Master's Degree Dissertation

Tisagenlecleucel (chimeric antigen receptor T-cells targeting CD19) for patients with relapsed/refractory B-cell acute lymphoblastic leukemia:

asystematic review and cost-utility analysis from a Spanish perspective

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TITLE: Tisagenlecleucel (chimeric antigen receptor T-cells targeting CD19) for patients with relapsed/refractory B-cell acute lymphoblastic leukemia: a systematic review and cost-utility analysis from a Spanish perspective

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DECLARATION OF ORIGINALITY: I formally declare that I have written the submitted piece of work independently. I did not use any outside support except for the quoted literature and other sources mentioned in the paper. I also declare that I have adapted the Excel templates and macros kindly provided by Prof. Carlos Crespo in his seminar "Modeling techniques in economic evaluation of pharmaceuticals and healthcare technologies", which is part of this Masters in Health Economics and Pharmacoeconomics.

AUTHORSHIP: I hereby certify that I am the sole author of this original manuscript.

DECLARATION OF CONFLICTS OF INTEREST: I am the principal investigator of a clinical trial (CART19-BE-01) that has evaluated the role of ARI-0001 cells in the treatment of relapsed/refractory acute lymphoblastic leukemia. This is an academic product that has exactly the same mechanism of action as tisa-cel (CART-cells targeting the CD19 antigen) and we wish to submit to the Spanish Medicines Agency for approval under the Hospital Exemption Rule. However, I would not benefit personally (in money or in kind) if our product is eventually approved.

I have no conflicts of interest in relation with the manufacturers of the pharmaceutical products evaluated in this paper, nor with any other pharmaceutical company.

ABSTRACT

Patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (ALL) have a poor prognosis with conventional therapies. In the summer of 2018, the European Medicines Agency approved tisagenlecleucel (tisa-cel, Kymriah®, Novartis), for the treatment of these patients based on a single-arm phase 2 international clinical trial with a short follow-up. The price tag for this product is €320,000 but under a pay-for-performance scheme in which the health care provider pays €192,000 upfront and the other €128,000 if the patient is alive and in remission 18 months later. The main objective of this study was to perform a cost-utility analysis of tisa-cel from a Spanish point of view. Tisa-cel resulted in a longer life expectancy (9.89 LYs) than the other two therapies evaluated (6.45 and 1.94 LYs for blinatumomab and clofarabine, respectively). The difference in relapse-free survival (RFS) led to 3.75 additional QALYs for patients receiving tisa-cel compared to blinatumomab at a cost of €55,779/QALY, and 7,15 additional QALYs compared to clofarabine at a cost of €35,787/QALY. The Markov process revealed very similar results: the difference in RFS resulted in 3.67 additional QALYs for tisa-cel compared to blinatumomab at a cost of €57,368/QALY (95% confidence interval [CI]: 52,779-61,956), and 7.3 additional QALYs compared to clofarabine at a cost of €35,504/QALY (95% CI: 35,153-35,854). One-way sensitivity analyses showed that the factor that had the greatest impact on the cost-effectiveness of tisa-cel (over blinatumomab) was its cost. In conclusion, tisa-cel could be considered cost-effective in the treatment of patients with R/R pediatric ALL when the WTP threshold is set at €50,000/QALY (or higher), but many uncertainties remain (lack of comparative data, short follow-up).

BACKGROUND

Pediatric acute lymphoblastic leukemia (ALL) is a very remarkable disease in many ways. On the one hand, it is the most common malignancy in children.[1] On the other hand, pediatric ALL is the cancer in which chemotherapy was used for the first time in history,[2] and also the disseminated tumor with the highest cure rate of all malignancies known to date, reaching 90% of patients in some series.[1] Paradoxically, ALL is so much more frequent than other pediatric malignancies that, despite having such high cure rates, it is also the most frequent cause of cancer-related mortality in children. This is because patients with relapsed/refractory (R/R) ALL have a poor prognosis with conventional chemotherapeutic (i.e. cytotoxic) agents.[1] As a rule of thumb, patients with R/R ALL are considered incurable unless they can be put into remission (i.e. no evidence of disease by conventional laboratory tests) and this remission can be consolidated with an allogeneic hematopoietic cell transplantation (alloHCT). Up until very recently, patients with R/R ALL were traditionally treated with salvage chemotherapy (e.g. combinations of fludarabine, cytarabine and idarubicin, or FLAG-Ida), but this strategy yielded low response rates, meaning that many patients never made it to the alloHCT, and was also associated with high toxicity rates, including non-negligible mortality rates. In the last decade, the advent of clofarabine, a purine analog with remarkable activity in several types of leukemia, has somehow improved the outcome of these patients,[3] increasing the percentage of patients able to proceed to the alloHCT.

More recently, several modalities of immunotherapy have been evaluated in patients with R/R ALL, and one of them has gained much praise by the medical community in view of its impressive efficacy, namely chimeric antigen receptor (CAR)T-cells.[4] These are T-cells collected from the patient and then genetically modified to target the CD19 antigen expressed on the surface of ALL tumor cells. Since this is a type of cell therapy ("a living drug") that is not very different from alloHCT, there is tremendous hope in the medical community that CART-cells might be able to cure patients with R/R ALL. This would mean that alloHCT may not be necessary anymore, a procedure that is associated with significant cost, morbidity and mortality.[5] On the other hand, there is no need to identify a donor because the cells come from the patient, and no need to administer immunosuppressive agents, thus minimizing the risk of infections post-transplantation and eliminating the risk of one of the most feared complications of alloHCT, which is graft-versus-host disease.

In the summer of 2018, the European Medicines Agency (EMA) approved one particular of CART-cells targeting the CD19 antigen, called tisagenlecleucel

(tisa-cel, Kymriah®, Novartis), for the treatment of pediatric patients (up to 25 years of age) with R/R ALL.[6] This approval was based on a single-arm phase 2 international trial.[7] In Spain, tisa-cel was approved for the treatment of R/R pediatric ALL in January 2019. The price tag for this product is €320,000 but under a pay-for-performance scheme in which the health care provider pays €192,000 upfront and the other €128,000 if the patient is alive and in remission 18 months later. In view of the staggering price of this new therapy, several cost-utility analyses (CUAs) have been performed in the USA and UK.[8–11] These studies have evaluated the cost-utility of tisa-cel in their own context and, more importantly, using their own price tags ($475,000/£282,000) and paying schemes. Not all these studies have concluded that tisa-cel is cost-effective using currently defined thresholds and, of course, these thresholds are very different from country to country.

On the other hand, the approval of tisa-cel comes at a time of good news for pediatric patients with R/R ALL because another agent, blinatumomab, a bispecific monoclonal antibody also targeting CD19 was recently approved for patients with R/R disease. Other forms of immunotherapy may appear in the future, such as the anti-CD22 monoclonal antibody inotuzumab ozogamicin, but they are not a reality at the time of writing this report.

AIMS

The objectives of this study were: (1) to systematically review all CUAs of tisa-cel available to date; and (2) to perform a CUA of tisa-cel from a Spanish point of view, considering local costs under different clinical situations and assumptions.

METHODS

Literature search and comparator arms

A literature search for cost-effectiveness analyses in patients with R/R pediatric ALL receiving tisa-cel was performed in Pubmed. Search terms were "cost-effectiveness", "cost-utility", "QALY" or "ICER" and "kymriah", "tisagenlecleucel" or "chimeric". The Global Health CEA Registry (Tufts Medical Center) was also searched. As comparator arms, registration trials evaluating clofarabine[3] and blinatumomab[12,13] were selected as in previous studies.[8–10,14]

Therapies evaluated

Three currently available treatments for R/R pediatric ALL were compared based on the results of their respective pivotal/registration clinical trials: tisagenlecleucel (tisa-cel),[15] blinatumomab[12] and clofarabine.[3] Inotuzumab ozogamicin was recently approved by the EMA for the treatment of R/R ALL and is currently available in Spain, but only for adults, and was therefore excluded from this study. Since the median follow-up in these trials is short (13, 23 and less than one year, respectively), the probabilities of being-relapse free at different time points were visually extracted from all three pivotal trials and extrapolated using the beta distribution as displayed in Table 1.

Model structure

I modeled a hypothetical cohort of 10,000 Spanish pediatric patients with R/R ALL through a decision-tree followed by a Markov process that evaluated the cohort every 3 months over a period of 50 years (Figure 1). After each treatment, some patients achieve a remission (state M1 in the state transition diagram [Figure 1B]) and the rest are refractory (state M2) or die. While in remission, patients receiving any of these 3 options may undergo alloHCT, and the probability of this happening, as well as all the other probabilities or rates were also extracted from the same clinical trials.[3,12,15] Patients who do not respond to therapy face a very low probability of responding to subsequent therapies and usually receive palliative chemotherapy until death.

Costs and utilities

My analysis adopts a Spanish health care payer perspective, accounting for direct health care costs such as drugs, drug administration in the Day Unit or in the Hospital Ward, adverse events, alloHCT and follow-up care (Table 1). A more detailed explanation of these costs can be found in Supplementary Table 1. The

model reflects the pay-per-results scheme Novartis agreed with the Spanish Ministry of Health in which 60% of the drug cost is payed upfront and the remaining 40% is only payed if the patient is in sustained remission 18 months later. The average cost reflects the fact that only 50% of patients were in remission at that time-point in the registration trial.[15] Costs related to the lymphodepleting chemotherapy were added to the drug cost in the case of tisa-cel, and the cost of grade 3-4 adverse events was also added depending on their incidence to all three drug costs (Supplementary Table 2). I also searched the literature to assign preference-weighted utilities to each health state modeled, but I basically tried to replicate the utilities proposed by Lin et al[8] in order to make my results more easily comparable.

Main outcomes

Outcomes were life-years (LYs), costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER) over a horizon of 50 years. Costs and effects were discounted at 3% annually (0.75% per trimester).[16] I pre-defined the long-term effectiveness and prices at which tisa-cel would be cost effective at 2 different willingness-to-pay (WTP) thresholds that are commonly used in the UK and Europe: €30,000/QALY and €50,000/QALY.

Sensitivity analyses

I performed one-way sensitivity analyses to evaluate how variations in my assumptions altered my conclusions. I also performed probabilistic sensitivity analyses in which I sampled model inputs from uncertainty distributions, as displayed in Table 1, and also thanks to a Monte Carlo simulation. All calculations were done in Microsoft Excel by adapting the templates and macros kindly provided by Prof. Carlos Crespo (Dept. of Statistics, University of Barcelona).

RESULTS

Literature search

I identified four different CUAs of tisa-cel: three performed in the US[8–10] and one in the UK (Supplementary Table 3).[11] Unfortunately, not only the currency was different, but also the comparator arms were different across the studies and it was impossible to perform a meta-analysis. This is a summary of these four studies:

- In the first study, tisa-cel was compared with blinatumomab and clofarabine from a US health payer perspective following a Markov model.[8] The authors evaluated three different scenarios for tisa-cel: a 5-year relapse-free survival (RFS) of 40%, 20% and 0%, respectively. Under the first assumption, tisa-cel increased life expectancy by 12.1 years at a cost (ICER) of $61,000/QALY gained compared to blinatumomab (clofarabine was dominated under all assumptions). The cost increased to $151,000/QALY gained under the 20% 5-year RFS assumption; and to 184,000/QALY gained under the 0% assumption. The authors also concluded that, under the 20% and 0% assumptions, the cost of tisa-cel would have to drop down to $200,000- $350,000 (from the $475,000 current price in the US) to meet a $100,000-$150,000/QALY WTP threshold.
- In the second study, the outcome with tisa-cel was extrapolated from pooled data (three different trials) and compared with clofarabine only, again from a US health payer perspective, this time following a semi-Markov partitioned survival model.[10] The authors only modeled the 40% 5-year RFS assumption, which led to an ICER of $42,000 per LY gained and $46,000 per QALY gained for tisa-cel compared to clofarabine.
- In the third study,[9] the outcome of patients receiving tisa-cel was compared with a small cohort of patients treated with clofarabine, etoposide and cyclophosphamide,[17] from a US health payer perspective, following an individual-based state-transition microsimulation model. According to this study, tisa-cel improved effectiveness by 8.18 QALYs, resulting in an ICER of $64,600/QALY. A probabilistic sensitivity analysis revealed that tisa-cel was cost-effective in 95% of iterations at a WTP of $100,000/QALY.
- In the fourth study, the Evidence Review Group summarized their independent evaluation of the evidence submitted by Novartis to the National Institute for Health an Care Excellence (NICE).[14] As comparator arm they chose chemotherapy (not including clofarabine) and blinatumomab following a hybrid model combining a decision tree and three-state partitioned Markov model. The deterministic ICER was £45,397/QALY gained

versus chemotherapy and £27,732 versus blinatumomab. The probabilistic ICERs were £48,265/QALY and £29,501/QALY versus chemotherapy and blinatumomab, respectively. In view of the immaturity of ongoing clinical trials, the committee did not recommend tisa-cel for routine use on the UK's National Health Service, but recommended its use under the Cancer Drugs Fund until de conclusion of the ELIANA trial[7] in June 2023.

In conclusion, tisa-cel can be considered cost-effective under different assumptions and statistical models and using accepted WTP thresholds in the US, and less so in the UK, although the drug is currently available in both countries.

Base case analysis

In my deterministic analysis (Figure 2), tisa-cel resulted in a longer life expectancy (9.89 LYs) than the other two therapies evaluated (6.45 and 1.94 LYs for blinatumomab and clofarabine, respectively) (Table 2). Moreover, tisa-cel was also the most expensive treatment strategy (€314,216) compared to the others (€105,258 and 58,287€ for blinatumomab and clofarabine, respectively). The difference in relapse-free survival (RFS) led to 3.75 additional QALYs for patients receiving tisa-cel compared to blinatumomab at a cost of €55,779/QALY, and 7,15 additional QALYs compared to clofarabine at a cost of €35,787/QALY.

In my probabilistic analysis (Markov process, after running a Monte Carlo simulation), the results were consistent with the previous. The difference in RFS resulted in 3.67 additional QALYs for tisa-cel compared to blinatumomab at a cost of €57,368/QALY (95% confidence interval [CI]: 52,779-61,956), and 7.3 additional QALYs compared to clofarabine at a cost of €35,504/QALY (95% CI: 35,153-35,854).

Sensitivity analyses

As expected, in one-way sensitivity analyses the factors that had a greater impact on the cost-effectiveness of tisa-cel (over blinatumomab) were its cost, the cost of alloHCT, which is commonly performed after either tisa-cel or blinatumomab, and the cost of blinatumomab (see Tornado plot in Figure 3). Other important factors were costs of hospitalization, since patients with R/R ALL are generally admitted to hospital to receive any therapy, and the costs of managing severe (grade 3 or 4) side effects, which are also very common in patients receiving tisa-cel, blinatumomab or indeed any treatment for R/R ALL.

I also undertook a probabilistic sensitivity analysis and, when I considered a WTP threshold of €50,000/QALY, tisa-cel was cost-effective in 34% and dominant in 1% of simulations, as can be seen in the cost-effectiveness plane (Figure 4). In

contrast, when I considered a lower WTP threshold (€30,000/QALY), tisa-cel was cost-effective in virtually none of the simulations. Moreover, using the same WTP threshold of €50,000/QALY, blinatumomab achieved the greatest net benefit in 51% of all simulations, tisa-cel in 49% and clofarabine in none of them. The acceptability curve (Figure 5) shows how blinatumomab remains the most cost-effective option of all three drugs when the WTP threshold is set around €30,000/QALY, while the WTP threshold in which tisa-cel and blinatumomab become equally cost-effective is roughly around €50,000/QALY.

DISCUSSION

Oncology as a whole represents the fastest growing sector of health-care spending, with expensive immunotherapy drugs currently being standard of care in many prevalent malignancies.[18–20] Furthermore, CART-cells in general, and tisa-cel in particular, are one of the most expensive therapeutic options ever introduced to the market. According to my study, tisa-cel provides significant gains, both in terms of LYs and QALYs, for children with R/R ALL compared to another novel agent (blinatumomab) and also to a more conventional chemotherapeutic agent (clofarabine). Although blinatumomab and clofarabine were both evaluated as comparator arms, most analyses focused on blinatumomab because it has been recently approved for the treatment of R/R pediatric ALL, and also because both tisa-cel and blinatumomab have the same target (the CD19 antigen expressed on the surface of tumor cells). At the same time, the role of clofarabine as treatment for R/R ALL is declining, precisely because this drug is particularly lymphotoxic and could hamper a subsequent treatment with tisa-cel.[21] However, it is also evident with at its current price and payment structure, this novel drug appears to start being cost-effective from a WTP threshold of €50,000/QALY or higher. In addition, if long-term follow-up results from the current pivotal trial or future clinical trials fail to meet their goal of confirming that tisa-cel can cure ALL without the need for alloHCT, and tisa-cel must be used as a bridge to alloHCT, then the cost-effectiveness will be even harder to achieve.

There is really no need to perform an economic analysis to realize that the economic value of tisa-cel, at its current cost, remains uncertain. Not surprisingly, our sensitivity analysis confirmed that the price of tisa-cel is the single factor with the highest impact on the cost-effectiveness of the drug (Figure 3). Indeed, in Spain the administration of tisa-cel for pediatric patients with R/R ALL is currently limited to only four centers in the entire country, and all patients must be evaluated

and approved by an Independent National Experts Committee. Again, there is no doubt that this measure's main objective is to tightly control the number of patients who receive this treatment. On the other hand, each country is free to negotiate with the manufacturer the best possible paying scheme. In the US, the payer is only responsible for the price of tisa-cel only if the patient achieves an initial complete remission. However, because of tisa-cel's high remission rate (over 80%), this scheme is not really effective in reducing costs compared to the traditional model. In contrast, I believe that the outcomes-based scheme agreed by the Spanish authorities and Novartis, in which 40% of the price is paid only if the patient remains in remission 18 months later, possibly is a better option, effectively reducing its cost from €320,000 to $256,000 (on average). Indeed, Lin et al calculated that two different options would make tisa-cel cost-effective (at a $100,000-$150,000 WTP threshold) even in a worst-case scenario in which all patients relapse and tisa-cel serves as a bridge to alloHCT: (1) lowering the price to $200,000 (instead of the current $475,000), and (2) keeping the price as it is but within a scheme in which payment only occurs if the patient remains in remission 7 months after the infusion.[8]

This study also has a number of limitations, derived primarily from the type of clinical trial evaluated. Firstly, there is no comparative evidence between tisa-cel and the comparators, meaning that cross-trial differences in the patient populations, and not between treatments, could account for the difference in health outcomes observed. Indeed, the baseline characteristics of patients enrolled in these single-arm trials were rather different.[3,7,12] Of note, a phase 3 trial comparing tisa-cel and blinatumomab or inotuzumab is supposed to commence recruitment next year (OBERON trial, available at clinicaltrials.gov), although results are not expected until 2025. Secondly, the short follow-up in all trials required intensive modeling and this increased the uncertainty even further. Moreover, at its current price, its long-term efficacy is a critical determinant of its cost-effectiveness. Consequently, this analysis should be repeated once more mature data becomes available. Thirdly, most evaluations focused on blinatumomab as comparator because phase 2 data suggest that this is the best option, and also because the use of clofarabine is declining. Unfortunately, even though blinatumomab is already approved by the EMA for the treatment of R/R pediatric ALL, there is still no agreement between the manufacturer and the Spanish Ministry of Health in terms of price. For this reason, I was forced to use the French price, but I hope that the drug will be commercially available in Spain soon, and also that the Spanish price will be in the same order of magnitude. Lastly, my model inputs include probabilities, rates, costs and utilities arising from many heterogeneous sources,

which adds to variability and uncertainty regarding the results finally obtained.

In spite of these limitations, this evaluation concluded that tisa-cel could be considered cost-effective in the treatment of patients with R/R pediatric ALL when the WTP threshold is set at €50,000/QALY (or higher). The study should be repeated as soon as long-term follow-up data or phase III data becomes available.

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