HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
Update
October 2017

SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

BLINCYTO (blinatumomab), monoclonal antibody

High clinical benefit for relapsed or refractory Philadelphia chromosome-negative (Phi-) B-precursor acute lymphoblastic leukaemia and minor clinical added value compared to chemotherapy regimens

Main points

- BLINCYTO has been granted a marketing authorisation for the treatment of adults presenting with relapsed or refractory Philadelphia chromosome-negative B-precursor acute lymphoblastic leukaemia (Phi- B ALL).
- The median overall survival is increased with this medicinal product (+3.7 months) compared to standard chemotherapy regimens, without however retaining this benefit over time.
- No benefit has been observed compared to standard chemotherapy regimens on the number of patients receiving haematopoietic stem cell (HSC) transplantation, the only curative treatment at this stage of the disease.
- Its safety profile is marked by more frequent and more severe neurological adverse events and cytokine release syndromes than with standard chemotherapy regimens.
- Its role in the therapeutic strategy with respect to HSC transplantation is not known, either as a "bridge" to transplantation or deferred transplantation, or as a substitute for transplantation.

Therapeutic strategy

- The treatment of Phi- B ALL is based on long-term, intensive age-adapted polychemotherapy (using cyclophosphamide, vincristine, L-asparaginase, anthracyclines, methotrexate, cytarabine, etoposide, 6-mercaptopurine and corticosteroids).
  In patients under 60 years of age, the treatment is intended to be curative, based on intensive chemotherapy for a period of approximately 6 months including an induction phase followed by a consolidation phase.
  In patients over 60 years of age, the therapeutic approach is age-adapted, with reduced chemotherapy doses.
- The treatment of relapses of Phi- B ALL and of refractory forms is based on various remedial polychemotherapy regimens particularly including cytarabine, fludarabine, anthracyclines, and alkylating agents.
- **Role of the medicinal product in the therapeutic strategy**
  In view of the results of the clinical data and insofar as the post-transplantation data in respect of efficacy (relapse rate in particular) and toxicity (non-relapse-related post-transplantation mortality and morbidity) are not available, no formal or definitive conclusion can be reached on the positioning of BLINCYTO with respect to transplantation, either as a "bridge" to transplantation or deferred transplantation, or as a substitute for transplantation, particularly for ineligible patients.

Clinical data

- An open-label randomised study compared blinatumomab to a standard treatment in terms of overall survival. The patients received either blinatumomab, or a chemotherapy regimen chosen by the investigator from 4 predefined regimens according to the same administration schedule: 2 induction treatment cycles followed by up to 3 further consolidation cycles and up to 12 months of maintenance treatment subject to having obtained/retained a medullary response during the previous treatment phase.

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In total, 405 patients were randomised: 271 to the blinatumomab group and 134 to the standard treatment group and 29/405 (7%) patients received no treatment (4/271 [1.5%] in the blinatumomab group and 25/134 [18.7%] in the standard treatment group.

- Although a statistically significant increase in overall survival (primary endpoint) (7.7 months versus 4.0 months) and the haematological remission rate (43.9% versus 24.3%) was observed in the blinatumomab group compared to the standard treatment group, uncertainties remain in respect of the actual clinical benefit of blinatumomab. Indeed, the objective of patient treatment is to induce haematological remission in order to prepare patients for HSC transplantation, the best therapeutic opportunity for the population targeted by blinatumomab. It is observed that in the blinatumomab group and compared to the standard treatment group:
  - the rate of HSC transplantation was lower (42.0% versus 54.5% in patients attaining CR/HCR/ICR), whereas the haematological (CR/HCR/ICR) and molecular (MRD negative) responses were higher in the blinatumomab group;
  - access to HSC transplantation took longer in the blinatumomab group following the successful CR/HCR/ICR outcome (11.3 months versus 3.6 months);
  - mortality at 100 days post-transplantation without recourse to another anti-leukaemia treatment was higher (4 deaths versus 0 deaths), but these percentages do not reflect the mortality rates expected at this stage according to experts.
- The safety profile was consistent with that observed during the initial assessment with higher neurological toxicity and cytokine release syndrome in the blinatumomab group (61.0% versus 49.5% and 16.1% versus 0% respectively). The incidence of serious adverse effects arising under treatment was also higher in the blinatumomab group than in the standard treatment group (61.8% versus 45.0%).

Special prescription requirements

- Medicinal product for hospital use only
- Prescription reserved for haematology specialists or physicians with expertise in blood disorders

Benefit of the medicinal product

- The actual clinical benefit* of BLINCYTO is high
- BLINCYTO provides a minor clinical added value** (CAV IV) over chemotherapy regimens used for the treatment of adults presenting with relapsed or refractory Ph - ALL.
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 25 October 2017 (CT-16074) available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement".

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