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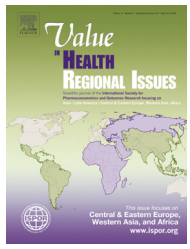

Pharmacoeconomics Evaluations of Oral Anticancer Agents: Systematic Review of Characteristics, Methodological Trends, and Reporting Quality

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ABSTRACT

Objectives: To review literature characteristics, describe methodological trends, and assess the reporting quality of the economic evaluations of oral anticancer drugs (OACDs). **Methods:** The review included comparative economic evaluations of OACDs. The search was conducted via PubMed, Embase, EconLit, and Economic Evaluation Database, and studies till December 2017 were included. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist, literature inclusion and data extraction were performed in duplicate by separate investigators. Outcome measures were literature characteristics, gaps and methodological trends, and reporting quality using the Consolidated Health Economic Evaluation Reporting Standards checklist. Data were summarized on the basis of methodological themes of interest. Descriptive statistics and tabulations were used for result presentation. **Results:** Out of 241 found articles, 21 were included. There is a recent increasing interest in the economics of OACDs, whereby the cost per quality-adjusted life-year, via cost-utility analysis, is the most used for decision making. Most of the studies were from the payer perspective, and the primary sources of data were clinical trials, expert panels, and medical charts. The dominance status (higher effect, lower cost) was a commonly reported outcome. Decision-analytic modeling was used in most of the studies, mostly including Markov modeling. Studies were highly heterogeneous in methodological aspects, and the included studies did not meet most of the reporting quality criteria. **Conclusions:** High heterogeneity in methods in studies may limit the robustness and transferability of results, potentially misleading decision makers toward wrong decisions on OACDs. The transferability and generalizability of results are further limited by a "less than ideal" adherence to current reporting standards.

Keywords: cancer, economic evaluation, methods, oral chemotherapy, systematic review.

Introduction

The oral chemotherapy landscape has developed over the years. The first approval of oral anticancer drugs (OACDs) by the Food and Drug Administration was in the early 1950s, which rapidly grew in the early 2000s, overtaking the growth of intravenous chemotherapy in the last 5 years [1,2]. It is estimated that more than a quarter of the 400 anticancer drugs now in the development pipeline are planned to be oral agents [3]. Seeing the minimized inconvenience of infusion, including pain, anxiety, and inpatient status, OACDs have been proposed to be associated with improved quality of life (QOL) in patients. The oral administration allows patients to receive their therapy at home, with only follow-ups taking place in a hospital setting. These, together with an increased incidence of cancer, availability of more therapeutic alternatives, and insufficiency of hospital resources, have led practices to move toward the use of OACDs [4,5].

Cancer care requires a significant amount of control, particularly for dosing and its timing. With OACDs, however, much of this control is in the hand of the patients. The lack of coordinated care results in a possible level of errors, nonadherence, and increased adverse events [6]. As a consequence, and despite the advantages, the use of oral chemotherapy has been controversial. Importantly, and within the context of the present research, the economic burden is especially a prominent issue that has an impact on the use and prescribing of OACDs, influencing patient access to the drugs. Oral chemotherapies tend to be costly. As of 2014, in the United States, for example, most of the newly marketed OACDs had a price that exceeded US $10,000/mo [7]. In addition to the financial burden, prescribing OACDs is believed to be partly shifting the economic paradigm of cancer care and medical service from the hospital setting to the community, creating a loss of potential resources for hospitals, which may create a barrier to the widespread use of the drugs and, hence, reduced patient access [8,9]. Also important, and partly a result of the aforementioned burdens, is that it is common for the cost of OACDs not to be covered by government reimbursement because OACDs are not administered in a hospital or a clinical setting,

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even if they are administered on the basis of accepted treatment protocols [10]. Nevertheless, OACDs still have considerable advantages, as discussed earlier, which have the likely potential for downstream cost-savings. Hence, although most of the evaluations of OACDs seem to be focusing on treatment adherence and safety, it is only logical that future research will focus more on the economic implications of OACDs, especially for guiding toward the right national reimbursement plans for oral chemotherapies in settings. It is, therefore, anticipated that there is and will continue to be an increasing interest in conducting economic evaluations of OACDs, as opposed to that of nonoral chemotherapies [11]. Several studies [12–25] have indeed been performed to find that the cost-savings with OACDs as associated with the reduced need to treat adverse events, and with the enhanced patient time and medical resource utilization, exceeded the relative increase in acquisition costs of the drugs as compared with the intravenous formulations.

Here, the absence of research technique standardization and poor consistency with established standards, filling knowledge gaps on literature characteristics, and methodological trends will be of functional incentive to researchers in arranging and sorting out their local explorations.

In the present study, the objective was to systematically review the literature characteristics, the methodological trends and gaps, and the reporting quality of the economic evaluations of oral chemotherapies in the literature. It is important to note that the clinical, practice, and policy aspects of studies are outside the scope of the present review.

Information about such literature characteristics and trends will be of practical value for consideration by researchers in settings that are looking to perform pharmacoeconomics research on OACDs. This information is added to enable a better understanding of the quality of evidence by decision makers as they contrast this against current gaps and quality of reporting in the literature. Results from the present study can also be inceptive to journal editors and commentators in enhancing the quality of distributed research.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting checklist was followed for the purpose of the present study (see Appendix I in Supplemental Materials found at 10.1016/j.vhri.2018.05.003) [26].

Search Strategy

A systematic review of the literature was conducted via the databases PubMed, Embase, EconLit, and the National Health Service Economic Evaluation Database (EED). The search was last updated in July 2017 for PubMed, Embase, and EconLit. The EED, however, ceased its search in December 2014 and did not include publications from later dates. Articles found via PubMed were differentiated by labeling them as "PubMed—indexed for MEDLINE" or "PubMed—in process." The former refers to articles that exist in MEDLINE, whereas the latter refers to articles that exist only in PubMed. The PubMed search terms were the Medical Subject Heading terms "antineoplastic agents," "administration, oral," "neoplasms," and "cost-benefit analysis," in addition to the free-text term "oral." The Embase index terms used were the Emtree terms "oral drug administration," "antineoplastic agent," "neoplasm," "cost-effectiveness analysis," "cost-benefit analysis," "cost-utility analysis," "cost-minimization analysis," "economic evaluation," "cost," and "pharmacoeconomics," in addition to the free-text terms "oral," "neoplasms," "cancer," "cancers," and "tumor." The EED search keywords were similar to those in Embase. The EconLit search terms were "antineoplastic agent," "anticancer," "oral," "neoplasm," "cancer," "tumor," "cost effectiveness," "cost utility," "cost benefit," and "economic evaluation." The full PubMed search strategy is given in Appendix II in Supplemental Materials found at 10.1016/j.vhri.2018.05.003.The same was adapted for the other databases. The database search included the gray literature, such as books, dissertations, conferences, working papers, and governmental publications, and was supplemented with a screening of references in the included articles and also a general Internet search using Google and Google Scholar, where free-text searching used the same search terms as in the primary search.

Selection Criteria

Inclusion criteria

The inclusion criteria were outlined in terms of the PICO (Population, Intervention, Comparison, Outcome) framework:

- *Population*: Cancer-based underlying disease.
- *Intervention*: Study of the use of at least one oral chemotherapy in cancer.
- *Comparison*: Therapy-based comparative studies.
- *Outcome*: Peer-reviewed publications of comparative studies till December 2017 were included. No considerations were made on whether the articles were freely available. No considerations were made on whether the studies were retrospective or prospective. Of interest in the included literature were the characteristics, methodological trends and gaps, and the reporting quality of the economic evaluations.

Exclusion criteria

The exclusion criteria included the following:

- Non-English language
- Nonhuman studies
- Noncomparative research (e.g., letters, general reviews, and editorials)
- Non–drug-based studies

Data Extraction

Screening for initial eligibility via the search terms was done by assessing the titles and abstracts first. Found articles via the database search were further screened for eligibility through a manual analysis of study abstracts. Then, for final inclusion in the study, a follow-up manual screening by reviewing the full text of the initially eligible articles was conducted. This process, in addition to data extraction, was separately performed for conformance by two of the authors. Disagreements were further discussed by the research team as led by one of the authors. Before formal data extraction, and for validation purposes, a random sample of three included articles was independently reviewed by each of the study authors before being discussed to ensure consistency and agreement among all.

Extracted data from included full texts were related to study characteristics and methodological features, such as comparators, study objectives, setting and perspective, type of evaluation, research design, types and sources of clinical and economic data, time adjustment, time horizon, limitations, and uncertainty analyses.

Descriptive statistics and tabulations were used to present the results.

Quality Assessment

Economic evaluations were scrutinized by using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)