HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
24 MARCH 2021

The legally binding text is the original French opinion version

tisagenlecleucel
KYMRIAH 1.2 x 10^6 - 6 x 10^8 cells dispersion for infusion

Re-evaluation

Key points

Favourable opinion for maintenance of reimbursement in the treatment of paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

What therapeutic improvement?

Maintenance of therapeutic progress in the treatment of paediatric and young adult patients up to and including 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse.

Role in the care pathway?

In the first-line treatment of B-cell ALL, the treatment strategy is based on:

- a 4 to 6-week induction phase with an intensive polychemotherapy regimen based on vincristin, corticosteroids, anthracyclines and asparaginase, its role is to achieve complete remission (≤ 5% of blasts in the bone marrow) and, if possible, undetectable minimal residual disease (MRD) (< 10-4);
- a consolidation phase following achievement of complete remission of a duration of 6 to 9 months with a polychemotherapy regimen, generally not used in the induction phase (mercaptopurine, thioguanine, methotrexate, cyclophosphamide, etoposide or cytarabine)
- a maintenance phase of approximately 2 years using less intense chemotherapy protocols, generally based oral methotrexate and mercaptopurine by the oral route.

Induction and consolidation treatments must be combined with a tyrosine kinase inhibitor targeting the BCR-ABL fusion protein in the event of Philadelphia chromosome-positive ALL.

In addition, to prevent central nervous system damage, intrathecal chemotherapy (generally with methotrexate) is recommended. In contrast, brain radiation is little used in paediatric patients since it is associated with a risk of secondary cancer and cognitive disturbances. The prognosis following a first line of treatment takes into account the characteristics of the leukaemia (leukocytosis, cytogenetic factors, etc.), age and sensitivity to treatments, primarily assessed by the quantity of residual disease after achieving complete remission. The benefit of allogeneic haematopoietic stem cell transplantation (HSCT) after initial remission has not been clearly established in paediatric and young adult patients, though it may be recommended in patients at high risk of relapse.

The complete remission rate after first-line treatment is high (90 to 95%), with the remaining 5 to 10% corresponding to patients having died due to chemotherapy-related adverse effects or patients refractory from the outset (with primary refractory disease). The prognosis for the latter is generally unfavourable. Their management includes a second induction chemotherapy regimen followed by allogeneic HSCT for eligible patients following the achievement of complete remission.

Around 15 to 20% of patients who have achieved complete remission after first-line treatment relapse. The treatment of relapse in paediatric and young adult patients is not standardised, but may include:

- a new induction polychemotherapy regimen (similar to the first-line regimen or otherwise, conventional or clofarabine-based), followed by allogeneic HSCT consolidation if a second complete remission is achieved and if the patient is eligible,
- anti-BCR-ABL TKIs in patients carrying the Philadelphia chromosome,
- inotuzumab ozogamicine in patients over the age of 18 years, in the event of CD22 expression,
- blinatumomab, in adults (18-25 years) with relapsed or refractory Philadelphia chromosome-negative ALL (see opinion of 25/10/2019) and in patients under 18 years of age with Philadelphia chromosome-negative CD19-positive B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation (see opinion of 08/01/2020).
- palliative supportive care.

Long-term remissions may be observed following an initial relapse if a second remission is achieved (approximately 50% in the event of late relapse and 25% for relapse during treatment) 11 12 13. At this stage of the disease, the prognosis depends, in particular, on the duration of the first remission, the site of the relapse (isolated extramedullary relapse has a better prognosis), the characteristics of the leukaemia and the sensitivity to chemotherapy.

In second relapse or refractory disease situations, full recovery is exceptional (between 0 and 15%)14 and the median survival time observed is generally less than 6 months (expert opinion). At this stage of the disease, there is no standardised treatment; allogeneic HSCT is recommended if not received after the first relapse, a second transplant may be discussed.

Role of KYMRIAH (tisagenlecleucel) in the care pathway:

KYMRIAH (tisagenlecleucel) is a first-line treatment in paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse. According to the inclusion criteria of clinical trials, this indication corresponds to patients:

- in second or later medullary relapse,
- in medullary relapse following allogeneic haematopoietic stem cell transplantation (HSCT), performed at least 6 months before injection of tisagenlecleucel,
- or with primary refractory disease, defined by the absence of complete remission after two cycles of chemotherapy,
- or with chemo-refractory disease, defined by the absence of complete remission after 1 cycle of chemotherapy in relapsed patients,
- or intolerant or not responding to two lines of a tyrosine kinase inhibitor in the event of Ph+ B-cell ALL,
- or ineligible for allogeneic HSCT due to comorbidities, contraindications to HSCT conditioning treatments, the absence of a compatible donor, a history of prior HSCT or patient's refusal to undergo HSCT.

Due to the timeframes between determination of patient eligibility for CAR-T cell treatment, leukapheresis, the production of the genetically modified cells and lymphodepleting chemotherapy through to transportation to the patient for reinjection, to be eligible for KYMRIAH, the general condition and life expectancy of patients must be compatible with these timeframes.

Unknowns and uncertainties persist:

Given the lack of comparative data, the role of KYMRIAH compared to its therapeutic alternatives is not known. Very few patients pretreated with an anti-CD19 (e.g.: blinatumomab) were included in the clinical studies (6 in the ENSIGN supportive study and none in the ELIANA pivotal study in accordance with the exclusion study). Consequently, the efficacy and safety of KYMRIAH has not been established in patients pretreated with BLINCYTO. In its opinion of 09/01/2020 relative to the paediatric indication extension of BLINCYTO (blinatumomab), the Committee considered that in the absence of comparative data versus KYMRIAH (tisagenlecleucel), the role of BLINCYTO compared to this proprietary medicinal product is not known. However, in patients with a general health status and life expectancy compatible with the administration of CAR-T treatment, the Committee considers that KYMRIAH (tisagenlecleucel) should be favoured.

In clinical studies, tumour expression of CD19 had to have been demonstrated within 3 months prior to inclusion for relapsed patients. Consequently, the efficacy and safety of KYMRIAH in the absence of tumour expression of CD19 is not known. The efficacy and safety data for KYMRIAH in patients aged under 3 years at the time of inclusion or over 21 years at the time of diagnosis remain limited, since these patients were excluded from clinical trials.

The Committee also highlights that:

- considering the high frequency of grade ≥ 3 adverse events (approximately 80% of patients), with, in particular, cytokine release syndromes, neurological adverse effects and possible hospitalisation in the ICU, as well as the constraints related to the need for a lengthy hospital stay and the potential distance from the patient's home of a qualified centre, it is essential to inform patients about these constraints and the risks,
- KYMRIAH (tisagenlecleucel) should be administered in a healthcare facility specifically qualified in the use of CAR-T cells,
- and that the summary of product characteristics (SPC) and the RMP must be complied with, and special monitoring during and after treatment is required.

Special recommendations

The use of KYMRIAH (tisagenlecleucel) is limited to a small number of centres specifically qualified in the use of CAR-T cells given the complexity of the procedure, as stipulated in the order of 8 August 2019. In this context, the Committee highlights the importance of overall care (in particular including travel and local accommodation near healthcare facilities, where required), as reported by patient and user associations.

The Committee highlights the importance of ensuring patients, and their carers if applicable, having access to appropriate information on the complexity of the CAR-T procedure, the constraints related to prolonged hospitalisation and the risks to patients.

The Committee would like to see all stakeholders mobilised to provide responses to these uncertainties at the next re-evaluation. To this end, the Committee calls for the participation of all qualified centres in the DESCAR-T registry in order to obtain exhaustive, high-quality observational data.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ B-cell ALL in paediatric and young adult patients is a serious blood disease. This disease is liable to be life-threatening to patients in the short term in the event of refractory disease, relapse post-transplant or second or later relapse.
◗ This is a curative treatment.
◗ The efficacy/adverse effects ratio remains high in the short and medium term. It remains to be determined in the longer term.
◗ There are therapeutic alternatives.
◗ This is a first-line treatment in paediatric and young adult patients up to and including 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse, in good general condition, with a life expectancy and disease progression compatible with the waiting time before administration of KYMRIAH.

◗ **Public health impact**

Considering:

- the seriousness of B-cell ALL in patients with refractory disease, relapse post-transplant or second or later relapse, and its low prevalence,
- the inadequately met medical need at this stage of the disease,
- the partial response to this need, taking into account:
    - the additional impact on morbidity and mortality in the short term, with a transposability to routine practice not guaranteed due to the still limited data from the shared French CAR-T cell registry,
    - the lack of demonstrated impact on quality of life in the absence of relevant data,
    - the methodological limitations of the indirect comparison of tisagenlecleucel, making precise quantification of the clinical effect difficult,
    - and persistent uncertainties with respect to the clinical consequences, particularly in terms of efficacy, production timeframes and the exact composition of the bags,
- the absence of an improvement in the care pathway of patients (as the dossier currently stands) due to:
    - hospitalisations in a qualified centre, sometimes far from the patient's home, with ICU stays possible (particularly during the first 10 days following infusion or in the event of the onset of early signs or symptoms of cytokine release syndrome and/or neurological effects),
    - the need to remain close to this hospital for monitoring for at least 4 weeks following infusion,
- the impact on the organisation of care, considering the need for:
    - accreditation of hospitals based on precise criteria,
    - close coordination between the various departments of centres authorised to treat patients with CART cells (laboratories, internal pharmacy, clinical departments, etc.),

KYMRIAH (tisagenlecleucel) is unlikely to have an impact on public health, on the basis of currently available data.

Considering all these elements, the Committee deems that the clinical benefit of KYMRIAH (tisagenlecleucel) is substantial in the treatment of paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication "treatment of paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia ALL that is refractory, in relapse post-transplant or in second or later relapse" and at the MA dosages.

Clinical Added Value

Considering:

- **the updated efficacy data from the ELIANA and ENSIGN studies confirming the previously analysed results, particularly in terms of complete remissions (60 to 67% of the ITT population maintained in at least a third of patients following median follow-up of more than 3 years) and overall survival (median of 29.9 months in patients treated in the ENSIGN study and still not achieved in the ELIANA study), in clinical situations that are life-threatening in the short term, for which the available treatment options are limited, and do not enable full recovery to be envisaged,**
- **the updated indirect comparison results, which, despite their limitations, suggest a benefit of KYMRIAH (tisagenlecleucel) compared to standard treatments,**
- **the safety profile marked by significant short-term toxicity,**
- **but the initial uncertainties identified, which persist despite the Transparency Committee's requests, particularly with respect to:**
    - **the exact effect size compared to historic management, in the absence of any robust comparison,**
    - **the real-world efficacy in view of the immaturity of the data in the DESCAR-T registry (18 patients treated, 6 centres activated, numerous missing and unmonitored data), not enabling the results of the clinical studies to be confirmed at this stage,**
    - **maintenance of the clinical efficacy in the medium and long term, particularly concerning achievement of full recovery for patients in lasting remission,**
    - **and the absence of medium and long-term safety data**

the Committee considers that its previous conclusions are not liable to be modified. On the basis of currently available data, KYMRIAH (tisagenlecleucel) still provides a moderate clinical added value (CAV III) in the care pathway for the treatment of paediatric and young adult patients with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse.