Available online at www.sciencedirect.com
ScienceDirect
Research in Social and Administrative Pharmacy 11 (2015) 303–314
RESEARCH IN SOCIAL & ADMINISTRATIVE PHARMACY

Review Article

Interventions for adherence with oral chemotherapy in hematological malignancies: A systematic review

Jan Kavookjian, Ph.D.*, Saranrat Wittayanukorn, M.S., Ph.D. (c.)
Health Outcomes Research & Policy, Harrison School of Pharmacy, Auburn University, AL, USA

Abstract

Background: Poor adherence to treatment for chronic diseases including some hematological malignancies impedes health outcomes and increases costs. Oral chemotherapy is an emerging trend that raises concern about nonadherence problems in these targeted patients.
Objectives: This systematic literature review explores evidence and gaps in the literature regarding interventions to enhance adherence with prescribed oral chemotherapy in patients with hematological malignancies.
Methods: Searches of databases and abstracts from conferences were performed for 1987 to January 2013 using a modified Cochrane method. Studies measuring interventions to improve adherence alone or together with clinical, humanistic, and economic outcomes were included. Assessment of methodological quality was performed for each retained study.
Results: The literature search generated 6 studies that met inclusion criteria. Four of these reported a statistically significant increase in the adherence outcome, compared with baseline. Tailored and educational interventions were widely used among the retained studies. Post-intervention adherence rates were 41–96.1%; intervention groups yielded higher rates than comparison groups. Two studies reported statistically significant improvement in clinical outcomes (cytogenetic response and survival time). One study reported that severity of illness was associated with survival time but not with adherence. Studies that used both tailored and educational interventions showed significant relationship between adherence and clinical outcomes; however, the study that used dosage simplification did not. None of the studies explored humanistic or economic outcomes.
Conclusions: Interventions to improve adherence with oral chemotherapies in hematological malignancies remain limited. Though they were heterogeneous in nature, interventions tested in the retained studies suggested a positive impact on the adherence outcome; some established a significant relationship between adherence and clinical outcomes. The results yielded limited evidences regarding characteristics of a specific intervention, but supported a general structure for methods to improve adherence and other outcomes in real-life settings. Further rigorous methodological studies are needed to fully examine impact on adherence and clinical outcomes.

Keywords: Oral chemotherapy; Hematological malignancies; Adherence; Intervention(s); Outcome(s)

* Corresponding author. Health Outcomes Research & Policy, Harrison School of Pharmacy, 031 Foy Hall, Auburn University, AL 36849-5506, USA. Tel.: +1 334 844 8301; fax: +1 334 844 8307.
E-mail address: kavooja@auburn.edu (J. Kavookjian).

1551-7411/$ - see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.sapharm.2014.08.006

Introduction

An estimated incidence of 140,310 new cases of hematological malignancies, including leukemia, lymphoma, or myeloma were diagnosed in the United States in 2011.[1] Moreover, approximately 1,012,533 Americans are living with leukemia, Hodgkin's and non-Hodgkin's lymphoma, and myeloma.[2] According to the American Cancer Society, for 2012, non-Hodgkin's lymphoma and leukemia are among the 10 leading causes of cancer death in both men and women.[3]

Treatment decisions for these conditions include a choice between oral and intravenous administration and rely upon several factors such as the oncologist's decision, patient preference, and/or insurance eligibility, a paradigm shift in oncology considers some cancers as chronic diseases requiring chronic therapy; this has resulted in greater use of oral agents.[4–7] It is estimated that more than 100 of the 400 anti-cancer drugs now in the development pipeline are planned as oral agents[7]; the nature of these cancers is such that chemotherapy is a primary treatment option and there are no surgical options as with solid tumor cancers, making adherence even more important, This emerging trend of targeted therapy administered orally is considered to have less myelosuppressive toxicity than classic chemotherapy. As a consequence, the perceived advantage and convenience of oral chemotherapy encourages oncologists to use this option as a monotherapy or in combination with other classic chemotherapy regimens for treatment, or for maintenance therapy after organ transplantation or cancer remission. It is unclear whether patients maintain the desired adherence level with oral agents when taking them on their own at home.[7–11]

The World Health Organization has defined adherence with long-term therapy as "the extent to which a person's behavior -taking medication, following a diet, and or executing lifestyle changes, corresponds with agreed recommendations" and suggests that the health outcomes and economics may be more influenced by enhancing adherence than advancing medical therapies.[12,13] Unfortunately, adherence to chronic medication therapy in ambulatory care is typically not as high as in the clinical setting.[6–9,12–14] This is because an oral mode requires patients and caregivers to be more responsible for self-management, including adherence to complicated dosage administration and monitoring of side effects instead of the handling of intravenous regimens by a health care provider in the hospital. It is suggested that an oral formulation might be successful in well-motivated and high literacy patients.[6,7,15–17]

Nonadherence or poor adherence with oral therapies results in unsatisfactory consequences. It is an important factor that compromises treatment outcomes that are typically monitored in patients with hematological malignancies, including clinical outcomes like cytogenetic response, pharmacologic response, and pharmacokinetic response, adverse physical effects, and survival time. Nonadherence is also associated with lower rates of disease-free survival and can result in biased assessment of the efficacy of treatment because practitioners might not be able to determine whether the patient actually relapsed or if refractory disease resulted from chemotherapy resistance or from nonadherence. In 2010, Marin and colleagues revealed that adherence was the only independent predictor for achieving complete and major molecular response in patients with chronic myeloid leukemia with stable cytogenetic response. Additionally, poor adherence appears to be the only independent predictor for inability to achieve sustained molecular response.[18] In particular, the degree of achieved complete molecular response is associated with improved duration of complete cytogenetic response which eventually leads to favorable prognosis and prolonged survival. Furthermore, nonadherence can prolong the duration and complexity of treatment regimens, can result in the development of drug resistance or toxicities, and can be costly from an economic sense.[6,7,13,19] Typically, rates of adherence to and persistence with oral antineoplastic drugs are estimated to range from 16% to 100%.[6] Interestingly, research has shown that full 100% adherence is rare in patients with chronic myeloid leukemia (CML) and more than one-third of patients are nonadherent.[20] However, little is known about the effect of nonadherence with oral antineoplastic agents in hematological malignancies; most studies of adherence in this field have been conducted with oral anti-cancer regimens for solid tumors.[6–8,21,22] Additionally, there has been no gold standard measure of adherence, self-report or otherwise.

Aim of the review

The aim of this review is to summarize the existing research literature and to identify

evidence and gaps regarding interventions for adherence with oral chemotherapy in patients with hematological malignancies. The review also proposes implications for practice and research for further implementation.

Methods

The methods and structure used within this review were derived from a modified Cochrane method of systematic review. The general Cochrane method is intended to answer a very narrowly defined and specific intervention research question with inclusion criteria for type of study design, type of intervention, type of target outcome(s), and within a specifically defined target population.[23] This review used the rigor of the Cochrane methods of search and review applied to an intention for describing evidence and gaps in the literature for heterogeneous interventions applied to the primary outcome of adherence with oral chemotherapy for a specific set of cancer types in adult patients. This review limited the target cancers to one general type, hematological cancers, because 1) the nature of these cancers is such that chemotherapy is a primary treatment option and there are no surgical options as with solid tumor cancers, making adherence even more important, and 2) the narrowing to one specific area strengthens the rigor of findings among studies where the intervention and outcomes measures are expected to be heterogeneous.

Selection criteria and definitions

The following criteria had to be met for inclusion in the early screen tiers:

1) Types of studies: Randomized controlled trials (RCTs) were initially sought; since only 1 was detected, the search strategy expanded to include controlled cohort studies, case-control studies, and quasi-experimental designs that conducted tests of interventions to improve adherence in the target population.
2) Types of participants: Adult patients with hematological malignancies who were prescribed oral chemotherapy.
3) Types of interventions: Any method of intervention studied for at least 2 months for its affect on adherence.
4) Types of outcomes measures: The primary target outcome included adherence; adherence along with other outcomes (clinical, economic, and humanistic) was also sought. The definition of adherence used in the studies had to comply with or mirror the WHO definition.
5) Oral chemotherapy included any oral chemotherapy used for hematological malignancies.
6) Those studies with mixed populations (i.e. other diseases) were excluded.
7) Studies must have included a description of the details of an adherence intervention.

Search strategy

Ten electronic databases were searched for relevant research articles published between 1987 and January 2013; this time frame was relevant because this time frame covers a period that included the use of classical oral agents (e.g., mephalan) as well as the recent release of novel oral agents. The databases included the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Registry, MEDLINE/Pubmed, CINAHL, psycINFO, International Pharmaceutical Abstracts (IPA), Academic Search Premier (EBSCO), and Dissertations & Theses (Proquest). The reference lists of articles and relevant reviews were also hand searched. Unpublished studies from ClinicalTrials.gov and meeting abstracts from the American Society of Hematology annual meetings were also reviewed. The search strategy used a combination of medical subject heading and general terms relating to the topics of interest. The search terms for the database search were as follows: (oral chemotherapy, or oral anti-cancer, or oral antineoplastic agent(s), or oral novel agent(s), or oral immunomodulating agent(s),or oral tyrosine kinase inhibitor(s), or oral cancer therapy) AND (hematological malignancies, or hematologic disease(s), or leukemia, or lymphoma, or CML, or CLL, or myeloma or cancer) AND (adherence, compliance, or patient self-report, or self-administration), AND (intervention(s), or outcomes, or treatment outcomes). The search was concentrated primarily on articles published in English.

Review of studies for inclusion and exclusion

The search and review of articles was initially performed by one researcher, checked by a second researcher, and with final discussion among both researchers. The first tiers identified articles related to the topic of interest by checking titles, and then abstracts, to determine relevance. If the article was not excluded, the full-text article was reviewed in the next screen tier. The inclusion and

exclusion criteria described above were applied for full-text study review in making the final decision to retain or reject a study.

Assessment of methodological quality

When a systematic review is conducted among published peer reviewed papers, it is important to evaluate the quality of the study designs/results reports before drawing conclusions among suggested results. While there are several study quality grading systems commonly used and reported among published systematic reviews, the authors of this report chose to use the Cochrane Collaboration method that assesses risk of bias per outcome among retained study methodologies.[24] The Cochrane system includes examining and assigning levels of bias risk based on important study design factors including randomization methods and sample size, allocation concealment, blinding of participants and practitioners to intervention and outcome, completion level of the outcome data, and treatment fidelity. The method uses a simple, symbolic approach to depict risk to validity of results for a particular outcome within retained studies (+ = low risk, ? = unknown, − = high risk). The risk of bias assessment used in this review examined risk of bias for the adherence outcome across the design characteristics noted above.

Results

The detailed PRISMA flow diagram results of the literature search are illustrated in Fig. 1. After removing duplicates, early screen tiers review of titles and abstracts excluded 71 articles based on title and 33 articles based on abstract due to non-relevance primarily due to other cancer type, non-adult patient population, short duration of study, inclusion of adherence with additional medications for other conditions. Of the initial 32 studies examined at the full-text screen tier, 23 studies were excluded as follows: 5 studies contained no original data (e.g., review articles); 10 studies had inadequate baseline data (e.g., did not clearly mention specific cancer type or medication); 4 studies were observation studies and did not have an intervention; 5 studies did not

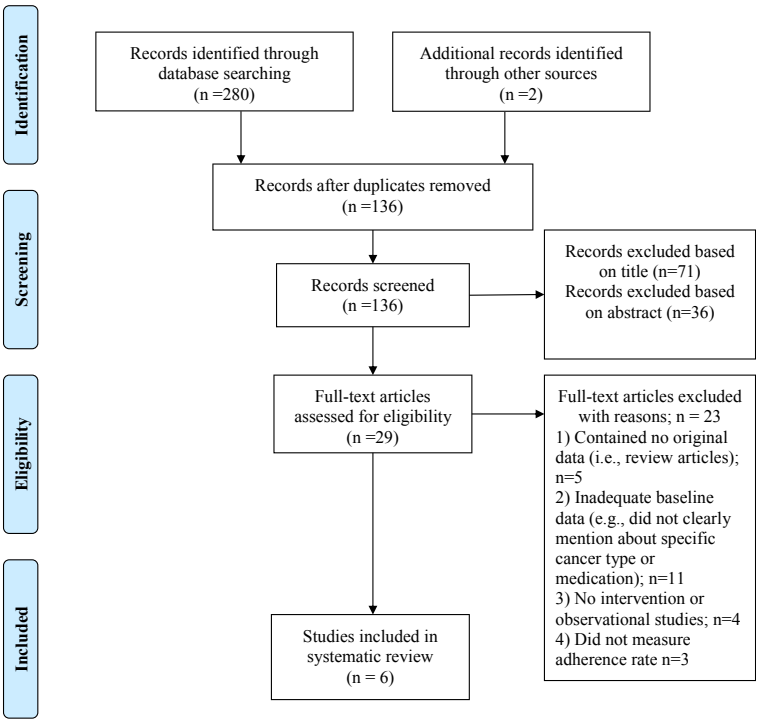

Fig 1. PRISMA flow diagram of potential studies to final number of eligible studies.

measure adherence rate. Therefore, the remaining 6 studies were fully analyzed and form the basis of this report.[25–30] The characteristics of retained studies are described in Table 1.

The quality of the retained studies varied as can be seen in Table 2. Each article was influenced by some sources of potential systematic bias. There was 1 randomized controlled trial (RCT). Consequently, an approach to allocation among the other studies may not have adequately controlled for confounding variables. Risk for selection bias, which may have contributed to differences in outcome, may have been present in some retained studies.[25,27–30] Some studies did not use an established way to measure outcomes (e.g., no validated instrument nor psychometric analysis of the properties of the measure used) which may result in performance bias.[28] None of the 6 retained studies suffered from risk of bias due to attrition. Lastly, there was a threat for detection bias in some trials because they couldn't blind researchers or subjects to the intervention, nor could results be controlled for the systematic difference between the comparison groups in outcome.[25,27,29,30]

Adherence interventions, measures, and outcomes

The interventions and target outcomes for the 6 retained studies are summarized in Table 3. The interventions in the retained studies could be generally described by grouping into one of 3 categories as following: (1) general patient education,[25,27–30] (2) tailored intervention (combinations of patient education and targeted behavior change intervention),[25,27–30] and (3) dosage/regimen simplification.[25] An approach comprised of tailored intervention methods was used in 4 studies. Adherence was measured and reported by patients[25,27–30] or researchers.[26,28] Behavioral measure (self-report) was used in 2 studies.[25,26] One used pill count and percentage of doses taken to measure adherence; the other used the Microelectronic Monitoring System (MEMS) cap and pill count. Three studies implemented combinations of biochemical and behavioral measures,[27,29,30] using blood serum sample to determine the level of drug and its metabolite.

Four of the studies reported a statistically significant difference in adherence between control and intervention groups.[25,27,28,30] The adherence rate ranged from 44 to 96.1%.[25,27,28,30] However, Klein and colleagues (2006) reported no significant difference in adherence between once and twice-a-day topotecan regimens.[26] In addition, Richardson and colleagues reported improved allopurinol adherence in patients receiving intervention compared with control, but no significant difference in prednisone adherence.

Clinical, humanistic, and economic outcomes

Clinical outcomes

Table 4 gives a summary of clinical outcomes addressed in the literature for oral chemotherapy; these consisted of cytogenetic response, pharmacologic response, pharmacokinetic response, adverse physical effects, and survival time. Doti and colleagues found a statistically significant increase in cytogenetic response in chronic myeloid leukemia patients in the tailored intervention arm.[25] Klein and colleagues evaluated an intervention involving dosage simplification in myelodysplastic syndrome patients.[26] Patients receiving once daily did not demonstrate any difference in pharmacological response (complete or partial response; hematologic improvement) and pharmacokinetic parameter compared with patients in the control group, who received twice daily topotecan. In term of toxicities, occurrences were similar between the two regimens. However, they found the twice-a-day resulted in a statistically significantly higher platelet transfusion requirement than the once-a-day regimen. The influence of adherence on survival time was investigated by Richardson and colleagues.[30] The data demonstrated that disease severity, high adherence, and intervention groups were associated with decreased risk of death and increased survival time. Adherent patients had statistically significantly longer survival time compared with non-adherent. Additionally, patients receiving educational and supportive programs demonstrated statistically significant improvement in survival time. On the contrary, high and moderate severities of disease may shorten survival time compared with those with low severity, but adherence was not related to severity of illness in this study. One study evaluated the influence of adverse physical effects due to disease or chemotherapy on adherence by using a questionnaire; however there was no significant difference between intervention and control groups concerning the impact of adverse physical effects.[29]

Humanistic and economic outcomes

None of the 6 studies reported assessments for humanistic outcomes (e.g., quality of life, patient satisfaction) or for economic outcomes.

Table 1
Characteristics of included studies

Source	Regimen	Study design	Sample	Duration (months)	Setting	Method (description of the intervention)	Adherence measure
Moon et al[28] (Korea, 2012)	Imatinib	- Cross sectional study - 4 centers	114 Chronic myeloid leukemia patients	36 months	Outpatient	I: happy club group (education via telephone counseling and mail letter) C: non-happy club group	- Overall adherence: mg taken/mg prescribed × number of days prescribed/365
Doti et al[25] (Argentina, 2007)	Imatinib	- Prospective, case-control study - single center	24 Chronic myeloid leukemia patients (F:10; M:14)	12	Outpatient	Case: tailored intervention C: no intervention	- Adherence: Pill count and mg taken/mg prescribed × 100 - Cytogenetic: Cytogenetic response
Klein et al[26] (USA, 2005)	Topotecan	- RCT - single center	90 myelodysplastic syndrome patients	4.2	Outpatient	I1:topotecan once daily I2: topotecan twice a day	- Adherence: MEMS, pill count - Pharmacologic response - Pharmacokinetic parameter
Richardson et al[30] (USA, 1990)	Prednisone and allopurinol	- Cohort study - single center	94 hematologic malignancies patients (F:35; M:59)	Adherence: 6 Survival: 48.6	Outpatient	I1: education + home visit I2: education + tailoring I3: education + tailoring + home visit C: no intervention	- Adherence: Serum metabolites and self-report - Survival status: Survival time
Richardson et al[29] (USA, 1988)	Prednisone and allopurinol	- Cohort study - single center	107 hematologic malignancies patients (F:41; M:66)	6	Outpatient	I1: education + home visit I2: education + tailoring I3: education + tailoring + home visit C: no intervention	- Adherence: Serum metabolites and self-report - Adverse physical effects: Questionnaire
Levine et al[27] (USA, 1987)	Prednisone and allopurinol	- Cohort study - single center	108 hematologic malignancies patients (F:41; M:67)	6	Outpatient	I1: education + home visit I2: education + tailoring I3: education + tailoring + home visit C: no intervention	- Adherence: Serum metabolites and self-report

AVR = automated voice response; C = control; I = intervention; F = female participants; M = male participants; MEMS = Microelectronic Monitoring System; MMAS-8 = the eight-item Morisky Medication Adherence Scale; NS = not significant at $P < 0.05$ level; RCT = Randomized Controlled Trial; Tailored intervention = discussion regarding non-adherence and revised dosing schedule.

Table 2
Methodological quality, risk of bias in adherence outcome results of retained studies

Source	Study design	Selection bias	Blinding	Performance bias	Attrition bias	Intervention fidelity
Moon et al[28] (Korea, 2012)	Cross-sectional	?	–	?	+	?
Doti et al[25] (Argentina, 2007)	Case-control	–	–	?	+	?
Klein et al[26] (USA, 2005)	RCT	+	–	?	+	?
Richardson et al[30] (USA, 1990)	Cohort	–	–	?	+	?
Richardson et al[29] (USA, 1988)	Cohort	–	–	?	+	?
Levine et al[27] (USA, 1987)	Cohort	–	–	?	+	?

Risk of bias: + = Low risk of bias; ? = unknown risk of bias, – = high risk of bias.

Discussion

Implications for practice

Four of the interventions reported statistically significant improvements in adherence outcomes compared to the control groups[25,27,28,30]; two of these demonstrated significantly positive outcomes for both adherence and clinical outcomes.[25,30] Overall, the evidence in the literature did not reveal one best-practice intervention design to improve adherence in oral chemotherapy. The intervention designs, methods, and measures were heterogeneous, making a direct comparison challenging, but a general tailored intervention structure that included education and targeted behavior change intervention was impactful in several of the studies; these included education and patient-centered decision-making about treatment choice and adherence support. Even though the details of those included in retained studies varied, tailoring and education could be considered as a general intervention structure for adherence with oral chemotherapy. This makes sense from what has been reported in the literature regarding education as an important foundational piece for adherence intervention, but not as a stand-alone intervention.[31] It is also challenging to draw definitive conclusions because the number of studies of adherence in hematological malignancies is very limited. Three of the 6 retained studies were conducted prior to the year 2000, while the others were performed after 2000. One possible explanation is because most of the research in this area has examined adherence with oral chemotherapy in solid cancer due to the existence in the market of oral agents targeting solid cancer tumors. Novel targeted agents in hematological malignancies had just been approved and introduced to the market after 2001.[6,7]

Indirect methods were commonly used to measure adherence rates. Although, some approaches such as drug level and MEMS provide a somewhat more precise measure of adherence than self-report, they are expensive and require labor-intensive efforts and may not be practical for use in daily practice.[14] Based on data from the retained studies, and supported by findings for other chronic diseases, educational and tailored interventions may be beneficial because they were more likely to have significant improvement in adherence and clinical outcomes.[19,32–34] In addition, there are several factors that authors suggested may have had influence on adherence. Richardson and colleagues reported that adherence with prednisone correlated inversely and significantly with regimen complexity. This means while complexity of the regimen increased, patient adherence decreased.[13,19,35] The majority of chemotherapy regimens for treating hematological malignancy are typically complex and sophisticated.[7] Concerning dosage simplification, Richardson's results suggested no statistically significant difference in adherence rate among number of doses taken daily. The results of this study are inconsistent with findings from the report by Claxton and colleagues who conducted a systematic review and found that adherence was conversely proportional to dosing frequencies ($P < 0.05$).[32]

For major clinical outcomes, cytogenetic responses and survival time were statistically significantly impacted or associated with adherence after the interventions, including tailored intervention, educational, and supportive interventions.[25,30] The studies emphasized the meaningful impact of improving adherence by providing interventions. Moreover, achievement of cytogenetic response is related to prolonged survival which is one of the goals of cancer therapy.[36] Notably, the result

Table 3
Summary of adherence outcomes

Source	Description of the intervention	Intervention group(s) vs control group	Adherence rate per group	Level of significance
Moon et al[28] (Korea, 2012)	I: happy club group (education via telephone counseling and mail letter) C: non-happy club group	I > C	Intervention group vs. Control group: 93.0% (±2.3) vs 76.2% (±7.4)	$P = 0.001$
Doti et al[25] (Argentina, 2007)	I: tailored intervention C: no intervention	I > C	Intervention group vs. Control group: 96.1% (±9.0%) vs. 80.0%	$P < 0.05$
Klein et al[26] (USA, 2005)	I1:topotecan once daily I2: Topotecan twice daily	I1 = I2	Adherence rate: 90.0%	NS
Richardson et al[30] (USA, 1990)	I1: education + home visit I2: education + tailoring I3: education + tailoring + home visit C: no intervention	Prednisone:I1 = I2 = I3 = C Allopurinol: I1 = I2 = I3 > C	Prednisone: 29.0–41.0% (I1-3) vs 32.6% (C) Allopurinol: 45.0% (I) vs 21.0% (C)	NS $P < 0.05$
Richardson et al[29] (USA, 1988)	I1: education + home visit I2: education + tailoring I3: education + tailoring + home visit C: no intervention	Prednisone:I1 = I2 = I3 = C Allopurinol: I1 = I2 = I3 > C	Prednisone:33.0% Allopurinol:41.0%	N/A
Levine et al[27] (USA, 1987)	I1: education + home visit I2: education + tailoring I3: education + tailoring + home visit C: no intervention	Prednisone:I1 = I2 = I3 = C Allopurinol: I1 = I2 = I3 > C	Prednisone: 32.7–38.0% (I1-3) vs 26.8% (C) Allopurinol: 44.0–48.0% (I1-3) vs = 16.8% (C)	NS $P < 0.01$

C = control; I = intervention; MEMS = Microelectronic Monitoring System; NS = not significant at $P < 0.05$ level; RCT = Randomized Controlled Trial; Tailored intervention = discussion regarding non-adherence and revised dosing schedule.

Table 4
Summary of clinical outcomes

Source	Description study group	General results	Clinical outcomes targeted	Intervention group(s) vs control group	Level of significance
Doti et al[25] (Argentina, 2007)	I: tailored-intervention C: no intervention	Case > Control	Cytogenetic response (% cytogenetic response)	Intervention group vs. Control group: 89.9 (±20%) vs. 60% (±25%)	$P < 0.05$
Klein et al[26] (USA, 2005)	I1: Topotecan once daily I2: Topotecan twice daily	I1 = I2	I. Pharmacologic response	1. Complete and partial response	NS
		I1 = I2	1. Response (% response)	I1 vs. I2: 3% vs. 10%	NS
		I1 = I2 EXCEPT that I2 received more transfusions than I1	2.1 Hematologic improvement (% improvement)	2.1 Hematologic improvement I1 vs. I2: 28% vs. 33%	NS $P < 0.05$
			2.2 Grade 3 and 4 toxicity (% achieving 3 and 4 toxicity)	2.2 Toxicities I1 = I2 EXCEPT transfusion requirement I1 vs. I2: 51% vs. 83%	
		I1 = I2	II. Pharmacokinetic response	Pharmacokinetic parameter: (CL/F; Vc/f; Ka) I1 = I2	NS
Richardson et al[30] (USA, 1990)	I1: education + home visit I2: education + tailoring I3: education + tailoring + home visit C: no intervention	I1 = I2 = I3 > C (allopurinol arm)	Survival time by group and characteristic comparisons	1. Intervention vs. Control: RR 0.39: 1.00; CI 95%: 0.17–0.89 2. Adherent vs. Nonadherent: RR 0.45: 1.00; CI 95%: 0.21–0.94 3. Disease severity (high vs low severity) RR 2.48; CI 95%: 1.13–5.46	$P < 0.05$ $P < 0.05$ $P < 0.05$
Richardson et al[29] (USA, 1988)	I1: education + home visit I2: education + tailoring I3: education + tailoring + home visit C: no intervention	I1 = I2 = I3 = C	Adverse physical effects	Non-significant relationship between adherence and hair loss, nausea, loss of appetite, fever, weakness, pain, bleeding, and infection	NS

C = control; CI = confidence interval; CL/F = apparent clearance; I = intervention; Ka = absorption rate constant; MEMS = Microelectronic Monitoring System; NS = not significant at $P < 0.05$ level; RCT = Randomized Controlled Trial; RR = Relative Risk; Tailored intervention = discussion regarding non-adherence and revised dosing schedule; Vc/F = apparent volume of distribution.

regarding influence of adherence on better cytogenetic responses in patients with chronic myeloid leukemia is consistent with data from the recent study by Marin and colleagues[18] as mentioned earlier; in addition, the ADAGIO study by Noens and colleagues indicated that nonadherence to imatinib treatment is related to suboptimal response and poorer treatment outcome.[37] Concerning dosage simplification, pharmacologic response, toxicities, and pharmacokinetic parameters were not significantly different; only transfusion requirements exhibited statistically significant differences.[26] However, there are other factors that might affect pharmacokinetic variability such as age or renal function.[38]

Implications for research

The objectives of this review intended to also examine evidence and gaps in the literature for research implications. The review of methodological quality suggested that risk of bias in the adherence outcome results may exist in the retained study designs. Allocation and blinding often pose challenges to a behavior intervention study; the inherent nature of behavior change requires knowledge on the part of the patient and practitioner regarding measurement and/or discussion of a particular target behavior. An obvious gap in the literature is evidenced by the minimal numbers of retained studies; only 6 studies met the inclusion criteria that were designed to explore a narrow focus (adherence with oral chemotherapy in adults with hematological cancers) with general applications (heterogeneous adherence measures, interventions, settings, study designs).

More research is needed to address the target research questions, and rigorous study designs will be required in order to draw appropriate conclusions. Well-conducted randomized controlled trials (RCTs) are needed in further research to better understand adherence impact and other essential outcomes in hematological cancers. In addition, future studies implementing adherence interventions should 1) define adherence and how it will be measured in advance of study design and launch[39] and 2) measure relevant practical outcomes such as humanistic or economic outcomes, to examine intervention effectiveness on the adherence behavior outcome as well as factors relevant to the patient and/or the health care delivery system. Moreover, the follow-up time periods reported in the retained studies of this review were relatively short-term periods (e.g., 6 months or less). Consequently, it is crucial to employ longitudinal studies to assess adherence after the intervention has been discontinued in order to examine sustainability of intervention effect for study participants. This would also make it feasible to examine long-term clinical outcomes commonly examined in cancer research, like five-year survival rates.

Additional research could fill gaps in the literature by evaluating patient or system factors often associated with adherence in other conditions or diseases; it would be relevant to examine factors like socioeconomic status, provider or system characteristics, disease/therapies, social support, comorbidities, and general patient characteristics specifically in patients with hematological cancers to examine their influence on adherence and other outcomes.[4–7,9,12,13,34,40] For example, in addition to factors noted in this review, recent technical reviews suggest that patient-related factors like cognitive impairment, comorbid conditions, gender, socioeconomic status, psychological conditions, and other medications can impact adherence. In addition, clinician-related factors can also have an impact, positively or negatively, on a patient's decision-making about medication adherence. For example, some providers are uncertain about long-term follow-up and required surveillance for cancer recurrence.[41] Interventions related to enhancing effective communication between health care providers and patients should be examined. This is particularly relevant because the interventions in the retained studies were performed by research teams and not the patients' health care providers. This atmosphere might not be generalizable to a typical daily practice setting where time constraints or other factors might influence intervention capability. Finally, studies focusing on comparative effectiveness between the impact of single and complex interventions should be performed to find the most impactful and feasible interventions to employ in a typical practice setting, while also striving for an optimal study design.

Limitations

First, decisions about articles to retain within this systematic review were initially made by one researcher, with a follow-up examination of those rejected by the second researcher after the fact. This was not as systematic an approach as could have been employed if comprehensive and simultaneous review and discussion had been employed

for retention/exclusion decisions. Second, a comparison outcome across studies or meta-analysis was not possible due to the heterogeneity and complexity of interventions and outcome measures. Third, there are insufficient evidences to draw rigorous conclusions concerning a single effective intervention to enhance adherence in antineoplastic agents. Fourth, most studies did not measure other patient, provider, or system factors that could have influenced adherence; it is unclear whether factors that typically influence adherence for other conditions have an impact in adherence among cancer patients in the retained studies. Fifth, study lengths were short, eliminating the possibility of making conclusions about interventions that produce sustained behavior change and outcomes. Finally, there may be sources of systematic bias in the review because non-randomized study methods were included in the retained studies.

Conclusions

An increasing use of oral chemotherapy raises awareness of the potential for non-adherence among cancer patients who take these medications on their own outside of a clinical setting. However, through a systematic search and analysis of existing literature, it is clear that there are a very limited number of well-conducted studies examining interventions to improve adherence in oral antineoplastic agents for hematological malignancies. Since oral chemotherapy is a first-line treatment in cancers that don't include solid tumors, it is important to consider the implications of adherence. Interventions tested in the retained studies suggested a positive impact on adherence outcomes; some, but not all, established a significant relationship between adherence and clinical outcomes. The results yielded non-specific evidence regarding general intervention structures that can be expected to impact adherence and potentially other outcomes when applied in real practice settings. Caution is required regarding generalizing the results to patients since the retained studies were conducted in experimental designs with researchers and not the patients' providers. Further rigorous methodological studies (e.g., randomized control trials) of longer duration need to be conducted to further examine the effectiveness of interventions on multiple outcomes including adherence behavior, clinical, humanistic, and economic.

References

1. The Leukemia & Lymphoma Society. Facts 2012. http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdf; Accessed 08.06.13.
2. Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations)*, 2011. http://seer.cancer.gov/csr/1975_2009_pops09/. Accessed 08.06.13.
3. American Cancer Society. Cancer facts & figures 2012. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf; Accessed 08.06.13.
4. Aisner J. Overview of the changing paradigm in cancer treatment: oral chemotherapy. *Am J Health Syst Pharm* 2007;64(9 suppl 5):S4–S7.
5. Partridge AH, Avorn J, Wang PS, et al. Adherence to therapy with oral antineoplastic agents. *J Natl Cancer Inst* 2002;94(9):652–661.
6. Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA Cancer J Clin* 2009;59(1):56–66.
7. Weingart SN, Brown E, Bach PB, et al. NCCN Task Force Report: Oral chemotherapy. *J Natl Compr Canc Netw* 2008;6(suppl 3):S1–S14.
8. Blecher C, Barefoot J, Davis D, et al. A team approach toward promoting patient adherence to oral chemotherapy protocols. *Oncol Nurs Forum* 2008;35(3):537, abstr 2985.
9. Lebovits AH, Strain JJ, Schleifer SJ, et al. Patient noncompliance with self-administered chemotherapy. *Cancer* 1990;65(1):17–22.
10. Liu G, Franssen E, Fitch MI, et al. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997;15(1):110–115.
11. Viele CS. Managing oral chemotherapy: the healthcare practitioner's role. *Am J Health Syst Pharm* 2007;64(9 suppl 5):S25–S32.
12. Haynes RB, Ackloo E, Sahota N, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2008;2:CD000011.
13. Sabaté E. *Adherence to Long-term Therapies – Evidence for Action*. World Health Organization, 2003. http://apps.who.int/medicinedocs/pdf/s4883e/s4883e.pdf. Accessed 08.06.13.
14. Escalada P, Griffiths P. Do people with cancer comply with oral chemotherapy treatments? *Br J Community Nurs* 2006;11(12):532–536.
15. Gater A, Heron L, Abetz-Webb L, et al. Adherence to oral tyrosine kinase inhibitor therapies in chronic myeloid leukemia. *Leuk Res* 2012;36(7):817–825.
16. Breccia M, Efficace F, Alimena G. Adherence to treatment is a complex and multifaceted issue that can substantially alter the outcome of chronic myeloid leukemia patients treated with tyrosine kinase inhibitors. *Leuk Res* 2012;36(7):804–805.
17. O'Brien S, Berman E, Moore JO, et al. NCCN Task Force report: tyrosine kinase inhibitor therapy

selection in the management of patients with chronic myelogenous leukemia. *J Natl Compr Canc Netw* 2011;9(suppl 2):S1–S25.
18. Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol* 2010;28(14):2381–2388.
19. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353(5):487–497.
20. Jabbour E, Saglio G, Hughes TP, et al. Suboptimal responses in chronic myeloid leukemia: implications and management strategies. *Cancer* 2012;118(5): 1181–1191.
21. Font R, Espinas JA, Gil-Gil M, et al. Prescription refill, patient self-report and physician report in assessing adherence to oral endocrine therapy in early breast cancer patients: a retrospective cohort study in Catalonia, Spain. *Br J Cancer* 2012;107(8): 1249–1256.
22. Simons S, Ringsdorf S, Braun M, et al. Enhancing adherence to capecitabine chemotherapy by means of multidisciplinary pharmaceutical care. *Support Care Cancer* 2011;19(7):1009–1018.
23. [Updated March 2011]*Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0*. The Cochrane Collaboration; 2011.
24. Higgins JPT, Altman DG, Sterne JE. Assessing risk of bias in included studies [Updated March 2011]. In: Green S, ed. *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0*. The Cochrane Collaboration; 2011.
25. Doti C, Stemmelin G, Shanley C, et al. Cytogenetic response in relation to the adherence to treatment with Imatinib Mesylate: a case control study. *Blood* 2007;110(11):4553.
26. Klein CE, Kastrissios H, Miller AA, et al. Pharmacokinetics, pharmacodynamics and adherence to oral topotecan in myelodysplastic syndromes: a Cancer and Leukemia Group B study. *Cancer Chemother Pharmacol* 2006;57(2):199–206.
27. Levine AM, Richardson JL, Marks G, et al. Compliance with oral drug therapy in patients with hematologic malignancy. *J Clin Oncol* 1987;5(9):1469–1476.
28. Moon JH, Sohn SK, Kim SN, et al. Patient counseling program to improve the compliance to imatinib in chronic myeloid leukemia patients. *Med Oncol* 2012;29(2):1179–1185.
29. Richardson JL, Marks G, Levine A. The influence of symptoms of disease and side effects of treatment on compliance with cancer therapy. *J Clin Oncol* 1988; 6(11):1746–1752.
30. Richardson JL, Shelton DR, Krailo M, et al. The effect of compliance with treatment on survival among patients with hematologic malignancies. *J Clin Oncol* 1990;8(2):356–364.
31. Krueger KP, Berger BA, Felkey B. Medication adherence and persistence: a comprehensive review. *Adv Ther* 2005;22(4):319–362.
32. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;23(8):1296–1310.
33. Ran MS, Xiang MZ, Chan CL, et al. Effectiveness of psychoeducational intervention for rural Chinese families experiencing schizophrenia–a randomised controlled trial. *Soc Psychiatry Psychiatr Epidemiol* 2003;38(2):69–75.
34. Williams A, Manias E, Walker R. Interventions to improve medication adherence in people with multiple chronic conditions: a systematic review. *J Adv Nurs* 2008;63(2):132–143.
35. Zeppetella G. How do terminally ill patients at home take their medication? *J Palliat Med* 1999;13(6): 469–475.
36. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006;355(23): 2408–2417.
37. Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood* 2009;113(22): 5401–5411.
38. Leger F, Loos WJ, Fourcade J, et al. Factors affecting pharmacokinetic variability of oral topotecan: a population analysis. *Br J Cancer* 2004;90(2):343–347.
39. Spoelstra SL, Given CW. Assessment and measurement of adherence to oral atineoplastic agents. *Semin Oncol Nurs* 2011;2:116–132.
40. Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med* 1990;150(4):841–845.
41. Schneider SM, Hess K, Gosselin T. Interventions to promote adherence with oral agents. *Semin Oncol Nurs* 2011;2:133–141.