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Challenges to the Design and Testing Supportive Interventions for Cancer Patients Treated with Oral Oncolytic Agents

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Abstract

Conducting research into supportive care for patients as they initiate treatment with oral oncolytic agents poses numerous new challenges. Some of these medications have very complex dosing schedules and produce symptoms that patients need to manage at home with less reliance on oncology clinicians. We describe lessons learned from a multi-site trial designed to improve adherence to these medications and self-management of symptoms among patients newly prescribed oral oncolytic agents. Identifying these challenges can assist researchers to improve the integrity of their future supportive care trials.

Keywords

Oral; Oncolytic; Agents; Cancer; Interventions

Introduction

This commentary summarizes challenges encountered during implementations of a multi-site trial designed to improve adherence and self-management of symptoms among patients newly prescribed oral oncolytic agents (OA). Identifying these challenges may be of value to others as they plan similar supportive care trials of patients on OAs.

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CONFLICT OF INTEREST DISCLOSURE

The authors of this commentary certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Recruitment/Enrollment

This trial was approved by the Institutional Review Board (IRB) of the investigators' university and each cancer center. Patients (N=272) were recruited from six NCI designated comprehensive cancer centers. Informed consent was discussed with each prospective patient. All trial participants signed an informed consent form.

Unlike trials with patients on infusion chemotherapy there was much less opportunity to meet patients prescribed OAs. In collaboration with the Site Investigators at each center strategies were developed. The most successful approach relied on well-trained seasoned recruiters; oncologists and nurses helped explain the study and introduced the recruiter to patients.

A second approach, approved by the institution's IRB, notified the recruiter electronically when a prescription for a new OA was written and sent to the cancer center pharmacy. The recruiter met the patient at the pharmacy, explained the study, and obtained consent to participate.

In one center, oncologists employed pharmacists to educate patients regarding their OAs. The Pharmacy Director agreed to have pharmacists introduce the study and to refer patients to the recruiter who answered questions and consented patients.

Other approaches to identifying and recruiting patients might incorporate alerts into electronic medical records, after visit summaries, or involving specialty pharmacies that fill scripts and call the patients to explain how to take their OA's [1].

Accrual of patients was challenging and unique to each center. This is reflected in the rates of accrual compared with our previous similar studies among patients undergoing infusion chemotherapy where 93% of consented patients completed their baseline interview [2] while only 84% of consented patients prescribed OAs completed their baseline interview in the current study. Multiple factors could account for this difference, including the interval from enrollment to receipt of the medication. Nevertheless, accrual of patients initiating OAs deserves careful planning to reach pre-specified sample sizes. On a positive note, following completion of the baseline interview, rates of attrition over comparable periods in this and our previous studies were identical at 23%.

Trial Implementation Challenges

Once baseline interviews were completed, patients were randomized 1:1 to the experimental or standard care arm. Assignment was balanced according to recruitment location, depression, site of cancer, concurrent IV chemotherapy (yes/no) and OA regimen (continuous versus intermittent). Patients assigned to the experimental arm received reminder calls daily for 4 weeks, with option of every other day for weeks 5–8. Weekly automated telephone assessments of symptoms were conducted for 12 weeks in both arms. In the experimental arm, patients reporting elevated symptoms were referred to *Medication Management and Symptom Management Toolkit*. Telephone interviews were conducted at: 4, 8 weeks (end of intervention) and 12 weeks.

Early on, we noted some patients were not answering their daily reminder calls. When queried, patients indicated that since daily calls came at a designated time, the call alone was a sufficient reminder. Patients in the experimental arm reported lower symptom severity at 8 weeks but not later. In neither instance could we link calls or referrals to the Toolkit to patient engagement. This is a challenge facing self-management trials. Until research links patients' uptake of self-care strategies to units of change in clinical parameters, service use, and quality of life, this line of investigation will remain haunted by claims that outcomes result from a "Hawthorne effect".

Adherence to OAs

Adherence to OAs were assessed via pill counts at 4, 8, and 12 weeks. Patients were asked to count the number of pills remaining in each bottle or blister pack, as well as provide information from the prescription label on the number of pills and number of refills. Using this approach we were able to assess both the number of refills, the date of refill and thus the numbers of pills taken and number prescribed between each refill. Adherence measures were threatened in the following ways: 90 (33%) of patients underwent temporary stoppages and 67 (25%) had at least one medication in the protocol permanently stopped. Thus, both regimen changes and dose interruptions had to be included to calculate the number of pills patients were eligible to take in a given period.

When interruptions or stoppages occurred, pharmacies often were not notified and continued to ship refills. Unfortunately, despite requests not to, patients combined new refills with pills remaining in their current bottle. When this occurred it was difficult to identify how many pills patients took and, if the previous prescription bottle was not available, assessing number of pills taken against the script became difficult. On occasion oncologists altered patients doses but this change was not recorded in the medical record, which further complicated adherence calculations. Finally, pill counts were conducted by patients over the phone leaving room for error in counts.

In the literature reports of patient adherence vary widely [3–9]. Currently bundled strategies that combine, smartphone reminders, motivational interviewing, and strategies to manage symptoms are being tested for assessing adherence [10–14]. Emerging strategies that are under testing and refinement for assessing adherence include the use of Radio Frequency Identification chips [15–17].

Overall, despite these problems, adherence was high in our trial, patients took over 94% of doses prescribed by oncologists. However, due to treatment interruptions and other factors, oncologists prescribed on average less than 90% of the FDA-approved dose.

These observations lead to important and emerging issues in treating patients with OAs. For some patients, might tailored doses lead to fewer interruptions and dose adjustments and better treatment outcomes as defined by tumor scans? Further, do age, sex, body mass index, comorbid conditions, contribute to toxicities and symptoms that lead to treatment interruptions, reduced doses, and poorer outcomes [7, 18]?

OAs are transforming how cancer treatment is delivered. Our work points to the challenges that accompany testing interventions to assist patients and families as they seek to manage treatment and address symptoms and side effects, which may adversely affect outcomes. Future tests of supportive care interventions may benefit from knowledge about these challenges and thus adapt protocols and designs accordingly. For patients with solid tumor cancers, OAs are a late and often last line of therapy. This fact opens questions of value that are currently being debated [19–20]. Hopefully, the points we have raised can guide designs for researchers wishing to test how supportive interventions can improve outcomes among patients taking OAs.

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