EDITORIAL

Symptom Monitoring With Patient-Reported Outcomes During Pediatric Cancer Care

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Over the past 5 decades, clinical outcomes have significantly improved for children with cancer through the availability of new treatment regimens.[1] However, these advancements come with treatment-related symptomatic toxicities such as nausea, fatigue, and pain that often go undetected by care teams, leading to preventable suffering and avoidable downstream consequences such as hospitalizations.[2]

Consider the true case of a grade school-aged child cared for at one of our institutions and cured of an aggressive metastatic solid tumor following surgical resection, radiation, and chemotherapy. Despite receiving otherwise excellent treatment, the child experienced ongoing pain, nausea, vomiting, and decreased appetite while at home between chemotherapy administrations. The parents did not reach out to the care team about these symptoms between visits, and when the child was ultimately admitted to the hospital for severe dehydration, the parents noted that they were uncertain about when it would be appropriate to call the office as they did not want to bother the team.

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To improve detection of symptoms in children receiving cancer treatment, and thereby improve quality of care for patients like the child in the above anecdote, systematic monitoring with electronic-based patient-reported outcome (ePRO) surveys and, in some cases, caregiver observer-reported outcome surveys has been suggested.[3] This approach generally entails use of a web-based system that sends regularly scheduled reminders to patients and/or their caregivers (depending on the child's age) to complete symptom surveys. Symptom scores above a predetermined threshold on these surveys trigger alert notifications to the care team to inform clinical actions at the discretion of the team. Prior research of this approach in adult cancer populations has demonstrated improvements in symptom control, health-related quality of life, hospitalization rates, and, in some cases, survival.[4] However, to our knowledge, there have not been multicenter evaluations of this approach in pediatric cancer populations.

Two clinical trials reported by Dupuis and colleagues in the current issues of *JAMA*[5] and *JAMA Pediatrics*[6] provide such evidence. In the first trial,[5] 20 US pediatric oncology practices were cluster randomized to receive either an ePRO symptom monitoring intervention or usual care control. Enrollment included 445 children aged 8 to 18 years undergoing systemic cancer treatment. Patients in the intervention group received ePRO symptom surveys 3 times per week, with notification alerts to care teams for concerning symptoms that also included management recommendations.

The protocol-specified primary outcome was the 8-week mean difference between the groups in the validated Symptom Screening in Pediatrics Tool (SSPedi) score, which captures 15 symptoms that are aggregated into a single score ranging from 0 to 60 points. The authors reported a statistically significant 3.8-point (95% CI, 1.2-6.4) mean score difference in this metric in favor of the intervention group. This difference remained favorable for the intervention after adjusting for an imbalance in baseline scores (which the authors attributed to symptom management pathways that were implemented before baseline in sites assigned to the intervention group only), with a mean difference of 3.0 points (95% CI, 0.8-5.2). Benefits were even greater for individual symptom scores from the SSPedi in favor of the intervention, with the largest differences for pain, neuropathy, vomiting, and cognitive function. No differences were seen in the secondary outcome of quality of life, which is not a surprise because this is a broad outcome that frequently does not change in ePRO trials. Similarly, it was not surprising to see no differences in fatigue, because this symptom is not typically targeted by medication interventions, so it would not be expected to change substantially with a symptom monitoring intervention.

There are a several minor concerns about the design of this trial. First, it is not clear why symptom management pathways were implemented only at intervention sites, and why they were implemented prior to baseline outcome assessments. Ideally, these would have been implemented at all practices and started after baseline. The approach used in this trial leaves open the question of how the symptom pathways may have affected differences between practices independent of the ePRO intervention. Given this approach, symptom management pathways may be considered an integral component of the intervention. Second, it is not known what mean score differences in the SSPedi are clinically meaningful.[7] The protocol did prespecify 3 points as a minimal clinically important difference as the basis for power calculations (equivalent to a 5% difference on the SSPedi scale), which the trial achieved. Future research could evaluate what SSPedi score thresholds are clinically meaningful using appropriate anchors including patient input. It is worth noting that a 5% difference in mean scores that results from a nontoxic intervention such as ePROs that affects symptom control might on its face be considered meaningful. Third, there was a small excess in emergency department visits in the intervention group of unclear etiology; it is possible that these were appropriate admissions based on intensified symptom monitoring or were due to imbalances in

practice patterns between practice clusters. This finding is contrary to research in adult populations, in which ePRO monitoring generally decreases emergency department visits, and therefore future work is warranted in this area.

In the second trial,[6] 345 children receiving ambulatory or inpatient cancer treatment at 8 practice sites were randomly assigned either to receive the ePRO intervention described for the above trial or to usual care. Symptom management pathways were implemented at all participating sites. The protocol-specified primary end point was mean difference between groups in the SSPedi score at day 5. Findings included a 2.5-point (95% CI, 1.2-3.8) mean difference in this metric in favor of the ePRO intervention. Differences in individual SSPedi symptom scores also favored the intervention.

Again, it is not known what SSPedi score mean difference is clinically meaningful. The slightly smaller score difference compared with the other trial may have been related to implementation of symptom management pathways in both groups (which may have led to improved scores for all patients) or to contamination from the intervention group to the control group because randomization was at the patient level (ie, greater vigilance for symptom control). As with the other trial, a lack of difference in quality of life between groups was not surprising. However, a lack of difference in pain between the groups was surprising, given observed benefits in the above and prior ePRO trials, and may have been related to the brief timeframe of this trial.

Taken together, these 2 trials provide compelling evidence that ePRO symptom monitoring confers benefits on symptom management for children receiving cancer treatment. The authors are to be congratulated on the conduct of these complex trials in the service of improving the experiences of children with cancer. As future steps, adjustments to the implementation approach to optimize these benefits could be explored with a goal to further increase the benefits and usability of the intervention.[8] For example, the ePRO software could be integrated with electronic health record systems to ease access to notifications by the care team. Use of patient-friendly modes of survey administration, such as automated telephone interfaces, could be added to increase uptake by populations with limited internet access, restrictive data plans, visual impairment, or limited literacy. Automated advice to patients and caregivers for self-management could be triggered when concerning symptoms are reported. Caregiver reporting could be added as an option to increase contextual information for care teams or serve as a backup when children are unable to self-report. This includes the extension of routine symptom monitoring to children younger than 8 years when children may need assistance from their caregivers or the caregivers can report based on what they observe in the children.[9] More broadly, increasing the use of navigation services during pediatric cancer care would likely further improve symptom management outcomes as it has in adult populations.[10]

These trials in *JAMA* and *JAMA Pediatrics* are practice-changing and provide the first level 1 evidence in children of the benefits of remote symptom monitoring with electronic patient-reported outcomes on clinical outcomes. Now that this evidence exists, adding to the literature of benefits among adults with cancer,[4] the next steps will be development of implementation guides and widely available software to help practices adopt this approach.[11] In the service of alleviating the symptoms of children with cancer and bringing the voice of the child into cancer care, these studies have taken a meaningful stride.

ARTICLE INFORMATION

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