The anti-CD19 antibody-drug conjugate SAR3419 prevents hematolymphoid relapse post-induction therapy in preclinical models of pediatric acute lymphoblastic leukemia.

Richard B Lock1, Barbara Szymanska1, Hernan Carol1, Ingrid Boehm1, Kathryn Evans1, Peter J Houghton1, and Malcolm A Smith1

1Children’s Cancer Institute Australia for Medical Research, University of New South Wales, Sydney, Australia; 2Nationwide Children’s Hospital, Columbus, Ohio, US; 3Cancer Therapy Evaluation Program, NCI, Bethesda, Maryland, US.

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INTRODUCTION

SAR3419 is an antibody-drug conjugate (ADC) of a humanized anti-CD19 antibody and the maytansinoid DM4 currently in clinical trials for relapsed or refractory B cell non-Hodgkin’s lymphoma and adult acute lymphoblastic leukemia. SAR3419 was previously shown by the Pediatric Preclinical Testing Program (PPTP) to be highly effective in delaying the progression of CD19+ B cell precursor ALL (BCP-ALL) xenografts in NOD/SCID mice, while being ineffective against CD19+ T-ALL in NOD/SCID ALL. In the current study we evaluated the efficacy of SAR3419 against additional BCP-ALL and infant mixed lineage leukemia (MLL) xenografts, assessed its therapeutic range, and studied its efficacy in combination with an induction-type regimen of vincristine/doxorubicin/l-asparaginase (VLS).

METHODS

Engraftment and responses of xenografts to drug treatments were assessed by enumeration of the proportion of human versus mouse CD45+ cells in PB or NOD/SCID mice. Mice with established systemic disease received vehicle, SAR3419 (2.5-10 mg/kg, weekly x 3), or VXL (0.15 mg/kg, weekly; 5 mg/kg, daily x 5; 100 µg/kg, daily x 5; p.i. x 2 weeks) followed by SAR3419 (10 mg/kg) either for 3 weeks or continuous treatment. The aim was to evaluate residual disease. The three measures of anti-leukemic activity were used: (1) an objective response measure (ORM) modified after the clinical setting; (2) time to event based on the median event-free survival (EFS) of treated or control groups; and (3) a leukemia growth delay (LGD) measure comparing the EFS of treated and control groups.

RESULTS

SAR3419 exerts significant in vivo single-agent efficacy against MLL xenografts. SAR3419 as a single agent significantly delayed the progression of three MLL xenografts by 22.1 to 36.5 days and induced objective responses in all three xenograft models.

CD19 expression correlates with in vivo response to SAR3419. Relative surface CD19 expression across the BCP-ALL xenograft panel significantly correlated with both LGD and ORM scores, indicating that CD19 density is an important determinant of SAR3419 efficacy.

SAR3419 is effective against ALL-4 in vivo over a broad dose range. SAR3419 was highly effective against a chemoresistant BCP-ALL11 xenograft (ALL-4), inducing complete responses (CRs) over a wide range of doses (2.5-10 mg/kg), while the unconjugated antibody (HuM195) had limited efficacy, indicating that DM4 is critical for the high efficacy of the ADC.

SAR3419 prevents hematolymphoid relapse of BCP-ALL xenografts following remission induction with VXL therapy. Mice receiving VXL followed by 3 weekly doses of SAR3419 eventually relapsed with dissemination of leukemia into hematolymphoid organs. However, mice that received continuous weekly SAR3419 treatment post-VXL were already relapsed with leukemia induction to the central nervous system (CNS) and splenic failure, but without evidence of infiltration of major organs (bone marrow, spleen, liver, kidney, lung, PB).

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CONCLUSIONS

• SAR3419 was highly effective against aggressive and chemoresistant CD19+ pediatric ALL xenografts over a wide range of doses.
• When used as maintenance therapy following VXL, SAR3419 prevented hematolymphoid relapse.
• These findings suggest that SAR3419 may be effective for high-risk CD19+ ALL in both the remission induction and the post-remission settings.