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Orally Administered Cancer Therapy: Breaking Down Barriers to Adherence and Quality of Life

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Over the past 2 decades, many orally administered cancer therapy options have become available.[1] As of 2010, 20% to 25% of cancer therapeutics in development were oral formulations,[2] and the number of oral therapies has increased dramatically over the past decade with the addition of small-molecule biologics.[1] Possibly in part because intravenous medications are often perceived to increase medical complications, inconvenience, cost, and poor quality-of-life (QoL), studies have confirmed that many patients prefer oral to intravenous chemotherapy,[3,4] This has, in turn, led to trials comparing the efficacy and outcomes of oral versus intravenous therapies because patients did not want to sacrifice efficacy for convenience.[4] Although many comparative trials have shown equal or better outcomes with oral therapies,[3] several challenges remain, including patient safety, monitoring of adverse effects, and medication adherence.[5]

Adherence is a global medical issue across disease sites.[6] Within cancer care, the earliest reports of nonadherence rates were documented in breast cancer with endocrine therapies, ranging from 12% to 59% with tamoxifen and 9% to 50% with aromatase inhibitors.[7] In a systematic review by Greer et al,[1] adherence estimates were widely variable among studies (49%–100%), due to the diverse methods for assessing adherence, lack of standardization in defining optimal adherence, considerable differences in length of follow-up, and poor quality of studies. Nonetheless, poor adherence rates have been confirmed and have been linked to downstream consequences, such as poorer clinical outcomes, development of medication resistance, increased consumption of healthcare resources, and lower QoL.[7,8] Therefore, clinicians need to identify barriers to adherence and establish standard protocol and documentation procedures for prescribing oral therapeutic agents, educating patients on appropriate use, monitoring adverse effects, and tracking adherence.[1]

Barriers to adherence are multidimensional and include patient-related factors (comorbidities, cognitive abilities, and health literacy), disease-related factors (severity of symptoms, points of progression of disease), therapy-related factors (complex regimens, inconsistent prescription labelling, drug–drug or drug–food interactions, adverse effects), healthcare-related factors (inadequate training, ineffective communication), and social and economic factors (limited insurance, lack of access to good care).[1,2] Ideally a standardized, comprehensive oral cancer therapy delivery program should be developed that can be tailored to the patient and their specific barriers. However, few intervention studies have been effective, due to methodological concerns.[1] Only 1 of 12 intervention studies reviewed by Greer et al[1] may have had an effect on adherence. This signifies the need for further knowledge of what factors have the most impact on adherence.

In this issue of *JNCCN*, Jacobs et al[9] aimed to measure adherence rates of patients on oral cancer therapies across various cancer types, identify the physical and psychological symptoms of these patients, and describe correlates to adherence and QoL. They hypothesized that poor adherence would likely be associated with

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high symptom distress, poorer QoL, and increased psychological symptom burden. The patients analyzed were part of a randomized controlled trial of adherence and symptom management comparing a smartphone mobile application intervention versus standard oncology care (ClinicalTrials.gov identifier: NCT02157519). The rates and correlates of symptom burden, adherence, and QoL of the patients for this analysis were obtained from baseline data before randomization and intervention in the trial. Although no gold standard method has been established to measure adherence, pill bottles with electronic caps were used in this study. This method allowed for an objective measure that remained noninvasive. The reported baseline rates of adherence in this trial were similar to those previously reported[9] (26% of the sample was <90% adherent; 17% of the sample was <80% adherent).

This analysis by Jacobs et al[9] highlights a few points that medical oncologists and other healthcare providers can focus on in everyday practice. First, greater cancer-related symptom severity was associated with lower adherence, and higher symptom burden was associated with worse QoL especially in patients with anxiety and depression. These associations, along with previous conclusions that side effects are a major barrier to adherence,[7] suggests that closer monitoring of patients with a greater symptom burden during treatment (whether due to malignancy or medication) is needed. At the start of therapy, patients should be provided with patient-centered resources on behavior strategies to cope with adverse effects.[10] During therapy, interventions in the form of regularly timed medical visits, check-in calls, or appropriately implemented patient-reported outcome (PRO) measures should be in place.[10] Adjustments of the treatment plan or timing of future interventions should be based on the results of these visits, call-ins, or PROs in real time to minimize the impact of symptoms and side effects on adherence and QoL. Many PRO measures have been developed and are well validated in practice, with feasibility proven for use in clinical settings.[11] They have been successfully implemented, improving patient–physician communication, physician awareness of symptoms, symptom management, patient satisfaction and QoL, and overall survival.[12] Evidence has also established that patient assessment of symptoms and QoL can significantly differ from physician assessment.[12] Therefore, implementing a PRO may decrease this bias and allow for more personalized care.

Jacobs et al[9] also noted that lower satisfaction with both treatment and communication with clinicians was associated with worse overall QoL. This finding is consistent with a study showing significantly lower rates of clinician documentation of treatment plan discussions for oral chemotherapy than for intravenous chemotherapy, per measures outlined in the ASCO Quality Oncology Practice Initiative.[1] However, the continued shortage of medical oncologists and the number of high-volume clinics with major time constraints[2] suggest that improving provider communication skills and documentation can have only a limited effect on helping patients understand treatment options and the significance that treatment may have on overall outcomes.

Although healthcare models have been successfully moving toward a multidisciplinary team approach, many resources have been underused in terms of better support for patients during therapy. Other team members, such as clinical oncology pharmacists and seasoned clinical nursing staff, should be integrated into the care team to support communication of personalized treatment plans, dosing schedules, FDA labeling instructions, expected side effect profiles, and management of side effects.[2] Similarly, other team members, such as social workers, can help in other QoL domains. Regular evaluation of a patient's social support is vital to identify deficiencies that may require additional measures, such as more frequent check-ins or assistance with transportation. In the analysis by Jacobs et al,[9] a 1-point increase in anxiety symptoms was associated with a 7.10-point reduction in QoL, indicating that a stepwise structured pathway for referral to support groups, social work, cognitive

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behavioral therapy, and mental health providers should be available for patients with psychosocial issues.

Some limitations of the study include a cross-sectional nature, which only allows for correlation rather than a cause-and-effect relationship. In addition, most patients had stage IV disease over a wide variety of cancer types. As the authors point out, this argues that perhaps symptom distress and worse QoL may be related to advanced disease stage rather than issues with oral therapies. Patients were also enrolled at different points during their treatment course—an inherent bias favoring adherence among patients without adverse events. Additionally, agents treating different cancer types show different degrees of adverse effect potential. For example, patients receiving curative-intent adjuvant endocrine oral therapies may experience milder side effects and less symptom burden overall relative to patients with metastatic disease on cytotoxic or targeted small molecule oral therapies, such as capecitabine or everolimus.

Despite these confounding variables—and Jacobs et al[9] noted that adherence rates did not differ by cancer type or other clinical or treatment-related characteristic—the findings of this analysis remain in line with what is known regarding patient-related factors affecting adherence and QoL in patients on oral therapy. In future efforts to develop a standardized comprehensive oral therapy delivery program, these analyses help focus attention on areas within the multidimensional barriers to adherence where interventions may have the most impact on adherence and ultimately QoL for our patients.

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