Patients' needs in hematology: whose perspectives?

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To highlight the commitment of hematologists in addressing the issue of quality of life (QoL) of patients affected by hematologic disorders, the European Hematology Association designated "Quality of life" as the theme of the year for 2012-2013. Fortuitously, the first edition of the "Guidelines for measurement of *Patient-Reported Outcomes in Hematology*" was published in June 2012 by the European Hematology Association Scientific Working Group (EHA SWG) "Quality of Life and Symptoms" to mark the initiation of the EHA theme.

Patient-reported outcomes (PROs) are amongst the most important outcomes of treatments in hematologic disorders. Responding to the patient's voice by means of PROs is a suitable approach to improve the quality of care in hematology. PRO is an umbrella term encompassing a number of patient self-reported parameters related to a patient's health status and perception of treatment side effects.[1-4] As defined by the US Food and Drug Administration (FDA), PRO is "a measurement based on a report that comes directly from the patient about the status of a patient's condition without amendment or interpretation of the patient's response by a clinician or anyone else".[5,6] PRO assessments introduce the patients' perspective into the clinical process via standardized self-report instruments that are scored by the patient, not a clinician, or a researcher. The use of a PRO instrument is thus recommended when measuring a concept that is best known to the patient or best measured from the patient's perspective.[5] As stated by the FDA, some "treatment effects are known only to the patient", and such information can be lost when the patient's perspective "is filtered through a clinician's evaluation of the patient's response to clinical interview questions".[5] PROs include QoL, symptoms, satisfaction with and adherence to treatments, and any other treatment or outcome evaluation obtained directly from patients.[5,7-9]

In hematology, PROs serve a number of important purposes both in clinical trials and in clinical practice. They are a bridge towards acquiring understanding of the nature and the extent of functional impairment (i.e. both physical and psycho-social) that patients may encounter during disease, throughout and after treatment, and in the long term. QoL measures have also been shown to be of prognostic value for the outcome of treatment (survival) in specific hematologic diseases and may become a valuable guide in treatment selection. Furthermore, identification of risk factors for such dysfunctional behavior can help to identify high-risk patients for whom counseling and psycho-social support would be required.

In patients with hematologic disorders, the physician-patient partnership is crucial to provide patient-centered care and to reduce suffering due to the disease. This could be reinforced by the implementation of PRO assessment in routine practice, ensuring that clinicians use this information in their decision-making process. Furthermore, accurate evaluation of symptom severity is critical for optimal care of patients with hematologic disorders, and for alleviating symptom burden of disease and treatment-related adverse events, ultimately improving the QoL in this patient population.

During the last decade, PROs have been increasingly included in clinical trials and post marketing research in hematology to measure treatment benefits and risks. Often, PROs complement primary clinical outcomes such as survival, disease activity, clinician ratings and physiological or biomedical measures. In situations in which there are multiple treatment options with similar survival outcome, or if a new therapeutic strategy needs to be evaluated, the inclusion of QoL as an end point can provide additional data and help in clinical decision-making. In some settings, in particular that of palliative care, PRO assessment may be the sole indicator for initiating or changing treatment. At present, in hematology, PROs are more frequently

Table 1. Key steps when planning clinical trials with a patient-reported outcome component.

Step	Considerations	Comments
Developing an end-point model	Primary or secondary end point	PRO end point should be incorporated in the model within the hierarchy of all end points
Choosing an appropriate PRO instrument(s)	Generic QoL questionnaire(s)and/or disease-specific QoL questionnaire(s) and/or symptom assessment questionnaire(s)	Special attention should be given when choosing the instrument(s) for children/adolescents and elderly patients
Timing of administering PRO instrument(s)	Depends on study goals as well as on the interventions and the illness trajectory	Timing should be linked to physician visits or treatment dates (preferable to have the measurements completed at the same point in time relative to these events i.e. before the physician's interview and examination, and before the scheduled treatment).
Planning and monitoring data collection	Rigorous protocol instructions and qualified staff necessary	Particular emphasis should be given to the mechanisms that will ensure a minimum of missing information.
Analyzing and interpreting PRO data	Scientifically sound, feasible, clinically meaningful and policy relevant approaches	The PRO data should be presented to scientific community and health-care providers in a clear and transparent way.

PRO: patient-reported outcome; QoL: quality of life.

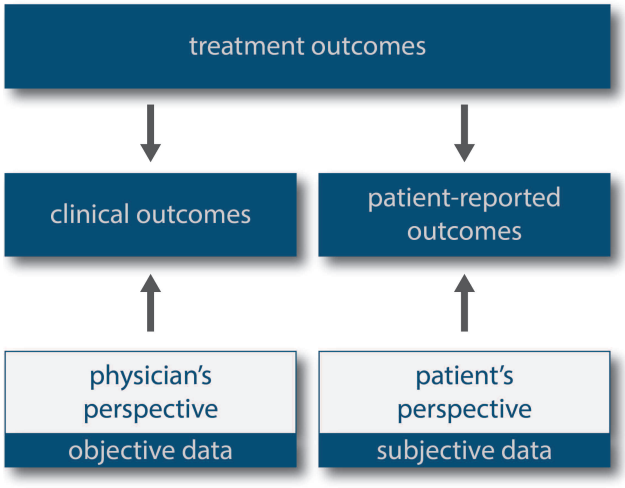

Figure 1. A dichotomous model for evaluating treatment outcomes in patients with hematologic diseases.

used in phase III and IV studies. There are also examples of phase II studies in which it is useful to evaluate the patient's viewpoint. Using PRO as an outcome measure in a clinical trial is the only way of obtaining evidence-based data from the patient's perspective on the effect of treatments in hematology. In hematology, PROs have been used as primary outcomes in clinical trials, particularly when no surrogate measure of direct benefit is available to capture the patient's well-being. It is, therefore, recommended that all clinical studies include some form of PRO measure.

In a number of international recommendations for various hematologic diseases, namely, hemophilia,[10] immune thrombocytopenia,[11] myelodysplastic syndromes,[12] chronic lymphocytic leukemia,[13] acute leukemia,[14] non-Hodgkin's lymphoma,[15] Hodgkin's lymphoma[16,17] and multiple myeloma,[18] the importance of PRO issues is highlighted and these indicate the need for more research in the field. However, the international hematology community has not introduced any standards or guidelines for the assessment of PROs. To address this issue, a 3-year project was launched in 2010 by the EHA SWG "Quality of Life and Symptoms" to identify, evaluate and summarize the highest and most current quality evidence in order to issue a set of consensus statements to standardize PRO assessment in clinical trials of new treatments for hematologic disorders. It was envisaged that this in turn would raise the quality of care in patients with such diseases. An expert panel of clinicians and researchers from 17 countries met in consensus conferences, in close collaboration with advisory groups, comprising representatives of patients' organizations and the pharmaceutical industry, nurses, psychologists and hematologists. The Guidelines, "Patient-Reported Outcomes in Hematology", focus on methodological issues of measuring PROs in clinical trials of new treatments for hematologic conditions.

Since PRO data may influence clinical and regulatory decisions, standardization of PRO measurement is essential for producing valid and reproducible results. Measuring PROs in clinical trials should follow the same rigorous procedures as when measuring any traditional clinical end point. Key issues to be considered when planning clinical trials with a PRO component are carefully described in the Guidelines, as summarized in Table 1. All aspects of PRO measurement should be taken into account and integrated during the stage of the development of the protocol and standard components of the protocol, as well as practical aspects of feasibility and data collection, are discussed. An overview of currently available PRO instruments for patients with hematologic diseases, with their pros and cons, is presented. Furthermore, guidance is provided for interpreting PRO data.

The Guidelines propose a dichotomous model to evaluate treatment outcomes in patients with hematologic disorders (Figure 1): the concept of "clinical outcomes" (reported by physicians) is the physician's perspective of treatment efficacy, and is considered to be the objective component of the model; PROs are the patients' perspective, and are the subjective component. As part of the Guidelines, it is recommended that, in clinical trials, clinical outcomes should be evaluated in terms of clinical response, whereas PROs should be measured by QoL changes and symptom response. Furthermore, a clinical trial with a PRO component should be designed with the advice of a PRO Consensus Group consisting of clinicians, PRO experts, patient representatives and the respective sponsor. The state-of-the art of studies with a PRO component, summary of available instruments and practical considerations for PRO measurement in patients with leukemias, lymphomas, multiple myeloma, myelodysplastic syndromes, bleeding disorders (hemophilia, von Willebrand's disease and immune thrombocytopenia), anemia of chronic disease, bone marrow transplantation/hematopoietic stem cell transplantation, as well as in patients receiving anticoagulants, are described separately. It is worth noting that a separate chapter is dedicated to PRO assessment in long-term blood cancer survivors and the final chapter covers PROs in children/adolescents with hematologic malignancies.

In conclusion, evidence-based data from a patient's perspective on the effects of treatment may only be obtained by PROs. Though survival is a hard end point, the absence of PRO data in clinical trials produces an imprecise measurement of the benefits and risks of treatment. The development of these Guidelines is the first step towards ensuring quality standards for PRO assessment in clinical trials in hematology. The next, but no less important step is the implementation of PROs in routine clinical practice in hematology. The use of PRO information in the real world setting will be an effective approach to improve quality of care for hematologic patients and to ensure patient-centeredness as a fundamental component of providing optimal patient care for this heterogeneous and challenging patient population.

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