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RESEARCH

Patient Reported Outcomes in Metastatic Breast Cancer Studies: Evaluating the Impact of the FDA Guidance for Industry

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Introduction: Over the last two decades, a number of new therapies have demonstrated improved overall survival in metastatic breast cancer (MBC) [10]. Despite these advances, MBC remains incurable with a median survival of less than three years [7, 10, 11, 15]. Prolonging survival and maintaining quality of life (QoL) continue to be the central goals of therapy. Unlike the early stages of breast cancer, the management of MBC is less clearly defined, with no specific treatment recognized as the standard of care [15]. Several studies have sought to determine an optimal regimen for the management of MBC with aims to prolong survival, however relatively few adequately powered studies have directly addressed QoL [8].

Patient reported outcomes (PROs) are instruments used to elicit the patient experience thereby gaining insight into a particular health state and aiding in the assessment of QoL [5]. As the prevalence of PROs grew, the FDA released in December 2009 an industry guidance on the implementation of PROs in clinical trials for the development of medical products and to support labeling claims [1]. This study was undertaken with aims to evaluate the impact of the FDA guidance on the use of PROs as standard endpoints in randomized phase two or three clinical trials assessing therapeutic options in MBC.

Methods: Clinicaltrials.gov's advanced search tool was used to capture registered interventional phase two or three clinical trials in adult patients with MBC conducted in the United States that began recruitment between January 1, 2002 and December 31, 2017. Trials with QoL or PROs listed as primary or secondary endpoints on Clinicaltrials.gov were subsequently identified. Segmented regression analysis of the interrupted time series data [18] was used to estimate dynamic changes pre and post adoption of the FDA guidance.

Results: A total of 677 studies were identified, 72 of which used PROs. Prior to adoption of the FDA guidance, there is a nonsignificant trend towards increasing PRO use at a rate of 0.4% per year ($p > 0.05$). At the time of adoption, there is a one-time nonsignificant increase of 0.6% in PRO use ($p > 0.05$). After adoption, there is a nonsignificant trend towards decreasing PRO use at a rate of 0.3% per year ($p > 0.05$).

Discussion: Our study results demonstrated that despite the FDA guidance, there has been little change in the use of PROs as endpoints in MBC studies. This missed opportunity to elicit the patient experience inherently limits evidence often used to counsel patients and support their decision-making framework as they focus on their priorities in selecting treatment options.

Keywords: Breast cancer; Metastatic; Patient Reported Outcomes; Oncology; Quality of life

Although the importance of QoL to cancer patients is established [19], this has yet to translate into increased PRO implementation. Commonly used provider graded adverse event criteria do not necessarily provide enough information on the change in QoL experienced as a consequence of therapy. To better inform decisions made by patients and providers, understanding the impact of treatment on the patient experience is essential and can be facilitated through the use of PROs.

While many studies did not include PROs, some recent trials that have explored targeted therapies such as oral cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) inhibitor palbociclib and oral poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitor talazoparib have demonstrated some improvement in QoL and increased time to definitive clinically meaningful deterioration [12, 14]. The inclusion of PROs in these studies allowed for the investigators to demonstrate that in their case prolonging progression-free survival was coupled with maintenance of QoL. These significant findings are particularly appreciated when these regimens are implemented into clinical practice. Responding

to questions spanning from physical and emotional function to pain, nausea, vomiting and hair loss from the patient's perspective is made possible by the implementation of these PROs. Conveying the true overall impact of treatment on a patient's wellbeing, beyond clinician reported toxicities, allows physicians to better address some of most pressing concerns patients have when considering treatment options.

Previously reported barriers to implementing PROs in clinical research include engaging providers, the concern of burdening existing workflows, the need for additional staff and increasing costs [3, 4]. Discordance between regulators and industry has also surfaced as a potential challenge [6]. Furthermore, the availability of culturally appropriate validated instruments in languages other than English is another barrier to consider. To overcome these barriers, the concepts of PROs and QoL should be incorporated in educational curricula focusing on patient centered care in preparation for these complexities encountered while engaging in shared decision-making. Groups such as Basch et al. [5] have since published recommendations specifically addressing the implementation of PROs in clinical trials in adult oncology with aims to further engage providers, regulators and payers. Since 2009, the FDA has held disease-specific patient-focused drug development meetings to more systematically gather patients' perspectives [2]. In addition, the American Society of Clinical Oncology has subsequently held webinars and workshops intended for providers on the use of PROs in clinical research [13, 17]. The use of electronic PROs and standardized measures through initiatives such as The National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS) [9] may help surmount logistical barriers to implementation. Providing culturally appropriate instruments in languages other than English may continue to be a barrier as the adaptation process can be lengthy and costly [16].

Study limitations include the possibility of implementation delay following the FDA guidance and the lack of inclusion of PROs as an endpoint in Clinicaltrials.gov's registry used to collect this data. It is perhaps too soon to fully appreciate the impact of the FDA guidance and subsequent physician led efforts given the possibility of lag time between policy publication and implementation. The time frame used of eight years pre and eight years post adoption of the FDA guidance may limit the ability to capture a meaningful trend. The provision of additional time points in future studies could strengthen the statistical analysis and interpretation of this data.

Conclusion

The FDA Guidance for Industry has yet to translate into significant intermediate term growth in the use of PROs as endpoints in phase two or three studies assessing therapeutic options in MBC. The use of PROs in future clinical trials is necessary to quantify outcomes and allow providers to address issues of importance to patients suffering from MBC.

Competing Interests

The authors have no competing interests to declare.

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