ANZCHOG Australian & New Zealand Children's Haematology/ Oncology Group

ANZCHOG Leukaemia Lymphoma Group position on the use of blinatumomab in infants, children and adolescents with B-cell acute lymphoblastic leukaemia

Version 1.1 - 04/09/2024

Treatment for children with B-cell acute lymphoblastic leukaemia (B-ALL) comprises cyclical multi-agent chemotherapy. Recent clinical trials have investigated whether the addition of a form of immunotherapy, blinatumomab, can improve the outcome for children with B-ALL. Blinatumomab is a single chain recombinant antibody construct, known as a bispecific T-cell engager, with binding sites for CD19, which is expressed on B cells including malignant B-lymphoblasts, and CD3, which is expressed on endogenous T-cells. Blinatumomab enables T-cell mediated destruction of B-ALL cells.

Blinatumomab has previously been demonstrated to improve outcomes in children with relapsed/refractory B-ALL.[1, 2] Results from two pivotal paediatric frontline studies have now shown significant improvement in survival outcome with the addition of blinatumomab to chemotherapy for both infants, defined as patients diagnosed prior to their first birthday, and children (Children's Oncology Group (COG) AALL1731 study) with B-ALL.[3, 4] For infants with *KMT2A*-rearranged ALL, there was an over 30% improvement in 2-year disease-free survival (DFS) with the addition of a single cycle of blinatumomab to the conventional Interfant-06 chemotherapy backbone compared to historical controls treated with the Interfant-06 chemotherapy backbone alone.[3] On the COG AALL1731 study, an interim analysis by the data safety monitoring board identified a significant and clinically meaningful improvement in 3-year DFS for children with Standard Risk-High B-ALL treated with two non-sequential cycles of blinatumomab following consolidation and also those with Standard Risk-Average B-ALL who were minimal residual disease (MRD) positive at the end of Induction, using the Adaptive ClonoSeq High Throughput Next Generation Sequencing (HTS) platform, which is 10-100-fold more sensitive than conventional flow cytometry.[4]

There is also now robust evidence that blinatumomab is safe and at least as effective as standard chemotherapy, with comparable survival outcomes when used in lieu of standard treatment in chemotherapy-intolerant patients.[5, 6]

To ensure consistency of therapy for infants, children and adolescents being treated for B-ALL across Australia and New Zealand and to enable equity of access, the ANZCHOG Leukaemia & Lymphoma group have developed the following recommendations regarding the use of blinatumomab in this setting. These recommendations are current at the time of writing, however, may be subject to change as further evidence emerges with time.

(i) All infants, children and adolescents with B-ALL should be offered the opportunity to enrol on an open clinical trial where available and eligible.

(ii) All infants with CD19+ *KMT2A*-rearranged B-ALL should receive one cycle of blinatumomab following Induction therapy.[3]

(iii) Children and adolescents with CD19+ B-ALL, who are being treated according to COG protocols and have not been classified as being of favourable risk (Standard Risk-Favourable or High Risk-Favourable) and have not yet commenced maintenance therapy should receive one to two non-sequential cycles of blinatumomab following consolidation and prior to maintenance therapy.[4] This indication is independent of flow cytometry MRD status.

(iv) Children and adolescents with CD19+ B-ALL, who are being treated according to the AIEOP-BFM ALL 2017 ['Study 10'] protocol and who have not been classified as being of Standard Risk and have not yet commenced maintenance therapy should receive two to three cycles of blinatumomab following consolidation and prior to maintenance therapy. This indication is independent of MRD status.

(v) Considerations around addition of blinatumomab to other standard of care or clinical trial protocols (i.e., non-COG or non-BFM) should take into account institutional and/or cooperative group consensus recommendations where applicable, as well as individual patient risk prognostication, treatment burden and feasibility. It is

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recommended where available that individual patient eligibility is discussed at the relevant statewide multi-disciplinary meeting.

(vi) In children with CD19+ B-ALL who are suffering from chemotherapy-induced or infectious toxicity and are consequently unable to receive further intensive chemotherapy, blinatumomab may be considered for interim therapy until they have recovered from the toxicity in question and been deemed clinically fit to receive further chemotherapy by their treating team.[5, 6]

Currently the Pharmaceutical Benefits Scheme (PBS) provides reimbursement for the use of blinatumomab only in patients who are MRD positive. An application has been made by Amgen to the Pharmaceutical Benefits Advisory Committee (PBAC) and the Therapeutic Goods Administration (TGA) for PBS reimbursement of blinatumomab for patients who are MRD negative, based on positive results from the E1910 study that has been conducted in adults with B-ALL.[7] The application has been made agnostic of age and cytogenetic status and if approved as current, will result in infants and children ultimately being able to access PBS reimbursed blinatumomab for the aforementioned recommendations.

Further details regarding the interim results of the COG AALL1731 study or the AIEOP-BFM ALL 2017 ['Study 10'] study can also be provided and discussed in confidence by your institution's oncology team.

References

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3. van der Sluis IM, de Lorenzo P, Kotecha RS, Attarbaschi A, Escherich G, Nysom K, et al. Blinatumomab added to chemotherapy in infant lymphoblastic leukemia. N Engl J Med 2023;388(17):1572-1581.
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6. Hodder A, Mishra AK, Enshaei A, Baird S, Elbeshlawi I, Bonney D, et al. Blinatumomab for first-line treatment of children and young persons with B-ALL. J Clin Oncol 2024;42(8):907-914.
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