Journal for ImmunoTherapy of Cancer

POSTER PRESENTATION Open Access

Immunotherapy using bispecific T cell engager (BiTE®) antibodies: preclinical and clinical experience in acute leukemia

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From Society for Immunotherapy of Cancer 29th Annual Meeting
National Harbor, MD, USA. 6-9 November 2014

BiTE® antibodies are novel recombinant single chain Ig domain constructs that leverage the endogenous cytotoxic potential of polyclonal T cells to target malignant cells by utilizing the specific binding properties of variable domains from two different antibodies. Antibody-based immunotherapy represents a promising strategy in cancer. BiTE® antibodies have demonstrated efficacy in hematologic malignancies, both preclinically and clinically.

Two investigational BiTE antibodies are under development targeting leukemia. The most advanced BiTE® antibody, Blinatumomab, directs cytotoxic T cells to CD19-expressing target cells. Blinatumomab has shown anti-leukemia activity in adult relapsed/refractory (r/r) B-precursor ALL. Its efficacy and toxicity was evaluated in a large confirmatory Phase II study. Patients with Ph-negative r/r ALL (N = 189; refractory; 1st relapse

Given the anti-leukemia activity of single-agent Blinatumomab in a difficult-to-treat population with r/r ALL, another BiTE® antibody targeting CD33, AMG 330, was developed for its suitability as immunotherapy in AML. To simulate the natural setting of target and T cells in AML patients, a long-term culture system was developed that supports the growth of primary AML cells *ex-vivo* for up to 5 weeks. AMG 330 activated and expanded residual autologous T cells within primary AML patient samples and eliminated CD33+ blasts even at very low effector to target ratios. The functional relevance of CD33 expression levels was shown by faster lysis kinetics of $CD33^{BRIGHT}$ versus $CD33^{DIM}$ AML cell lines and primary AML cells in ex-vivo cytotoxicity assays. However, by extending the exposure time to AMG 330, potent anti-leukemic activity was observed in both $CD33^{BRIGHT}$ and $CD33^{DIM}$ cells. AMG 330 treated T cells were shown to up-regulate the activation markers CD25, PD-1, TIM3 and LAG3, which was partially reversible after complete target cell elimination

Clinical experience with Blinatumomab in ALL and ex-vivo activity of AMG 330 in primary AML samples supports further development of BiTE® antibodies for targeted T cell-mediated immunotherapy of patients with malignancies.

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Published: 6 November 2014

doi:10.1186/2051-1426-2-S3-P115
Cite this article as: Subklewe *et al.*: Immunotherapy using bispecific T cell engager (BiTE®) antibodies: preclinical and clinical experience in acute leukemia. *Journal for ImmunoTherapy of Cancer* 2014 2(Suppl 3):P115.

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