrine disorders (including diabetes), and arthritis. Any of these conditions may contribute to fatigue.

More than half of newly diagnosed patients with cancer exhibit symptoms of nutritional deficits. Significant weight loss (>10% of body weight) within the 6 months prior to diagnosis is considered a high-risk attribute and often is indicative of more aggressive or advanced disease. A body mass index (BMI) of less than 20 kg/m² or weight loss of more than 5% of body weight over the previous 6 months is considered an indication of cancer cachexia. All cancer survivors are likely to benefit from a nutritional analysis and recommendations tailored to their disease, treatment plan, and comorbidities. However, studies that support a direct correlation between specific dietary measures and either increased or decreased fatigue are lacking.

A high intake of ω-6 relative to ω-3 polyunsaturated fatty acids (PUFA) has been suggested in previous studies as a surrogate for increased inflammation and a higher risk of illness. Omega-6 PUFA mostly comes as linoleic acid from plant oils, such as corn oil, soybean oil, and sunflower oil, and from nuts and seeds. Omega-3 PUFA comes primarily from fatty fish, such as salmon, mackerel, and tuna, and from walnuts and flaxseed in lesser amounts. Alfano and colleagues evaluated 633 breast cancer survivors participating in the Health, Eating, Activity, and Lifestyle (HEAL) Study who used a diary to
capture diet and activity, and used self-ratings on the Piper Fatigue Scale and Short Form-36 vitality scale to evaluate multidimensional fatigue.\cite{11} The researchers also measured serum C-reactive protein (CRP) and amyloid A levels as surrogates for inflammation at study entry and again 30 months after study entry. Increased intake of ω-3 PUFA relative to dietary ω-6 PUFA was associated with lower serum CRP levels; a 2.6-fold increased risk of fatigue was found among individuals with the highest ω-6:ω-3 ratio who were not taking ω-3 supplements. Lower CRP levels were associated with decreased fatigue.

A pilot study examining the association between diet and persistent cancer-related fatigue in 40 female cancer survivors suggested that consumption of whole grains, vegetables, and food rich in certain anti-inflammatory nutrients was associated with decreased levels of fatigue.\cite{11} Only increased vegetable consumption reached statistical significance when comparing fatigued cancer survivors and non-fatigued cancer survivors in this pilot study. Both of these trials cite the limitation of including only female cancer survivors and suggest that, to better understand the relationship to fatigue, clinical trials should include both dietary intake (including supplement use) and measures of inflammatory cytokines in diverse populations of cancer survivors. Until these studies have been conducted, the authors suggest following the current American Cancer Society guidelines for diet and nutrition.

**Pathophysiology of cancer-related fatigue: An evolving science**

Cancer-related fatigue is a complex, multidimensional phenomenon for which the underlying pathophysiology is not yet well understood. Although a number of studies have incorporated biomarkers thought to be correlated with fatigue, which in some cases have reached statistically significant associations, the results have been limited by small sample size, narrow population definitions (breast cancer survivors most commonly), and variable measures of fatigue. Thus no current guidelines or recommendations exist for the widespread use of specific biomarkers for fatigue.

Dysregulation in inflammation, hypothalamic-pituitary-adrenal function (cortisol production and glucocorticoid receptors), and immune factors (cellular immune system and latent herpes viruses) are thought to play a primary role in the underlying mechanism of fatigue.\cite{3} Tumor necrosis factor alpha (TNFα), interleukin-6 (IL6), and nuclear factor-kB (NFkB) have been suggested as biomarkers for inflammation in a number of animal models and human trials.\cite{3} Polymorphisms in these cytokine genes are being explored as possible surrogates for inflammation. Bower and Lamkin\cite{9} propose a conceptual model linking cancer, cancer treatment, and inflammation to fatigue, but emphasize the need to also incorporate biobehavioral factors, such as sleep, depression, stress, and BMI, that have well-established associations with fatigue. Sleep disturbance also has been linked to increased inflammation with increased daytime production of IL6 and night-time production of NFκB, particularly in women.\cite{12} Depression has been linked to elevated levels of CRP and IL6 in cancer survivors.\cite{13}

Both IL6 and TNFa are known to play an important role in the expansion and maintenance of MM cells. Wang and colleagues evaluated 51 patients with MM who had undergone an autologous hematopoietic stem cell transplant (HSCT) using the Charlson co-morbidity score, the MDASI-MM, and an inflammatory marker assay based on potentially relevant associations with symptom burden.\cite{5} Elevated TNFa was the only biomarker predictive of a high symptom burden and was positively associated with fatigue, muscle weakness, and bone pain.

**Correlates of fatigue in multiple myeloma survivors**

In a study of 187 newly diagnosed patients with MM, fatigue was common at baseline (mean Functional Assessment of Cancer Therapy-Fatigue [FACT-F] scores of 32.1 for women and 38.7 for men) and was severe in 19% of patients.\cite{14} Anemia was present in greater than 50% of subjects at the time of diagnosis, and was more common in women. In regression analysis, patients with anemia, pain, mood disturbance, diminished strength, diminished endurance, decreased sleep efficiency at night, and advanced disease (International Staging System [ISS] Stage III) had more severe fatigue at the time of diagnosis.

Patients with MM who have undergone multiple lines of therapy, including hematopoietic stem cell transplantation, are at particular risk for increased symptom burden and fatigue. Boland and colleagues evaluated 32 post-HSCT MM patients who required additional treatment following transplantation.\cite{15} With an average time from diagnosis of 5.5 years, fatigue, as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30), together with pain, had the greatest negative impact on physical functioning, compromised work abilities, and concern for loss of independence.\cite{15} Serum IL6 levels were not correlated with fatigue but were inversely correlated with physical functioning and positively correlated with pain, insomnia, and loss of appetite.\cite{15} Pain, insomnia, inadequate nutrition, and decreased physical activity have been shown to be associated with fatigue in other studies.\cite{16}

Sustained fatigue in patients with MM has been reported. A registry-based study comparing quality of life for an age- and sex-matched normative population (n=500) to 156 patients with MM up to 10 years from initial diagnosis compared scores on the EORTC QLQ-30 and EORTC QLQ-MY20, a 20-item MM-specific tool, at baseline and again 1 year later.\cite{17} Baseline scores for all EORTC QLQ-C30 scales showed lower QOL in the patients with MM. Eighty of the patients completed the 1-year follow-up questionnaire. Among these patients, fatigue increased from baseline in 50%. Feeling drowsy was
Fatigue, by definition, is a subjective phenomenon. Thus, it is not possible to provide a simple list of physical findings that would indicate the presence of fatigue. Rather, systematic assessment using patient-reported symptoms, together with evaluation of common contributing factors, patient characteristics, and physical findings should guide the assessment and management of cancer-related fatigue (Table 2). Similar to accepted practices for patient-reported pain, the subjective nature of the experience of fatigue requires patient reported symptom burden to effectively quantify the severity of fatigue. Since factors contributing to fatigue vary for each patient, a tailored assessment of fatigue based on these individual characteristics is required.

### Clinical presentation, screening and assessment of fatigue

The clinical manifestations of fatigue are heterogeneous based on the underlying contributing factors previously described. Fatigue, by definition, is a subjective phenomenon. Thus, it is not possible to provide a simple list of physical findings that would indicate the presence of fatigue. Rather, systematic assessment using patient-reported symptoms, together with evaluation of common contributing factors, patient characteristics, and physical findings should guide the assessment and management of cancer-related fatigue (Table 2). Similar to accepted practices for patient-reported pain, the subjective nature of the experience of fatigue requires patient reported symptom burden to effectively quantify the severity of fatigue. Since factors contributing to fatigue vary for each patient, a tailored assessment of fatigue based on these individual characteristics is required.

### Management of cancer-related fatigue in multiple myeloma survivors

The NCCN has established guidelines for the treatment of fatigue, recognizing the importance of preventive care in patients with cancer. The most recent guidelines provide recommendations for all cancer patients, regardless of age, disease, or treatment status. The current guidelines proposed by the American Society of Clinical Oncology (ASCO) for cancer-related fatigue are suggested for patients who have completed their primary cancer treatment and are in clinical remission. They provide useful general recommendations for evaluating and treating fatigue in cancer survivors who are disease-free or have completed therapy; however, MM remains an incurable disease characterized by multiple relapses and continued treatment over the course of the disease, in many cases for more than 10 years. Therefore, these recommendations require adaptation for MM survivors. Assessment and management of fatigue should also be adapted to the phase of cancer survivorship (from diagnosis to end-of-life) and severity of symptoms (mild to severe). Particular focus on potentially treatable contributing factors is emphasized.

### Table 1. The incidence of fatigue for novel agents used in the treatment of multiple myeloma

<table>
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<tr>
<th>Agent</th>
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<th>Grade 3/4</th>
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<tbody>
<tr>
<td>Bortezomib</td>
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Adapted from Kurtin & Billotti, with permission.

Recommendations for assessment are incorporated into each clinical management recommendation. Fatigue assessment should be performed at baseline and each clinical visit, similar to the assessment of pain. As discussed earlier, a number of tools have been validated to measure fatigue in clinical trials (EORTC QLQ-MY20, FACT-F, etc.); however, practical application to a day-to-day clinical setting can be limited due to the time required for completion and the requirement for tool familiarity. Therefore, a simple patient-reported numeric scale (0=no fatigue, 10=severe fatigue) is recommended, similar to the numeric scale used to assess the level of pain. For patients experiencing fatigue, additional questions are suggested to elucidate patient-specific characteristics.

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Table 2. Components of a comprehensive assessment of cancer-related fatigue

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
</table>
| Characteristics of fatigue       | • Patient self-reported severity: numeric scale (0-10)  
• Onset, pattern (change over time), and duration  
• Associated or alleviating factors  
• Interference with function |
| Disease- and treatment-related   | • Stage of disease: International Staging System (ISS) stage, risk category  
• Phase of survivorship: newly diagnosed, active treatment, relapsed refractory, end-of life  
• Drug-specific toxicities  
• Hematopoietic stem cell transplant  
• Radiation |
| factors                          |                                                                                                                                               |
| Performance status               | • Independence in activities of daily living (ADLs) and independent activities of daily living (IADLs)  
• Physical activity level  
• Measures of frailty  
• Deconditioning  
• Immobility |
| Comorbid conditions              | • Anemia  
• Arthritis  
• Cardiac dysfunction (arrhythmia, hypertension, coronary artery disease, congestive heart failure)  
• Endocrine dysfunction (hypogonadism, hypothyroidism, adrenal insufficiency)  
• Hepatic dysfunction (hyperbilirubinemia, transaminitis, hepatitis)  
• Infection (pneumonia, herpes zoster, bacteremia, urinary tract infections, fungal infections, etc.)  
• Neuromuscular dysfunction (neuropathy, proximal muscle weakness, other neuromuscular)  
• Pulmonary dysfunction (dyspnea, pneumonitis, chronic obstructive pulmonary disease)  
• Renal dysfunction (acute or chronic renal injury, electrolyte abnormalities)  
• Thromboembolism (deep vein thrombosis, pulmonary emboli) |
| Physical symptoms                | • Pain  
• Fever  
• Dyspnea  
• Appetite loss  
• Dysphagia  
• Dehydration |
| Nutritional status               | • Weight loss, presence of cachexia  
• Anorexia  
• Nausea/vomiting  
• Taste alteration  
• Xerostomia  
• Dietary restrictions |
| Lifestyle                        | • Alcohol abuse  
• Substance abuse  
• Exercise  
• Diet |
### Component

<table>
<thead>
<tr>
<th>Psychosocial and/or bio-behavioral factors</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disturbance</td>
<td></td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td></td>
</tr>
<tr>
<td>Consider use of the Distress Thermometer Screening Tool</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Available resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social support</td>
</tr>
<tr>
<td>Caregiver availability</td>
</tr>
<tr>
<td>Economic resources</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional consideration in the assessment of fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology commonly used to describe fatigue by patients</td>
</tr>
<tr>
<td>Weak</td>
</tr>
<tr>
<td>Exhausted</td>
</tr>
<tr>
<td>Lazy</td>
</tr>
<tr>
<td>Weary</td>
</tr>
<tr>
<td>Worn-out</td>
</tr>
<tr>
<td>Heavy</td>
</tr>
<tr>
<td>Slow</td>
</tr>
<tr>
<td>Like they do not have any energy or any get-up-and-go</td>
</tr>
</tbody>
</table>

Concepts that include fatigue used by healthcare professionals

<table>
<thead>
<tr>
<th>Asthenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lassitude</td>
</tr>
<tr>
<td>Malaise</td>
</tr>
<tr>
<td>Prostration</td>
</tr>
<tr>
<td>Exercise intolerance</td>
</tr>
<tr>
<td>Lack of energy</td>
</tr>
<tr>
<td>Weakness</td>
</tr>
</tbody>
</table>

Question that may elicit the severity of fatigue:

| On a scale of 0–10, how would you rank your fatigue in the last 7 days? (0=no fatigue, 10=worst fatigue imaginable) |

Questions that may elicit the impact of fatigue

<table>
<thead>
<tr>
<th>How often do you feel tired?</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often do you experience extreme exhaustion?</td>
</tr>
<tr>
<td>How often do you run out of energy?</td>
</tr>
<tr>
<td>How often does fatigue limit you at work?</td>
</tr>
<tr>
<td>How often are you too tired to think clearly?</td>
</tr>
<tr>
<td>How often do you feel tired when you hadn’t done anything?</td>
</tr>
<tr>
<td>How often do you have to push yourself to get things done because of your fatigue?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider performing laboratory testing based on the presence of symptoms, comorbid conditions, or other suspected contributing factors to fatigue:</td>
</tr>
<tr>
<td>Complete blood count differential, and platelet count</td>
</tr>
<tr>
<td>Comprehensive metabolic panel to assess renal, hepatic, and electrolyte values</td>
</tr>
<tr>
<td>Iron, ferritin, total iron binding capacity (TIBC), B12, folate, reticulocyte count (anemia panel)</td>
</tr>
<tr>
<td>Thyroid panel</td>
</tr>
<tr>
<td>Testosterone levels in older men</td>
</tr>
<tr>
<td>Other measures necessary to establish severity of disease</td>
</tr>
</tbody>
</table>

Adapted from NCCN, Bower & Lamkin, Koomsra et al, NCI, and Christodoulou et al.
References


