Featured Article

Lack of patient-reported outcomes assessment in phase III breast cancer studies: a missed opportunity for informed decision making

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Abstract: A phase III study comparing capecitabine monotherapy to combination treatment with capecitabine and sunitinib in patients with metastatic breast cancer failed to demonstrate a benefit in terms of progression-free or overall survival. Both regimens were reasonably well tolerated with some differences noted in the specific toxicity profiles. However, the study failed to incorporate an assessment of patient-reported outcomes (PROs) such as self-reported pain, quality of life, or employment outcomes. This is a missed opportunity. If more clinical trials included such measures, they would provide valuable information to patients and clinicians choosing from a wide array of available and otherwise similarly effective systemic therapies for metastatic breast cancer.

Keywords: Breast cancer; oral chemotherapy; patient reported outcomes (PROs); employment; palliative treatment

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Therapy for metastatic breast cancer is, by definition, given with palliative intent. As oncologists, our goal is to prolong life while also minimizing cancer- and treatment-related symptoms. While some recent therapeutic advances have led to longer survival times for our patients, many unfortunately have not. In this setting, survivorship issues, such as quality of life and employment outcomes, can be determinant.

Although adherence can be a concern, an orally administered regimen is associated with obvious advantages in terms of convenience and ease of administration, particularly for patients with triple-negative breast cancer for whom chemotherapy is the only treatment option. However, few such oral regimens exist. The most widely used oral chemotherapy agent in the U.S. is capecitabine. It is active and reasonably well tolerated as demonstrated in trials administering it as a single agent or paired with parenteral chemotherapy or other targeted agents. Combining it with another oral therapy to attempt to increase the associated survival benefit could also result in significant improvements in quality of life and related outcomes for patients with metastatic breast cancer.

Crown *et al.* recently published a phase III study of patients with pretreated metastatic breast cancer in the *Journal of Clinical Oncology*, comparing treatment with single-agent capecitabine to treatment with combination capecitabine and sunitinib, an oral tyrosine kinase inhibitor with broad targeting including angiogenesis that is approved for treatment of other malignancies, such as renal cell carcinoma (1). The primary outcome of the study was progression-free survival (PFS). Study participants had previously been treated with both an anthracycline and a taxane and had received one or two prior chemotherapy regimens in the metastatic setting. Of 442 participants, 27%

in each arm had triple-negative breast cancer.

Unfortunately, the study failed to demonstrate a benefit associated with the combination regimen. PFS was 5.5 months in the combination therapy arm and 5.9 months in the monotherapy arm (P=0.9). Overall survival was likewise not significantly different between the two arms (16.4 months for the combination arm and 16.5 months for capecitabine alone, P=0.5). Subgroup analyses did not suggest a significant benefit associated with combination therapy for any specific group of patients. Although both regimens were well tolerated, patients in the single agent arm, who received a higher dose of capecitabine, experienced higher rates of hand-foot syndrome, while those in the combination arm had higher rates of neutropenia and thrombocytopenia.

These results are disappointing in that they did not lead to improved overall outcomes for patients with metastatic breast cancer. In this study even a small statistically significant difference in favor of the combination arm could have been celebrated as a step forward scientifically. The authors elegantly described the biological rationale for choosing this combination. They noted that sunitinib has several targets that have previously been shown to be important in breast cancer, and preclinical data have demonstrated a synergistic effect of the combination of sunitinib with fluorouracil, of which capecitabine is the prodrug (2-6). A positive trial result would have contributed to the scientific evidence in support of simultaneously targeting neoangiogenesis and neoplastic cellular proliferation.

However, apart from the specifics in this case, there is also an obvious practical rationale for the use of two oral agents rather than two parenteral therapies or a combination of an oral and a parenteral therapy: such a regimen is an attractive option for patients who wish to minimize trips to the oncologist. In general, an entirely oral chemotherapy regimen is likely to be more convenient for the patient and to allow him or her to continue to live a life that is as close to "normal" as possible during treatment. The availability of oral treatment options has clear implications for patient reported outcomes (PROs) such as quality of life and employment.

Patient reported symptoms have gained prominence in clinical trials; PROs such as pain have been used as study endpoints and incorporated into drug labeling (7-9). However, other PROs, such as employment outcomes, have been virtually ignored in the clinical trials arena. My colleagues in health services research and I have been studying return to work in the adjuvant setting for several years. The Institute of Medicine cited employment concerns as paramount in their 2006 report, *From Cancer Patient to Cancer Survivor: Lost in Transition*, and recommended that "employers, legal advocates, health care providers, sponsors of support services, and government agencies should act to eliminate discrimination and minimize adverse effects of cancer on employment, while supporting cancer survivors with short-term and long-term limitations in ability to work" (10). To achieve this goal, however, we need to better understand the adverse effects of cancer treatment on employment. While we have generated some data on employment outcomes after adjuvant treatment for breast cancer, we know almost nothing about the work experiences of patients undergoing breast cancer treatment in the metastatic setting.

At Memorial Sloan-Kettering Cancer Center we have started to investigate the employment concerns of cancer patients undergoing palliative care. We surveyed 97 patients in our palliative care clinics and found that, although 79% were working at diagnosis, only 42% were still working at the time of the survey (11). Patients who continued to work reported a greater sense of normalcy and less financial distress, and 39% said they would have liked to work more hours than they were working. Factors significantly associated with not working included pain, side effects of analgesics, and fatigue. Based on these results, we can surmise that cancer-directed therapies that decrease pain and the need for analgesics might positively affect cancer patients' ability to work. On the other hand, treatments that are associated with high levels of fatigue might impair patients' ability to work. However, due to the lack of PRO data in the majority of clinical trials, we cannot draw any conclusions about the likelihood that an individual patient will experience decreased pain and/or be able to continue working while being treated with a specific regimen.

Despite the disappointing results of the study by Crown *et al.*, the push to include orally administered regimens in the armamentarium of therapeutics for metastatic breast cancer is encouraging and likely to continue. It would be useful going forward if investigators would include an assessment of quality of life as well as other relevant PROs among their study measures. Without such an assessment, we should ask ourselves how we would have incorporated the results of a similar study with positive results into our clinical practice and, indeed, how we might counsel patients. Crown *et al.* sought to demonstrate a 50% improvement in median PFS, from four to six months, with the combination

arm, deeming that such an improvement would be "clinically significant". Overall survival was a secondary endpoint in this study. Would we, as clinicians, feel comfortable recommending a treatment to our patients based on an improvement in progression-free but not overall survival without understanding the impact of either therapy on their quality of life? Indeed, PFS is sometimes cited as a surrogate for quality of life, but is it always? Using the data that are currently available in oncology, we are forced to make similar choices and guesses every day. Yet an alternative approach exists through which we could ultimately help our patients make more informed decisions.

PRO data are becoming increasingly standardized and easy to collect in the setting of a clinical trial. Basch *et al.* previously showed that patients undergoing chemotherapy can self-report symptoms using an online platform; more than 95% of patients and clinicians in their study were satisfied with the self-reporting system (12). Their research and that of other groups caught the attention of the Food and Drug Administration, which in 2009 issued a guidance document for use of PROs in the development of medical products and to support drug labeling (13). Basch *et al.* recently published recommendations in the *Journal of Clinical Oncology* for the incorporation of PROs into comparative effectiveness studies in adult oncology, including in randomized controlled trials (14). The inclusion of such measures could provide valuable insight into patients' experiences while undergoing treatment with commonly used and novel therapies. For example, in this study, although patients in the combination arm were more likely to experience hematologic toxicity, those in the single-agent arm had higher rates of hand-foot syndrome. From the perspective of a patient with metastatic breast cancer who is trying to continue to live a "normal" life, including maintaining commitments to family and to work, a lower rate of an uncomfortable and visibly disfiguring complication may be more important than a lower rate of thrombocytopenia without clinical sequelae. The inclusion of a quality-of-life measure in the study assessments would have given us a better understanding of the experiences of the patients in the two study arms. Had the trial been positive, this information would have been useful to oncologists and patients making decisions in the clinic.

Clinical trials are, by definition, patient-centered research, yet the patient experience during treatment remains incompletely understood. Our ignorance is an especially serious problem in the setting of treatment for metastatic disease. Until we demonstrate that we are able to cure patients with metastatic breast cancer, all treatment in this setting will remain palliative. As we strive to prolong our patients' lives, we cannot lose sight of the fact that one key goal should be to increase their comfort and the quality of their lives for whatever time they have remaining. The balance between these two goals is at the crux of how we practice every day in our clinics, and this same balance should be the focus of our clinical trials. The therapies we prescribe to our patients have toxicities that extend beyond what we as clinicians can see when we assess our patients, and it is our responsibility to advise patients of these toxicities when we discuss different treatment options and make clinical recommendations. However, we cannot hope to truly inform our patients if we do not have access to reliable toxicity information from clinical trials.

In their guidance document for use of PROs in drug labeling, the FDA asserted, "*Use of a PRO instrument is advised when measuring a concept best known by the patient or best measured from the patient perspective*". Based on this recommendation, many of the side effects currently reported by clinicians in the study setting, such as pain, nausea, and fatigue, should be reported by patients using accepted PRO measures. I would argue that such PROs should be incorporated into clinical trials regardless of whether or not one of these outcomes is the intended indication for drug labeling. We cannot expect this change to come from within the pharmaceutical industry, where the incentives may be different (unless we demonstrate the value of this approach to them). As clinicians, it is our responsibility to advocate for our patients by demanding that studies provide us with the information we need to make better and more informed recommendations. As researchers, it is our responsibility to ensure that clinical trials will yield the best information to advance the science of oncology, including not only our knowledge of biological targets but also our understanding of the real impact the treatments we study have on our patients' lives.

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References

1. Crown JP, Diéras V, Staroslawska E, et al. Phase III trial of sunitinib in combination with capecitabine versus capecitabine monotherapy for the treatment of patients with pretreated metastatic breast cancer. J Clin Oncol

2013;31:2870-8.
2. Abrams TJ, Murray LJ, Pesenti E, et al. Preclinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with "standard of care" therapeutic agents for the treatment of breast cancer. Mol Cancer Ther 2003;2:1011-21.
3. Banerjee S, Dowsett M, Ashworth A, et al. Mechanisms of disease: angiogenesis and the management of breast cancer. Nat Clin Pract Oncol 2007;4:536-50.
4. Goswami S, Sahai E, Wyckoff JB, et al. Macrophages promote the invasion of breast carcinoma cells via a colony-stimulating factor-1/epidermal growth factor paracrine loop. Cancer Res 2005;65:5278-83.
5. Paulsson J, Sjöblom T, Micke P, et al. Prognostic significance of stromal platelet-derived growth factor beta-receptor expression in human breast cancer. Am J Pathol 2009;175:334-41.
6. Tsuda H, Morita D, Kimura M, et al. Correlation of KIT and EGFR overexpression with invasive ductal breast carcinoma of the solid-tubular subtype, nuclear grade 3, and mesenchymal or myoepithelial differentiation. Cancer Sci 2005;96:48-53.
7. Novantrone: mitoxantrone for injection concentrate. Silver Spring, MD, Food and Drug Administration, 2008.
8. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. J Clin Oncol 1999;17:2506-13.
9. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996;14:1756-64.
10. Hewitt M, Greenfield S, Stovall E, eds. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C. The National Academies Press, 2006.
11. Glare PA, Alickaj A, Blinder VS, et al. Survey of palliative care patients WHO work. J Clin Oncol 2013;31:abstr e20677.
12. Basch E, Artz D, Iasonos A, et al. Evaluation of an online platform for cancer patient self-reporting of chemotherapy toxicities. J Am Med Inform Assoc 2007;14:264-8.
13. Guidance for industry—patient-reported outcomes measures: use in medical product development to support labeling claims. Silver Spring, MD, Food and Drug Administration, 2009.
14. Basch E, Abernethy AP, Mullins CD, et al. Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. J Clin Oncol 2012;30:4249-55.

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