Quality of life in higher resolution: the next generation of comparative effectiveness research in malignant hematology

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Quality of Life (QOL) is among the most important considerations for patients facing a cancer diagnosis.[1] Given the high response rates and even curability of many hematologic cancers, however, QOL considerations often take a back seat to active disease treatment, particularly in the curative-intent treatment setting. This is not necessarily unreasonable, as long as it is consistent with patients' goals and preferences. However, we must consciously face the reality that cure sometimes comes at significant cost in terms of QOL, and should discuss this trade-off openly with patients as we work to define less toxic yet effective regimens.

Consider the patient who undergoes allogeneic stem cell transplantation to cure her acute myelogenous leukemia (AML), but suffers debilitating chronic graft-*versus*-host disease thereafter. Think of the patient who suffers severe cardiomyopathy after receiving anthracycline-based combination chemotherapy to cure his aggressive lymphoma, or who develops post-traumatic stress disorder thereafter (which may be seen in upwards of one-third of non-Hodgkin's lymphoma survivors at five years).[2] Or, outside the curative-intent setting, consider the myeloma patient who suffers with severe neuropathy after multiple lines of palliative chemotherapy. As we increasingly recognize these survivorship trade-offs in clinical practice, we must study them in greater detail to inform our application of therapies that are both life-extending and toxic; longevity is only one part of the equation.

In contemplating these issues, it becomes apparent that relatively little is known about the impact of our therapies on patients' QOL, both during treatment and after. In other words, while we can often tell a patient that they will likely live longer with treatment A *versus* treatment B, we generally lack sufficient understanding, or an adequate evidence base, to provide guidance about the longer-term trade-offs of different regimens. The 'next generation' of comparative effectiveness research is beginning to address this issue in a more meaningful way. This work must look beyond the 'cure-at-all-costs' mentality to provide a more focused view of the unique benefits and drawbacks of our different therapies, better enabling us to match patients' goals and preferences with particular treatment regimens.

In a visionary fashion, the European Hematology Association (EHA) has recognized the importance of QOL considerations in hematology, naming it as this year's theme for the annual assembly.[3] At the June 2012 meeting, only 27 abstracts addressed topics related to QOL, out of 2,075 submissions.[3] Clearly, there is much more work to be done, but the EHA's step is a significant one in the right direction. Granted, QOL is not a new topic of study.[4] Indeed, measures such as the EORTC-QLQC30 and the FACIT family of questionnaires have been validated and in use for many years in the clinical trials setting,[5,6] and have been tested and applied to the blood cancer population.[7] What *has* changed recently, however, is technology, and it is changing the landscape regarding the ways in which we approach this work. Novel information technology (IT) solutions allow us to study QOL in much higher resolution, in more discrete, digestible, meaningful ways that include extensive symptom assessments and patient-descriptions of the impact of their illness on their lives, with trends over time, rather than just summary QOL scores and incomplete snapshots. IT developments now allow us to collect, organize, and explore information about patients' experiences in ways that were impracticable using standard methods like paper case report forms or telephone surveys. Using electronic tablet computers and other web-enabled devices, investigators can now collect data on patients' symptom burden, trajectory, performance status, and Quality of Life in a robust, reliable, validated manner, at relatively low cost, as part of daily cancer care.

Our group has experience in this type of work and has shown it to be reproducible and robust; it is useful to clinicians, saving time while providing a more detailed review of systems' assessment, and is simultaneously appreciated by patients as a meaningful part of their cancer care, perhaps even preferred for sensitive items such as sexual functioning.[8-11] Often called "electronic patient reported outcomes" (ePROs), these novel techniques allow data collection directly from patients, ensuring higher fidelity and remarkable completeness. These datasets can be electronically combined with other information, such as electronic health record data, administrative data, and biospecimen information, to create longitudinal information-rich summaries of a patient's journey.[12,13] Technology thus positions our field to perform the much-needed 'next generation' of comparative effectiveness research which considers the differential impact of therapies from the standpoint of a much richer depiction of the patient experience during and after treatment. As a more detailed depiction of symptom burdens, trajectories, and experiences across treatment lines emerges, our ability to develop targeted interventions is also enhanced. In other words, these are not just data, these are actionable items. When we have a greater understanding of who tends to suffer from what symptom with which regimen, we can better target early or preventive interventions. These electronic solutions can even be adopted to facilitate directed education, along with self-management and triage to other providers when extra help is needed, as in the case of distress screening.

Unfortunately, most studies and cancer registries to date have not included detailed symptom assessments, thus we remain somewhat ignorant of the longitudinal experience of our patients as they undergo chemotherapeutic treatment, especially across disease types and specific treatment regimens. Particularly in cases where cure is not possible, we need more information about these factors to help guide patients' decision-making. In cases in which different treatments are reasonably equivalent with regards to response rate and survival, patients' experiences become arguably even more important. It is critical to note that this importance extends beyond the usual adverse event and toxicity data collected in most clinical trials;

of course, anemia and neutropenia and neuropathy are all important, but so are dyspnea and fatigue, appetite, sexual functioning, distress, and change in physical functioning, but the latter types of measurements are conspicuously absent or underrepresented in the clinical trials literature in our field.

One particular area that is ripe for this type of inquiry is the continuum of myelodysplastic syndrome and AML, especially in older individuals, wherein patients often choose between intense, toxic therapies with a small but real chance of cure, compared to less intense but frequent treatments aimed at prolonging life and maintaining QOL, or even purely palliative strategies. We know comparatively little about the differential experiences of these patients across the disease spectrum, and across the different intensities of therapy,[14] and have reason to think that patients' choices may be inconsistent with their stated preferences regarding the balance between QOL and longevity.[15] Evidence also suggests that hematologic malignancies have a significant negative emotional impact, perhaps beyond that seen in solid tumors.[16-18] These phenomena remain underexplored. Having more detailed information about the patient experience will help us more effectively guide patients and family members about treatment decisions and goals of care.

Similarly, we know very little about the longitudinal experience of patients with more indolent leukemias and lymphomas, such as follicular non-Hodgkin's lymphoma or chronic lymphocytic leukemia, which may now have median survival rates of a decade or more in lower risk subgroups. How do QOL and symptom burden vary across the different treatments commonly used for these diseases? Emerging data on survivorship demonstrate a significant burden of symptoms even years after diagnosis in the setting of non-Hodgkin's lymphoma (NHL), including a surprising prevalence of post-traumatic stress disorder.[19,20]

A better understanding of patients' longitudinal experiences means we can more effectively target interventions. By combining patient-reported data with other information in the electronic health record, such as laboratory findings and clinical assessments, we paint a more detailed picture of the patient and his or her experiences, better heralding the future and preparing clinicians to more expertly manage the impact of hematologic malignancies and their treatments over time. We can also more effectively involve colleagues with expertise in the growing field of Hospice and Palliative Medicine who are increasingly involved in the care of patients with incurable solid tumors as a standard of care, but who far less often become involved in the care of patients with hematologic cancers. The more we know and understand about the symptom burden across different disease types and therapies, the better we can engage these experts in symptom management, and do so earlier in the course of treatment, across the spectrum of survivorship, where symptom burden may remain high.

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