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Editorial

Modelling uncertainty in survival and cost-effectiveness is vital in the era of gene therapies: the case of axicabtagene ciloleucel

Chimeric antigen T-cell (CAR-T) therapy in patients with cancer represents an avenue of significant advancement, with the most promising area currently being in hematological cancers [1]. While CAR-T therapy is promising, this must be tempered against its high cost and potential burden on health systems, the complexities of CAR-T therapy, such as manufacturing challenges, and the uncertainty around the long term effectiveness of therapy [1]. Given these issues, we read with interest a recent article by Whittington et al. [2]. The authors performed an economic evaluation of the novel chimeric antigen receptor T-cell (CAR-T) therapy, axicabtagene ciloleucel (Yescarta, Gilead Sciences Inc.), compared with chemotherapy in adult patients with diffuse large B-cell lymphoma. It is clear that the authors embarked on a difficult task, given the limited data available on both costs and outcomes for CAR-T therapy. Their paper is an important departure point for future discussions concerning value and gene therapies. Gene therapies pose enormous challenges for decision-makers in many countries, especially regarding the desire for robust evidence on effectiveness, cost-effectiveness, and budget impact. These challenges are sufficiently significant that we must carefully scrutinize and interpret all new research as gene therapies become a reality.

The importance of economic evaluation in health care decision-making is well-recognized. While individual jurisdictions might weight the results of economic evaluation differently, the importance of economic evaluation is contingent on it being conducted in a way that is rigorous, such that decision-makers can be confident in the generated evidence. While there is excitement about CAR-T therapy, and gene therapies more widely, this excitement needs to be balanced with an appreciation of the uncertainty in the therapy's effectiveness, particularly in the long term, and the associated opportunity costs. With regard to these considerations, we have identified three issues in the analysis by Whittington et al. [2] that we feel need to be highlighted and discussed to help both researchers and decision-makers understand the limitations of their analysis and improve future economic evaluations of CAR-T (and similar) therapies.

The first arises with respect to the modelling approach. While partitioned survival models are often used for the economic evaluation oncology treatments, this modelling approach often fails to properly incorporate the complexity of the disease and technology under investigation [3]. That is, partitioned survival models in cancer typically comprise three health states: alive, disease progression, and death. This modelling framework is unlikely to truly reflect the health states of a typical cancer patient and therefore has limited relevance to clinical decisions. Moreover, the assumption that endpoints are independent does not reflect reality; events or health states may occur that affect downstream events, such as disease progression affecting a patient's risk of death [4]. Finally, the most important limitation of partitioned survival models (addressed further below) is the inability to adequately incorporate uncertainty into the modelling approach [4]. Therefore, while partitioned survival models are not inherently incorrect or biased, they typically do not reflect the reality of patient trajectories, nor can they properly incorporate uncertainty around parameter estimates. Economic evaluations should be conducted using more rigorous methods that reduce decision uncertainty.

The second issue is that modelling for CAR-T therapies needs to incorporate a wider breadth of costs and resources than modelling for typical health interventions. The idea of incorporating infrastructure and capital costs for medical technologies, specifically for medical devices, has been presented previously [5]. An interesting aspect of CAR-T therapy is that it spans traditional categories of drugs and devices. For example, in Canada, when the first CAR-T therapy (tisagenlecleucel) was evaluated by the Canadian Agency for Drugs and Technologies in Health (CADTH), it was reviewed by the body charged with evaluating medical devices (the Health Technology Expert Review Panel or HTERP) as opposed to the body that typically evaluates cancer therapies (the pan Canadian Oncology Drug Review or pCODR) [6]. While the analysis by Whittington et al. [2] did appropriately incorporate the potential for patients to discontinue treatment due to failure of the manufacturing process, a proper evaluation of this technology requires a more in-depth consideration of the resources that are necessary to provide the therapy. The availability of CAR-T therapy, as a result of the requirement for considerable investment in infrastructure, may also have important equity considerations, particularly since many people have limited access to major academic or tertiary care hospitals. While not mandatory in an economic evaluation, equity considerations are becoming increasingly recognised as important issues by health technology assessment agencies and payers.

Finally, and in our opinion most importantly, an economic evaluation cannot be conducted without being accompanied by sensitivity analyses for the model input parameters. Specifically, probabilistic analysis is a necessity for every economic evaluation,

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and we believe this to be especially true in the context of novel therapies such as CAR-T where evidence and data are limited and often immature. While there is optimism and promise with these new approaches to treating different cancers, there is still a high degree of uncertainty associated with their efficacy and effectiveness, particularly over the long term. The economic evaluation used data for the new intervention, axicabtagene ciloleucel, from a phase II clinical trial (the ZUMA-1 trial) [7]. Current best practices for conducting an economic evaluation stipulate that probabilistic (sensitivity) analysis must be conducted. Probabilistic analysis is vital to characterizing and quantifying decision uncertainty about whether or not a new therapy should be reimbursed and has been long understood to be important for economic evaluation and subsequent decision-making [8]. Certainly, probabilistic analysis is a requirement for the primary analysis in a number of jurisdictions (i.e., in Canada by CADTH). Similarly, we believe that to make informed decisions about the provision of health services, this uncertainty needs to be understood by decision-makers, for all parameters that are included in the model. Scenario analyses can be conducted to inform decision-makers about changes in specific model parameters, such as the drug's cost. A probabilistic analysis, as compared to one-way or deterministic sensitivity analysis, has the advantage of being able address the problem of correlation between model parameters, and can articulate the probability that an intervention is cost-effective through intuitive and graphical presentations, such as cost-effectiveness acceptability curves [8].

As stated, the purpose of this editorial is to highlight some concerns in current economic evaluations of CAR-T therapies with the intention of ensuring a high standard in the methods of economic evaluation and evidence synthesis relating to CAR-T therapies, and gene therapies more generally, moving forward. This is becoming increasingly important for two reasons. First, it is well-known that drugs and technologies are becoming more expensive. However, in many cases, the magnitude of benefit is becoming increasingly uncertain. Payers are under pressure to approve new therapies based on earlier, less mature evidence (i.e., from phase II trials). Second, new technologies are spanning traditional lines of drugs and medical devices, and may involve more intensive processes, requiring infrastructure upgrades, increased human resources, etc. As such, economic evaluations need to properly specify the decision problem, and modelling needs to be appropriately sophisticated to incorporate uncertainty and the complexities of implementing the new technology. Our objective is to ensure that future analyses of CAR-T therapies, and gene therapies more generally, are of a higher standard and the information they provide can be used with confidence by decision-makers.

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