

# Blinatumomab: A Promising New Drug in the Therapeutic Armamentarium for Acute Lymphoblastic Leukemia

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#### Abstract

The anti CD19/CD3-bispecific T cell-engager monoclonal antibody blinatumomab is an effective drug with an acceptable toxic profile for the treatment of patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. This high efficacy has also been observed in patients with minimal residual disease. These favorable results have led to the investigation of the activity of this drug in early phases of the disease.

### Key words:

Acute lymphoblastic leukemia; B-cell precursor; Relapsed; Refractory; Immunotherapy

#### Introduction

Acute lymphoblastic leukemia (ALL) is a highly curable disease in children (80%-90%), while the cure rate in adults ranges between 35% and 50% [1]. Relapse or resistance (occurring in 10%-15% of children and in 50%-60% of adults) is the most important cause of therapeutic failure and represents an important problem in ALL management. Salvage chemotherapy followed by allogeneic hematopoietic stem cell transplantation (alloHSCT) in responding patients is the standard therapy for children with early relapses and for all adults with relapsed/ refractory (R/R) ALL. However, only 50-60% of children and 30-40% of adults achieve a second complete remission (CR), and only half of these patients can be transplanted. In all, only 20% of children with early relapse and 10% of adults with relapsed/refractory ALL can be cured with standard therapies [2]. Consequently, the development of effective and relatively non-toxic rescue therapies for R/R ALL patients is clearly needed.

Immunotherapy is a promising modality of treatment of neoplastic diseases. Among the several strategies used, the engagement of cytotoxic T cells irrespective of their T-cell receptor (TCR) specificity to the neoplastic cells has shown the highest therapeutic potential. Two therapeutic modalities have been especially useful for the treatment of B-cell precursor ALL [3,4]. One uses the ectopic expression of a CD19specific chimeric antigen receptor construct in transfected autologous T-cells of patients (CART). The other approach uses a CD19/CD3bispecific T cell-engager (BiTE\*) monoclonal antibody (MoAb) blinatumomab, which can transiently engage any cytotoxic T cell to CD19<sup>+</sup> target B cells [5-10].

The clinical development program of blinatumomab in ALL was initially focused on adult patients with R/R ALL and in ALL patients with high levels of minimal residual disease (MRD), a situation associated with a high risk of relapse [11]. The first two trials were conducted by the German Multicenter Adult Acute Lymphoblastic Leukemia (GMALL) Group, with complete responses (CR) of 42% (69% if CR with incomplete hematological recovery -CRh- was considered) in R/R patients [12] and of 80% in patients with MRDpositive ALL [13,14]. A global phase II study in R/R adult ALL patients was activated and of the 189 patients treated, 81 (43%) achieved CR/CRh within the first two cycles [15]. AlloHSCT was performed in 32 (40%) of the 81 patients with CR/CRh. At a median follow-up of 8.9 months the median RFS was 5.9 months. The median OS was 6.1 months (median follow-up 9.8 months), without differences after censoring the follow-up at alloHSCT. The OS was significantly better for patients achieving CR/CRh after two treatment cycles (median of 9.9 months vs. 2.7 months). In turn, the preliminary results of a confirmatory multicenter phase II study in adult patients with MRDpositive B-cell precursor ALL has shown that 89 out of 106 patients (80%) had complete MRD response after 2 cycles (88 [78%] after 1 cycle) [16]. The results of a phase II study of blinatumomab in pediatric patients with R/R B-precursor ALL have shown similar results than those of the adult trials [17]. Based on these results blinatumomab was approved by the US Food and Drug Administration (FDA) on December 3, 2014 following an accelerated review process, for patients with R/R, Philadelphia chromosomenegative B-cell precursor ALL.

A phase II single-arm, multicenter trial aimed to evaluate the efficacy of blinatumomab in adults with R/R ALL and Philadelphia chromosome is currently being conducted, and the accrual of the 41 patients has been completed. In addition, a phase III, randomized, multicenter, open-label study investigating the efficacy of blinatumomab vs. standard of care (SOC) chemotherapy in adults with R/R, Philadelphia chromosome-negative, B-cell precursor ALL is now underway, and several trials in children with R/R ALL in both the US and Europe are in the activation process. The next logical step is to evaluate the activity of blinatumomab in early phases of ALL. An ongoing phase III study of combination chemotherapy with or without blinatumomab in patients with newly diagnosed Ph-, B-lineage ALL is being conducted in the US by the Eastern Cooperative Oncology Group (ECOG).

Blinatumomab has a specific safety profile. The most significant toxicities reported in the studies performed in R/R ALL and in MRDpositive ALL using the dose of 15 ug/m<sup>2</sup>/day CIV during 4 weeks with 2 weeks off between cycles were central nervous system (CNS) events and the cytokine release syndrome (CRS). The adverse CNS events consisted of encephalopathy, aphasia, tremor, and disorientation, and were reversible in most cases but led to early discontinuation of the drug in others [18]. Neurological events are managed with temporary interruption of blinatumomab and dexamethasone treatment. The CRS is thought to occur due to rapid lysis of tumor cells by T- lymphocytes during the first infusion, being more pronounced during the beginning of the first cycle of treatment [19]. Baseline disease burden is associated with risk of CRS and pre-phase dexamethasone is required for patients with more than 50% blasts or a peripheral blast count over  $15 \times 10^9$ /L. The reduction in the dose of blinatumomab to 5 µg/m<sup>2</sup>/day (or 9 µg/day) in the first week of the first cycle also prevents the development of CRS.

Despite the promising results of treatment with blinatumomab and the high rate of HSCT in responding patients, a significant number of patients do not respond or experience relapse. In a significant proportion of relapsed patients the leukemic blasts are CD19 negative, suggesting that a selection of CD19-negative sub clones are present at low levels at relapse. On the other hand, some of the relapses after blinatumomab are extra medullary, especially in CNS, suggesting an insufficient activity of blinatumomab in sanctuary sites.

## Conclusion

Together with other immunotherapeutic approaches, blinatumomab provides a window of hope for patients with R/R B-precursor ALL, allowing a significant proportion of responses with an acceptable safety profile and increasing the proportion of patients that could be successfully rescued by alloHSCT. These results can hopefully be translated to early phases of the treatment of all.

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## References

- 1. Hoelzer D (2015) Personalized medicine in adult acute lymphoblastic leukemia. Haematologica 100: 855-858.
- Frey NV, Luger SM (2015) How I treat adults with relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia. Blood 126: 589-596.
- Maude SL, Teachey DT, Porter DL, Grupp SA (2015) CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. Blood 125: 4017-4023.
- Sadelain M, Brentjens R, Rivière I, Park J (2015) CD19 CAR Therapy for Acute Lymphoblastic Leukemia. Am Soc Clin Oncol Educ Book 35: e360-363.

- 5. Jabbour E, O'Brien S, Ravandi F, Kantarjian H (2015) Monoclonal antibodies in acute lymphoblastic leukemia. Blood 125: 4010-4016.
- Stieglmaier J, Benjamin J, Nagorsen D (2015) Utilizing the BiTE (bispecific T-cell engager) platform for immunotherapy of cancer. Expert Opin Biol Ther 15: 1093-1099.
- Bumma N, Papadantonakis N, Advani AS (2015) Structure, development, preclinical and clinical efficacy of blinatumomab in acute lymphoblastic leukemia. Future Oncol 11: 1729-1739.
- Buie LW, Pecoraro JJ, Horvat TZ, Daley RJ (2015) Blinatumomab: A Firstin-Class Bispecific T-Cell Engager for Precursor B-Cell Acute Lymphoblastic Leukemia. Ann Pharmacother 49: 1057-1067.
- Dahl J, Mace M, Kantarjian H, Jabbour E (2015) Blinatumomab for the treatment of adult acute lymphoblastic leukemia. Drugs Today (Barc) 51: 231-241.
- Rogala B, Freyer CW, Ontiveros EP, Griffiths EA, Wang ES, et al. (2015) Blinatumomab: enlisting serial killer T-cells in the war against hematologic malignancies. Expert Opin Biol Ther 15: 895-908.
- 11. van Dongen JJ, van der Velden VH, Brüggemann M, Orfao A (2015) Minimal residual disease diagnostics in acute lymphoblastic leukemia: need for sensitive, fast, and standardized technologies. Blood 125: 3996-4009.
- 12. Topp MS, Gökbuget N, Zugmaier G, Klappers P, Stelljes M, et al. (2014) Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. J Clin Oncol 32: 4134-4140.
- 13. Topp MS, Kufer P, Gökbuget N, Goebeler M, Klinger M, et al. (2011) Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol 29: 2493-2498.
- 14. Topp MS, Gökbuget N, Zugmaier G, Degenhard E, Goebeler ME, et al. (2012) Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. Blood 120: 5185-5187.
- 15. Topp MS, Gökbuget N, Stein AS, Zugmaier G, O'Brien S, et al. (2015) Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 16: 57-66.
- 16. Goekbuget N, Dombret H, Bonifacio M, Reichle A, Graux C, et al. (2014) BLAST: A Confirmatory, Single-Arm, Phase 2 Study of Blinatumomab, a Bispecific T-Cell Engager (BiTE\*) Antibody Construct, in Patients with Minimal Residual Disease B-Precursor Acute Lymphoblastic Leukemia. Blood 124: 379.
- Gore L, Locatelli F, Zugmaier G, Zwaan CM, Bhojwani D, et al. (2014) Initial Results from a Phase 2 Study of Blinatumomab in Pediatric Patients with Relapsed/Refractory B-Cell Precursor Acute Lymphoblastic Leukemia. Blood 124: 3703.
- Barrett DM, Teachey DT, Grupp SA (2014) Toxicity management for patients receiving novel T-cell engaging therapies. Curr Opin Pediatr 26: 43-49.
- 19. Teachey DT, Rheingold SR, Maude SL, Zugmaier G, Barrett DM, et al. (2013) Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokinedirected therapy. Blood 121: 5154-5157.