Molecular Immunology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Review

Clinical overview of anti-CD19 BiTE® and ex vivo data from anti-CD33 BiTE® as examples for retargeting T cells in hematologic malignancies

Gerhard Zugmaier[a], Matthias Klinger[a,*], Margit Schmidt[a], Marion Subklewe[b,c]

[a] Amgen Research (Munich) GmbH, Munich, Germany
[b] Department of Internal Medicine III, Klinikum der Universität München, Munich, Germany
[c] Clinical Cooperation Group Immunotherapy, Helmholtz Institute Munich, Munich, Germany

ARTICLE INFO

Article history:
Received 10 November 2014
Received in revised form 20 February 2015
Accepted 28 February 2015
Available online xxx

Keywords:
BiTE
Immunotherapy
NHL
ALL
AML
Blinatumomab
AMG 330

ABSTRACT

Blinatumomab, a bispecific antibody construct targeting CD19, is the most advanced member of bispecific T-cell engager (BiTE®) molecules. The clinical development program includes B-precursor acute lymphoblastic leukemia (ALL) and B-cell non-Hodgkin lymphoma (NHL). Minimal residual disease (MRD) response in patients with MRD-positive B-precursor ALL has translated into long-term clinical benefits as demonstrated by an estimated relapse-free survival (RFS) of 60% with sustained MRD negativity at a follow-up of 31 months. Remissions induced in pediatric and adult patients with relapsed/refractory B-precursor ALL have allowed for successful allogeneic hematopoietic stem cell transplantation (HSCT) in this setting. Blinatumomab has also induced durable responses in low-grade B-cell NHL. Blinatumomab recently gained approval in the United States by the U.S. Food and Drug Administration for treatment of Philadelphia chromosome-negative B-precursor relapsed/refractory acute lymphoblastic leukemia. AMG 330 is an investigational anti-CD33 BiTE® antibody construct. Targeting CD33 ex vivo in primary samples from patients with acute myeloid leukemia (AML) has shown AMG 330-mediated T-cell expansion and T-cell cytotoxicity against AML cells.

1. Introduction

Clinical observations reaching back more than one hundred years have shown cases of tumor regression after systemic infection. The first successful immunotherapy against cancer was developed by William Cooley in 1891 and consisted of streptococcal cultures used for injection in sarcoma patients (DeWeerdt, 2014).

Cytotoxic T-lymphocytes can inhibit tumor growth, and this property can be employed to achieve immunotherapy. This has been demonstrated in patients with melanoma by transfer of ex vivo expanded tumor-derived lymphocytes (Dudley et al., 2005) or of T-cell receptor gene-transfected T cells to melanoma patients (Morgan et al., 2006).

The development of T-cell-engaging antibodies (Muller and Kontermann, 2007; Staerz et al., 1985) has given a novel spin to the use of cytotoxic T cells. Due to lack of Fcγ receptors, conventional antibodies cannot be used for direct recruitment of T cells. Bispecific T-cell engagers (BiTE®) are built as single-chain antibody constructs (Baeuerle et al., 2008; Mack et al., 1995) that redirect T cells to tumor cells, by connecting a T cell via CD3 to a tumor-specific antigen on the surface of the tumor cell. This induces the formation of a transient cytolytic synapse between the cytotoxic T cell and the tumor cell resulting in T-cell activation, proliferation, and serial lysis of tumor cells (Fig. 1). BiTE®-mediated tumor cell lysis involves fusion of vesicles (which contain granzymes and perforins) with the tumor cell membrane resulting in pore-formation by perforins and granzyme B-induced apoptosis. Simultaneously, T-cell activation results in up-regulation of activation markers and adhesion molecules on the T-cell surface, production of additional granzymes and perforins and release of cytokines. Furthermore, T cells enter into cell cycle and T-cell proliferation is induced (Brandl et al., 2007; Brischwein et al., 2007; Haas et al., 2009; Hoffmann et al., 2005).

BiTE® molecules directly engage any cytotoxic T cell and thus do not require generation of tumor-specific T-cell clones by priming of naïve T cells through antigen-presenting cells, as known for other T-cell–based therapeutic strategies (Baeuerle et al., 2009). Furthermore, BiTE®-mediated T-cell activation does not rely on the presence of MHC class I molecules and tumor-specific peptide antigens (Baeuerle et al., 2009). BiTE® molecules currently under clinical evaluation target a variety of tumor-specific antigens, most importantly CD19 (expressed on B cells) and CD33 (expressed on

* Corresponding author at: Amgen Research (Munich) GmbH, Staffelseestrasse 2, 81477 Munich, Germany. Tel.: +49 089 895277 530; fax: +49 089 895277 605.
E-mail address: matthias.klinger@amgen.com (M. Klinger).

http://dx.doi.org/10.1016/j.molimm.2015.02.033
0161-5890/

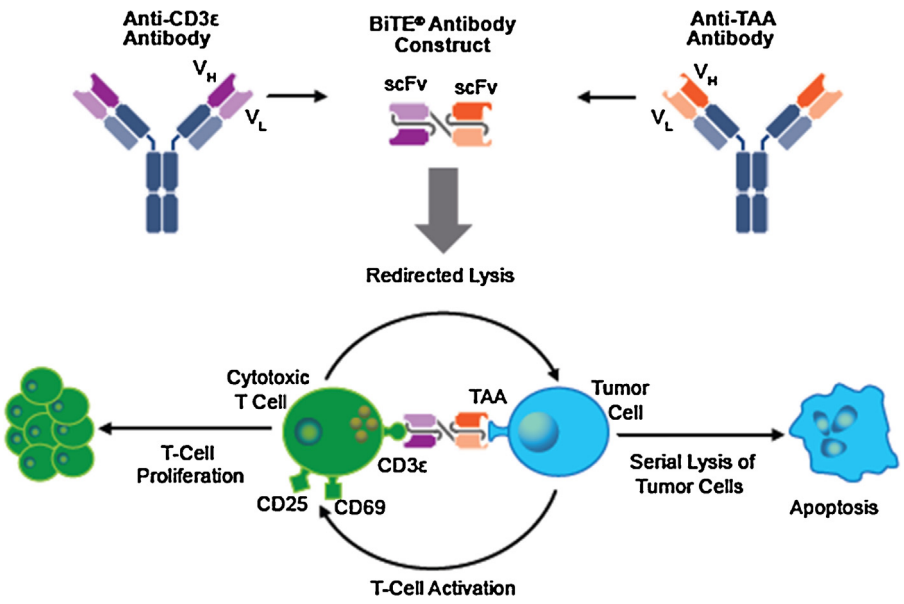

Fig. 1. Design and mode of action of BiTE® antibody constructs. TAA, tumor-associated antigens.

myeloid-derived cells) as well as specific antigens associated with solid tumors, such as epithelial cell adhesion molecule (EpCAM; CD326), prostate-specific membrane antigen (PSMA), and carcinoembryonic antigen (CEA; CD66e) (Frankel and Baeuerle, 2013). Tumor-associated antigens targeted by other bispecific antibody formats include the interleukin-3 receptor α (CD123) or the human C-type lectin-like molecule 1 (CLL-1) in the setting of AML (Lu et al., 2014; Stein et al., 2010). Bispecific antibody formats for treatment of various solid tumor types are currently also in development (Garber, 2014).

In this review we provide an overview of recent preclinical and clinical results for the investigational BiTE® antibody constructs blinatumomab (which has dual specificity for CD19 and CD3) in B-cell malignancies, and AMG 330 (which has dual specificity for CD33 and CD3) in myeloid malignancies.

2. Anti-CD19 BiTE® blinatumomab

Blinatumomab is an investigational single-chain antibody construct of the BiTE® class that is designed to direct T cells to target B cells. Blinatumomab combines in one polypeptide chain the binding specificity for both the pan–B-cell antigen CD19 and the CD3 epsilon chain of the T-cell receptor complex, with a molecular weight of approximately 55 kDa (Nagorsen et al., 2012). Biological activity of blinatumomab comprises release of different cytokines (e.g., TNF-α, IFN-γ, IL-6, IL-10) by T cells in the presence of targeT cells, induction of activation markers (e.g., CD69, CD25) and expression of adhesion molecules (e.g., CD2, LFA-1) on the T-cell surface (Brandl et al., 2007). Furthermore, blinatumomab has been shown to exhibit high cytotoxic activity at very low concentrations, and activity has been demonstrated to be independent of T-cell co-stimulation (Dreier et al., 2002, 2003; Loffler et al., 2000).

2.1. Administration of blinatumomab

The majority of monoclonal antibodies for cancer therapy are administered to patients by intravenous (IV) injection. During early clinical development of blinatumomab, short-term infusions with blinatumomab were investigated in patients with relapsed or refractory non-Hodgkin lymphoma (NHL). Blinatumomab was administered at different doses, given once or twice weekly, as a 2- or 4-h IV infusion. Given blinatumomab's half-life of approximately 2 h, this administration strategy was unlikely to have achieved constant serum concentrations across a given 24-h period. Although blinatumomab exhibited biologic activity (i.e., cytokine release, T-cell activation), clinical responses did not occur. Based on these observations, the administration schedule of blinatumomab was modified to continuous IV (cIV) infusion. This change of administration strategy resulted in a prolonged T-cell activation and sustained B-cell depletion, and clinical activity in the form of partial remissions (PRs) and complete remissions (CRs) was observed. Systemic exposure to blinatumomab via cIV infusion was dose proportional and stable with time (Nagorsen et al., 2012).

Continuous blinatumomab infusion is administered via a portable mini-pump (Nagorsen et al., 2012). The pump is preprogrammed to ensure the flow rate is continuous and uniform throughout the infusion. The patient can move about freely while the infusion pump is in use because it is portable, lightweight, and supported in a pouch with a shoulder strap or belt. Patients therefore can be treated either in the hospital or at home. In the clinical setting, patients are treated initially as an inpatient with close monitoring. After a required observation period, the patient may return home at any time depending on the clinical assessment and judgment of the investigator. Alternatively, treatment may also be continued in the hospital, depending on the health status of the patient. At home, the patient may be visited by a home healthcare provider or return to the outpatient clinic to ensure that blinatumomab is administered continuously and the IV bags are changed according to schedule. Current data from ongoing clinical trials demonstrate that the mean duration of treatment in the hospital lessens with each subsequent cycle (through cycle 4), and patients spend progressively more time in a home setting with each cycle.

The pharmacokinetic and pharmacodynamic properties of blinatumomab have important clinical implications. A continuous infusion over 4 weeks provides sufficient serum exposure for sustained B-cell depletion and prolonged T-cell activation, and has the potential to provide meaningful therapeutic benefits in relapsed or refractory acute lymphoblastic leukemia (ALL). In clinical studies, an integrated strategy to support the safe handling and administration of blinatumomab has been developed. A key component of this strategy is the ability to administer blinatumomab on a

Please cite this article in press as: Zugmaier, G., et al., Clinical overview of anti-CD19 BiTE® and ex vivo data from anti-CD33 BiTE® as examples for retargeting T cells in hematologic malignancies. Mol. Immunol. (2015), http://dx.doi.org/10.1016/j.molimm.2015.02.033