# Health-related quality of life in patients with multiple myeloma - does it matter?

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Survival of patients with multiple myeloma (MM) has been extended markedly in the last 15 years and patients living with the disease for 10-15 years are no longer rare.[1] However, in the absence of a curative treatment, the aim of therapy is to induce an objective response with the expectation that this leads to a prolongation of survival and, furthermore, to improve the patients' quality of life.

Myeloma patients experience a variety of disease-related events and symptoms, such as bone destruction leading to pain, height reduction and body shape changes, and bone marrow failure, renal failure, immunodeficiency, as well as the psychosocial burden of a diagnosis of cancer. These aspects may have different importance for the patient in different periods of the disease. Furthermore, therapeutic interventions may produce troublesome side effects and functional impairments.[2] Although prolongation of overall survival will always be a main goal of cancer treatment, health-related quality of life (HRQoL) is becoming increasingly important. To illustrate this, the US Food and Drug Administration (FDA) has emphasized HRQoL as an important end-point for approval of new anticancer drugs.[3]

HRQoL is a complex and elusive matter and its evaluation is critically dependent on our tools and how the results are interpreted. Assessing HRQoL introduces the patients' perspective into the clinical process via standardized self-reported instruments (questionnaires) that are scored by the patient. It is generally accepted that the patient should be the primary source of information regarding his or her HRQoL, without interpretation of the patient's response by a clinician or anyone else.[4,5]

A systematic review recently analyzed the impact of thalidomide, bortezomib and lenalidomide on HRQoL in MM patients.[6] The review demonstrated the complementary value of HRQoL when assessing clinical response, progression, overall survival and toxicity. However, they concluded that, to date, there has been a relatively small body of HRQoL data published on novel MM treatments, and that weaknesses and inconsistencies of analysis and presentation of HRQoL data were observed. This review was consistent with our systematic review in which 15 randomized clinical trials (RCT) published between 1996-2008 with HRQoL as a study endpoint, were identified.[7] In 13 of the trials, the authors stated that HRQoL results should influence clinical decision-making. We found, however, that the HRQoL data had had limited impact on published treatment guidelines regarding important treatment aspects such as bisphosphonates, high-dose treatment, interferon, erythropoiesis-stimulating agents and novel agents.

In this issue of the Journal, Delforge *et al.* report HRQoL in transplant-ineligible patients with newly diagnosed MM included in the FIRST trial.[8] The randomized phase III trial compared the efficacy and safety of lenalidomide in combination with low-dose dexamethasone (Rd), with melphalan, prednisone and thalidomide (MPT).[9] In this three-arm study, 1,623 patients were randomized to Rd until disease progression (535 patients), to the same combination for 72 weeks (541 patients), or to MPT for 72 weeks (547 patients). The primary end-point was progression-free survival with continuous Rd *versus* MPT. The results from this trial were published in the *New England Journal of Medicine* in 2014 and showed that continuous Rd given until disease progression was associated with a significant improvement in progression-free survival as compared to that achieved with MPT. An interim analysis also demonstrated improvement in overall survival.

In the FIRST trial, HRQoL was a secondary endpoint using the psychometric validated and most commonly used instruments in MM; EORTC QLQ-C30, EORTC QLQ-MY20 and EQ-5D.[10] Six clinically relevant HRQoL domains were selected before the data analysis; Disease Symptoms and Side Effects of Treatment (from QLQ-MY20); and Global Health Status, Physical Functioning, Fatigue and Pain (from QLQ-C30). In their analysis Delforge *et al.* showed that both Rd regimens and MPT improved patients' HRQoL from baseline over the duration of the study across all preselected domains of the QLQ-C30 and EQ-5D questionnaires, and that HRQoL dropped at progression. In order to assess whether statistically significant differences translated into clinically meaningful differences, the minimal important difference (MID) associated with each domain was considered.

When analyzing HRQoL data, it is important to recognize that a statistically significant change does not necessarily imply a clinically significant change. In larger clinical trials, an observed difference in HRQoL scores is often found to be statistically significant. However, these changes in HRQoL scores are often so small that clinicians are hesitant to apply them to clinical decision-making. For example, when the mean score of a HRQoL domain increases 7 points on a 0-100 scale compared to the control group, is this a small, moderate or large effect? For this reason, interpretation of changes or differences in HRQoL scores should be based on the MID.[11]

Historically there has been a lack of consensus regarding what degree of difference is clinically relevant, and this has been an important field of interest within HRQoL research. There is no universal MID for a particular HRQoL instrument or scale, and MID varies by population and context. We have previously published results from a clinical trial using different methods to estimate MID in HRQoL scores for the EORTC QLQ-C30.[12] We

concluded that a difference of 6-17 points (0-100 scale) in the EORTC QLQ-C30 represents a clinically meaningful change in patients with MM. Our findings imply that mean score changes smaller than 6 are unlikely to be important to the patients, even if these changes are statistically significant.

Delforge *et al.* showed that when a MID score of 12 for pain (0-100 scale) was applied, Rd produced clinically significant decreases in pain at months 6 and 12 after the start of treatment. When we know that about 70% of the patients have pain at the time of diagnosis,[13] this is an important finding. As the Rd arm showed a significant improvement in progression-free survival and no evidence of inferiority to MPT in the preselected HRQoL domains, the oral Rd regimen emerges as an efficient and well-tolerated first-line treatment.

The results from the FIRST study are in line with the work by Dimopoulos *et al.* regarding HRQoL outcomes in the MM-015 phase III trial.[14] This study was a double blinded RCT determining the efficacy and safety of melphalan, prednisone and lenalidomide (MPR) *versus* melphalan, prednisone and lenalidomide followed by lenalidomide maintenance (MPR-R) *versus* melphalan and prednisone (MP). Progression-free survival improved significantly in the MPR-R arm compared to the MPR and MP arms, but no survival differences were noted. HRQoL was assessed using the EORTC QLQ-C30 and QLQ-MY20 and clinically meaningful improvements of the MID were more frequently observed in patients treated with MPR-R than in those receiving MP. As in the FIRST study, progressive disease had a negative impact on HRQoL.

Interpretation of the clinical value of HRQoL scores requires that HRQoL data from clinical trials are reported clearly using both statistical and descriptive tools. To improve the reporting of HRQoL data from RCT, the Consolidated Standards of Reporting Trials Patient-reported Outcomes (CONSORT PRO) have been developed.[15] Five CONSORT PRO checklist items were selected for RCT in which HRQoL are primary or secondary endpoints, and it is recommended by the authors that the CONSORT PRO guidance should supplement the standard CONSORT guidelines for reporting RCT when HRQoL data are included. Improved reporting of HRQoL data will facilitate a more standardized and robust interpretation of the results from RCT and will be informative for patients' care.

Clinical trials in MM patients should include HRQoL as a study endpoint making it possible to compare the study treatments taking into account the patients' perspective. Because many of the new treatments in MM may not give substantial prolongation of survival, HRQoL should be the primary endpoint in more studies. The bisphosphonate study by the Nordic group is a good example of altered decision-making based on HRQoL analyses.[16] This randomized study compared the effect of 90 mg *versus* 30 mg of pamidronate on HRQoL and skeletal morbidity in patients with newly diagnosed MM. In this trial, the primary endpoint was physical function estimated by the EORTC QLQ-C30 questionnaire 12 months after the start of treatment. The result was no difference in the primary endpoint and this was accompanied by no difference in skeletal-related events. Due to firm evidence based on HRQoL in a double-blind study, the recommendation for pamidronate treatment in MM was changed from 90 mg to 30 mg monthly in Nordic countries. The patients were spared overtreatment and unnecessary side effects which are also risks for myeloma patients when so many treatment options are available.

Does it matter? To answer our initial question, there is no doubt that HRQoL adds an important dimension to the traditional endpoints in clinical trials and these measures should be combined in future studies. HRQoL could even serve as a primary endpoint in many trials.

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