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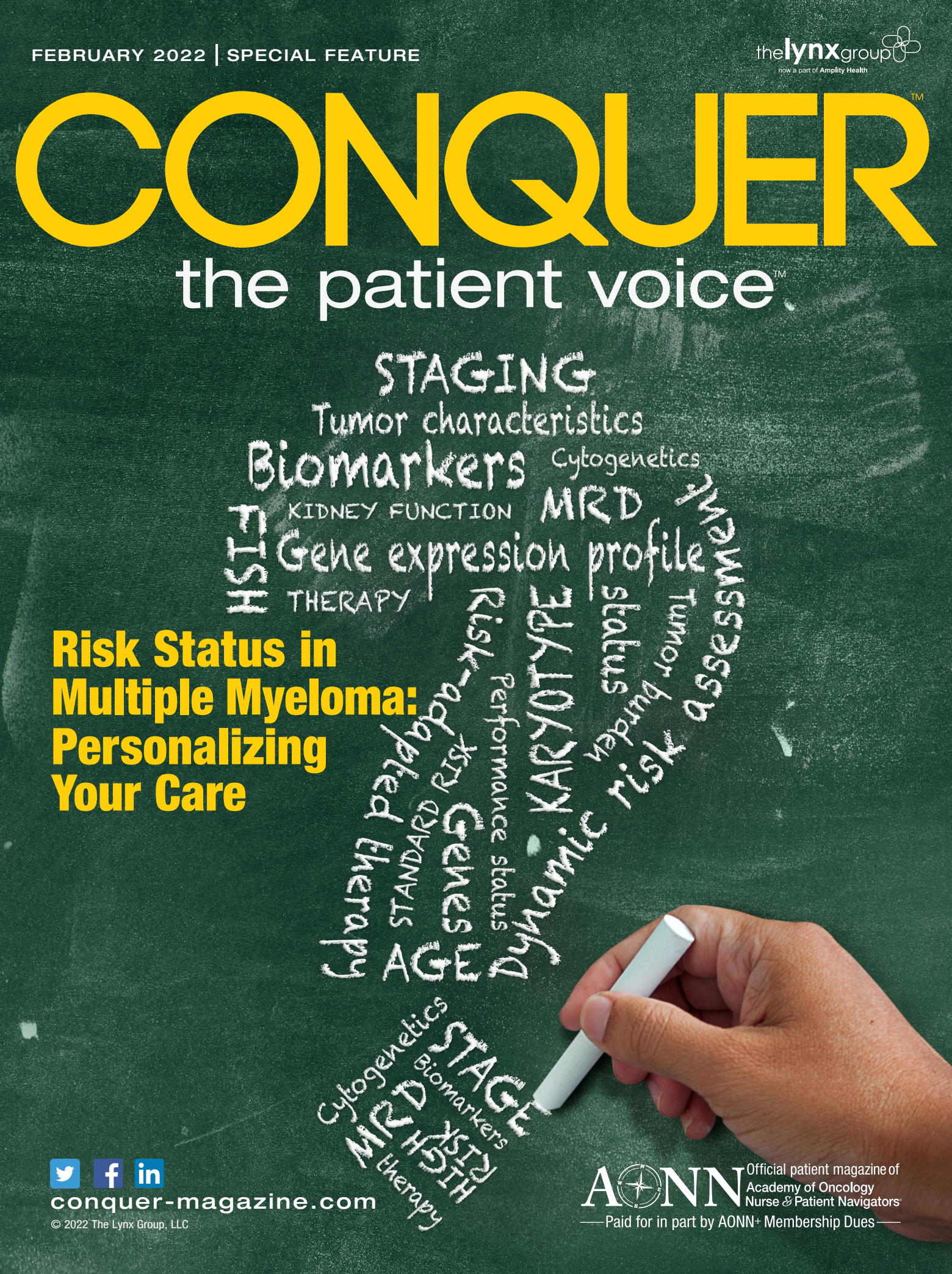

Risk Status in Multiple Myeloma: Personalizing Your Care

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AONN Official patient magazine of Academy of Oncology Nurse & Patient Navigators®
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table of contents

EDITORIAL CORRESPONDENCE should be addressed to **EDITORIAL DIRECTOR**, *CONQUER*, 1249 South River Rd, Suite 202A, Cranbury, NJ 08512. E-mail: **editorial@conquer-magazine.com**. Phone: **732-992-1892**. Correspondence regarding permission to reprint all or part of any article published in this journal should be addressed to **REPRINT PERMISSIONS DEPARTMENT**, Green Hill Healthcare Communications, LLC, 1249 South River Rd, Suite 202A, Cranbury, NJ 08512.

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CPS1438

Risk Status in Multiple Myeloma: Personalizing Your Care

INTRODUCTION

Multiple myeloma is a relatively rare type of blood cancer that affects plasma cells, which are immune cells that produce antibodies (immunoglobulins). In multiple myeloma, these malignant plasma cells increase in number in the bone marrow and crowd out normal blood cells. They also produce large quantities of abnormal antibodies that can be found in the blood and urine. The presence of high levels of these abnormal antibodies, referred to as monoclonal or "M"-proteins, is a hallmark of the disease.

Multiple myeloma is a very diverse disease, and every case is different with regard to how fast the myeloma cells increase in number and the extent to which they spread in the bone marrow, and how they respond to therapy. Taken together, these factors affect the length of response to treatment and survival. Because of these differences, physicians carefully characterize each patient's myeloma to determine the best treatment plan for them.

Part of this process involves staging, or determining the extent of the myeloma, and determining an individual's risk status. Patients are categorized as having either standard-risk myeloma or high-risk myeloma. Patients with high-risk multiple myeloma tend to have poorer outcomes than those with standard-risk disease and require a different treatment strategy. Much progress has been made in identifying and treating patients with high-risk multiple myeloma to the point that, in some cases, survival can approach that seen in standard-risk disease. However, it is important to note that risk status alone does not define an individual's myeloma, and many factors can affect outcomes.

Approximately 15% of individuals with myeloma are considered to have high-risk disease at the time they are diagnosed.[1] Because this represents a minority of patients, the concept of risk status in multiple myeloma is often not well known. To better understand patients' understanding of, and experience with, risk status assessment in multiple myeloma, The Lynx Group and Takeda Oncology conducted an Internet-based survey. The survey was developed in conjunction with Takeda's Patient Leadership Council, whose members are patient advocates living with multiple myeloma who lead myeloma support groups. Deployed during June and October 2020, the survey was completed by 264 individuals in the United States with myeloma or their care partners.

By explaining what risk assessment is and how it is used to guide treatment strategy, we hope to convey the importance of risk status assessment in multiple myeloma and the potential implications for optimal outcomes. As a patient, you are a partner with your clinicians in your healthcare management. Being well-informed about your risk status may help you have quality conversations with your team about your myeloma and its treatment, and assist your providers in helping you achieve the best outcome while maintaining optimal quality of life.

Survey Facts: Who Responded to the Survey?

87% were patients with myeloma

Most had been living with myeloma for ≥1 years; 29% have had myeloma for >10 years

Most (80%) had active myeloma

Almost all (97%) were aged >40 years

Half were men and half were women

The majority (86%) were white; 7% were black or African American; 4% were Asian/Pacific Islander; and 2% were Hispanic or Latino

64% lived in a suburban area; 23% in an urban area; and 13% in a rural area

38% primarily see a myeloma specialist; 26% primarily see a community oncologist; and 36% see both

RISK STATUS IN MULTIPLE MYELOMA: WHY IS KNOWING YOUR RISK STATUS IMPORTANT?

Risk Status versus Risk Factor

Note that *risk status* in myeloma is different from having a *risk factor* for development of myeloma. A risk factor is something that increases a person's chance of developing a disease. For example, the risk for developing multiple myeloma increases with a person's age, and myeloma is slightly more common in men and more than twice as common in African Americans than in white Americans.[2]

Determining a patient's risk status is also referred to as "risk stratification." Knowing risk status at the time of diagnosis provides information on a patient's prognosis, or the predicted course of a disease or outcome. Knowing this information helps a patient and their doctor understand and discuss the overall outlook and what might be expected. It also helps doctors tailor therapy to each patient. "A patient knowing about their risk status and discussing that with their physician while reviewing their specific treatment options and plan makes for a more meaningful and insightful conversation for both the physician and patient in discussing treatment goals and setting realistic expectations," noted Kena C. Miller, RN, MSN, FNP, US Medical Affairs, Medical Science Liaison at Takeda.

Survey Fact: 66% of respondents would like to know if they have high-risk multiple myeloma.

Compared with patients with standard-risk myeloma, patients with high-risk multiple myeloma tend to respond to therapy for a shorter length of time, have more frequent relapses, and have shorter survival. If a patient's myeloma is determined to be standard risk, they will be offered a treatment plan that is sufficient to control their myeloma without the risk of being overtreated. However, if a patient's myeloma is found to be high risk, a more aggressive treatment plan that has been shown to be effective in high-risk myeloma may be offered. Referred to as a "risk-adapted approach," the goal is to optimize outcomes and quality of life while minimizing potential short- and long-term side effects.

WHAT FACTORS CONTRIBUTE TO RISK IN MULTIPLE MYELOMA?

Several different factors have been found to influence risk and help predict outcomes in myeloma. These factors can be grouped into 3 categories (**Figure 1**)[3]:

1. Patient-related factors
2. Tumor burden
3. Tumor characteristics or biology

Patient-related factors refer to things that are related specifically to the patient and their overall health. These include factors such as the patient's age and how well their kidneys are functioning. It also includes how well they are able to perform ordinary tasks and carry out their daily activities, also known as their performance status. Older age, impaired organ function, or poor performance status can contribute to overall risk and affect a patient's ability to tolerate certain treatments.

Figure 1. Factors That Contribute to Risk in Multiple Myeloma

Patient-Related Factors
- Age
- Kidney function
- Performance status

Tumor Burden
- Stage
  - Beta2-microglobulin
  - Albumin
- Presence of disease outside the bone marrow

Tumor Characteristics
- Cytogenetic features
- Lactate dehydrogenase level

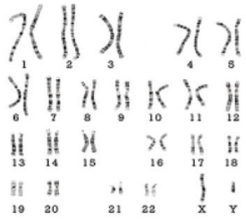
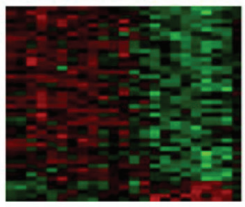
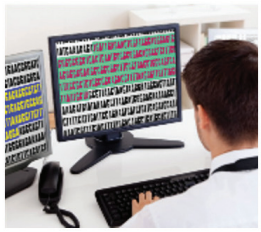
Tumor burden refers to the amount of cancer in the body. This could be represented simply by the size of a tumor, but this is not possible with blood cancers such as myeloma. In these cases, tumor burden may be better represented by the stage of the disease. Traditional staging of myeloma, such as with the Durie-Salmon staging system, is based on markers that indicate the extent of disease and kidney function, such as blood counts, calcium level, level of M-protein, and presence of bone lesions. Another staging system is based on levels of blood markers such as beta2-microglobulin and albumin. Tumor burden can also be defined by whether any abnormal plasma cells are found outside the bone marrow.

Tumor characteristics are features of the myeloma itself, such as things that might show how aggressive it is or how fast it might grow. Perhaps the most important of these are the specific genetics of the myeloma cells. Cytogenetics is a type of genetic analysis that focuses on the study of chromosomes and chromosomal abnormalities. Chromosomes are long strands of DNA and protein that contain most of the genetic information in a cell. Because they are malignant cells, most myeloma cells have chromosomal abnormalities. These abnormalities are not hereditary abnormalities that are passed down from one generation to the next but are specific to the myeloma cells and play an important role in the development and prognosis of multiple myeloma. Looking at cytogenetics is an important way to determine risk.

CYTOGENETIC TESTS THAT PROVIDE INFORMATION ON RISK IN MULTIPLE MYELOMA

A number of laboratory tests can be performed on a patient's bone marrow to help identify chromosomal abnormalities in myeloma cells and help determine risk (**Figure 2**).[4,5] Two of these, cytogenetic analysis, also known as karyotyping, and fluorescence in situ hybridization (FISH), are the most commonly used. National guidelines recommend that all patients undergo chromosome analysis by FISH for risk assessment at initial diagnosis and state that karyotyping may provide additional information.[4] In addition, several newer tests that may be available in research centers can also be used to help identify

Figure 2. Cytogenetic Tests That Provide Information on Risk in Multiple Myeloma

Standard Laboratory Tests		May Provide Additional Information		
Cytogenetic Analysis (Karyotyping)	**Fluorescence In Situ Hybridization (FISH)**	**Gene Expression Profiling (GEP)**	**Next-Generation Sequencing (NGS) Panel**	**Single Nucleotide Polymorphism (SNP) Array**
				
The process of analyzing cells to look for changes in chromosomes, including broken, rearranged (translocations), missing (deletions), or extra chromosomes (gains)[5]	Shows where a specific gene is located on a chromosome, how many copies of the gene are present, and whether there are any abnormalities[5]	Shows the pattern of activity (expression) of many genes in a cell at one time; also known as gene array analysis[5]	Provides a more detailed evaluation of myeloma genetics[4]	

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distinct molecular subgroups of myeloma that have different prognoses and help in planning treatment. It typically takes only a few days to receive results of FISH testing and about 2 to 3 weeks to get the results of cytogenetic analysis.

Survey Facts: 41% of respondents had not heard of these cytogenetic tests. FISH was familiar to almost half of respondents and karyotyping was familiar to a third. Of those who were familiar with these tests, half had learned about them from their hematologist and 21% had researched the information themselves online. A greater proportion of respondents who saw a myeloma specialist were familiar with these tests, as were respondents with high-risk myeloma.

PUTTING IT ALL TOGETHER TO DEFINE RISK IN MULTIPLE MYELOMA

Taken together, patient factors, tumor burden, and tumor characteristics may be used to categorize myeloma. Several guidelines have been developed that define specific sets of criteria to denote high-risk and standard-risk multiple myeloma. The most common are:

- International Myeloma Working Group (IMWG)[6]
- Mayo Stratification and Risk-Adapted Therapy (mSMART)[7]

However, the specific definitions for these risk categories can vary across guidelines and among treatment centers. In addition, risk definitions continue to evolve as newer therapies have been shown to equalize outcomes between high-risk and standard-risk disease. For this reason, it is now more common to stratify a person's myeloma based on the presence of individual cytogenetic abnormalities.

A number of cytogenetic abnormalities have been associated with poorer outcomes in multiple myeloma and are used to identify high-risk disease (see **Sidebar**). In general, myeloma that does not have any of these cytogenetic abnormalities is referred to as standard-risk disease. Although risk can be defined and characterized in several ways, approximately 15% of patients with myeloma are considered to have high-risk disease at the time they are diagnosed.[1]

High-Risk Cytogenetic Abnormalities in Multiple Myeloma

Cells in the human body contain 23 pairs of chromosomes. Each chromosome pair is joined together in the middle, so it looks like an X with 4 arms. Several different types of chromosomal (cytogenetic) abnormalities have been found in multiple myeloma, including:

- Rearrangements known as translocations (t), whereby a piece from one chromosome arm is swapped with a piece from another chromosome arm
- Loss of a part of a chromosome (deletion or del)
- Gain of a part of a chromosome (gain)
- Extra chromosome arms or pairs (hyperdiploid)
- Loss of a chromosome arm or pair (hypodiploid)

When defining these abnormalities, the abbreviations are used along with the chromosome number(s) that is affected. For example, t(4;14) refers to a rearrangement of parts of chromosomes 4 and 14. Sometimes the chromosome arm (shorter arm [p] or longer arm [q]) is also included. So, gain(1q) means there is an extra part of the long arm of chromosome 1.

According to IMWG guidelines, the following cytogenetic abnormalities are associated with high-risk multiple myeloma[6]:

Test	Feature
Karyotype	del(13) Hypodiploid karyotype
FISH	t(4;14) t(14;16) t(14;20) del(17/17p) gain(1q)
Gene expression profile	High-risk signature

However, some risk classifications may be modified when certain treatments are given. For example, if a person's myeloma is found to have the high-risk t(4;14) feature and they are treated with novel agents, such as bortezomib, or a combination of a proteasome inhibitor, an immunomodulatory drug, and dexamethasone, their myeloma's behavior falls somewhere between standard and high risk. Thus, these agents partly overcome the adverse effect of having t(4;14).[6]

Survey Facts: 17% of survey respondents said they had high-risk myeloma. Only 25% of respondents understand very well what is meant by standard-risk versus high-risk disease; an additional 39% have a basic understanding of this concept. Most (78%) knowledgeable patients learned about myeloma risk from their hematologist/oncologist.

High-Risk Smoldering Multiple Myeloma: How Is It Different from High-Risk Multiple Myeloma?

Smoldering multiple myeloma is a precursor of myeloma, whereby patients have an increased number of plasma cells in their bone marrow or elevated M-protein in the blood but do not yet show any symptoms of the disease.[8] In the past, patients with smoldering myeloma did not receive treatment right away but were closely followed.

About half of patients with smoldering multiple myeloma progress to myeloma and develop symptoms within 5 years, whereas half do not. Researchers have identified characteristics that can identify smoldering myeloma that is more likely to progress to myeloma. Patients who have those characteristics are said to have high-risk smoldering myeloma and may be offered treatment.

Survey Fact: Only 3% of respondents were aware that high-risk smoldering myeloma is different from high-risk myeloma.

WHEN SHOULD RISK STATUS BE DETERMINED?

As noted earlier, myeloma treatment guidelines recommend that all patients undergo chromosome analysis by FISH for risk assessment when they are initially diagnosed. Other cytogenetic tests are optional, but they may provide additional information regarding prognosis and choice of therapy.[4]

More recently, it has been found that, after the initial diagnosis and risk assessment, additional factors during the time an individual receives therapy and beyond may affect their prognosis to the extent that a person's risk status may change over time. For this reason, the concept of "dynamic risk assessment" is evolving as an ongoing way to define risk.[1]

One factor that can be used in dynamic risk assessment is the amount of residual myeloma disease that is present after treatment. Individuals who have a complete response to therapy may still have low levels of myeloma cells present. These low levels of disease can be detected by sensitive techniques such as minimal residual disease (MRD) assessment and functional imaging with PET/CT scans. In general, if a person's disease becomes undetectable by either of these methods, they tend to have a better prognosis than if their disease remains detectable. In addition, studies show that individuals who have high-risk myeloma who become MRD-negative after initial therapy have a more favorable outcome that is similar to individuals with standard-risk disease who are MRD-negative.[1] For individuals who remain MRD-positive after therapy, their risk category at diagnosis continues to predict outcome.

Another factor that contributes to risk is the length of time between initial diagnosis and disease relapse. Myeloma that relapses early in the course of treatment tends to be associated with poorer outcomes than myeloma that relapses late. Individuals whose myeloma relapses within 18 months of diagnosis are considered to have "functional high-risk multiple myeloma" regardless of their risk status at diagnosis.[1] This may be as a result of a person's myeloma gaining cytogenetic abnormalities and evolving from standard-risk to high-risk disease over time or as a result of therapy. For this reason, cytogenetic testing and risk assessment should also be performed at relapse.[9] The presence of cytogenetic abnormalities associated with high-risk disease would indicate an aggressive relapse that requires more aggressive treatment. Ms Miller noted, "If a patient's cytogenetic profile changed from standard- to high-risk based on testing, you would treat accordingly."

Survey Facts: Of respondents who knew whether cytogenetic tests were performed when they were diagnosed with myeloma, most (78%) said they had these tests performed. However, of respondents with relapsed myeloma who knew whether cytogenetic tests were performed when they had relapsed, only half said they actually had these tests performed.

RISK-ADAPTED THERAPY FOR MULTIPLE MYELOMA

After patient- and tumor-related factors are used to assess risk, myeloma treatment can be tailored according to a patient's genetic abnormalities and other risk factors. Different treatment strategies can be used in high-risk multiple myeloma to help improve outcomes. In general, patients with high-risk disease typically receive more aggressive therapy that may be given continuously or for a longer period of time.

Survey Facts: Only 42% of survey respondents were aware that individuals with high-risk myeloma may receive different treatment than those with standard-risk disease. Of those with high-risk disease, only a minority (29%) said they were told they were receiving a different treatment for their disease.

Because high-risk disease represents a minority of patients with myeloma, very few clinical studies of myeloma treatments have been done just in high-risk patients. Most clinical trials usually involve small numbers of patients with high-risk disease. However, results from a number of large studies have helped identify treatments that can improve outcomes in high-risk myeloma.

Several studies have shown that the combination of a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and dexamethasone, a common therapy for myeloma, provides a survival benefit to individuals with high-risk myeloma compared with certain individual agents and other drug combinations.[1] In these studies, survival in the high-risk groups approached or equaled that seen in the groups with standard-risk disease.[1]

This survival benefit is thought to be due to the ability of some drugs to partly overcome the adverse effects of certain cytogenetic abnormalities. For example, if a person's myeloma is found to have the high-risk t(4;14) feature and they are treated with the PI bortezomib or a triple combination of a PI, IMiD, and dexamethasone, their myeloma's behavior falls somewhere between standard and high risk.[6]

Other strategies that are being used to improve outcomes in high-risk myeloma include[7]:

- The addition of a fourth drug, such as a monoclonal antibody, to a PI, IMiD, and dexamethasone combination as initial therapy
- Performing a second autologous stem-cell transplant ("tandem ASCT")
- Continuing initial combination therapy over a longer period of time rather than giving a set number of cycles
- Use of single-agent or double-agent maintenance therapy following ASCT

The combination of a PI, IMiD, and dexamethasone may also provide a survival benefit in high-risk relapsed disease. For example, individuals with high-risk relapsed multiple myeloma who received the PI ixazomib, the IMiD lenalidomide, and dexamethasone had survival that was similar to the entire study population.[4]

Questions to Ask Your Doctor

If you are not sure of your risk status or would just like to learn more about your myeloma, here are some questions you can ask your care team.

- Have cytogenetic tests been performed on my bone marrow?
  - If so, which ones?
  - Have any cytogenetic abnormalities been identified?
  - Were these tests also performed if/when I relapsed?
- Was MRD testing performed on my bone marrow if/when restaging my disease at relapse?
- Do I have high-risk multiple myeloma?
  - If so, which cytogenetic abnormalities have been identified?
  - Is the therapy I am receiving based on these cytogenetic abnormalities?

CONCLUSION

Risk assessment is an important means to tailor therapy and improve outcomes in high-risk multiple myeloma. We have learned through diligent research some of the biomarkers in myeloma that can identify patients at high risk of early disease progression and death. This knowledge will continue to evolve with retrospective analysis, where we look back to see how the disease behaved, to determine characteristics of high-risk disease and exceptional responders to treatment to strategically determine appropriate therapy accordingly. Looking forward, trials can be designed to help determine the best combination treatments for high-risk myeloma that are tolerable and convenient and can be taken long-term. ◆

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