Jennifer A. Belsky*, DO, MS, Joseph R. Stanek, MS and Melissa J. Rose, DO

Investigating the safety and feasibility of osteopathic medicine in the pediatric oncology outpatient setting

https://doi.org/10.1515/jom-2021-0246
Received October 7, 2021; accepted March 22, 2022; published online April 15, 2022

Abstract

Context: Pediatric patients receiving chemotherapy experience unwanted therapy-induced side effects, commonly constipation and pain that diminish quality of life. To date, few studies have investigated the safety and feasibility of osteopathic manipulative treatment (OMT) in pediatric oncology.

Objectives: The primary objective of this study is to investigate the safety and feasibility of OMT in pediatric oncology outpatient clinics.

Methods: This is a single institutional pilot study evaluating children aged ≥2–21 years receiving chemotherapy for an oncological diagnosis at Nationwide Children’s Hospital (NCH). Permission was obtained from the NCH Institutional Review Board. Participants were enrolled for 8 weeks and received weekly OMT. OMT was deemed feasible by participating in six out of eight weekly treatments, and safety was assessed through adverse event grading per Common Terminology Criteria for Adverse Events (CTCAE). During the clinic visit, participants answered validated surveys on constipation (Bristol Stool Scale) and pain (FACES Scale) pre/post-OMT. Feasibility was analyzed utilizing a one-sided exact binomial test while validated tools and adverse events were summarized descriptively.

Results: A total of 23 patients were enrolled, with 21 included in feasibility analyses. The majority of the patients were female (n=13, 61.9%), with a median age of 12 years at enrollment (range, 2.7–20.8 years). There were no serious adverse events attributed to OMT intervention, and among the patients assessed for feasibility, 100% of them participated in at least two-thirds of their weekly OMT treatments, meeting our defined feasibility criteria. The intervention lasted an average of 14.2 min (range, 7.2–19.2 min). There were no FACES or Bristol Stool Scale scores that correlated with worsening pain on constipation post-OMT intervention.

Conclusions: Pediatric oncology patients were feasibly and safely able to receive OMT during a regularly scheduled chemotherapy visit. The limitations include the small sample size. These findings support the need to further investigate the safety and feasibility, as well as efficacy, of OMT in the pediatric oncology clinical setting.

Keywords: osteopathic manipulative treatment; pediatric oncology; supportive care.

Survival rates for childhood cancer continue to rise, yet the side effects and long-term sequelae of anti-cancer chemotherapy remain areas of concern in pediatric oncology. Children experience numerous unwanted side effects secondary to chemotherapy, radiation, and prolonged hospitalizations. Common chemotherapy side effects include constipation, pain, nausea, vomiting, and fatigue [1], Vincristine, one of the most commonly utilized chemotherapeutic agents in leukemia treatment, has the highest potential for chemotherapy-induced constipation [2]. Pharmacologic interventions utilized to combat side effects each come with their own potential side-effect profile. Numerous supportive care studies have demonstrated a need for improved therapies to prevent these side effects, improve symptom control, and in turn improve overall quality of life in oncology patients [3, 4].

Osteopathic medicine is a distinct form of medical practice, defined by the National Center for Complementary and Integrative Health as a “mind and body” complementary method that offers the added benefit of a hands-on approach to the diagnosis and treatment of many medical conditions [5]. Osteopathic manipulative
treatment (OMT) incorporates techniques such as gentle stretching and manipulation to target specific muscle and nerve groups [6]. Many research studies have published the utility of OMT in noncancer patients by demonstrating reduction in reported pain [7, 8], decreasing constipation [9, 10], reducing cost, decreasing length of hospitalizations [11], and improving quality of life [12].

A recent administrative database study of 4,647 pediatric patients with acute lymphoblastic leukemia (ALL) identified that 81% of patients in induction therapy were diagnosed with constipation and required medical intervention [13]. Current treatment options for chemotherapy-induced constipation include both pharmacologic and nonpharmacologic therapies. Nonpharmacologic interventions include increased physical activity, increased fluid and fiber consumption, as well as eliminating medical factors that may be contributing to constipation. These interventions pose unique challenges in children with cancer as a result of nausea, prolonged hospitalization, poor oral intake, and decreased mobility with fatigue. OMT studies focusing on constipation in the adult noncancer patient populations have demonstrated statistical significance in the improvement of severe constipation with overall symptom reduction and the potential to decrease abdominal pain, bloating, and drug use in pilot studies [14, 15].

Within the oncology population, the need for alternative therapies to combat chemotherapy side effects is evident from both patients and clinicians, however, published literature on the effects of OMT in the adult oncology field is sparse [16, 17]. A qualitative study investigating 16 patients found that when delivered alongside existing medical care, osteopathic medicine may have health benefits for patients with complex conditions such as cancer [17]. To date, few studies have explored adjunctive osteopathic therapies in pediatric oncology patients. Our recent needs assessment in the pediatric oncology field demonstrated that the majority of pediatric oncology clinicians, patients, and caregivers are interested in further OMT research, specifically for its use in managing constipation and pain [16]. Given the paucity of OMT research in the field, we investigated the safety and feasibility of an 8-week OMT intervention in outpatient pediatric oncology patients, and we explored potential changes in reported pain and constipation.

**Methods**

This prospective, single-institution pilot study from September 2019 to August 2020 evaluated children aged 2–21 years receiving chemotherapy for an oncologic diagnosis at Nationwide Children’s Hospital (NCH). This study was approved by the NCH Institutional Review Board. All participants in this study were provided written informed consent/assent prior to participation. The inclusion criteria included: (1) patients aged ≥2 years to ≤21 years as study tools for the assessment of constipation and pain validated for this age group; (2) patients currently receiving chemotherapy for a confirmed oncologic diagnosis; (3) patients who scheduled weekly clinic visits in the 2 months following enrollment; and (4) patients scheduled to receive at least one dose of vincristine during the study time period. The exclusion criteria were: (1) pregnant or breastfeeding women, due to the lack of data of OMT in pregnant oncology patients; (2) prior malignancies or pre-existing conditions including, but not limited to, inflammatory bowel disease, diabetes, chronic pain syndromes, chronic neuropathic pain, trisomy 21, and additional genetic conditions, which were excluded due to the potential for confounding variables; and (3) the inability to comprehend survey tools due to the language barrier.

Potential patients were screened by a member of the research team for eligibility at weekly oncology team meetings. Patients were approached for enrollment during a previously scheduled, routine chemotherapy clinic visit in the ambulatory clinic setting. A brief video (Supplemental 1) demonstrating the concept of OMT was shown to interested patients and caregivers, along with a script detailing OMT (Supplemental 2). Informed assent/consent was obtained at enrollment.

**Intervention**

The total study duration consisted of 10 total weeks. Following enrollment, patients were approached to receive OMT at scheduled clinic visits for eight consecutive weeks. Osteopathic intervention lasted a maximum time allotment of 20 min per visit and was performed by a single osteopathic physician to ensure uniformity across visits and patients. A research team member administered validated constipation and pain scales. Participants were given an encrypted Apple iPad and completed pre- and postintervention surveys without research team assistance. These surveys consisted of the FACES pain scale and detailed questions about their bowel habits including the Bristol Stool Scale. The Bristol Stool Scale is a validated constipation scale utilized by participants ≥6 years of age for self-reported symptoms or reported by caregivers for children <6 years of age and administered at each visit prior to OMT [18]. It consists of scores 1–2 indicating clinical constipation, 3–4 representing normal stool, and 5–6 describing loose stool taking no more than 1 min to complete. The FACES pain scale was administered prior to OMT intervention to assess pain before OMT, and again after OMT to assess posttreatment pain, taking 10–30 s to complete [19]. The FACES pain scale is validated for children aged ≥3 years of age for self-reporting, and caregiver reporting for children <3 years of age [19]. Concomitant medications were updated at each visit, including details of as-needed medication use in the past week. Following each intervention visit, the charge nurse and bedside nurse were asked to complete a brief questionnaire via REDCap regarding interruptions in workflow. If a patient was admitted to an inpatient service or intensive care unit, OMT was not offered that week to maintain true feasibility of an outpatient intervention. Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes, and general supportive care including massage and physical therapy were utilized as clinically indicated by their primary medical team.
Osteopathic techniques

OMT consisted of myofascial release, muscle energy, balanced ligamentous tension, and visceral manipulation. Due to the collateral ganglia in the abdomen influencing regional visceral dysfunction, visceral manipulation included a ventral abdominal release and inhibitor pressure directed at the celiac, superior, and inferior mesenteric ganglia. Lymphatic pump and high velocity, low amplitude (HVLA) techniques were excluded due to the small hypothetical risk of inducing metastasis by increasing lymphatic flow in patients with assumed microscopic disease, and to protect the bony skeleton in patients receiving steroids and presumed decreased bone density [20].

Study endpoints

For the purposes of this study, feasibility is defined as the ability to incorporate OMT intervention into regularly scheduled chemotherapy outpatient appointments. Oncology clinics are multidisciplinary and require coordination between many providers, nurses, and administrative staff. The primary feasibility endpoint was defined as the percentage of patients that were available and agreed to receive OMT at two of their three ambulatory visits over the total 10-week study period. There are no previously published data to guide the definition of feasibility, therefore two of their three visits were decided among the study team to represent feasibility based on the belief that completion of over half of the eligible visits: (1) would indicate a reasonable degree of patient interest in receiving treatment, (2) show evidence of the flexibility to schedule OMT sessions without disruptions to the regular clinic workflow, and (3) may warrant further research in the benefit of investing hospital staff and resources to implement OMT as a supportive-care option for patients into oncology clinics. Safety outcomes were assessed at each study visit according to the required adverse event reporting tool, Common Terminology Criteria for Adverse Events (CTCAE) criteria, as mandated by the National Cancer Institute (NCI) [21].

Sample size

With an a priori goal of 23 enrolled subjects, there was approximately 80% power to detect if the percentage of subjects who agree to two of their three offered OMT treatments would be significantly greater than 50% utilizing a one-sided exact binomial test with a 5% type I error and an effect size of 25% (i.e., H0:50% of patients agree to at least two out of three OMT treatments vs H1:75% of patients agree to at least two out of three OMT treatments).

Statistical considerations

The proportion of subjects who agreed to two of the three offered OMT treatments was summarized and presented with a corresponding exact binomial 95% confidence interval, and the primary hypothesis was tested utilizing a one-sided exact binomial test. Descriptive statistics were utilized for additional safety and feasibility analyses. To be included in the safety analysis, patients must have received at least one OMT intervention. The feasibility analysis included patients who were eligible for at least six clinic visits. Adverse effects were noted at each study visit. The survey tools utilized included the Bristol Stool Scale for constipation and the FACES pain scale. A nonvalidated questionnaire was utilized to assess clinic flow and nursing views to better understand the feasibility of incorporating OMT in the clinic. The length of clinic visits, frequency of adverse events, nurse assessments of clinical flow, and patient satisfaction scores were summarized descriptively. All p values are two-sided and those less than 0.05 were considered statistically significant. Statistical analyses were performed utilizing SAS software, version 9.4 (SAS Institute, Cary, NC) or the base R statistical package (R Foundation for Statistical Computing, Vienna, Austria).

Results

Participant characteristics

A total of 30 patients were screened for eligibility, 24 patients met the eligibility criteria, and 23 total patients were enrolled into the study, with one patient declining enrollment due to possible transfer of care outside of the state. The majority of patients were female (n=13, 56.5%), with a median age of 12 years at enrollment (range, 2.7–20.8 years). Patients had a variety of cancer diagnoses including leukemia (n=9, 39.1%), lymphoma (n=7, 30.4%), sarcoma (n=6, 26.1%), and neuroblastoma (n=1, 4.3%). Patient characteristics are summarized in Table 1.

Primary outcome safety

Patients exhibited adverse events prior to enrollment secondary to chemotherapy treatment, such as deep vein thrombosis, leg pain, and constipation. None of these prior conditions were noted to be exacerbated while the patients were in the study. No patient developed a serious adverse event, per the NCI guideline criteria, that was attributed to OMT (Figure 1). Unrelated adverse events including Clostridium difficile (n=1), typhlitis (n=1), and fatigue and...
nausea (n=1) were observed and attributed to expected disease and/or chemotherapy side effects.

**Primary outcome feasibility**

Of 23 enrolled patients, two were not included in the feasibility and safety analysis due to not having at least six evaluable visits. One patient withdrew shortly after enrollment per parental request, and one patient became ineligible prior to the first visit due to alteration in therapy that no longer included vincristine. Thus, a total of 21 patients were eligible to complete at least six visits and were included in feasibility analysis. All (100%) patients agreed to OMT in at least two of their three available treatment weeks (Figure 1), which is significantly greater than the null hypothesis of 50% of patients (p<0.0001). Among the 21 patients included in feasibility analysis, three patients were unable to complete the final three study visits – one patient was taken off study due to discontinuation of chemotherapy and transitioned to palliative care, and two patients’ final study visits were impacted by the COVID-19 pandemic. The majority of the missed OMT intervention studies were secondary to either canceled clinic visits due to chemotherapy-induced myelosuppression, or the OMT physician was unavailable to see the patient due to other commitments.

OMT intervention lasted an average of 14.2 min (range, 7.2–19.2 min). No bedside or outpatient charge nurse had concern for delays with clinic workflow during the visits. No patient was detained past their expected visit time to complete study requirements.

**Descriptive patient reported data**

Among the 148 total Bristol Stool Scales collected, the median was 3 at both the first and final visits. Nearly all patients (17 patients, 37 individual visits) had at least one occurrence of self-reporting no constipation although their Bristol Stool Scale indicated the presence of constipation with score of 1 or 2. However, there were no instances in which patients self-reported constipation but the score was reported as a 3 or greater. Overall, there was disagreement in 25% (37/148) of self-reported constipation and Bristol Stool Scale scores. When known, patients reported that
they had a stool within 24 h after the previous OMT intervention at nearly every visit. Median FACES scores pre- and post-OMT were both 0. In 51 study visits, the FACES pain score decreased after OMT compared to the reported pain score prior to receiving OMT. There were zero instances in which the FACES pain score increased following OMT.

**Discussion**

The aim of this study was to examine the safety and feasibility of an 8-week OMT intervention in outpatient pediatric oncology patients and to explore the potential treatment benefits on pain and constipation. There were no serious adverse events per CTCAE criteria attributed to OMT intervention, and 100% of the patients with at least six study visits participated in two of their three weekly OMT treatments, meeting our defined feasibility criteria. In addition, both the bedside and charge nurses reported no interruptions or delays in their routine patient care. Furthermore, following OMT, all patients had improvement in their pain and constipation scores.

In pediatric oncology, as in most ambulatory clinics, patient satisfaction is directly correlated to wait times [22]. Our previous needs assessment regarding integration of OMT into pediatric oncology supportive care demonstrated concerns with feasibility regarding implementation into ambulatory clinics [4]. Although oncology ambulatory clinics operate differently with an ever-changing workflow, anecdotally, patients and caregivers have unwanted downtime, without medical staff present or interventions occurring. As an institutional baseline, the average oncology clinic visits at NCH last approximately 80 min. The average OMT intervention time in this study was 14.2 min, which is a relatively feasible timeframe to incorporate into a routine clinic visit. Comparatively, external ambulatory clinics have published longer wait times, with average clinic visits ranging between 94 and 140 min [22, 23]. OMT can feasibly be integrated into this clinic time and potentially improve satisfaction as patients wait for their primary provider to see them, accessing central lines, labs to result, chemotherapy, and/or blood product administration.

Current supportive care measures alone are frequently insufficient in treating pediatric chemotherapy side effects, particularly pain and constipation [24, 25]. As with a majority of pharmacologic interventions, constipation and pain medications come with an array of unwanted side effects. Descriptively, no patient had worsening pain post-OMT intervention, and at nearly all study visits, the patients (or their caregiver) reported having a bowel movement within 24 h of the previous OMT visit. It should be noted that there was one patient who opted to withdraw their enrollment after the initial visit because the patient was unable to tolerate the OMT intervention secondary to medical anxiety, thus this intervention may be best suited for patients without anxiety.

The evidence regarding the efficacy of pediatric constipation medications is lacking. A previous meta-analysis assessing the adverse events of pediatric patients receiving polyethylene glycol reported adverse events including diarrhea, abdominal pain, nausea or vomiting, pain or straining at defecation, bloating or flatulence, hard stool consistency, bad palatability, and rectal bleeding [26]. It has been reported that stimulant laxatives have caused up to 72% of patients to experience similar side effects, with diarrhea and abdominal pain cited most frequently. Additionally, stimulant laxatives are approved for short-term use (no longer than 4 weeks), and the prolonged use of these agents is associated with long-term negative colonic effects [27]. Most medications to treat constipation are oral formulations, which can be problematic for patients unable to swallow or tolerate oral medications due to mucositis or nausea. Oncology patients are also often too fatigued or weak to perform any reasonable physical activity in an attempt to improve their gastric motility. Furthermore, side effects such as mucositis, anorexia, and nausea can be barriers to incorporating increased fluid and fiber consumption, leaving patients without a viable option to help with their constipation.

Interestingly, a quarter of patients had a discrepancy with regard to their perception of constipation and the validated Bristol Stool Scale score, suggesting they were clinically constipated despite their perceived bowel habits. This highlights a concern of whether oncology patients and caregivers are (1) appropriately educated regarding signs and symptoms of constipation, (2) comfortable knowing when to administer as-needed constipation medications, and (3) discussing their bowel habits and regimens with their clinician appropriately.

Regarding pain, opioids are commonly a necessity for patients suffering from mucositis or postsurgical pain. Side effects are common and can result in constipation, pruritis, sedation, urinary retention, and respiratory depression. In addition, nonopioid pain medications have a wide range of side effects ranging from hepatotoxic effects from acetaminophen to limiting platelet defects with nonsteroidal anti-inflammatory therapies [28]. OMT techniques in this pilot study were well tolerated by most patients and could provide a favorable safety profile to supplement or reduce the need for pharmacologic therapies and the associated side effects.
The literature reports increased compliance, adherence, and outcomes when chemotherapy side effects are controlled in children. Pediatric patients, particularly those ≥9 years of age, dislike taking oral medications, leading to poor adherence to therapy [29]. In conjunction with uncontrolled side effects, there are many non-pharmacologic, supportive-care options including OMT that could potentially improve medication adherence [30, 31], particularly as interest in complementary medicine options in pediatric patients continue to increase [32]. As oncology clinicians, caregivers, and patients increasingly utilize nontraditional therapy options, further scientific studies must be conducted to ensure the safety, feasibility, and efficacy of such treatments, including OMT.

Limitations

Despite promising findings, the authors acknowledge the limitations of the study. This is a small sample size, singleinstitutional study that may not be representative of the wider pediatric oncology population or other oncology clinics. Nonetheless, our study was able to include a wide range of patients in age and cancer diagnoses.

Another limitation was that the lead investigator was an osteopathic physician, which could lead to implicit bias from patients. To best negate this, all quantitative survey tools and question responses were blinded and analyzed at the end of the study. We recognize the many limitations to descriptive analyses of OMT effects on constipation and pain, including modification of the prescribed bowel regimen, other supportive care modalities including massage and physical therapy, home diet implementations, recall bias with post-OMT bowel movements, and most notably the fact that patients receive different chemotherapy regimens with various timing, dosing, and frequency of vincristine.

Conclusions

Pediatric oncology patients receiving chemotherapy experience many unwanted side effects that deserve supplemental, evidence-based, nonpharmacologic interventions. OMT was feasibly integrated into an outpatient oncology clinic with no serious safety events. Future directions should focus on investigating the efficacy of OMT for therapy side effects in children receiving chemotherapy to supplement medical interventions.

Research funding: Financial support was received from the American Academy of Osteopathy.

Author contributions: All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; J.A.B. drafted the article or revised it critically for important intellectual content; all authors contributed to the analysis and interpretation of data; all authors gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests: None reported.

Ethical approval: This study was reviewed and approved by the Ohio State Institutional Review Board (#OSU-19247).

Informed consent: All patients in this study provided written informed consent prior to participation.

References

1. Ramirez LY, Huestis SE, Yap TY, Zyzanski S, Drotar D, Kodish E. Potential chemotherapy side effects: what do oncologists tell parents? Pediatr Blood Cancer 2009;52:497–502.
2. Mora E, Smith EM, Donohoe C, Hertz DL. Vincristine-induced peripheral neuropathy in pediatric cancer patients. Am J Cancer Res 2016;6:2416–30.
3. Loeffen EAH, Kremer LCM, Mulder RL, Font-Gonzalez A, Dupuis LL, Sung L, et al. The importance of evidence-based supportive care practice guidelines in childhood cancer—a plea for their development and implementation. Support Care Cancer 2017;25:1121–5.
4. Belsky JA, Stanek J, Skeens MA, Gerhardt CA, Rose MJ. Supportive care and osteopathic medicine in pediatric oncology: perspectives of current oncology clinicians, caregivers, and patients. Support Care Cancer 2021;29:1121–8.
5. Health NCICCal. Complementary, alternative, or integrative health: what’s in a name? 2019. [Accessed 22 Jan 2020].
6. DiGiovanna EL SS, Dowling DJ. An osteopathic approach to diagnosis and treatment, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.
7. Goldstein FJ, Jeck S, Nicholas AS, Berman MJ, Lerario M. Preoperative intravenous morphine sulfate with postoperative osteopathic manipulative treatment reduces patient analgesic use after total abdominal hysterectomy. J Am Osteopath Assoc 2005;105:273–9.
8. Arienti C, Bosiio T, Ratti S, Migliori R, Negroni S. Osteopathic manipulative treatment effect on pain relief and quality of life in oncology geriatric patients: a nonrandomized controlled clinical trial. Integr Cancer Ther 2018;17:1163–71.
9. Cohen-Lewe A. Osteopathic manipulative treatment for colonic inertia. J Am Osteopath Assoc 2013;113:216–20.

10. Müller A, Degenhardt BF, Morley TF, Blais FX, Hortos KA, Hensel K, et al. Efficacy of osteopathic manipulation as an adjunctive treatment for hospitalized patients with pneumonia: a randomized controlled trial. Osteopath Med Prim Care 2010;4:2.

11. Noll DR, Degenhardt BF, Morley TF, Blais FX, Hortos KA, Hensel K, et al. Osteopathic manipulative treatment for irritable bowel syndrome: a systematic review. J Am Osteopath Assoc 2014;114:470–9.

12. Daraï C, Deboute O, Zacharopoulou C, Laas E, Canlorbe G, Belghiti J, et al. Impact of osteopathic manipulative therapy on quality of life of patients with deep infiltrating endometriosis with colorectal involvement: results of a pilot study. Eur J Obstet Gynecol Reprod Biol 2015;188:70–3.

13. Belsky JA, Stanek JR, O’Brien SH. Prevalence and management of constipation in pediatric acute lymphoblastic leukemia in U.S. children’s hospitals. Pediatr Blood Cancer 2020;67:e28659.

14. Piche T, Pishvaie D, Tirouvaziam D, Filippi J, Dainese R, Tonohouhan M, et al. Osteopathy decreases the severity of IBS-like symptoms associated with Crohn’s disease in patients in remission. Eur J Gastroenterol Hepatol 2014;26:1392–8.

15. Attali TV, Bouchoucha M, Benamouzig R. Treatment of refractory irritable bowel syndrome with visceral osteopathy: short-term and long-term results of a randomized trial. J Dig Dis 2013;14:654–61.

16. Belsky JA, Stanek J, Skeens MA, Gerhardt CA, Rose MJ. Supportive care and osteopathic medicine in pediatric oncology: perspectives of current oncology clinicians, caregivers, and patients. Support Care Cancer 2021;29:1121–8.

17. Steel A, Tricou C, Monserrat T, Ruer M, Deslandes C, Sisoix C, et al. The perceptions and experiences of osteopathic treatment among cancer patients in palliative care: a qualitative study. Support Care Cancer 2018;26:3627–33.

18. Lane MM, Czyzewski DI, Chumpitazi BP, Shulman RJ. Reliability and validity of a modified Bristol stool form scale for children. J Pediatr 2011;159:437–41.e431.

19. Garra G, Singer AJ, Taira BR, Chohan J, Cardoz H, Chisena E, et al. Validation of the wong-baker FACES pain rating scale in pediatric emergency department patients. Acad Emerg Med 2010;17:50–4.

20. Seffinger M. Foundations of osteopathic medicine, 4 ed. Lippincott Williams and Wilkins; 2018.

21. Basch E, Reeve BB, Mitchell SA, Ciauser SB, Minasian LM, Dueck AC, et al. Development of the national cancer institute’s patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014;106:dju244.

22. Elsaid M, Morgan J, Colorado N, Woolsey J, Canterberry N, Rice P, et al. Chemotherapy wait times in a network of pediatric oncology clinics. J Pediatr Hematol Oncol 2020;42:e475–8.

23. DePadova S. Evaluation of patient throughput in an outpatient pediatric hematology, oncology, and bone marrow transplant clinic. Washington, DC: Himmelfarb Health Sciences Library, The George Washington University Health Sciences Research Commons; 2019.

24. Wolfe J, Grier HE, Klar N, Levin SB, Ellenbogen JM, Salem-Schatz S, et al. Symptoms and suffering at the end of life in children with cancer. N Engl J Med 2000;342:326–33.

25. Sitaresmi MN, Mostert S, Gundy C, Sutary S, Veertman A. Chemotherapy-related side effects in childhood acute lymphoblastic leukemia in Indonesia: parental perception. Pediatr Blood Cancer 2007;49:526.

26. Chen SL, Cai SR, Deng L, Zhang XH, Luo TD, Peng JJ, et al. Efficacy and complications of polyethylene glycols for treatment of constipation in children: a meta-analysis. Medicine (Baltim) 2014;93:e65.

27. Noergaard M, Traerp Andersen J, Jimenez-Solem E, Bring Christensen M. Long term treatment with stimulant laxatives - clinical evidence for effectiveness and safety? Scand J Gastroenterol 2019;54:27–34.

28. Schafer AI. Effects of nonsteroidal anti-inflammatory therapy on platelets. Am J Med 1999;106:25s–36.

29. Regnier Denois V, Poirson J, Nouriassat A, Jacquin JP, Guastalla JP, Chauvin F. Adherence with oral chemotherapy: results from a qualitative study of the behaviour and representations of patients and oncologists. Eur J Cancer Care 2011;20:520–7.

30. Yun H, Romero SAD, Record B, Kearney J, Raghunathan NJ, Sands S, et al. Utilization of integrative medicine differs by age among pediatric oncology patients. Pediatr Blood Cancer 2019;66: e27639.

31. Atzori B, Hoffman HG, Vagnoli L, Patterson DR, Alhalabi W, Messeri A, et al. Virtual reality analgesia during venipuncture in pediatric patients with onco-hematological diseases. Front Psychol 2018;9:2508.

32. Schütze T, Langler A, Zuzak TJ, Schmidt P, Zernikow B. Use of complementary and alternative medicine by pediatric oncology patients during palliative care. Support Care Cancer 2016;24:2869–75.

**Supplementary Material:** The online version of this article offers supplementary material (https://doi.org/10.1515/jom-2021-0246).