Health Technology Assessment of Curative Interventions–an Old Problem With New Issues

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A broad range of data collection programs, methodological tools, and commercial arrangements have been proposed and adopted to inform recent health technology assessment decision making regarding such curative interventions.

Interventions with curative intent have been around for as long as evidence-based medicine and health technology assessment (HTA). The first technology appraisal conducted by the National Institute for Health and Care Excellence in the United Kingdom (UK) was on the topic of wisdom tooth extraction, and one of the first recorded randomized controlled trials (RCTs) was conducted by James Lind in 1747 regarding the consumption of citrus fruit to treat scurvy.

While early HTAs looked at similar "curative" interventions (such as different types of surgery), the term has been used (or implied) to describe a broad range of interventions that do not necessarily meet the traditional definition of a cure. Some provide patients with a "functional cure," such as emtricitabine/tenofovir (Truvada®) for human immunodeficiency virus (HIV). Others may facilitate the increased use of pre-existing curative interventions, such as brentuximab vedotin (Adcetris®), which allows an increased bridging to (curative) stem cell transplant in CD30-positive Hodgkin lymphoma. There are also some treatments which may provide durable clinical responses resulting in "long-term survivors" in indications with no precedence for such outcomes, such as axicabtagene ciloleucel (Yescarta®) for diffuse large B-cell lymphoma.

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Recent developments in cancer immunotherapy, gene therapy, and novel biologics have placed pressure on HTA agencies to recommend these potentially curative interventions with uncertain long-term benefits, yet high upfront costs. The unique characteristics of these more recent interventions pose a number of difficulties in conducting HTA. This article presents a summary of key challenges, along with initiatives undertaken to address them with illustrative case studies presented.

UNCERTAINTY IN LONG-TERM CLINICAL EFFECTIVENESS

One of the common issues encountered within HTA is the uncertainty in clinical effects beyond the trial duration. While applicable to all interventions for which future benefits are anticipated, the consequences of a difference between cure or no cure has a profound impact on cost-effectiveness. Uncertainty may feature in a number of different ways—for example, uncertainty in the proportion of patients who are "cured"/"functionally cured," as well as uncertainty in the duration of the "cure-like" effect as the possibility of relapse cannot necessarily be ruled out.

To address these concerns, various initiatives have been introduced to collect further evidence—often while interventions are allocated provisional funding. In the United Kingdom, the Cancer Drugs Fund was established to defer decisions by 2 years while data are collected either regarding the use of interventions in routine clinical practice, or through extended clinical trial follow-up. In Australia, managed access programs exist where reimbursement is conditional upon the outcomes observed in real-world clinical practice. An example of this conditional reimbursement is ipilimumab (Yervoy®) for the treatment of metastatic melanoma, which was funded conditionally on 2-year overall survival (OS) in real-world clinical practice being similar to 2-year OS in the RCT.[1]

Further work is still required to establish

how best to understand (and express) the uncertainty in longer-term clinical outcomes. Real-world evidence collection efforts are becoming increasingly popular, although their collection is not always proactively undertaken in anticipation of addressing evidence gaps or enforceable by payers. There are also practical issues regarding how to proceed if the technology underperforms, resulting in payers preferring to defer funding decisions.

APPLICABILITY OF TRADITIONAL MODELLING METHODS

While the uncertainty of the clinical effect of curative interventions is a key issue in determining their likely clinical effectiveness, this issue is exacerbated further by acknowledging the array of alternative techniques that may be applied to quantify this benefit to inform cost-effectiveness analysis. Traditional curative interventions may be modelled using an explicit "cured" health state within a modelling exercise, where the term "cure" is not contested. However, the same does not necessarily apply for newer curative interventions, and so alternative methods have been utilized to inform cost-effectiveness analysis.

In the field of cancer immunotherapy, a range of methods have been proposed to extrapolate OS. These include "flexible" extrapolation functions (eg, splines) that aim to better reflect complex survival patterns versus "traditional" extrapolation functions (eg, Weibull), mixture models that aim to reflect the heterogeneity in patient populations by simultaneously modelling outcomes for 2 (or more) distinct groups, as well as extrapolation functions that involve the use of a clinically relevant landmark (such as response) to separate groups of patients by likely prognosis.[2] Each of these methods have been evaluated by HTA agencies in assessments of treatments, and are subject to limitations relating to both technical and practical issues—for instance, the plausibility of patients having a "normal" life expectancy (ie, being "cured") from baseline (as implied by some cure-based models).

To date, the primary focus of many published studies has been placed upon estimating clinical outcomes using statistical methods (as described above). However, more recently, economic model-based methods have gained popularity. These include models that incorporate health states based on response, and multistate modelling wherein individual transitions between clinically relevant health states are predicted simultaneously. Similarly, an evidence report by the Institute for Clinical and Economic Review in the United States adopted a structure wherein beyond a given point in time, patients were assumed to be effectively cured.[3] Further research is still needed to ascertain the pros and cons of adopting statistical- and/or model-based methods to best reflect outcomes associated with curative interventions. The accuracy of both approaches also needs to be demonstrated once longer-term follow-up data allow such validation.

HIGH COST OF TREATMENT

As well as the issues raised in quantifying clinical benefits, the high cost of acquisition is another common issue faced when conducting HTA of curative interventions. Interventions may be broadly categorized as those with upfront costs (such as chimeric antigen receptor T-cell [CAR-T] therapies), or those that are expected to be given repeatedly but perhaps only for a specific time period, after which the clinical effect is expected to be maintained (such as immune-checkpoint inhibitors). In both cases, however, the benefits of treatment are accrued for a much long time period versus the period over which they are paid for. The high budget impact of interventions for more common conditions constitutes a further issue in relation to patient access; a study regarding the treatment of hepatitis C in United States' prisons found that treating all inmates would have cost 13 times the overall pharmacy budget.[4]

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Among the tools proposed to provide patient access while ensuring value for the money are risk-sharing agreements. These agreements can take many forms, broadly classified as financial-based (eg, expenditure or treatment caps) or outcomes-based (eg, only paying for cured patients). Compared to fragmented healthcare systems, such as those in the United States, these agreements have been implemented more frequently in the single-payer systems of Europe, Canada, and Australia. In the aforementioned case of ipilimumab in Australia, if there was a discrepancy between the observed versus predicted OS benefits, then the company would have to rebate the difference in costs, such that it would have been cost-effective from the date first funded.[1] However, this is an exception; despite Australia having reasonable information systems to track patient outcomes, the ability to price by indication, and the ability to enforce deals through deeds of agreement, there remains limited uptake of outcomes-based risk-sharing arrangements. This seems to be due to the administrative burden compared to expenditure caps or discounts, and for many markets outside of Australia, these administrative systems and associated policies are not yet established.

The confidential nature of many pricing arrangements between companies and payers has to date prevented detailed examination of approaches used. More transparent conceptual guidelines for acceptable pricing agreements (perhaps in the form of position statements from various payers or HTA bodies) may lead to improved access to curative interventions by finding sustainable agreements between different stakeholders.

CONCLUSIONS

The issues associated with undertaking HTA for curative interventions have existed for a very long time, although in recent history the context to which these issues apply has changed. Modern curative interventions offer previously unattainable clinical benefits to patients who would otherwise face diagnoses likely to be terminal. Appropriate clinical- and cost-effectiveness assessment frameworks are of utmost importance to allow timely decision making regarding curative interventions. >

The generation of evidence to inform HTA is constantly evolving, and decisions are increasingly being made based on maturing evidence which is often not collected within RCTs, or relies on small patient numbers (either recruited into the RCT due to biomarkers, or due to a low number with data because of administrative censoring or mortality). Increased data collection efforts are required to allow continued methodological development and the validation of proposed methods to best address the clinical- and cost-effectiveness of curative therapies. Substantial progress has been made but there is still a long way to go before we will truly be able to reliably determine the clinical- and cost-effectiveness of these newer (potentially) curative interventions and utilize appropriate payment mechanisms—by which point medical science will have inevitably advanced yet again, providing us with an entirely new set of challenges.

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