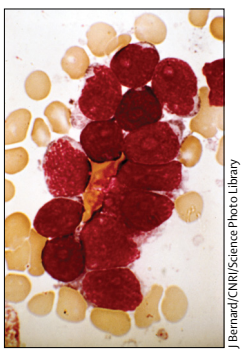
Blinatumomab: a new era of treatment for adult ALL?



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Standard chemotherapy for acute lymphoblastic leukaemia (ALL) is, at present, far from ideal. Although intensified cytotoxic therapy has improved the prognosis of children with ALL, this approach has provided little benefit in adults, despite the recent introduction of paediatric-inspired regimens for adults.[1] Most patients respond to induction chemotherapy, but up to 50% experience relapse with chemoresistant disease.[2] Persistence or reappearance of minimal residual disease (MRD) is the most important adverse prognostic factor.[3] Chemotherapy regimens produce particularly poor results for patients with relapsed or refractory disease.[4] Thus refractory or relapsed and MRD-positive ALL remain an unsolved therapeutic problem, for which therapies with an alternative mechanism of action are needed.

Medical haematology has recently undergone profound changes. Among these changes, recent developments in monoclonal antibody therapy are particularly exciting, and could improve remission rates and thus increase uptake of allogeneic stem-cell transplantation (SCT). Blinatumomab is a novel, bispecific, single chain T-cell engager antibody with dual binding specificities. Blinatumomab uses patients' own cytotoxic T cells to kill CD19-positive, malignant B-cells. T cells are bound by its anti-CD3 moiety, whereas malignant B cells are bound by the anti-CD19 moiety. Blinatumomab-mediated T-cell activation involves the transient proliferation of T cells and release of inflammatory cytokines. In *The Lancet Oncology*, Max Topp and colleagues report findings from a phase 2 trial of 189 patients given blinatumomab, and describe impressive clinical activity with high MRD response, even in heavily pretreated patients.[5] After two cycles, 81 (43%, 95% CI 36–50) patients had achieved the primary endpoint of complete response or haematological complete response. The most important adverse events were reversible neurological toxicities and aplasia.

Despite these encouraging results, some issues should be mentioned. First, which patients will benefit from blinatumomab has yet to be defined. Severe life-threatening reactions can potentially result from massive release of cytokines, as reported with other monoclonal antibodies.[6] Blinatumomab also causes B-cell depletion, leading to further decreases in immunoglobulin levels, increasing the risk of infections. Blinatumomab has a fairly short half-life, making continuous infusion over 4-week cycles through a portable mini-pump the optimum mode of delivery.[7] These features could present challenges in frail patients or in the paediatric population. Second, questions remain about how best to use blinatumomab: as a single agent or in combination therapy, for induction, consolidation, or maintenance, or as part of a large combination or succession of treatments? The incorporation of blinatumomab into conventional chemotherapy backbones, potentially including other monoclonal antibodies, should produce opportunities to assess the feasibility of such combinations and to increase treatment efficacy. Furthermore, combinations of several drugs might reduce the risk of resistant clonal outgrowth. However, the dependence of blinatumomab on circulating immune cells seems to limit our ability to directly combine blinatumomab with myelosuppressive therapies. It seems more likely that we should use blinatumomab sequentially with chemotherapy instead of concurrently. The striking efficacy of immuno-modulatory approaches has generated interest for a potential role in the management of MRD-positive disease. Activation of T cells stimulates proliferation of CD4-positive and CD8-positive cytotoxic cells as long as target cells are available. A potential role of blinatumomab could be in molecular relapses after SCT to potentiate the effect of donor lymphocyte infusions. In addition, allogeneic SCT remains the main goal of therapy in high-risk ALL. An emerging point is the feasibility of SCT after blinatumomab treatment. As with other monoclonal antibody therapies, blinatumomab results in a fast and deep response, but a short duration of effect. Blinatumomab might be useful in combinations to obtain even deeper response and remissions that are long enough to allow organisation of transplantation. Blinatumomab could thus find a place in a window period and serve as a bridge to SCT. Several factors should be considered for this approach, including the likelihood of achieving remission, organ toxic effects, and the time needed to screen, enroll, and treat patients before SCT. Finally, new therapeutic strategies might focus on exploiting targets governing stem-cell renewal and differentiation. An important issue in favour of

combination therapy is that blinatumomab can target bulk leukaemia cells, but not the leukaemia stem cell. This supposition is supported by the short duration of effect with blinatumomab. Furthermore, the ability to target sanctuary sites remains a major challenge.

Many drugs have become available that have the potential to change the standard of care for adult patients with ALL. Combination of several agents targeting more than one antigenic determinant, gene mutation, or signal transduction pathway might be the most effective strategy, and could hold the promise of substantial benefit, and could represent a targeted solution similar to the total therapy approach pioneered by Don Pinkel in the 1960s with chemotherapeutic agents.

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I declare no competing interests.

1 Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J Clin Oncol* 2009; **27:** 911–18.
2 Gökbuget N, Hoelzer D. Treatment of adult acute lymphoblastic leukemia. *Semin Hematol* 2009; **46:** 64–75.
3 Gökbuget N, Kneba M, Raff T, et al. Adults with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. *Blood* 2012; **20:** 1868–76.
4 Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL): an MRC UKALL 12/ECOG 2993 study. *Blood* 2007; **109:** 944–50.
5 Topp MS, Gökbuget N, Stein AS, et al. 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* 2014; published online Dec 16. http://dx.doi.org/10.1016/S1470-2045(14)71170-2.
6 Winkler U, Jensen M, Manzke O, et al. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). *Blood* 1999; **94:** 2217–24.
7 Nagorsen D, Baeuerle PA. Immunomodulatory therapy of cancer with T cell-engaging BiTE antibody blinatumomab. *Exp Cell Res* 2011; **317:** 1255–60.