Assessing the Quality and Value of Quality-of-Life Measurement in Breast Cancer Clinical Trials

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decision making. In the previous review (4), QOL outcomes were most likely to influence clinical decision making in the setting of primary treatments (eg, surgery, radiation) or in symptom management and psychosocial intervention trials, whereas in the adjuvant and metastatic settings, QOL outcomes were infrequently identified as being influential in decision making. The authors concluded that disease outcomes trumped QOL outcomes (4). In the updated review, the findings were similar in that there was limited added value from including QOL assessments in adjuvant therapy trials, with the exception that in those that compared endocrine therapy with chemotherapy, the QOL outcomes were generally useful in clinical decision making. The conclusions of the original review are strengthened by the added number of articles in this update. The authors provide the following recommendations based on their updated review findings: 1) QOL should be included as a secondary endpoint in adjuvant therapy trials only when the treatment expectation is equivalence or noninferiority, for example, when treatment decisions will be based on differences in patient outcomes between study arms or when the trial focuses on a vulnerable population (eg, elderly women) or is testing substantially different modalities (eg, endocrine vs chemotherapy) or a new treatment for which descriptive information is needed; 2) QOL assessments should be included in metastatic breast cancer treatment trials only when a minimal survival difference is expected or the treatments have substantial differences in toxicity or descriptive information about a new treatment is needed; 3) QOL-specific sample size calculations should be performed and QOL should be measured only in the subset of the study population that was defined by these calculations; 4) when QOL is not the primary trial endpoint, the results should ideally appear in a companion article published at the same time as the medical outcomes article, so that a complete appraisal of the risks and benefits of the intervention can be evaluated (5).

Although many challenges remain in the integration of QOL and patient-reported outcomes into breast cancer clinical trials, much has been achieved in the past decade. The large increase in the number of published studies identified in this high-quality systematic review reflects the increased acceptance of the patient’s voice in assessing the outcome of trials as well as the participation of expert QOL investigators in the design, conduct, and analysis of clinical trials. Many of the challenges noted by Lemieux et al. (5) were discussed at a National Cancer Institute–sponsored conference focused on these issues (9) and reported in several articles of a special issue of the *Journal of Clinical Oncology* (10,11). It should be noted that although the review by Lemieux et al. is a comprehensive update, many of the studies they identified reported on trials that were designed in the mid to late 1990s and, as a result, may not reflect the many improvements in study design and data collection that are now standard in clinical trials that incorporate patient-reported outcomes.

One might ask why QOL assessment adds little value to most randomized trials of adjuvant chemotherapy in breast cancer (ie, chemotherapy regimen X vs chemotherapy regimen Y; 16 trials found in this review), where it has been extensively incorporated? Although there is a mature literature on the multidimensional measurement of QOL in breast cancer patients with breast cancer treatment–specific QOL tools (12,13), the ability of these measures to detect differences in outcomes among adjuvant treatments has been very limited. For example, Land et al. (14) [reference 48 in Lemieux et al. (5)] described QOL and symptom outcomes in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-23 trial in patients with node-negative estrogen receptor–negative disease who were randomly assigned to four cycles of doxorubicin and cyclophosphamide (AC) vs six cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). The functional assessment of cancer therapy for breast cancer (FACT-B) (13), a measure of fatigue, and a symptom checklist were used to track QOL outcomes in this study. There were no differences between the two study arms detected by the FACT-B, a multidimensional breast cancer–specific QOL tool. However, the fatigue scale identified greater severity of this symptom during treatment with AC, and the symptom checklist identified statistically significantly more bladder problems and diarrhea in the CMF arm vs the AC arm (14). Because these two treatments were found to be equivalent in terms of treatment outcomes, among other factors, the difference in symptoms might lead to a preference for the shorter-duration AC, which had more limited toxicity. Symptom assessment is not included routinely in the current conceptualization of QOL; although several instruments [eg, the European Organization for Research and Treatment of Cancer (EORTC)-BR23 (12) and the FACT-B (13)] contain disease-specific items, some of which are symptoms; however, they are not usually analyzed separately.

There has been increasing interest in the value of patient-reported symptom assessment in clinical treatment trials and calls for including symptom assessments as primary or secondary outcomes in new trials (15,16). Indeed, for breast cancer patients, many of whom will survive their adjuvant therapy with no major impacts on QOL (as noted by Lemieux et al.), there will be persistent symptoms, such as fatigue, cognitive complaints, sexual dysfunction, sleep problems, and neuropathy, months and years after treatment ends (17–22). Similarly, for patients with advanced breast cancer, where deterioration in overall health may mask the measurement of QOL benefits or harms, it may be much more useful to include patient-reported symptom assessments to gauge the toxicity of treatment regimens that are being compared and to determine whether the measured difference in survival is outweighed by added symptom burden.

These observations about the discrepancy between QOL assessment and symptom reporting are not new. The NSABP P-1 Breast Cancer Prevention Trial included a validated multidimensional assessment of QOL (the MOS SF-36) (23), as well as a standardized measure of depressive symptoms (the CES-D) (24), a measure of sexual functioning, and a 32-item symptom checklist (25–28). The symptom checklist and measures of depression and sexual function were included to ensure that any untoward side effects of tamoxifen would be captured in this placebo-controlled trial among middle-aged women who were at high risk for development of breast cancer. The symptom checklist drew on items that were in use in other trials of hormone therapy and menopause symptom management, as well as items that were developed specifically for safety monitoring in this trial. At the conclusion of the P-1 trial, no statistically significant differences were found in the QOL outcomes between tamoxifen- and placebo-treated...
women; however, there were substantial differences in symptoms, which varied by treatment and age group (≤50, 50–59, and ≥60 years). The results from the symptom assessment in more than 13,000 women who participated in the P-1 trial are the only major source of patient-reported outcome data regarding tamoxifen available today, which can assist in clinical decision making regarding tamoxifen use in healthy high-risk women, as well as in women with early-stage breast cancer. Clearly, symptom assessment in this setting added value beyond the standard QOL assessment.

After about three decades of effort to promote the incorporation of QOL endpoints in clinical trials, why do we find that psychometrically reliable and valid QOL assessment tools sometimes fail to capture clinically important differences between treatments in the setting of breast cancer clinical trials? The tools to measure QOL that are available are generally multidimensional and assess important domains such as physical, emotional, and social functioning. Although these tools have been designed to robustly capture differences in QOL between patients with minimal disease burden and those with advanced disease, or declines or improvements in function over time in groups of patients, they may not have the precision to assess differences within the clinical trial setting, where the patient population is homogeneous and the comparative treatments are equally bothersome in their impact on general domains of QOL. In addition, patients may respond differently to scale items that ask them to provide overall QOL assessments, whereas the specificity of questions about symptom severity may be easier to rate accurately, allowing finer distinctions between different treatment strategies. For many clinical trials, symptom-focused patient-reported outcomes may be the assessment where should be focused, both from the perspective of patients, clinicians, and government regulators (6).

In conclusion, the large body of research on QOL outcomes in breast cancer clinical trials, as reviewed by Lemieux et al. (5), provides support for the feasibility and value of including QOL in future studies. As we strive to provide better patient-centered care for our patients, this type of information is very important to collect. However, we should heed the lessons from this review and ensure that future trials that include QOL and patient-reported outcomes focus on high-quality statistical design and analysis plans and choose outcome measures that are likely to provide valuable information at the completion of the trial. Continuing to measure QOL in all breast cancer clinical trials (eg, standard adjuvant chemotherapy trials) is unnecessary, and the conclusions of this review should be used to guide future measurement strategies. In addition, inclusion of well-validated measures of relevant symptoms should be a high priority for assessing the burden of breast cancer treatments, whether in survivors of breast cancer or in women with advanced disease receiving palliative care.

References


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