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Review

Deficiencies of methods applied in cost effectiveness analysis of hematological malignancies

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ABSTRACT

Background: As novel therapies in oncology and in particular hematological malignancies impose a high financial burden with a limited increase in life expectancy. Therefore, CEA is important to evaluate the value of new therapies. However, there is a dire need to critically evaluate how valid are such studies.
Aims: To review and critically analyze the methodology used to conduct CEAs within the hematologic malignancies disease.
Methods: We conducted a PubMed search using the following keywords and combined searches: CEAs, hematological malignancies leukemia, lymphoma and myeloma.
Results: Available data showed that systemic reviews of CEA of hematological malignancies to assess whether reviewers have not sufficiently cited deficiencies in their methodologies, or stated clearly the impact of sponsorship and publication biases.
Conclusion: Despite the paucity of the literature, sponsorship bias was found to be a major concern in the validity of these analyses.

Contents

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Introduction

The overall cost of cancer treatment in America has nearly doubled over the past two decades [1,2]. In fact, health care expenditure is expected to encompass 20% of the US gross domestic product by 2015 [3–5], with an increase of use of care near the end of life [6,7].

Hematological malignancies are a diverse group where leukemia was found to be the fifth most expensive condition in terms of acute hospital costs [8]. In this regard, the increase of the average length of stay brings the cost higher [9], as well as the frequency of some lymphoid malignancies [10,11]. Therefore, there is a need especially recently for cost effectiveness analyses (CEAs) to examine thiscost [12]. In effect, this type of studies have helped to craft health care policies [13–19]. CEAs provide a standardized method to evaluate cost and beneficial effect of treatment [17,20,21].

An important notion is the Incremental cost-effectiveness ratio (ICER), which compares the difference between the costs and health outcomes of two treatments [12,16,22,23]. While evaluating methodological strength of CEA in oncology remains a concern; an improvement was noted in regards to the proportion reporting ICERs [12]. However, not reporting the time horizon (the time period over which costs and effectiveness are analyzed), the discount costs or quality-adjusted life years (QALYs) were among the noted deficiencies. Perhaps, CEAs of hematological malignancies are not different from other CEA studies. However, our team of physicians at Roswell Park Cancer Institute in the division of leukemia was intrigued to explore this area of CEA and oncology. Therefore, we reviewed Pubmed to examine the methods implemented to evaluate CEA methodologies, and systemic reviews of CEAs of hematological malignancies.

Standardized methods for evaluating CEA methodologies

There are several standardized methods that evaluate methodologies of CEAs: such as the Drummond method [24,25], the *British Medical Journal* checklist [26,27], the Eddy checklist [28] or a combination of methods [29–34]. Other guidelines based on exist based on randomized controlled trials [35]. Other criteria such Knight's criteria [31,33,36] were used to analyze NHL. In brief, standardized criteria that are used to report cost utility analysis (CUA) include a comparison with the best practice, a societal perspective, a lifetime horizon, a calculated QALYs based on RCTs, a calculate ICER and comparing it to an established threshold, and finally reporting any conflicts of interests or funding sources [12]. Our paper reviewed the literature but did not apply those criteria to analyze these CEAs.

Cost effectiveness analysis in hematologic malignancies

Most reviewers described some methodological flaws, and commented on the paucity of relevant studies regarding their hematologic malignancy of interest

A. Systemic reviews using standardized methods to assess CEAs

Analyzing the quality of CEA in multiple myeloma [25] found that 18 studies have met the inclusions criteria. In general, 60% of CEAs were compliant with each of the 10 criteria. Some criteria were deficient (such as discounting on costs and consequences, discussion of generalizability, and utilizing a time horizon greater than one year) [25]. However, in another analysis 15% of reviewed studies did not state the time horizon [12]. Moreover, these CEAs have become less frequent [25]. Unfortunately, out of the initial 65 abstracts they screened, the vast majority did not meet the inclusion criteria and CEAs failed to properly describe its methodology. For example, a review about rituximab in non- Hodgkin's Lymphoma used proper checklist criteria submitted the pharmaceutical company; however, certain assumptions were to suggest outcome in favor of this drug [26,28,29]. In another review of imatinib, a probable underestimation of the duration of palliative care was noted when analyzing studies of chronic myeloid leukemia [32,34].

In fact, this has been a reflection of many subjective assumptions when modeling CEAs.

B. Individual deficiencies in the methodologies of CEAs

Overall, the majority of reviews of theses CEAs cited a limited amount of data in the literature [8,25,29,30,37–47] .The most common concern was a general lack of published cost data. Moreover, a lack of relevant quality of life data was noted in many studies that neglected to calculate QALYs [8,25,29,37–40,42–44]. Other concerns include a lack of indirect cost analysis [8,25,39–41,45]. Other commented on the short time horizons [37], and the lack of long term patient follow-up data [23]. Importantly, a large concern was the lack of relevant randomized control trial data [39,41,45,46,48].

On the other hand, a relative lack of variety in the literature was noted where the highest numbers of publications focused on heavily utilized drugs such as rituximab [45]. Although, methodological integrity was still relatively noted in respective hematologic malignancy [41]. However, a review about multiple myeloma noted that if trends of poor quality CEA methodology persist in the future, then study results may be of little value when making economic decision [25].

Sponsoring bias

Minimizing bias is always a concern when conducting and analyzing a study. CEAs are particularly susceptible to sponsorship bias, especially that industry sponsorship studies may influence the results of their research [49]. In fact, the CEA was perceived as a form of marketing within the industry as they usually generate favorable results [22,49–57]. On the other hand, funding source was not identified in about a third of these studies [22]. Although no specific study pertaining to hematological malignancy could be identified, however, other recent evaluations of CEAs in oncology have demonstrated this bias [58].

Importantly, the validity of a CEA relies on the assumption that the modeled clinical trial is valid. In fact, Low-quality trials have overestimated the therapeutic benefit [59]. While industry-funded studies are also more likely to examine drugs where the intervention and the control are considered equivocal [60]. Moreover, interventions deemed likely not to be cost effective may never be brought to market [49,61,62]. This prepublication removal of less favorable data may also contribute to uneven distribution of ICERs.

Additionally, modeled studies are susceptible to this type of bias unlike those based on clinical trials [54]. Therefore, methodological checklists recommend reporting source of funding, and any conflict of interests [12,34,36,63,64].