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Adherence influencing factors in patients taking oral anticancer agents: A systematic review

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ABSTRACT

Background: The use of oral anticancer agents increased steadily in the last decades. Although oral anticancer agent adherence is important for a successful treatment, many patients are insufficiently adherent.

Purpose: To evaluate adherence influencing factors in patients taking oral anticancer agents.

Methods: A systematic literature search was performed in Medline and Embase. Titles and abstracts and in case of relevance, full-texts were screened according to predefined inclusion criteria. The risk of bias was assessed. Both were carried out independently by two reviewers. Relevant data on study characteristics and results were extracted in standardized tables by one reviewer and checked by a second. A meta-analysis was not performed because of clinical and methodological heterogeneity between the studies to avoid misleading results. Data were synthesized in narrative way using a standardized procedure.

Results: Twenty-two relevant studies were identified. The study quality was moderate. Especially the risk of bias regarding the measurement of influencing factors and adherence was mostly unclear. Social support, intake of aromatase inhibitors, and lower out-of-pocket costs for OACA seem to have a positive effect on adherence. Depression and the number of different medications seem to have a negative effect on adherence.

Low age and very high age seem to be associated with lower adherence.

The remaining factors showed either mostly no influence or were heterogeneous regarding the effect direction and statistical significance.

Conclusions: There are some factors that seem to have influence on adherence in patients taking OACA. However, due to the heterogeneity no general conclusions can be made also for these factors that can be applied to all indications, medications, settings, countries etc. The results should rather be considered as indications for factors that can have an influence on adherence to OACA.

1. Introduction

The use of oral anticancer agents (OACA) has increased steadily. One quarter of newly developed anticancer agents can be taken orally [1]. The use of OACA will probably increase further. Most patients prefer to take their medication orally [2]. Adherence, defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [3] is lower in patients taking OACA compared to patients treated with intravenous chemotherapy [4]. It is estimated that adherence rates in patients taking OACA lie in a range between less than 20% and 100%, depending on patient characteristics, therapy and adherence measurement and definition [5,6]. For some cancer types adherence to OACA turns out to be crucial factor for the success of treatment [7–9], especially given the long period in which OACA have to be taken correctly. Consequently, adherence has become a key issue in modern oncology treatment. There are several factors that can potentially influence patient adherence [10]. In clinical practice the knowledge about factors that influence patient adherence can help to identify patients at risk for non-adherence and also help to develop methods to improve adherence in affected populations.

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The objective of this systematic review was to identify adherence influencing factors in patients taking OACA.

2. Material and methods

2.1. Sources

This systematic review was prepared according to the standards of the Cochrane collaboration, recommendations for systematic reviews of prognostic factors, and reported according MOOSE [11–13].

A systematic literature search was performed in MEDLINE (via Pubmed) and Embase (via Embase). The search strategy comprised several terms and medical subject headings related to adherence and OACA (the full search strategies are available in Supplement I). The search was performed in December 2012. Study type, publication date and language were not limited in the search strategy because it was intended to maximize sensitivity. In addition, the reference lists of all included publications were hand-searched and a Google scholar search was performed to identify gray literature.

2.2. Study selection

To be eligible for this review the studies had to meet the following inclusion criteria:

1. Patients: Adult patients (≥18 years) with malignant neoplasms
2. Medication: Intake of OACA
3. Exposure: Potential adherence influencing factor/s
4. Outcome: Quantitative patient adherence measure
5. Study type: Quantitative analyses between exposure and adherence e.g. correlation (no interventional trials)
6. Published in English or German

All types of malignant neoplasms and OACA were included. Non-adherence can be intentional or non-intentional. Prior research revealed that non-adherence is mostly non-intentional [14]. To ensure comparability exclusively intentional non-adherence measures (e.g. patient stated reasons) were excluded, if distinguishable. A study was accepted as quantitative if there were either an association measure between the exposure and adherence or if values were stated separately for exposure as well as adherence.

Firstly, the titles and abstracts were screened. Secondly, the full-texts of all potentially relevant articles were obtained and screened. Two independent reviewers performed the study selection according to the a priori defined inclusion criteria. Any differences between the reviewers were discussed until consensus. The authors were contacted in case of any missing information regarding the inclusion criteria.

2.3. Assessment of risk of bias

The risk of bias of included studies was assessed using a six item methodology checklist for prognostic studies (evaluation questions for the instruments are available Supplement II) [15]. The measurement of adherence was only considered without bias if measured with a medication event monitoring system (MEMS, e.g. electronic tablet bottles) or with blood samples, because MEMS is considered as gold standard and blood samples are direct and objective [16]. The risk of bias assessment was performed independently by two reviewers. Disagreements were resolved in a discussion or by involving a third person.

2.4. Data extraction and synthesis

The data on study characteristics and results were extracted in beforehand compiled standardized tables. The number of analyzed patients, demographic, socioeconomic and clinical inclusion criteria, cancer type, the OACA, the country where the study took place, the used adherence measure and mathematical operationalization as well as the adherence rate of the study population were extracted for each study. Because in some studies many different OACA were used by a small part of the study population, the type of OACA was extracted only if taken by ≥5% of study population. For each analyzed influencing factor the effect on adherence (effect direction or compared categories; effect size and measure) and the statistical significance (p-value) were extracted. To describe the effect direction uniformly all data in the tables were commutated so that it refers throughout to the influence on adherence regarding an increase of the respective factor independently whether the factor is positive (e.g. educational level) or negative (adverse events). In the case the studies used univariate as well as multivariate analysis methods, only the results of the last mentioned were extracted. Data extraction were performed by one reviewer and verified by a second.

A quantitative data synthesis using a meta-analysis was planned a priori but was not performed because no statistically significant results were mostly reported and consequently pooling would have been biased. Furthermore, there was strong heterogeneity regarding the included patients, adherence measurements and definitions/operationalization, measurement of influencing factors, and statistical analysis methods (e.g. adjustments, categorizations). Thus, it was decided not to pool the results to avoid misleading summary estimations. For all factors that were analyzed in at least two studies a summary estimation effect direction and effect size was made. Two reviewers rated the evidence for an effect, considering the consistency of the effect direction (within and between studies), the effect size, the statistical significance, the sample size and the risk of bias of included studies that analyzed the respective factor. Discrepant ratings were discussed until consensus.

A p-level of <0.05 was considered statistically significant.

3. Results

3.1. Literature search

After deducing duplicates the search in electronic databases resulted in 2309 hits. After title and abstract screening 95 seemed potentially relevant and full-text versions were screened in detail. Finally 23 publications of 22 studies were included [7,8,17–37]. The manual search and reference-check revealed no further relevant publications. The flowchart illustrates the selection process (Fig. 1).

3.2. Description of studies

The characteristics of the included studies are presented in Table 1. The number of analyzed patients ranged between 11 [27] and 13.479 [23] patients. Breast cancer was the most analyzed cancer type followed by colorectal and lung cancer and hematologic malignancies. In two studies a specific study population was examined. Consequently, the most prescribed drugs were tamoxifen, capecitabine and imatinib. Partridge et al. [31] included only low income indigent patients and Xu et al. [8] only men with breast cancer. With four exceptions [8,24,30,36] all studies were performed in WHO mortality stratum A (very low child mortality and low adult mortality) [38]. Most studies used either pill counts or self-reports to measure adherence. Only three studies used