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Tisagenlecleucel for the treatment of relapsed or refractory diffuse large B-cell lymphoma

English summary

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

Direction des services de santé et de l'évaluation des technologies

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This is the English summary of the guidance entitled Tisagenlecleucel pour le traitement du lymphome diffus à grandes cellules B récidivant ou réfractaire published in January 2019.

The complete version of this guidance (in French) is available on the website of INESSS in the Publications section.

Membres de l'équipe de projet

Auteurs principaux
Nina N. Mombo, Ph. D.
Richard Bisaillon, Ph. D.
Sara Beha, M. Sc.
Marie-Ève Brouard, B.A., M.A
Sylvie Arbour, Ph. D.
Mélanie Béland, Ph. D.

Collaborateurs internes
Marie-Claude Aubin, Ph. D.
Sylvie Bouchard, B. Pharm., D.P.H., M. Sc., M.B.A.
Paula Louise Bush, Ph. D.
Olivier Demers-Payette, Ph. D.
Isabelle Ganache, Ph. D.
Mireille Goetghebeur, Ph. D.
Emmanuelle Jost, M.Sc.
Anne-Marie Lemieux, M. Sc.
Geneviève Martin, Ph. D.
Julie Nieminen, Ph. D.
Geneviève Plamondon, M. Sc.

Adjointe à la direction
Marième Simoncelli, B. Pharm, M. Sc.

Coordonnateurs scientifiques
Yannick Auclair, Ph. D.
Jim Boulanger, Ph. D.

Directrice
Michèle de Guise, M. D., FRCPC, M.M.

Repérage d'information scientifique
Caroline Dion, M.B.S.I., *bibl. prof.*
Mathieu Plamondon, M.S.I.
Lysane St-Amour, M.B.S.I.
Julien Chevrier, M.S.I.
Flavie Jouandon, *tech. doc.*

Gestion de l'information
José Pérez, M. Sc.
Mike Benigeri, Ph. D.
Frédérique Baril, M. Sc.

SUMMARY

Background

Diffuse large B-cell lymphoma (DLBCL) is a highly aggressive form of non-Hodgkin's lymphoma (NHL) that mainly affects adults. It consists of several subtypes with morphological, molecular and immunohistochemical differences. It is important to take these characteristics into consideration when choosing the treatment and predicting the course of the disease. Having poor prognostic factors can diminish the effectiveness of the therapies administered and lead to treatment failure or a relapse after an initial response to chemotherapy. DLBCL can also result from the histological transformation of follicular lymphoma (transformed FL) following a relapse or a progression of the disesase.

The treatment of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) consists of the administration of a combination of antineoplastic agents, followed by an autologous stem cell transplantation, the only curative treatment recognized at the present time. However, autologous transplantation is an option only for a subgroup of age-selected patients with no comorbidities. The 1-year overall survival rate remains below 40% in patients who have experienced two or more relapses. The lack of effective therapeutic options for treating patients with r/r DLBCL or who are ineligible for transplantation is a clinical issue that cannot be solved with the current therapies.

Tisagenlecleucel (Kymriah™), which was recently approved by Health Canada, is a gene immunotherapy based on the expression of a chimeric anti-CD19 receptor on the surface of T-cells (CAR-T). It is used to treat hematologic cancers, including r/r DLBCL. The patient's T-cells are collected by leukapheresis, genetically engineered, cultured and then reintroduced into the patient. The CAR-T cells recognize the CD19 antigen on the surface of the B lymphocytes. An immune response is induced following the activation of the CAR-T cells, which causes the death of the CD19-positive cells, including the malignant B cells.

Task

For the first formal requests to Institut national d'excellence en santé et en services sociaux (INESSS) to evaluate cell therapies, such as those of the CAR-T type, it was agreed with the Ministère de la Santé et des Services sociaux (MSSS) that a consultative arrangement with the different ministerial teams concerned would be put in place to rule both on the advisability of the evaluation and the relevance of widening its scope, specifically, by giving special attention to the organizational issues relating to implementation. Since this approach was more in line with a conventional health technology assessment, INESSS gave the Direction des services de santé et de l'évaluation des technologies (DSSET) the task of evaluating this therapy using a tailored process that meets the same levels of quality and rigour that are characteristic of INESSS' work and that encourages the combining of different types of knowledge

and perspectives, including those provided by clinicians, patients and the general public.

Methods

The literature data and the data provided by the manufacturer were reviewed to document the efficacy, safety and efficiency of tisagenlecleucel. Data on the patient and general public perspectives were gathered by means of two consultative panels. The data from Lymphoma Canada surveys were studied as well. The ethical aspects were examined by way of a narrative review. In addition, a cost-utility analysis and a budget impact analysis are presented, as are contextual data from the consultations with health professionals in the field.

Results

Efficacy

The tumour response to treatment as measured by the overall response rate (JULIET: 52%; A2101J: 50%, based on a per-protocol analysis), is considered substantial in patients with an advanced stage of the disease. The response rate appeared to be lower in the intent-to-treat analysis (JULIET: 34%; A2101J: figure not reported). Nonetheless, the response was rapid (occurring as early as 3 months after treatment) and long-lasting (median not achieved; median follow-up 13.9 months in JULIET and 28.6 months in A2101J). The results of study A2101J showed that the response to treatment can be long-lasting (median: 22.2 months) without subsequent treatments. The overall survival data are, however, immature, with rates estimated at 62% at 6 months and 49% at 1 year in the JULIET study, and the extent of the response to treatment is difficult to determine because there is no direct comparison. In the JULIET study, close to one-half of the patients who received tisagenlecleucel died, most following disease progression. It should be noted that this treatment could not be administered to 30% of the patients enrolled in the JULIET study, mainly because of disease progression, death due to DLBCL or production failures.

The data on tisagenlecleucel are from uncontrolled trials with a weak level of evidence. However, the experts consider their designs acceptable, given the absence of a standard, effective third-line treatment.

Safety

In the JULIET study, all the patients who were treated with tisagenlecleucel experienced adverse events, most of which were grade 3 or higher. Cytokine release syndrome is a potentially serious adverse event frequently associated with CAR-T therapy. The proportion of patients who experienced this syndrome (approximately 20%) was similar in the JULIET and A2101J studies. The severe form of this syndrome requires admission to an intensive care unit and the administration of tocilizumab, which has yet to be approved by Health Canada for this indication. The patients (11.7%) who experienced severe neurological events (grade 3 and higher) were also

closely monitored in the intensive care unit. Another potential complication is prolonged B-cell aplasia, which can lead to infections and requires symptomatic management with monthly immunoglobulin injections. No deaths related to tisagenlecleucel therapy have been reported in the studies.

Quality of life

The data from the JULIET study indicate that an improvement in quality of life is achieved 3 months after tisagenlecleucel is administered. However, the significance of these results is limited by the small number of patients questioned and the short duration of follow-up.

Therapeutic value

The naïve indirect comparison of the JULIET and A2101J studies with the two extension studies of the CORAL trial and the SCHOLAR-1 study seems to show higher overall response rates and a more durable response with tisagenlecleucel than with the third-line chemotherapies. However, this comparison has several limitations, which affects the significance of the conclusions. The risk-benefit ratio for tisagenlecleucel nonetheless seems favourable in the short term. It will need to be reassessed in light of new, more robust data.

Economic data

Given the absence of comparative clinical data with salvage chemotherapies, the results of the pharmacoeconomic analysis are highly uncertain. Nevertheless, the pharmacoeconomic model, which INESSS considers acceptable, was used to construct exploratory scenarios, including probabilistic analyses. Therefore, if the promise of the therapy's long-term value is confirmed, the incremental cost-utility ratio would be close to $180,000/QALY gained. When all the sources of uncertainty identified by INESSS are taken into account, the results of the probabilistic analysis show that there is a 7% probability that the ratio would be less than $200,000/QALY gained. For the record, the probability would be 92% for a ratio of less than $300,000/QALY gained. If, however, the promise of value is not confirmed, the incremental cost-utility ratio could be more than $3 million/QALY gained.

Tisagenlecleucel is a costly technology intended for a population estimated at more than 60 patients a year. The total additional costs to the public health and social services system would be [redacted] for the first 3 years after tisagenlecleucel is listed. When all the sources of uncertainty identified by INESSS are taken into consideration, the results of the probabilistic analysis show that there is an 80% probability that the costs would range from $76 million to $101 million.

Data obtained from patients, patient associations and members of the general public

The patients who had received CAR-T-type therapy reported having chosen this option because they had exhausted all the other available treatment options. Some of the

patients consulted indicated that being in remission outweighed the adverse effects that they experienced. The representatives of patient associations consulted said, in fact, that, given the last-resort context, the uncertainties associated with the long-term efficacy and safety of this therapy should not be a major concern. For their part, the patients consulted who did not try this therapy and their families indicated that they would be willing to try it and to put up with the potential adverse effects, even if the benefits were short-lived and the disease relapsed or became refractory.

The members of the general public consulted said that they were concerned about many aspects of the therapy, mainly because of the limited data on it, despite the fact that the results are promising. They added that they were also concerned about the production process taking place outside the country (the cross-border transport of the cells, the loss of control over the process, and the ownership of the cells). They also expressed their opinion about the potential impact of the therapy on the healthcare system and on society, be it the potential hospital overcrowding, the economic consequences or access to the therapy. Some of them even raised the issue of public expenditures associated with CAR-T therapy, which could be used to fund the manufacturer's clinical studies for an investigational treatment. Nonetheless, the members of the general public stressed the importance of maintaining Quebec hospitals' expertise and competitiveness in the area of cell therapy.

Ethical considerations

Different ethical and social issues surrounding tisagenlecleucel were identified, including the current situation in which the manufacturer has a monopoly, the potential serious long-term adverse effects, and the constraints in patients' access to the therapy. Given the last-resort context and the high degree of vulnerability of patients and their families, special attention should be given to free and informed decision-making.

Deliberation

A weak majority of the members of the deliberative committee[1] recognized the promise that tisagenlecleucel (Kymriah™) holds for the treatment of adult patients with r/r DLBCL who are deemed to be at a therapeutic impasse. The members considered that the submitted and available evidence was too immature for them to confidently recognize the therapeutic value of this therapy. However, they did recognize the severity of the disease and the significance of the unmet need.

The members of the deliberative committee are of the opinion that this therapy should be available for r/r DLBCL patients, but only with coverage conditions that would take into account the high degree of uncertainty regarding the situation.

[1] 10 members for and 7 against.

Reasons for the majority position

- The committee members who expressed support for tisagenlecleucel pointed out that the results of the initial studies are promising, with overall response rates of approximately 50%, despite the failure of several previous treatments. Even if a longer follow-up is necessary, the data further suggest that the remission lasts for several months in some patients. However, the members observed that it is presently not possible to estimate the size of the actual effect or the duration of remission or to identify which patients will respond to the therapy. Yet, some pointed out that this reality is commonplace in the field of oncology.
- Given that the data are immature, the committee members stated that there is considerable uncertainty regarding tisagenlecleucel's long-term safety. They nonetheless considered its safety profile acceptable, the absence of therapeutic options greatly contributing to patients' increased willingness to accept the risk.

Reasons for the minority position

- The committee members who were not in favour of tisagenlecleucel did not recognize the promising nature of this therapy, given the low level of evidence. They were of the opinion that the clinical efficacy data are based on scientific evidence of low quality and that more robust data are needed. In addition, some members pointed out that the efficacy of tisagenlecleucel is similar to that of the existing treatments when the data are reported on an intent-to-treat basis.

As well, the committee members expressed numerous concerns in regard to incorporating this therapy into the basket of services, including the following, among others:

- The burden of demonstrating the value of a costly therapy whose efficacy, safety and efficiency are marked by uncertainties should not be borne by the government.
- The cost of the therapy is considered very high relative to the clinical benefits projected on the basis of the available data. Its cost-effectiveness is subject to a wide margin of uncertainty. Furthermore, the budget impact is considerable.
- The therapy is associated with a high level of acute toxicity that requires cutting-edge expertise to control the complications. The impact on hospital management, in particular, on the use of human and material resources in intensive care units, is a major concern, especially from the perspective of an offer of service at the Canadian level.
- The issues of unfair access persist for patients who live far from treatment centres, which are presently concentrated in Montreal. Financial compensation is provided in this regard, but it is probably not enough to mitigate the patients' financial burden.

- A number of issues were identified, such as those concerning the handling of cells, the ownership of the biological material, the cross-border transport of the cells, the quality assurance processes and the prioritization of orders in a context where a single facility serves the needs of all of North America.
- It is essential to disclose all the available information on the clinical benefits, the uncertainties and the risks associated with this treatment modality so that patients can make a truly free and informed choice.
- The disruptiveness of this type of innovative therapy and the importance of solidifying Quebec's expertise and competitiveness in a field where it is a leader at the Canadian and international levels are important considerations.

INESSS'S RECOMMENDATION

Despite the uncertainty regarding tisagenlecleucel's therapeutic value, and given the great promise it holds in the treatment of patients with r/r DLBCL, INESSS considers that covering it could be a fair and reasonable option to the extent that the following goals are met:

- a considerable mitigation of the economic burden.
- the introduction of a temporary status for such coverage until more robust data are available (3-year time horizon).
- thecontinued development of evidence concerning tisagenlecleucel's therapeutic value and safety.

Indication recognized for coverage

The indication for coverage proposed for tisagenlecleucel (Kymriah™) is as follows:

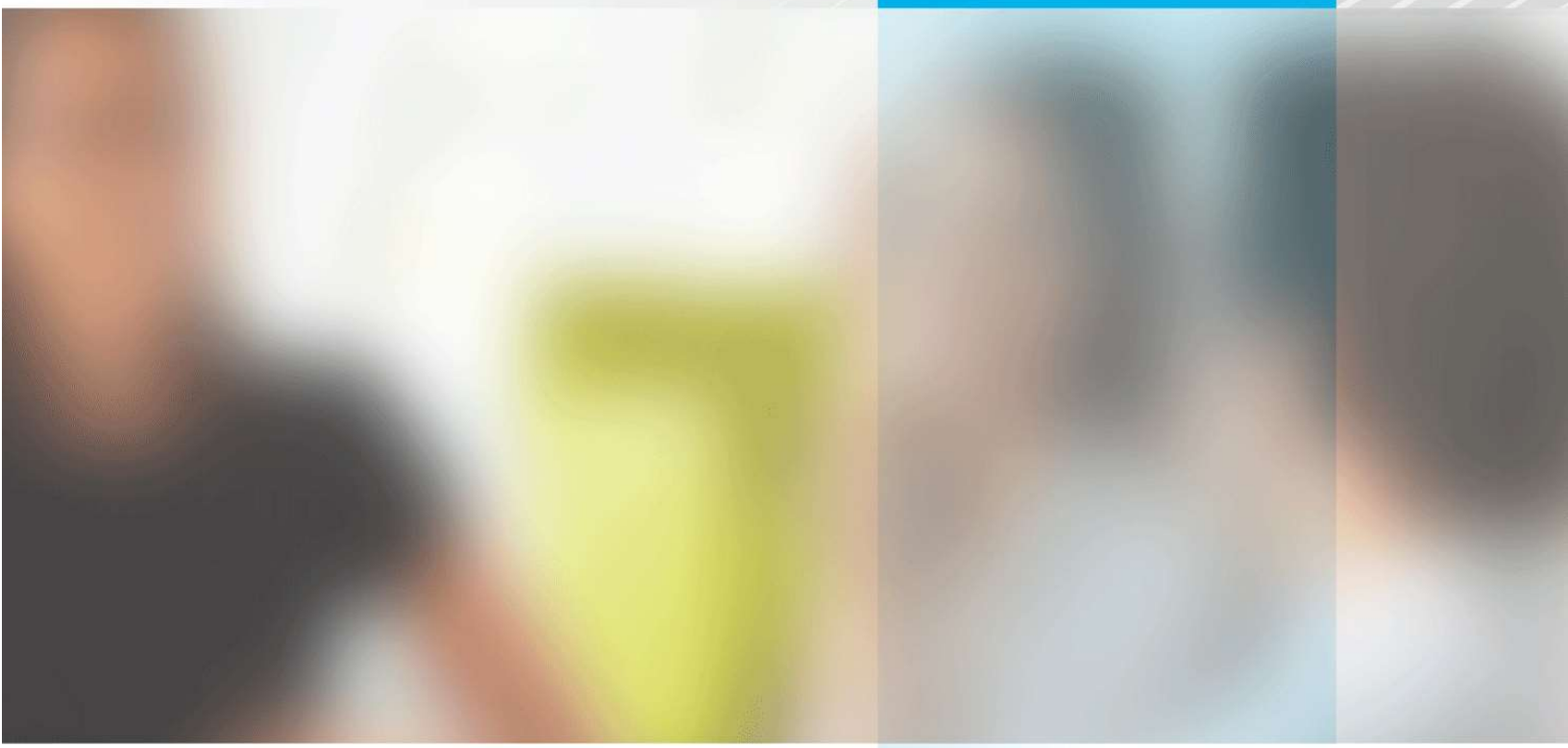
- for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.In addition, patients must meet all of the following criteria:
  - disease positive for the CD19 marker;
  - ECOG performance status 0 or 1;
  - life expectancy of at least 12 weeks;
  - no previous anti-CD19 therapy.

Implementation considerations

1. The impact of introducing tisagenlecleucel on hospital management, specifically, in intensive care units, is a major concern. Any offer of service should be carefully planned to ensure that the necessary resources are acquired so as not to compromise access to routine care and services at the hospitals concerned.
2. Sustained data-gathering by the manufacturer in real-world healthcare settings could help optimize the implementation and management of the use of this therapy

by providing additional information applicable to the Quebec context. At a minimum, the collected data should include:

- the time to the administration of the therapy;
- the duration of the clinical response;
- the 1- and 3-year overall survival rates;
- the number and types of subsequent treatments (e.g., chemotherapy and transplantation);
- the incidence of serious complications.



Siège social

2535, boulevard Laurier, 5e étage
Québec (Québec) G1V 4M3
418 643-1339

Bureau de Montréal

2021, avenue Union, 12e étage, bureau 1200
Montréal (Québec) H3A 2S9
514 873-2563
inesss.qc.ca

Institut national d'excellence en santé et en services sociaux
Québec