Current Clinical Trials

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The BLAST trial for MRD+ adult B-precursor acute lymphoblastic leukaemia (B-ALL) patients investigates a bi-specific anti-CD19/anti-CD3 BiTE® antibody (blinatumomab®)

B-cell precursor acute lymphoblastic leukaemia; BCP-ALL; minimal residual disease; MRD; BiTE®

Background:

Blinatumomab is bi-specific single chain BiTE® antibody designed to redirect cytotoxic T-cells for lysis of B-precursor ALL cells by crosslinking CD3 present on all normal T-cells with CD19 expressed on leukemic cells. This results in perforin- and granzyme-mediated death of the target cell.[1]

Blinatumomab® corresponds to a new class of therapeutic antibodies called 'bispecific T cell engagers' (BiTEs) capable of redirecting any cytotoxic T cell to tumour cells. BiTE® antibodies directed against other target antigens than CD19 are currently investigated in solid tumour indications.[2]

BiTE® antibodies represent a completely new immunotherapeutic approach for cancer therapy that exploits characteristics of both humoral and cellular immune responses, resembling to some extent the tumour allo-specific CTL response expected after hematopoietic stem cell transplantation (HSCT) but without its inherent toxicity.

Blinatumomab has shown a remarkable activity in a phase II study with B-precursor ALL patients for the eradication of minimal residual disease (MRD). The results of the initial phase II study MT103-202 are impressive with 80% of MRD negativity achieved after the first treatment course.[3] Blinatumomab is also currently tested in the context of haematologic relapse/refractory disease in Germany (study MT103-206). Here the activity of blinatumomab is also impressive.[4,5]

Persistence or reappearance of MRD of B-ALL is an indicator of resistance to chemotherapy. In this case, HSCT offers a chance of cure but many patients remain MRD+ and experience relapse before transplantation or are not eligible for transplantation because of older age or lack of donor. Even after transplantation, the prognosis of patients with positive MRD before the procedure remains poor. This is especially the case for relapsed B-ALL.

In this situation where conventional treatment approaches fails, blinatumomab offers a very high rate of conversion to MRD negativity, sometimes sustained, and can be used as a bridge to HSCT.

The BLAST trial:

The BLAST trial is a confirmatory European multicenter, single-arm study to assess the efficacy, safety, and tolerability of the BiTE® antibody blinatumomab® in adult BCP-ALL patients who, after intensive treatment (consisting of at least three blocks of intensive chemotherapy), are in hematologic remission but still have a positive MRD (>10-3).

Blinatumomab is administered as a continuous infusion. If a HSCT is planned, blinatumomab serves as a 'bridge to transplant' by lowering the MRD level before transplant. If there is no graft, four courses of the antibody are planned. It is possible to retreat in case of molecular relapse after blinatumomab.

Practically:

In order to assess the MRD response by molecular techniques, DNA obtained at diagnosis or relapse has to be sent prospectively to the central laboratory in Germany (Kiel) to establish a clonospecific PCR test and confirm the level of MRD at the time of inclusion.

To increase the number of B-ALL patients that can potentially benefit from the drug, the sponsor gives the opportunity to all hematologic centres (this proposal also applies to all the centres where the protocol is not open!) to send DNA from the newly diagnosed B-ALL to the central lab in Kiel, already at the time of diagnosis or relapse, for the lab to establish clonospecific PCR (creation of primers specific to the patient

Then at the end of induction (which must have included at least three blocks of intensive chemotherapy) or at the end of re-induction (when the patient is in hematologic remission) a new sample must be sent to Kiel to determine the MRD. If it is >10-3,

the patient is includable in the protocol.
The shipment could be done via the nearest centre where the protocol is open. For a list of involved centres in Belgium see below.

Conclusions / recommendations

Blinatumomab is a real opportunity for patients with B-cell precursor acute lymphoblastic leukaemia who are MRD positive.
The BLAST study offers two advantages for our future new BCP-ALL patients:

1. Patients can benefit from a clonospecific PCR for the monitoring of their treatment (not done routinely in the adult context).
2. It offers a very promising alternative therapy in case of treatment failure (i.e., MRD positivity). In case of relapse, it may be the only way to get patients into MRD negativity before HSCT or, if a HSCT is not possible, to keep patients in remission as long as possible.

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List of participating centres in Belgium

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