Patient-Reported Outcomes in Multiple Myeloma

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Abstract
Multiple myeloma is an incurable malignancy of plasma cells. People with multiple myeloma may experience a variety of disease-related symptoms because of bony destruction, bone marrow infiltration, renal failure, immunodeficiency, and the psychosocial burden of a cancer diagnosis. Exciting new therapies and treatment approaches are becoming available but often bring unwanted side effects. Because the goal of treating multiple myeloma is still symptom palliation and prolongation of life rather than cure, it is important to consider the tradeoffs between treatment toxicity and disease control when caring for the person with myeloma. The traditional endpoints of clinical trials are disease response, prolongation of disease-free and overall survival, and other objective criteria. However, subjective patient-reported measures, such as symptoms, quality of life, and functional status, are increasingly recognized as important dimensions by which to judge the impact of cancer and its treatment. In multiple myeloma, several patient-reported measures have been used to enrich our understanding of the disease’s impact on patients’ lives and the risks and benefits of specific treatments. (JNCCN 2004;2:379–383).

The Definition and Importance of Patient-Reported Outcomes

The most recent cancer statistics predict 15,270 cases of multiple myeloma (MM) will be diagnosed in the United States in 2004, and 11,070 people will die of the disease.1 The median age at diagnosis is 65 years, and incidence increases with age. Disease-related death results from infection, renal failure, uncontrolled disease, and complications of therapy. Seventy percent of patients experience bony pain, which is the major symptom of MM, although anemia, metabolic imbalances, and side effects of treatment also may be disabling.

Although MM remains incurable, the number of therapeutic options is increasing, and exciting laboratory progress into the pathophysiology of the disease suggests that more breakthroughs are forthcoming.2,3 Given the broad range of treatments available, including high-dose transplantation approaches and clinical trials,4,5 weighing the risks and benefits of any specific therapy relative to other options requires a more holistic understanding of what patients are experiencing.

The term, “patient-reported outcomes” refer to subjective, self-reported effects of disease and its treatment and are also called as “patient-oriented measures” and “patient-centered outcomes.” These outcomes generally encompass symptoms, multidimensional quality of life, and functional status, but their hallmark is that measurement requires patient input. Information cannot be collected retrospectively from chart review, laboratory studies, or other objective data. However, by the very nature of being subjective, patient-reported outcomes are sometimes considered “soft” endpoints because they are assessed by means of surveys, interviews, or patient diaries. Interpretation may be complicated by a variety of methodologic limitations. Information needs to be collected in real time because retrospective assessments are often inaccurate. Missing data are common because of logistical mixups and patient noncompliance at the time of assessment. Self-reported endpoints are influenced by extraneous influences in people’s lives and psychological factors in a way that biologic measurements are not. Nevertheless, patient-reported outcomes attempt to capture what people actually experience with a treatment
approach and are arguably the most important measure of successful anti-cancer therapy.

In 1996, the American Society of Clinical Oncology produced a policy statement that distinguished cancer outcomes from patient outcomes, and advocated for the latter as primary endpoints in clinical trials. Cancer outcomes represent the effect of treatment on the cancer itself and include the traditional measures of complete and partial response, response duration, time to progression, and tumor markers. In contrast, patient outcomes measure the effect of the treatment on the person and include survival, toxicity, functional status, and quality of life. The position statement noted that the goal of treatment should be to prolong survival, improve function, decrease symptoms, or improve quality of life, not simply to shrink tumor burden.

The Food and Drug Administration (FDA) has been influenced also by demonstrable differences in patient-reported outcomes when approving drugs. The FDA noted, “Increasing attention to the quality of life of patients on pivotal clinical trials ought to promote the submission of much stronger new drug applications. If a trial shows no statistically significant difference in efficacy between test and control, with a sample size that can adequately rule out medically important differences, the demonstration of better symptom control, less treatment-related toxicity, or a better quality of life score as measured by some previously validated instrument may be a potent argument in favor of the test treatment and ought to carry great weight from a regulatory perspective.”

Patient-Reported Outcomes Used in Multiple Myeloma

EORTC QLQ-C30
The European Organization for Research and Treatment of Cancer (EORTC) core form (QLQ-C30), currently in its third version, has been used extensively to measure quality of life (QOL) in people with multiple myeloma. "The survey is a 30-item multidimensional instrument that provides scores for functional status (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and global QOL using four-point Likert scales (not at all, a little, quite a bit, and very much). The average completion time is 11 minutes, and the survey can be self-administered without assistance." Possible scores range from 0 to 100. If at least half the items in a subscale are answered, a score may be calculated. Higher scores on the global health and functional scales reflect better QOL, and lower scores on the symptom scales reflect lower symptom burden.

MY24
Stead et al. developed a 24-item myeloma-specific subscale (MY24) for use with the EORTC QLQ-C30 core form. Rigorous procedures were used to develop the subscale, including identification of important domains to people with myeloma, pretesting, and psychometric validation. The MY24 yields four scores: pain, treatment side effects, social support, and future perspective. The module is currently undergoing international validation.

FACT
The 27-item Functional Assessment of Chronic Illness Therapy (FACT) tool is a multidimensional instrument comprised of 4 domains: physical, social (including sexual satisfaction), emotional, and functional (including work, sleep, and leisure activities). Statements are phrased in the active, first-person voice (“I have a lack of energy”) and measured on a 5-point Likert scale (not at all, a little bit, somewhat, quite a bit, very much). A variety of disease- and syndrome-specific subscales are available, including 2 scales relevant to anemia and fatigue. Higher scores indicate better functioning.

Pain Measures
Bone pain is the most common symptom of myeloma and many different instruments are available to assess pain severity, distribution, and impact. The Brief Pain Inventory (BPI) and a scale developed by the Radiation Therapy Oncology Group (RTOG) have been used in MM. The BPI asks patients to rate their current, worst, least, and average pain on a 10-point scale. The effect of pain on daily activities is also assessed. The RTOG developed four questions rated on a 0 to 3 scale to assess severity and frequency of pain, and type of pain medication and frequency of use. The pain score is calculated by multiplying scores of severity by frequency, and the narcotic score results from multiplying the medication type and frequency score, resulting in a score of 0 to 9 for each dimension. This scale was originally used to measure radiation therapy palliation in people with osseous...
metastases from heterogeneous primary cancer sites. Berenson et al. subsequently used this scale as an endpoint in a randomized trial assessing effects of pamidronate in people with stage III MM and osteolytic lesions.

Two other common pain measures are the McGill Pain Questionnaire and the Memorial Pain Assessment Card. The short-form McGill Pain Questionnaire contains 15 descriptors (11 sensory and 4 affective) rated on a four-point Likert scale (none, mild, moderate, or severe). It generates scores for sensory, affect, and total descriptors. The Memorial Pain Assessment Card measures pain intensity, pain relief, and mood using visual analogue scales. Eight pain severity descriptors, ranging from “no pain” to “excruciating,” are provided, and the patient circles the descriptor that most closely describes current pain severity.

Using Patient-Reported Measures in Multiple Myeloma Studies

Descriptive Studies
Poulos et al. surveyed a sample of 206 people identified from an institutional database treated within the last four years (response rate, 64%). They administered measures of pain, mood, and quality of life. Twenty-nine percent of respondents reported moderate to severe pain intensity, and pain experience was significantly associated with mood disturbance scores. As has been found in other studies, older people with MM tended to report better QOL.

Prognostic Factors
The Nordic Myeloma Study Group measured QOL in a randomized study of melphalan and prednisone with or without interferon α-2b (see below). Careful attention to collecting patient-reported outcomes resulted in 83% of all patients enrolled in the trial completing all administered surveys. Because the parent study showed no difference in survival between the 2 arms of the trial, data were combined for the prognostic factor study. In multivariate analysis, 3 biologic variables (β2-microglobulin, skeletal disease, age) and 2 functional variables (World Health Organization performance status and physical functioning assessed by the EORTC QLQ C30) were independently associated with survival. The investigators also performed a landmark analysis at 12 months. In multivariate analysis, response to treatment, performance status, and physical functioning at 12 months were the most important predictors of subsequent survival.

Phase II
Quality of life was measured in a phase II study of bortezomib (Velcade; Millennium Pharmaceuticals, Cambridge, MA). Participants were heavily pretreated, receiving a median of 6 previous treatment courses, with a median time of response of only 3 months to previous therapy. A 35% disease response rate was found (complete, partial, and minimal responses), and responses were associated with improved QOL as measured by the EORTC QLQC30 and MY24.

Phase III
Berenson et al. randomized 392 people with stage III myeloma and at least one osteolytic lesion to monthly pamidronate or placebo. Bone pain severity and frequency, performance status, analgesic use, and scores for QOL were assessed monthly. They reported that skeletal events and bone pain were decreased in the pamidronate group, and the placebo group experienced worsening of bone pain, analgesic use, performance status, and QOL.

The Nordic Myeloma Study Group used the EORTC QLQC30 and an interferon toxicity module to compare QOL between newly diagnosed people with MM randomized to melphalan/prednisone to melphalan/prednisone/interferon α-2b. Quality of life was measured before treatment and again at 1, 6, 12, 24, 36, and 48 months after randomization. Patient participation in the QOL component of the study was extremely high (90%). Many expected toxicities of interferon therapy were noted associated with a moderate reduction in global QOL during the first year. After the first year, only dizziness was increased in the interferon group. Given that overall survival was the same and late QOL was similar, the authors concluded that the early toxicity of interferon was not compensated by later improvements in QOL.

Osterborg et al. performed a randomized, double-blinded, placebo-controlled trial of recombinant erythropoietin in people with hematologic malignancies who were transfusion-dependent and had low serum erythropoietin levels. The study included 117 people with MM in addition to patients with non-Hodgkin’s lymphoma and chronic lymphocytic leukemia. Quality of life was measured at baseline and every 4 weeks.
with the core FACT instrument and anemia (FACT-An) and fatigue (FACT-F) subscales. No differences in QOL were found at baseline, and both groups improved over the course of the study. However, people randomized to the erythropoietin arm reported better QOL in total FACT scores, driven by the social, emotional, and physical subscales. Interestingly, no detectable differences were found in the fatigue and anemia subscales.\textsuperscript{23}

**Comparative Reports of Separate Trials**

Gulbrandsen et al.\textsuperscript{24} compared results for 221 people treated with autologous peripheral blood stem cell transplantation with those for 113 people receiving conventional melphalan/prednisone on five separate trials. Conventionally treated patients were selected for analysis if they would have qualified for inclusion in the intensive therapy trials. A proportion of both groups received interferon \(\alpha-2b\) after completion of therapy. Quality of life was assessed with the EORTC QLQ C30. No pretreatment differences in QOL were found. At 6 months, the intensively treated group had lower global QOL role functioning, and social functioning, and more appetite loss, but this group also showed a trend toward higher functioning scores and less pain and fatigue at 36 months, suggesting a long-term benefit to intensive therapy.\textsuperscript{24}

**Q-TWiST**

Q-TWiST is the acronym for “quality time without symptoms or toxicity.” It is a statistical method of combining considerations of symptom burden, disease-free survival, and overall survival into a single metric. Using primary clinical trial data, survival time is partitioned into time with symptoms of treatment (TOX), alive without symptoms and free of disease (TWiST), and in relapse (REL). The time in TOX or REL is down-weighted to reflect the lesser value of being in these states relative to TWiST. Summing the adjusted time in TOX, TWiST, and REL results in a Q-TWiST value reflecting both the benefits and toxicities of therapy.

Zee et al.\textsuperscript{25} performed a Q-TWiST analysis of a randomized clinical trial of interferon versus placebo. Primary patient-reported data determined time in TOX because a subject diary was used to ask the group randomized to interferon about muscle aches, headaches, nausea, vomiting, fever, chills, diarrhea, and fatigue on a 5-point scale (none, mild, moderate, severe, life-threatening). Any day on which a symptomatic grade 2 toxicity or higher was reported was considered a TOX day. The authors concluded that the clinical benefits of interferon probably outweigh the negative side effects because of the prolongation of symptom-free, relapse-free survival.\textsuperscript{25}

In a similar Q-TWiST analysis using estimated treatment burden, Porcher et al.\textsuperscript{26} concluded that high-dose autologous transplantation therapy provided a benefit over conventional therapy. Although people experienced transient toxicity with the high-dose therapy, their symptom profile improved after completion of therapy, and relapse was delayed.\textsuperscript{26}

**Implications for Clinical Trials and Patient Care**

Patient-reported outcomes are increasingly recognized as important in assessing the burden of myeloma on patients and the risks and benefits of treatments. The availability of validated self-administered instruments and the growing experience with measuring patient-reported outcomes in people with myeloma will help ensure that greater attention is paid to these areas, particularly in the design of clinical trials and translation of results back to the care of individual patients. The hope is that physicians and patients with myeloma can make more informed treatment decisions if provided with a broader description of the effects of treatment, both good and bad, and considering the entire person rather than just the disease.

**References**


