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Determinants and associated factors influencing medication adherence and persistence to oral anticancer drugs: A systematic review

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ABSTRACT

Background and aims: The use of oral anticancer drugs has increased in modern oncology treatment. The move from intravenous treatments towards oral anticancer drugs has increased the patients' own responsibility to take oral anticancer drugs as being prescribed. High rates of non-adherence to oral anticancer drugs have been reported. A systematic literature review was conducted to gain insight into determinants and associated factors of non-adherence and non-persistence in patients taking oral anticancer therapy.

Review methods: PubMed, Cochrane, Web of Science and Cinahl were systematically searched for studies focusing on determinants and associated factors of medication non-adherence and non-persistence to oral anticancer drugs. The methodological quality of the included studies was assessed by two independent reviewers. No studies were excluded based on the quality assessment.

Results: Twenty-five studies were included and systematically reviewed. The quality of the studies was moderate. Associated factors influencing medication non-adherence and non-persistence to oral anticancer drugs are multifactorial and interrelated. Older and younger age, and the influence of therapy related side effects were found to be predominant factors.

Conclusion: Non-adherence and non-persistence to oral anticancer drug therapy are complex phenomena. More qualitative research is needed to facilitate the development of patient tailored complex interventions by exploring patients' needs and underlying processes influencing medication non-adherence and non-persistence to oral anticancer drugs.

Introduction

The use and the number of different oral anticancer drugs (OACD) have increased in modern oncology.[1] Currently, 25% of the cancer chemotherapy in development can be taken orally.[1] Many of the available OACD are primarily cytostatic in nature and most effective when given over long-term periods.[2] OACD such as imatinib, has transformed chronic myeloid leukemia (CML) from a lethal to a chronic disease.[3] The use of OACD improves the quality of life of cancer patients by reducing hospital stay and give them a greater sense of control over their treatment while guaranteeing the treatment efficacy,[4] however also poses important challenges such as managing side effects, the prolonged treatment period and adherence issues.

Several studies show that most patients (range 54–89%) prefer to be on an oral therapy compared to intravenous therapy[5–8]; this mainly because medication can be taken at home and no needle has to be placed.[5,8,9] The shift from intravenous treatments towards OACD therapy increases patients' responsibility to take their OACD rigorously as being prescribed by their physician.[2] Because of the association between adherence and treatment success, concerns about non-adherence to OACD therapy have become an increasingly important issue in oncology.[2,10,12]

Until now, multiple definitions exist[11,13] but there is no universally accepted definition of medication (non-)adherence.[10] For this review, non-adherence has been operationalized based on the definition by Ruddy et al. (2009), who consider a patient to be non-adherent if "doses are missed, extra doses are taken or doses are taken in the wrong quantity or at the wrong time". This definition

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was chosen because of its concreteness. Non-persistence occurs when patients "don't take their medication as long as prescribed".[11] The terms non-persistence and early discontinuation are used interchangeably in the literature.

A literature review by Foulon et al. (2011) reports on OACD therapy non-adherence rates between 0% and 84%. The variation is mainly related to (1) differences in the type of OACD therapy (e.g. side effects, complexity of regimen), (2) differences in the definition of adherence being applied in the primary studies, and (3) differences in the assessment of medication adherence. OACD therapy non-adherence rate in breast cancer patients was found to be as high as 23% over a one year period.[14] Treatment discontinuity was found in 17% of the patients after two years[15]; and even in 31% after five years.[16] Marin et al. (2010) reported that 26.4% of the CML patients was ⩽90% adherent with their prescribed OACD therapy. Similar results have been found in a Belgian setting.[17] One third of the patients with CML appeared to be non-adherent with their treatment; only 14.2% was found to be completely adherent.[17]

Non-adherence and non-persistence significantly reduce the efficacy of OACD therapies.[2] Non-adherent patients with CML, treated with the OACD imanitib, were less likely to achieve complete cytogenetic responses (CCyR), resulting in a reduced success rate.[18–20] In the study by Noens et al. (2009), patients taking 74.0–76.8% of the prescribed dose had a less good response than patients taking 89.9–92.7% of the prescribed dose. In breast cancer patients, lower survival rates were found for patients being <80% adherent to the oral drug tamoxifen.[21] Non-adherence to OACD therapy was also related to higher healthcare costs due to the increased number of doctor visits, longer hospital stays and more frequent hospitalization.[22,23]

Given the magnitude and consequences of non-adherence in patients on an OACD therapy, an exploration of associated factors and underlying processes of medication non-adherence is needed. Factors influencing medication non-adherence and non-persistence are complex due to the multifactorial and interrelated character.[24] Understanding the complexity of non-adherence and non-persistence to OACD is important as it can inform the development of an intervention to enhance adherence and persistence with this type of medication. A literature review is therefore a crucial step in the development of such interventions.[25]

Literature reviews on medication non-adherence or non-persistence with OACD therapy are often not conducted and/or reported in a rigorous systematic way.[2,11,26] To our knowledge, only one systematic review including literature up until 2002 on non-adherence and non-persistence in patients taking OACD, has been conducted.[12] In the latter review different OACD have been considered.

The aim of our review is to provide an updated overview of determinants and associated factors of medication (non-)adherence and (non-)persistence in patients taking different types of OACD.

Methods

Search strategy

Four electronic databases were searched: PubMed, the Cochrane database, Web of Science, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search strategy consisted of MeSH terms and free text words subsequently combined (see Table 1).

All titles and abstracts were screened independently by two reviewers (MV & KL). If the abstract did not provide enough information to decide upon inclusion/exclusion, the full paper was retrieved for further screening. Disagreements about inclusion or exclusion were discussed between the reviewers until consensus was reached. The reference lists of the included articles were reviewed and additional articles were considered if appropriate.

Selection criteria

Articles were included if they addressed OACD therapy, focused on determinants and associated factors of medication adherence/compliance and/or medication persistence of patients aged 18 and older, and were evaluated as being of strong or moderate methodological quality. Factors considered to evaluate methodological quality for quantitative studies were: the presence of selection bias, allocation bias, confounders, study design, blinding, data collection methods, withdrawals and drop-outs, and the appropriateness of the analysis to the research question.[27] For qualitative studies, methodological quality was evaluated considering clear statement of the aims, the relationship between researcher and participants, ethical issues, rigorousness of the data analysis, clear statements of the findings, value of the study, appropriate methodology, design, recruitment strategy and data collection.[28]

The primary outcomes of the primary studies had to be (non-) adherence and (non-)persistence to OACD therapy to be eligible for inclusion. Only original research articles published between 1990 and April 2012 and written in English, French, German or Dutch were included. Study design was not used as a selection criterion. Studies conducted in developing countries were excluded because of the different context and differences in healthcare delivery systems.

Quality assessment

The methodological quality of each study was independently evaluated by two reviewers (MV & KL) using (1) the Quality Assessment Tool developed by Vyncke et al.[27] for quantitative studies, and (2) the Critical Appraisal Skills Programme (CASP) developed by the Public Health Resource Unit[28], National Health Service, England (2006) for qualitative studies.

The Quality Assessment Tool of Vyncke et al.[27] is based on a tool developed by the Effective Public Health Practice Project[29] and used by Mirza et al.[30] This tool was chosen because of (1) the extensiveness of the assessment of methodological quality and, (2) the usability for quality assessment of different quantitative research designs. The tool considers presence of selection bias and confounders, study design, blinding, data collection methods, withdrawals and drop-outs, appropriateness of the analysis to the research question, and the integrity of the intervention. The item on integrity of the intervention was not applicable for this review. For each item, two reviewers (MV & KL) assigned a rating of strong, moderate or weak based on the evaluation criteria of the quality assessment tool. Discrepancies in the reviewers' evaluations were discussed until consensus was reached.

The CASP includes 10 questions to assess (1) rigorousness, (2) credibility and, (3) relevance of the qualitative study by answering yes/no for each question. The first two questions are general screening questions considering whether the goal of the study is clear, and whether a qualitative methodology is appropriate for the study. When both questions are positively answered, it is worth proceeding to the remaining detailed questions to consider methodological quality.[28]

Data abstraction and synthesis

Two reviewers (MV and KL) independently extracted the data from each article. Findings were summarized using a data extraction sheet (Table 2). This sheet included the following items: author(s) and publication date, research focus, design, the definition of medication non-adherence and non-persistence, measurement, participants (n), factors associated with medication