

Driving and Disabling Factors of Noncurative Oral Chemotherapy Adherence: A Qualitative Evidence Synthesis

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PROBLEM IDENTIFICATION: Adherence to oral chemotherapy is influenced by many factors. This qualitative evidence synthesis aimed to contribute to an interpretive understanding of the factors that act as facilitators or barriers to adherence among people with cancer taking lifelong, noncurative oral chemotherapy.

LITERATURE SEARCH: A systematic search strategy was developed, and searching was undertaken across several electronic databases (CINAHL®, Cochrane Library, EMBASE, ETHOS, ProQuest, PsycINFO®, PubMed, Scopus, Web of Science including MEDLINE®).

DATA EVALUATION: 12 reports on 10 qualitative studies were included in the synthesis. A total of 206 patients were included, with 109 taking an oral tyrosine kinase inhibitor, along with a total of 57 healthcare professionals.

SYNTHESIS: Two principal analytic themes (driving adherence and disabling adherence) and seven subthemes were identified.

IMPLICATIONS FOR PRACTICE: A trusting relationship between healthcare professionals and patients is important to adherence. Open discussions concerning treatment side effects and patients' perceived quality of life should occur at each visit.

KEYWORDS adherence; cancer; oral; chemotherapy; qualitative evidence synthesis

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Systemic oral anticancer treatments offer a new model for treatment (Arber, Odelius, Williams, Lemanska, & Faithfull, 2017), but adherence to these oral chemotherapy regimens, which are taken by patients outside of the healthcare setting, is vital because lack of adherence can cause the treatment to be ineffective. Although some patients may have doubts about the effectiveness of oral chemotherapy (Bassan et al., 2014), most embrace the chance to take their chemotherapy orally (Simchowicz et al., 2010). Oral chemotherapy treatment often results in better patient quality of life because of reduced visits to the hospital and avoidance of the complications associated with IV chemotherapy (Barillet, Prevost, Joly, & Clarisse, 2015). However, oral chemotherapy is associated with a high risk for error and toxicity (Rooop & Wu, 2014). Patients must assume the responsibility of taking their oral chemotherapy and managing their side effects. Some patients accept this autonomy and control over their treatment, but others do not, making adherence an issue for many patients (Greer et al., 2016).

Adherence can be defined as “the extent to which patients take their medications as prescribed by their healthcare providers either as part of clinical trial participation or routine care” (Atkinson et al., 2016, p. 576). Many factors may affect a patient's adherence to and persistence with oral chemotherapy, including sociodemographic issues, cognitive impairment, treatment expectations and understanding, patient age and comorbidities, side effects, and the patient-provider relationship (Barillet et al., 2015). Patients with calm, scheduled lives have been found to be more likely to adhere to oral chemotherapy, whereas those with irregular lives, with competing family and professional

obligations, are less likely to adhere (Bourmaud et al., 2015).

Measuring adherence is often challenging. In addition, no gold standard of adherence assessment exists (Barillet et al., 2015); numerous tools of varying specificity may be used to measure patient adherence to treatment, ranging from patient diaries to electronic medication caps that track how many times the patient opens the container to retrieve the medication to laboratory tests like drug metabolite assays (Bourmaud et al., 2015; Patel et al., 2013; Verbrugge, Verhaeghe, Lauwaert, Beeckman, & Van Hecke, 2013). Discord also can exist between patients' self-reported adherence rates and those of medication event monitoring systems (Eliasson, 2010). As a result, drawing conclusions from studies measuring adherence is difficult because of the many different methods of assessment available (Greer et al., 2016; Mathes, Antoine, Pieper, & Eikermann, 2014) and the varied accuracy of these tools (Patel et al., 2013). A more interpretive and comprehensive approach to understanding adherence is needed (Bassan et al., 2014). This qualitative evidence synthesis (QES) aims to contribute to an interpretive understanding of adherence.

Methods

Research Question

The objective of this QES was to uncover what factors act as facilitators or barriers to adherence among patients with cancer taking oral chemotherapy. Studies reporting healthcare professionals' views and experiences were included because their communication and relationships with patients influence adherence.

Thematic synthesis was the approach used for this QES (Thomas & Harden, 2008). This approach is aggregative, and although it does not require the deep interpretive transformation of interpretive approaches to QES, it does call for a level of interpretation (Sigurdson & Woodgate, 2015). Divisions between the two main approaches to QES (interpretive and aggregative) are not clearly defined, and many of the methods used in QES are heavily influenced by the interpretive meta-ethnography approach (Noblet & Hare, 1988).

Search Strategy

A search strategy was developed, and various electronic databases (CINAHL®, Cochrane Library, EMBASE, EThOS, ProQuest, PsycINFO®, PubMed, Scopus, Web of Science including MEDLINE®) were searched by two of the current authors (A.C. and E.M.). Search terms included the following: *cancer,*

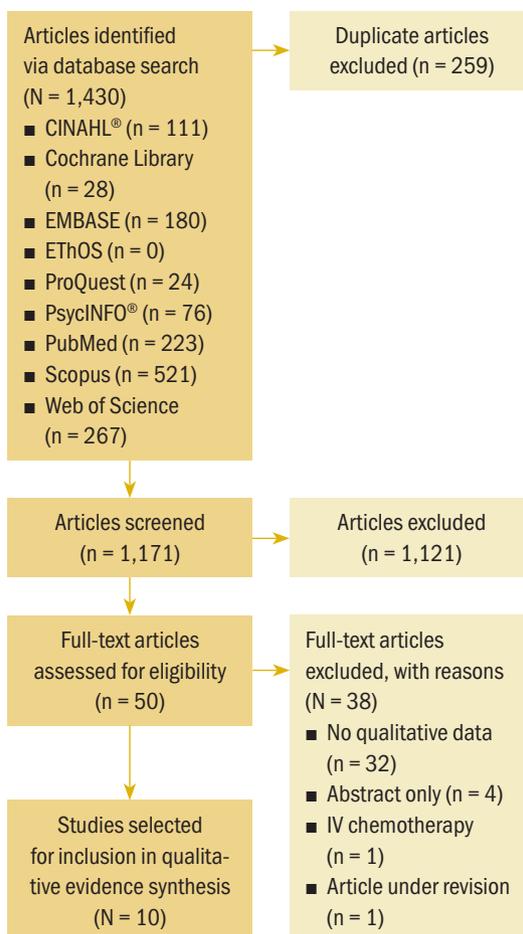
adherence, oral chemotherapy, anti-neoplastic, oral anti-cancer drugs, compliance, and concordance.

Screening Process

The electronic database search was conducted in July 2016. Results from the search are presented in Figure 1. The search resulted in 1,430 articles, which were managed using EndNote, version 8.0. Following removal of duplicates, the EndNote file with the selected sources was imported into the software package Covidence, which supports systematic reviewing and the blind screening and data extraction of large volumes of studies.

Title and abstract screening was undertaken by two of the current authors (M.D. and G.B.). A third

FIGURE 1. Flowchart of Literature Search



Note. 10 studies were selected for inclusion, but a total of 12 articles were used (2 studies were each discussed in 2 articles).

researcher (P.M.) was consulted with to decide on any conflicts. Fifty studies were selected for full-text review. One study was translated from French into English (Regnier-Denois, Poirson, Soum-Pouyalet, & Chauvin, 2009).

Study Eligibility Criteria

Articles were included in this review if they met the following criteria:

- Used qualitative methods (including mixed methods) to explore the perceptions or experiences of patients with cancer regarding their adherence to or compliance with oral chemotherapy
- Used qualitative methods (including mixed methods) to explore healthcare professionals' perceptions or experiences of educating about or monitoring adherence to oral chemotherapy among adults with cancer
- Included verbatim accounts from study participants

- Included study samples with adult patients (aged 18 years or older) who had been diagnosed with cancer (hematologic and nonhematologic) and were taking oral chemotherapy
- Published in peer-reviewed journals
- Had no time restriction (no time limit set regarding date of publication)
- Were written in English

Excluded articles were reviews and studies of patients with cancer taking other oral treatments prescribed for cancer (e.g., antiestrogens, antiandrogens) or to prevent severe side effects (e.g., allopurinol). Twelve articles on 10 studies were selected following full-text screening.

Appraisal Process

The selected studies were imported into NVivo, version 11.0, where appraisal, data extraction, and data synthesis were undertaken. Two of the current authors (M.D. and A.H.) extracted the data and undertook

TABLE 1. Critical Appraisal Skills Programme Quality Assessment of Selected Studies

Source and Quality Rating	1	2	3	4	5	6	7	8	9	10
Regnier-Denois et al., 2009; Regnier Denois et al., 2011 (9/10)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Eliasson, 2010; Eliasson et al., 2011 (9/10)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Oakley et al., 2010 (9/10)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Yagasaki & Komatsu, 2013 (5/10)	No	Yes	No	Yes	Yes	No	Yes	Yes	No	No
Chen et al., 2014 (10/10)	Yes									
Wickersham et al., 2014 (10/10)	Yes									
Hanan & Mullen, 2015 (8/10)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Wu et al., 2015 (10/10)	Yes									
Yagasaki et al., 2015 (9/10)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Verbrugge et al., 2016 (9/10)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

1—Was there a clear statement of the aims of the research? 2—Is a qualitative methodology appropriate? 3—Was the research design appropriate to address the aims of the research? 4—Was the recruitment strategy appropriate to the aims of the research? 5—Was the data collected in a way that addressed the research issue? 6—Has the relationship between researcher and participants been adequately considered? 7—Have ethical issues been taken into consideration? 8—Was the data analysis sufficiently rigorous? 9—Is there a clear statement of findings? 10—How valuable is the research?

Note. Categories answered with a “yes” response were given 1 point, and categories answered with a “no” response were given 0 points.

Note. Based on information from CASP UK, 2018.

FIGURE 2. GRADE-CERQual Summary of Qualitative Findings: Driving Adherence

Desire to Survive

High confidence; all studies with no or minor concerns about coherence, relevance, adequacy, and methodologic limitations

- “The doctor questioned my quality of life because I am so sick from this medication. She wanted to give me a lower dose . . . but I refused. I’ll hold on. It’s the only option if I want to have a chance” (Verbrugge et al., 2016, p. 159).
- “If I don’t take the drug, I risk the leukaemia coming back” (Wu et al., 2015, p. 258).
- “I will continue to take it at any price while enduring distressing side effects” (Yagasaki et al., 2015, p. 4).
- “You either take it and deal with any side effects . . . or you throw in the towel, give up . . . and I’m not going there” (Wickersham et al., 2014, p. S52).
- “I’m not going to take too much notice of side effects [because] I don’t want to let them get to me” (Oakley et al., 2010, p. 24).

Having a Routine

High confidence; 6 studies with no or minor concerns about coherence, relevance, adequacy, and methodologic limitations; 1 study (Hanan & Mullen, 2015) with minor concerns about coherence and relevance, moderate concerns about methodologic limitations, and substantial concerns about adequacy

- “[The medication is] just sitting on top my fridge and it’s just second nature to me now” (Wu et al., 2015, p. 258).
- “It’s easy to take medication. . . . I have never been nonadherent” (Yagasaki et al., 2015, p. 4).

- “My wife is my pill box” (Hanan & Mullen, 2015, p. 26).
- “It’s a matter of discipline” (Wickersham et al., 2014, p. S53).
- “The goal is for me to take it, so I eat my breakfast and I take it at the same time, or sometimes before or after. And it is the same in the evening” (Regnier-Denois et al., 2009, p. 172).
- “I have a system where I have a watch and when the alarm goes off, I take my pill” (Eliasson, 2010, p. 205).
- “I don’t forget. It’s part of my daily routine, like cleaning your teeth or combing your hair” (Eliasson et al., 2011, p. 629).
- “The diary acted as a way of documenting or letting me know I had taken [the medication] as sometimes I just couldn’t remember” (Oakley et al., 2010, p. 25).

Reciprocity in the Patient–Healthcare Professional Relationship

Medium confidence; all studies with no or minor concerns about relevance and methodologic limitations and moderate concerns about coherence and adequacy

- “I really trust my physician and receive treatment. He is a very good physician to me. I have to do my part too. I cannot betray his trust” (Yagasaki et al., 2015, p. 4).
- “I strongly feel that we need time and space to establish a trusting relationship with patients so that they can talk to us honestly” (Yagasaki & Komatsu, 2013, p. 514).
- “I decided a long time ago to put my faith in [the oncologist]. And when he said, ‘This is what I think you should do,’ that’s what I did” (Wickersham et al., 2014, p. S52).
- “I completely trust my patients. And it is mutual” (Regnier-Denois et al., 2009, p. 171).

GRADE-CERQual—Grading of Recommendations Assessment, Development, and Evaluation Confidence in the Evidence from Reviews of Qualitative research

simultaneous quality appraisal of the 12 studies. Any disagreements in data extraction between the two reviewers were resolved through discussion with two other authors (P.M. and L.B.).

Quality appraisal of all 10 studies was undertaken in tandem with data extraction using the Critical Appraisal Skills Programme (CASP) (see Table 1). In addition, overall confidence in the study findings was determined using the Grading of Recommendations Assessment, Development, and Evaluation Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approach, under the following headings (Lewin et al., 2015, 2018; Munthe-Kaas et al., 2018):

- Coherence
- Relevance

- Adequacy
- Methodologic limitations

Confidence in evidence was high across most identified themes (see Figures 2 and 3).

Synthesis

The steps outlined by Thomas and Harden (2008) were used to guide thematic synthesis. Thematic synthesis was iterative, interpretive, and inductive. The first and second stages of this process involved coding text and developing initial themes using NVivo to manage the data. Three of the current authors (M.D., A.H., and C.H.) undertook initial coding. Initial themes were then organized in a hierarchy, and the first and second authors (M.D.

and A.H.) undertook data extraction of each study's findings/results section. Following this, codes were examined for differences and similarities, and then preliminary subthemes were developed. Further distillation of subthemes and themes by cross-checking content, condensing, and merging nodes of similar content was then undertaken. The final stage involved generating the analytical themes. Once

initial interpretations were obtained, the interpretations of M.D. and A.H. were discussed with another author (C.H.) to agree on the analytical themes.

Nine descriptive themes (i.e., survival, having a routine, feeling hopeful, relationships with healthcare professionals, monitoring symptoms, reporting side effects, quality of life, planned partial nonadherence, nonintentional/unplanned partial nonadherence)

FIGURE 3. GRADE-CERQual Summary of Qualitative Findings: Disabling Adherence

Thoughts of Nonadherence

High confidence; all studies with no or minor concerns about coherence, relevance, adequacy, and methodologic limitations

- "I don't know how long I have to take this medication. The doctor said lifelong, but if my next [computed tomography] scan is positive I'll inquire whether I can stop the treatment for 1 or 2 months during the summer. Then I could enjoy a barbecue or have a glass of wine. Now, I'm often so tired and side effects are so intense. I just want to have a normal life again for a while" (Verbrugghe et al., 2016, p. 158).
- "I was told . . . this is my lifeline, [but] I wonder if there is ever a point that I can have a break" (Wu et al., 2015, p. 260).
- "I really wish I could skip [my medication]. I have such irresistible feelings" (Yagasaki et al., 2015, p. 5).

Unplanned Risky Behavior

Medium confidence; all studies with no or minor concerns about relevance and methodologic limitations and moderate concerns about coherence and adequacy

- "If I join my friend for tea and I decide to sleep over . . . then I forget [to take my medication] that night and the next morning" (Wu et al., 2015, p. 258).
- "I usually forget to take medication at night. I sometimes fall asleep right after a meal. I recognize that I have forgotten my medication, but it is too late" (Yagasaki et al., 2015, p. 5).
- "[The pharmacy] had no medication for me, so I went for nearly a week with no medication" (Eliasson, 2010, p. 190; Eliasson et al., 2011, p. 629).

Balancing Survival and Quality of Life

High confidence; all studies with no or minor concerns about coherence, relevance, adequacy, and methodologic limitations

- "I had no appetite anymore. I could not eat and drink anymore. It was terrible. Every afternoon, I had to lie on my bed because I was running on the end of my strength.

I had no life anymore. I was completely burned out. And then I decided to stop the therapy because it became too traumatic" (Verbrugghe et al., 2016, p. 157).

- "I went off my pills for three days . . . for the wedding [and] the food was beautiful and the wine was lovely and everything tasted so good [because] everything tastes so rotten when you are on [medication]" (Wu et al., 2015, p. 258).
- "I want to have a day off [medication] on Saturdays because I sometimes drink beer in the mornings. I try not to overlap, but sometimes they do overlap, so I just skip [the medication]" (Yagasaki et al., 2015, p. 5).
- "If I take [the medication] with an empty stomach, I will definitely vomit it out in 10 minutes" (Chen et al., 2014, p. 124).
- "You become . . . a little self-conscious because you know your face is all splotchy and red. . . . I don't want people looking at me" (Wickersham et al., 2014, p. S54).
- "I don't want to take it because it makes me feel sick" (Eliasson, 2010, p. 113; Eliasson et al., 2011, p. 629).

Maintaining Nonadherence

High confidence; all studies with no or minor concerns about coherence, relevance, adequacy, and methodologic limitations

- "The first time I forgot to take the medication, I thought something was going to happen. . . . But that was not so. Nothing happened" (Verbrugghe et al., 2016, p. 159).
- "I said I missed one and they said, 'Yeah, don't worry about it too much, just try to take them as soon as you can.' So I'm not too worried about missing one" (Wu et al., 2015, p. 258).
- "I am tending to miss more now, because at first I thought it was sort of life or death if you miss a tablet, but now the doctors have told me . . . it's not a big thing if you miss 1 or 2, so I tend to not worry as much about it as I did previously" (Eliasson, 2010, p. 133; Eliasson et al., 2011, p. 629).

GRADE-CERQual—Grading of Recommendations Assessment, Development, and Evaluation Confidence in the Evidence from Reviews of Qualitative research

were merged into two principal analytical themes and seven subthemes (see Figure 4).

Results

Characteristics of the Included Studies

A summary of the studies included in this review is provided in Table 2. The final sample for this synthesis consisted of 12 articles reporting on 10 studies. The studies were conducted from 2009–2016. A total of 206 patients were included, with 109 on an oral tyrosine kinase inhibitor. The largest patient group was made up of patients with chronic myeloid leukemia (CML) (N = 71). A total of 57 healthcare professionals were included (29 nurses, 19 physicians, and 9 pharmacists).

Most studies adopted a grounded theory approach; there was one ethnographic study and one study using interpretative phenomenological analysis.

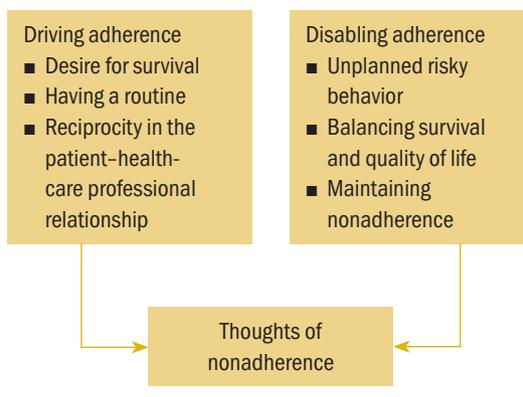
Driving Adherence

The first principal analytical theme, driving adherence, identified factors influencing the adherence of patients with cancer to their oral chemotherapy regimen and consisted of three subthemes (desire to survive, having a routine, and reciprocity in the patient–healthcare professional relationship).

Desire to survive: Treatment was viewed by many patients as essential to their survival and given the highest priority (Oakley, Johnson, & Ream, 2010; Verbrugghe et al., 2016; Wickersham et al., 2014; Wu et al., 2015; Yagasaki, Komatsu, & Takahashi, 2015). A variety of motivators related to survivorship were found to drive adherence, including a fear of disease progression (Wu et al., 2015; Yagasaki et al., 2015), a belief that this was the patient’s final chance to survive (Verbrugghe et al., 2016), the patient’s acceptance that the cancer was chronic (Chen, Chen, Huang, & Chang, 2014; Wickersham et al., 2014), and a sense of duty (Yagasaki et al., 2015). Many patients believed that they should put up with the side effects of treatment for improved chances of survival (Regnier Denois et al., 2011; Verbrugghe et al., 2016; Yagasaki & Komatsu, 2013).

In addition, patients whose main motivation was to survive experienced intense anxiety if they forgot to take their medication (Verbrugghe et al., 2016). These patients tended to view their side effects as unavoidable and were, therefore, more accepting of them than patients whose focus was more on quality of life (Verbrugghe et al., 2016). Good results on blood tests and scans were seen as positive reinforcement of their efforts in taking their medication (Chen et al., 2014; Eliasson, Clifford, Barber, & Marin, 2011; Regnier-Denois et al., 2009; Regnier Denois et

FIGURE 4. Factors Influencing Adherence to Oral Chemotherapy



al., 2011; Verbrugghe et al., 2016; Wu et al., 2015). In addition, patients often evaluated oral treatment as having less toxicity than IV chemotherapy (Regnier-Denois et al., 2009; Wu et al., 2015), and they tolerated side effects because they were happy that a treatment existed to help them survive (Wu et al., 2015).

A fear of developing resistance to the oral chemotherapy was an issue for some patients with CML, but these patients believed that interruptions or changes would result in resistance (Chen et al., 2014).

Having a routine: Establishing a routine was important for adherence (Hanan & Mullen, 2015; Oakley et al., 2010; Wu et al., 2015; Yagasaki et al., 2015), and patients used reminders or prompts to help them follow this routine (Eliasson et al., 2011; Hanan & Mullen, 2015; Oakley et al., 2010; Regnier-Denois et al., 2009; Regnier Denois et al., 2011; Wickersham et al., 2014; Wu et al., 2015). For some patients, the involvement of family members in reminders was essential for adherence (Hanan & Mullen, 2015; Oakley et al., 2010; Regnier Denois et al., 2011).

Reciprocity in the patient–healthcare professional relationship: Reciprocity in this relationship was important for some patients and healthcare professionals. Patients expressed their trust in their doctor (Wickersham et al., 2014; Yagasaki et al., 2015), and doctors emphasized that they needed to trust that the patient would follow instructions related to treatment (Regnier Denois et al., 2011). Nurses reported trust as being central to patients’ openness about their side effects (Yagasaki & Komatsu, 2013).

Disabling Adherence

The second principal analytical theme, disabling adherence, explored reasons for nonadherence to

TABLE 2. Characteristics of Studies Included in Thematic Synthesis

Study	Design	Sample and Context
Regnier-Denois et al., 2009; Regnier Denois et al., 2011 (France)	Focus group interviews and individual interviews; thematic and comparative analyses; purposively selected	N = 52; of the 42 patients, 32 had metastatic breast cancer, 6 had metastatic colon cancer, and 4 had adjuvant colon cancer; 20 patients had had cancer for at least 6 years, and 22 had had cancer for 5 or fewer years; 18 patients had been on chemotherapy for less than 6 months, 14 for 6–12 months, and 10 for more than 1 year continuously; 10 oncologists; total of 5 focus groups (1 with oncologists and 4 with patients); one-on-one interviews with 4 oncologists and 26 patients; involved patients undergoing oral chemotherapy and oncologists who prescribed this specific chemotherapy in 2 oncology-specialized care centers
Eliasson, 2010; Eliasson et al., 2011 (United Kingdom)	Unstructured exploratory interviews; constant comparative method of analysis; purposively selected following monitoring of 87 patients for adherence using a medication events monitoring device for 3 months; of the 23 nonadherent patients, 17 were interviewed; of the 64 adherent patients, 4 were interviewed.	N = 21; all participants were patients with CML prescribed imatinib; most patients (n = 17) were classified as nonadherent, whereas 4 were classified as adherent.
Oakley et al., 2010 (United Kingdom)	Observation, informal conversation, interview, field notes, and diary; ethnography; purposively selected and interviewed	N = 17; of the 8 patients, 5 were male and 3 were female; 5 had colorectal cancer and were treated with capecitabine; 3 had lymphoma and were prescribed oral chlorambucil; 5 nurses and 4 doctors with 2–10 years of experience; involved observation of each patient's outpatient clinic consultations; informal conversations immediately following observations; formal in-depth interview with each patient in his or her home 2 weeks into treatment
Yagasaki & Komatsu, 2013 (Japan)	Interpretive; 4 focus group interviews; grounded theory using theoretical sampling	N = 18; all participants were oncology nurses, certified by the Japanese Nurses Association, working in care settings where patients are on oral chemotherapy
Chen et al., 2014 (Taiwan)	Exploratory; semistructured interviews; purposively selected	N = 42; all participants were patients with CML on imatinib at the time of the interview; 23 were male; occurred at an outpatient oncology clinic
Wickersham et al., 2014 (United States)	Exploratory; in-depth semiformal interviews; grounded theory; purposively selected	N = 13; all participants were patients with non-small cell lung cancer (any type and stage) receiving oral epidermal growth factor receptor inhibitors (erlotinib); all were aged older than 21 years; 5 were male and 8 were female.
Hanan & Mullen, 2015 (Ireland)	Semistructured interviews with patients; telephone interviews with community pharmacists; focus group with the medical oncology team; thematic coding approach; purposively selected	N = 30; the 20 patients had lung, colorectal, or brain cancer or melanoma; 5 community pharmacists; 1 medical oncology consultant; 2 clinical nurse specialists; 1 hospital pharmacist; 1 nurse
Wu et al., 2015 (Australia)	Exploratory; cross-sectional; interpretive phenomenological analysis; consecutive sampling	N = 26; all of the 16 patients had CML and ranged in age from 26–71 years; 9 were male and 7 were female; all were treated with imatinib for 6–113 months; of the 10 healthcare professionals, 4 were hematologists, 3 were nurses, and 3 were pharmacists; occurred at a specialist cancer center

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TABLE 2. Characteristics of Studies Included in Thematic Synthesis (Continued)

Study	Design	Sample and Context
Yagasaki et al., 2015 (Japan)	Interpretive; semistructured interviews; grounded theory; purposively selected	N = 14; all participants were patients with advanced gastric cancer receiving more than 1 cycle of oral anticancer agents following surgery with a mean age of 63.4 years (range = 43–80 years) and were recruited at routine clinic appointments at a university hospital
Verbrugghe et al., 2016 (Belgium)	Exploratory; cross-sectional; grounded theory; purposively selected	N = 30; all participants were patients being treated with an oral tyrosine kinase inhibitor (12 with renal cell cancer, 8 with CML, 4 with breast cancer, 3 with skin cancer, and 1 each with gastrointestinal stromal tumor, hepatocellular carcinoma, and non-small cell lung cancer) attending 5 hospitals in Belgium
CML—chronic myeloid leukemia		

treatment and consisted of four subthemes (thoughts of nonadherence, unplanned risky behavior, balancing survival and quality of life, and maintaining nonadherence). For example, patients who viewed their cancer as a chronic illness and considered themselves to be experts on their disease were more likely to consider nonadherence to their oral chemotherapy treatment. Improving quality of life was the primary reason they considered nonadherence. This desire began as thoughts of taking a break or drug holiday and led to experimentation; for some patients, this nonadherence became a regular occurrence. For other patients, nonadherence was unintentional and was often attributable to forgetfulness.

Thoughts of nonadherence: Patients whose focus was their quality of life had hopeful thoughts about taking a break from their oral chemotherapy at some point in the future; they thought of experimenting with a drug holiday (Verbrugghe et al., 2016; Wu et al., 2015; Yagasaki et al., 2015).

Unplanned risky behavior: Nonadherence was often unplanned and mostly attributable to forgetfulness or to a change in the patient's treatment regimen (Eliasson, 2010; Regnier Denois et al., 2011; Wu et al., 2015; Yagasaki et al., 2015) or a problem with pharmacy dispensing (Eliasson, 2010). Some patients were adamant that forgetting to take their chemotherapy was a rare occurrence, reporting that, when it did happen, it was because of a change in their treatment regimen (Regnier Denois et al., 2011).

Balancing survival and quality of life: For many patients, nonadherence was planned but was mostly partial. Patients often engaged in planned nonadherence in response to their decreased quality of life, choosing to forgo treatment to get relief from the side

effects of treatment (Chen et al., 2014; Eliasson et al., 2011; Verbrugghe et al., 2016; Wu et al., 2015; Yagasaki et al., 2015); to drink alcohol at a social event, travel for work, or go on a vacation (Eliasson et al., 2011); or to avoid stigmatizing side effects known as social inhibitors (Wickersham et al., 2014). In addition, although some patients tended to be poorly informed about their medication (e.g., not knowing the reasons for a 12-hour interval between the first and second oral dose of a tyrosine kinase inhibitor [TKI]) (Verbrugghe et al., 2016), most patients who focused on finding a balance between survival and quality of life made medication adjustments that were informed and based on knowledge accumulated over time (Chen et al., 2014; Eliasson et al., 2011; Verbrugghe et al., 2016).

This focus on determining a balance between survival and quality of life tended to develop when patients had lived with their cancer for some time (Eliasson et al., 2011; Wu et al., 2015; Yagasaki et al., 2015) and had mostly accepted that their medication was for noncurative purposes (Verbrugghe et al., 2016; Yagasaki et al., 2015). However, finding this balance is challenging because side effects may arrive suddenly and be intense; the greater the intensity of side effects, the more likely it is that patients will decide not to adhere to their medication (Verbrugghe et al., 2016). For example, if other health problems arise (e.g., influenza), patients may feel like they cannot tolerate additional side effects and will choose to temporarily stop taking their oral chemotherapy (Verbrugghe et al., 2016).

Maintaining nonadherence: Continued nonadherence was most likely among patients on lifelong chemotherapy taking TKIs and those with CML.

Following initial episodes of nonadherence, patients were alert for physical feedback; if they did not experience severe or intense side effects as they expected, they would engage in further nonadherence (Eliasson et al., 2011; Regnier Denois et al., 2011; Verbrugghe et al., 2016; Wu et al., 2015). In addition, responses from healthcare professionals when patients did not take their medication sometimes reinforced nonadherent behavior (e.g., patients were reassured not to worry about occasional missed doses) (Eliasson, 2010; Eliasson et al., 2011; Verbrugghe et al., 2016; Wu et al., 2015).

Discussion

This QES has identified a number of facilitating and inhibiting factors that affect patients' adherence to oral chemotherapy. Some of the factors identified were also reported in a meta-summary of quantitative studies by Irwin and Johnson (2015) that highlighted various influences on adherence (good relationship between the patient and the healthcare professional, minimal side effects, information to support taking of the medication, family support). However, the current QES found that a strong desire for survival promotes adherence. This intense desire for survival even resulted in overadherence, with some patients deciding not to report their side effects because they feared a dose reduction that would affect their survival (Verbrugghe et al., 2016). Overadherence has been reported elsewhere (Bourmaud et al., 2015; Simchowitz et al., 2010) and can be an issue for patients whose cancer is metastatic and who are willing to tolerate severe adverse events in their pursuit of a cure (Patel et al., 2013).

One study in the current review included patients with metastatic cancer (Regnier-Denois et al., 2009; Regnier Denois et al., 2011), and another included patients with advanced gastric cancer (Yagasaki et al., 2015). Overadherence is also an issue when patients have high expectations of treatment outcomes, underestimate the risks of treatment, and will tolerate side effects of any severity because of the fear that their treatment regimen will be altered or stopped (Bourmaud et al., 2015).

The current review found that nonadherence was often unintentional and could be attributed to forgetfulness, which is a finding reported elsewhere as well (Arber et al., 2017). However, the current review determined that partial planned nonadherence was most likely to occur among patients who had lived with their cancer for some time (e.g., patients with CML); a similar finding is reported by

Bassan et al. (2014) in their review of the literature on adherence.

In addition, the current review determined that reciprocity in the patient–healthcare professional relationship promoted patient adherence, which is dependent on effective patient communication with healthcare professionals (Jacobs et al., 2017). Jacobs et al. (2017) found that patients who feel understood and respected by their oncologist and who believe that they are able to talk to physicians and nurses when needed are more adherent; this feeling of being understood is also linked to patients' overall satisfaction with treatment.

Another factor found to promote adherence was the use of reminders, which have elsewhere been highlighted as being essential to oral chemotherapy adherence (Simchowitz et al., 2010; Spoelstra & Sansoucie, 2015). Patients are often advised to use reminders, such as spreadsheets outlining when to take their oral chemotherapy (Arber et al., 2017). This review also found that informal caregivers acted as effective reminders.

Brief e-health interventions (Jacobs et al., 2017) and mobile applications (Nisotel et al., 2015) could also be useful in promoting adherence and could be used for prompt reporting of side effects (Arber et al., 2017).

This synthesis concluded that patients' nonadherence can develop over time and that patients on lifelong oral chemotherapy are at risk for nonadherence and should be closely monitored. This viewpoint is supported by Timmers et al. (2017), who determined that patients on lifelong oral chemotherapy, such as those with CML, need to be supported differently than patients with a shorter life expectancy, such as those with metastatic disease.

Limitations

The variety of malignancies (CML versus metastatic solid tumors) in the studies examined meant that patients had different diagnoses and were at different stages of their cancer trajectories. In addition, patient samples in some of the studies reviewed were heterogeneous. Different healthcare systems may also have influenced the experiences reported by study participants. Even so, the GRADE-CERQual approach revealed high confidence in most of the study findings. QES provides a methodology that allows conclusions to be drawn from a range of studies.

Implications for Nursing

Oncology nurses play a central role in monitoring patients on oral chemotherapy. This role includes

reinforcement of education, particularly in the early weeks following commencement of treatment and involving symptom management (Boucher, Lucca, Hooper, Pedulla, & Berry, 2015). Patients taking oral chemotherapy require new knowledge, including information on side effects (Bassan et al., 2014). However, patients often are not well informed about the side effects of their oral chemotherapy (Arber et al., 2017), and evidence supports the call for more patient education (Barillet et al., 2015; Bourmaud et al., 2015). Information is particularly needed when patients commence oral chemotherapy (Simchowicz et al., 2010). The Multinational Association for Supportive Care in Cancer Oral Agent Teaching Tool (MOATT) is reported to be useful when educating patients about oral chemotherapy (Boucher et al., 2015). Education focused on targeted behavior change is central to adherence (Arber et al., 2017; Kavookjian & Wittayanukorn, 2015). A nursing feasibility study using structured education with patients treated for lung cancer by Boucher et al. (2015) has reported that this type of intervention can enhance patients' adherence to oral chemotherapy. In addition, caregivers have been found to help patients with adherence (Berry, Blonquist, Hong, Halpenny, & Partridge, 2015; Bourmaud et al., 2015) and should be included in nurses' education sessions (Arber et al., 2017).

Nurses should ideally identify patients at most risk for nonadherence early and put supportive interventions in place. However, it is difficult to know which patients these will be without a tool that can accurately identify them. Distress and depression among patients with cancer is a factor that affects adherence (Bassan et al., 2014; Berry et al., 2015). Therefore, screening for depression and anxiety among patients is recommended (Arber et al., 2017). Other issues that nurses need to be aware of that may affect adherence include oropharyngeal and gastrointestinal problems, unreliable behavior, and lack of motivation in the past (Barillet et al., 2015).

A finding highlighted in this review is that patients on oral chemotherapy for metastatic cancer require a different approach to promote adherence than do patients on lifelong oral chemotherapy, such as those with CML. Patients with metastatic cancer are at risk for not reporting adverse events and for overadherence, whereas those on lifelong chemotherapy are at risk for intentional, planned nonadherence that may become an established routine. Reciprocity in communication between the patient and the healthcare professional should be the basis of

KNOWLEDGE TRANSLATION

- Patients with metastatic cancer are at risk for not reporting adverse events and for overadherence, requiring a different approach to promoting adherence from healthcare professionals compared to patients on long-term chemotherapy.
 - Patients on lifelong chemotherapy to manage their cancer, such as those with chronic myeloid leukemia, are at risk for intentional and planned nonadherence that can become an established routine.
 - Good communication and trust between healthcare professionals and patients is important so that patients can openly disclose adverse effects of their treatment and any thoughts of nonadherence.
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nurse-led education to promote adherence (Atkinson et al., 2016). Good communication and trust will help patients to feel that they can openly disclose adverse effects of their treatment and any thoughts of nonadherence with oncology nurses. Joint decision making between the nurse prescriber and the patient with cancer is highlighted as being central to adherence, and the nurse prescriber should identify the patient's routines and personal challenges (O'Reilly & Dowling, 2015). The active involvement of patients in decision making with the nurse prescriber has been shown to contribute to treatment adherence (Courtenay, Carey, Stenner, Lawton, & Peters, 2011). The oncology nurse prescriber may also educate patients about their disease and potential disease trajectory (O'Reilly & Dowling, 2015).

E-health could augment communication between nurses and patients and improve treatment adherence (Atkinson et al., 2016). Follow-up with patients can also act as a reminder for adherence (Barillet et al., 2015) and is an approach desired by patients, who prefer it to occur regularly between visits (Simchowicz et al., 2010). Monitoring by nurses via telephone is one recommended approach (Boucher et al., 2015; Roop & Wu, 2014).

Conclusion

This is the first known QES to explore the views and experiences of patients with cancer and healthcare professionals regarding patients' adherence to oral chemotherapy. Through an exploration of study findings, this synthesis provides oncology nurses with additional guidance about how they can facilitate patients' adherence to their oral chemotherapy.

The use of oral chemotherapy has expanded so rapidly that oncology services have not kept pace with patients' self-care needs (Barillet et al., 2015), and it has been argued that nurses play a key role in

ensuring that patients are adherent to their treatments (Atkinson et al., 2016). However, it is important to remember that adherence to oral chemotherapy should not be reliant on an individual healthcare professional's efforts but supported by the proper organization of care (Timmers et al., 2017).

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