Health-related quality of life and symptom assessment in clinical research of patients with hematologic malignancies: where are we now and where do we go from here?

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More than twenty years ago, the USA Food and Drug Administration (FDA) supported the use of health-related quality of life (HRQOL) assessment as an outcome measure in the evaluation of new anticancer drugs.[1] HRQOL is a multidimensional construct comprising at least four dimensions: physical function, psychological function, social role function and disease or treatment symptoms (e.g. pain and nausea).[2] Improvement in how patients feel and function is often viewed by patients as legitimate a clinical benefit as is survival, and the assessment of how patients feel and function is primarily accomplished through patients' reports. A shift towards more systematic patient-centered evaluation has entered the term *patient-reported outcome* (PRO) into the health care lexicon.[3]

PRO is an umbrella term encompassing a number of parameters related to the patient's self-reported health status and perception of treatment effects. These include the multidimensional construct of HRQOL as well as more focused, one-dimensional effects such as symptom severity and symptom impact. Importantly, PRO assessments introduce the patient's perspective into the clinical research process via standardized and methodologically sound self-report questionnaires.

Whereas PRO have traditionally been used in cancer clinical trials as an additional effectiveness end-point, many newer trials depend on PRO to measure a primary outcome, such as reduction of symptoms. Furthermore, newer agents for a primarily symptomatic benefit are now prominent in many pharmaceutical pipelines. Accordingly, the USA FDA recently published for comment their *Patient-Reported Outcome Measures: use in Medical Product Development to Support Labeling Claims*, to provide the guidance that researchers will need to justify the use of a particular PRO instrument in establishing a new drug's benefit from the patient's perspective.[4] Incorporating PRO as supplements to traditional clinical end-points in cancer research can provide valuable information to better inform and help guide clinical decision-making.[5,6] Because clinicians and patients commonly face challenging choices among treatments that are similar in effectiveness with regards to disease control and prolonging survival, differences in patients' health status during the survival period have become critical variables in making final, individualized treatment choices and in developing new therapies. Including PRO as measures of differences among treatments is paramount for effectively evaluating toxicity, overall treatment effectiveness, and quality of survival. A number of excellent examples describe how HRQOL outcomes have contributed to better management of patients.[7]

Assessing which PRO measure to use in a clinical trial setting requires careful consideration during the protocol design stage. Appropriate instrument selection will depend on issues such as disease stage, treatment type, concerns about respondent burden, and, most importantly, the HRQOL research hypothesis being tested. It is also important to have an idea of what symptoms or domains the treatment to be tested is liable to affect. A number of PRO measures are available to be used in hematology, including general cancer questionnaires, cancer site-specific or treatment-specific tools, and symptom-focused measures. General cancer measures (such as the widely used EORTC QLQ-C30) can be used across cancer populations and do not focus on specific interventions or cancer populations. Cancer site-specific or treatment-specific instruments address health aspects specific to a given cancer population or treatment and are more likely to capture subtle changes in a patient's health condition. Finally, also cancer-specific symptom measures are easy to administer, capture much of the patient's response to treatment, and can be used repeatedly to assess changes in a patient's status longitudinally over the course of the disease or treatment. Several multiple-symptom measures, including the M.D. Anderson Symptom Inventory, have recently been critically reviewed.[8]

HRQOL issues are of paramount importance to patients with hematologic malignancies, who generally experience a number of debilitating symptoms such as severe fatigue, neuropathy, sleep disturbance, nausea and

pain. A recent article well described the extent to which self-reported fatigue adversely affected HRQOL in a large sample of patients with myeloproliferative disorders, and also showed that fatigue cannot be merely explained by anemia or medication toxicity.[9] Patients with hematologic malignancies often require frequent hospital admissions and clinic visits as a result of intensive and aggressive treatment modalities and infections. Moreover, despite significant advances in treatment modalities and improved survival, many such patients cannot be cured. Those who do experience prolonged survival continue to have compromised function due to their treatment, and are confronted with their multifaceted challenge of living with the disease and the symptom burden of more *chronic* therapy. The impact of HRQOL for patients with solid tumors has been well studied, with many large randomized controlled trials (RCTs) that include HRQOL as an end-point;[10] however, our understanding of this issue in patients with hematologic cancers is lacking in comparison.[11] Very few RCTs in hematologic malignancies have included HRQOL as an end-point. In the literature, the paucity of scientific PRO data on patients with leukemia, lymphoma, myelodysplastic syndromes, myeloma or other hematologic diseases is, overall, in stark contrast to the amount of research available for patients with major solid tumors. Even though Burge and colleagues stated in 1975 that *quality of life in leukemia is as important as its quantity*,[12] several subsequent attempts to present information about HRQOL were based only on indirect measures, such as the number of days spent in hospital or clinician-reported observations,[13] suggesting that the patient's perspective has historically been much less emphasized in the field of onco-hematology.

What are the reasons behind this paucity of research? While it is a challenge to answer this question, we might speculate that this has probably been determined by a number of issues, which we can only partially address in this editorial. First, PRO assessment might not have been considered possible in certain diseases, such as acute leukemia, because of a historically very poor prognosis or an acute course. For example, obtaining a baseline (i.e., pretreatment) HRQOL assessment in a trial of acute promyelocytic leukemia cancer patients, in which the time lag between diagnosis and start of treatment is usually only hours, is a challenging task. Second, onco-hematologists, unlike medical oncologists treating patients with solid tumors, traditionally have had to depend on very aggressive and intensive treatments that necessarily have a strong negative impact on the patient's life. This may have contributed to a general perception that seriously compromising a patient's HRQOL was an indispensable step towards the cure. Conversely, the hematology community might have come to believe that a treatment's deleterious effect on HRQOL is an indicator of its effectiveness. It would then follow that hematologists might feel that they have *no room and no time* for formal assessment of the patients' perspective, thus hampering research in this area.

Despite the scarcity of robust PRO-based research, the long-term prognosis for patients with hematologic malignancies has improved greatly over the last decade. A higher number of potentially less toxic drugs are now available and newer treatments can potentially offer many patients the option to be treated with less aggressive approaches, making the patient's perspective much more critical in evaluating treatments. This is particularly true for patients with chronic myeloid leukemia, for whom the revolutionary tyrosine kinase inhibitors have greatly improved traditional clinical outcomes and have shown a far greater superiority in terms of HRQOL over previous interferon-based treatments.[14] It is also true for patients with other hematologic diseases, such as Hodgkin's and non-Hodgkin's lymphoma, acute promyelocytic leukemia, and acute lymphoblastic leukemia in children, for which there are potentially less aggressive treatments. As new agents in the same class emerge, it becomes more important to asses differences in treatment impact on patients. Furthermore, the number of elderly patients diagnosed as having a hematologic disease is increasing, raising challenging and compelling questions about trade-offs between the expected beneficial and harmful effects of treatment, overall survival, and HRQOL. Recent evidence in patients with chronic lymphocytic leukemia provides an excellent example of how HRQOL assessment can be implemented in a clinical trial setting, providing valuable data to better understand patient morbidity and overall treatment effectivness.[15]

For all of these reasons, it is of paramount importance for the patient and the physician to have access to empirical PRO data on established treatment benefits and effects, both positive and negative, on HRQOL and symptom burden. Information about side effects, symptoms, and treatment options can be of greatly help to both physicians and patients in making informed decisions. For example, cancer patients require information not only related to survival estimates, but also regarding HRQOL, symptoms, and expected treatment side effects.[16,17] Our ability to provide this information to patients from a robust evidence-based perspective will increase with the more systematic introduction of HRQOL and symptom evaluation in future prospective studies.

As an example, to provide a basis for the further development of methods using PROs in European hematological clinical research, the European Hematology Association (EHA) in 2006 established a Scientific Working Group on Quality of Life and Symptoms. This Working Group interacts with other EHA groups to mainly provide access to experts in symptom and HRQOL measurement.

The Working Group is presently co-chaired by Professor Charles Cleeland, Chair of the Department of Symptom Research at The University of Texas M.D. Anderson Cancer Center, Houston, and Professor Andrei Novik, Chair of the Department of Hematology at the National Medical Surgical Center, Moscow. The Working Group may be contacted through its secretary, Dr. Tatyana Ionova, in St. Petersburg, Russia at *mcqlr@peterstar.ru*.

In conclusion, we strongly encourage the onco-hematology community to face this challenge. While clinical and pharmaceutical research is achieving a number of important goals, the time is also mature for a more patient-centered approach, and we expect to see in the near future the patient's perspective becoming a more a relevant aspect in clinical research in hematology.

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