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Letter to the Editor

Technology and its interventional value in patient-reported outcomes in cancer research, what is next?

Sir,

For cancer patients, health-related quality of life (QOL) is a critical aspect of care management decision-making. In some cases, clinicians have even prioritized QOL over survival in patients with advanced cancer.[1] Over time, patient-reported outcomes (PRO) have gained prominence in cancer research to capture aspects of a patient's health condition, reported directly by the patient through a questionnaire through scales validated in different moments. PROs are currently used as a research tool in clinical trials for cancer drug development to monitor and assess the psychological and cognitive well-being of patients and detect significant symptoms.[2] In addition to QOL, several studies have suggested that PROs also improve patient outcomes and satisfaction.[3] Retrospective analyses have shown that QOL and its early palliative care are a prognostic factor for survival in cancer patients.[4-6] Although, such results were not confirmed by others who have reported after a systematic review of 24 controlled trials a limited statistically significant impact of PRO, and that the effect sizes of interventional PROs were small to moderate.[7]

Over the last two decades, there has been an introduction of the electronic form of PRO (ePROs) which elicits greater subject compliance by collecting information on side effects and medication time recorded on an electronic device than paper questionnaires. One of the main benefits of ePROs is the user-friendly platforms for patient self-reporting, such as phones, tablets and computers. Touchscreen-based devices have become the mainstay for remote PROs data collection in clinical trials. Some providers also offer an ePROs app that can be downloaded to patients' smartphones with the ability to take photos or videos and include personalized features to improve patient adherence by tailoring educational information and integrating patient reminder alerts. In addition, many ePROs systems can provide summary reports to patients' electronic health records and trigger real-time email alerts when patients report acute needs. ePROs can also improve communication between patients and doctors around the discussion of symptoms and QOL.[8]

Symptoms are the main component of QOL and are closely monitored by clinicians to assess response, relapse, and toxicity among patients receiving cancer treatment.[9] In some malignancies, symptoms such as loss of appetite and pain have been recognized as a prognostic factor for survival.[4] The hypothesis underlying the association between symptoms and survival is that the symptoms reported are not captured with traditional medical tests which may cause a delay in the diagnosis of progression and early treatment when tumour load and resistance is low. In that regard, and interestingly, the benefit of technology for close self-reporting and medical management of symptoms and better treatment compliance has contributed to the outcome of cancer patients demonstrated in two prospective, randomized clinical trials. In one study, memorial sloan Kettering cancer center in New York conducted a randomized trial in which patients reported 12 common symptoms between visits through a web-based PRO questionnaire platform. Patients with home computers received weekly email notices to report between visits. When participants in the PRO group reported a severe or worsening symptom, an email alert was sent to a clinical nurse responsible for that patient's care. Treating physicians received printouts of symptoms at visits, and nurses received email alerts when participants reported severe or worsening symptoms. The results showed that patients in the intervention group were hospitalized or admitted to the emergency room less often and stayed on chemotherapy longer than usual care. The study reported a statistical difference in which 75% of the intervention group versus 69% with usual care were alive at one year.[10] Overall survival analysis was assessed after the death of 517 of 766 participants (67%), at which time the median follow-up was seven years. Median overall survival was statistically different, with 31.2 months reported in the experimental arm versus 26.0 months in the control arm.[11] In another prospective, randomized, multi-institutional phase 3 study using a monitoring web application in which lung cancer patients self-assessed symptoms after surgery, chemotherapy, or radiation therapy collected weekly via smartphone (experimental group) compared with patients who were for routine clinical evaluation with computed tomography (control arm). Development of a web application helped detect symptomatic relapses, complications, and early supportive care in high-risk lung cancer patients between visits. Survival was 86.6% in the experimental arm and 59.1% in the control arm at one year, with a median survival of 16.7 months in the control arm and 22.4 months in the experimental arm, respectively.[12]

The transition from paper questionnaires to ePRO data collection systems has enhanced the integrity and accuracy of data collected in clinical trials.[13] According

to recent publication of prospective trials, the interventional value of ePROs for the early detection of progression-related symptoms correlates with survival. This information creates a paradigm which need a careful attention in the clinical development of new anticancer drugs. One caveat is that since the publication of these studies, no more comparable data have been published investigating how to achieve these goals. In a report from the 5th EORTC QOL in clinical cancer trials conference, 2019, together researchers, regulators, industry representatives, patients and patient advocates as well as health care professionals stated there were no standards, even in clinical trials, for PRO measurement, analysis and reporting, and a major issue on how to ensure that the right questions are asked, and the right answers are communicated.[14] There is also no doubt that improved technology and greater flexibility in measurement instruments are making PRO data more robust. However, many questions remain for further investigation for a better understanding of the survival value of ePRO in cancer research. For example, what symptoms should be reported and the standardization for PRO measurements to different type of malignancies? The type of malignancy, setting and treatment included in the trial? The impact of asymptomatic progression on study design? The risk of misinterpretation of by treating physician of a symptomatic progression when there is no radiological confirmation and the decision when to start further anti-cancer treatment of patients based solely on symptoms? Access to and use of technology for patient self-report of symptoms? The multicomponent approach together with prognostic biomarkers? In short, there is still a lot of research to be done on what technology can do to make PROs of significant value. In that context, developers should also consider stratifying the use of ePROs to report symptoms in their interventional clinical trials to recognize their significance and eventually enhance patient survival treated with new anticancer compounds.

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