EXPERIMENTAL CELL RESEARCH 317 (2011) 1255–1260

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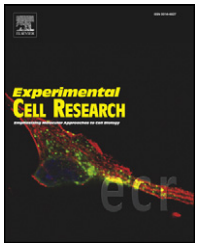

Review

Immunomodulatory therapy of cancer with T cell-engaging BiTE antibody blinatumomab☆

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ARTICLE INFORMATION

Article Chronology:
Received 7 January 2011
Revised version received 8 March 2011
Accepted 10 March 2011
Available online 16 March 2011

Keywords:
Bispecific
Antibody
BiTE

ABSTRACT

Severe side effects and few long-term remissions frequently limit the treatment of advanced malignant diseases. Bispecific antibodies are currently emerging as a new option for the treatment of malignant diseases, which can potentially engage all cytotoxic T cells of a patient for tumor cell lysis. Blinatumomab, a bispecific single-chain BiTE antibody construct with dual specificity for CD19 and CD3, is a front runner of this antibody class. We here summarize the current state of development of blinatumomab for the treatment of patients with B-cell non-Hodgkin's lymphoma (NHL) and B-precursor acute lymphocytic leukemia (ALL). High response rates and durable remissions are observed in first clinical trials, indicating that T cells can be potently redirected for efficient and lasting elimination of malignant cells.

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Introduction

Based on the observation that T cells are involved in cancer immune surveillance and their incidence within solid tumors can impact patients' survival, various approaches have been undertaken over the last decades to use this cell type of the immune system for controlling tumor growth or even induce tumor regression [1–4]. T cell-based therapeutic approaches include

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doi:10.1016/j.yexcr.2011.03.010

vaccines, adoptive transfer of autologous, ex-vivo expanded T cells, and T cell-activating antibodies [5–8]. Further attempts use a combination of vaccines in combination with IL-2, IFN2α GM-CSF, or CpG for stimulation of the activity of T cells or antigen presenting cells. While all such approaches have shown some limited activity, only bispecific T cell-engaging antibodies have demonstrated high response rates and durable remissions in patients with hematological malignancies [8,9].

The low response rates of most approaches trying to elicit or support tumor antigen-specific T cell responses in patients with malignant diseases are most likely due to escape variants of tumor cells that are selected under therapy and which later cause recurrence and disease progression. Tumor cells can be selected over time to express mechanisms allowing their escape from recognition by T cells, or their inactivation. These mechanisms include loss of molecules involved in T cell recognition, such as MHC class I, TAP transporter, ß2 microglobulin, or the expression by cancer cells of immunosuppressive molecules, such as IDO, IL-10, TGF-β, PD-L1/B7-H1, or FasL [10,11]. While all these escape mechanisms will inhibit in one or the other way the development of antigen-specific T cell responses, the direct engagement of pre-existing, polyclonal T cell clones with the help of bispecific antibodies may not be impacted to the same extent.

Bispecific antibodies are designed to bind with one arm to a surface antigen on cancer cells of the same kind as is recognized by monoclonal antibodies. These target antigens can, for instance, be overexpressed growth factor receptors, such as EGFR or HER-2, or cell differentiation antigen such as CD20, CD22 or CD19, where the ablation of an entire cell compartment along with cancer cells is tolerated by the patient. With the second arm, bispecific antibodies bind to an activating, invariant component of the T cell receptor. Through the temporarily forced interaction between T cell and cancer cell, any cytotoxic T cell will become activated and can now cause redirected lysis as otherwise performed by antigen-specific cytotoxic T cell clones. BiTE antibodies are one class of bispecific antibodies that have been very well characterized in this regard [8,12]. In the following, we will review the clinical experience with a CD19/CD3-bispecific BiTE antibody called blinatumomab (MT103) for the treatment of NHL and ALL patients.

CD19 as target antigen

The earliest B lineage-restricted antigen expressed on the surface of B lymphocytes is CD19. It primarily acts as a B cell co-receptor in conjunction with CD21 and CD81. Genetic analyses suggest that CD19 plays a role in maintaining the balance between immunity and autoimmunity [13]. With the exception of plasma cells, CD19 is expressed on all development stages of B cells, including all B-cell lineage-derived leukemias, where it is used as classification marker, and with high frequency also on all B-cell lineage-derived lymphomas. While several antibody-based therapies targeting CD20 are on the market, and CD22-targeting antibodies are in late-stage clinical development, CD19-targeting antibodies have only recently been advanced into clinical development. Several anti-CD19 IgG1 antibodies with cytotoxicity-improved Fcγ parts and one antibody drug conjugate are now in phase 1/2 trials. Furthest advanced is the anti-CD19/CD3 BiTE antibody blinatumumab, which is in a pivotal trial in patients with B-precursor ALL.

Mode of action of blinatumomab

Conventional antibodies of the IgG1 class predominantly kill target cells through antibody-dependent cellular cytotoxicity (ADCC), which is mediated by engagement of natural killer (NK) cells, macrophages and neutrophils. Complement dependent cytotoxicity (CDC) makes a poorly understood contribution to their mode of action. Conventional IgG1 antibodies fail to recruit T cells because T cells lack Fcγ receptors as needed for binding the antibodies' Fc domain. As a novel approach to leverage the high cytotoxic potential of T cells bispecific antibodies have been developed that can directly connect any T cell with a cancer cell independently of peptide antigen presentation by tumor cells, or the specificity of T cells.

The clinically most advanced technology for selectively engaging T cells to lymphoma or leukemia cells is based on blinatumomab, a single-chain bispecific antibody constructs of the BiTE class (please see Fig. 1) [8]. BiTE antibodies function as short adaptor molecules that force T cells and tumor cells into close proximity and thereby potently trigger the signaling cascade of the T cell receptor complex by binding to the invariant CD3 component of the receptor (Fig. 1). This redirects basically all antigen-experienced cytotoxic T cells that are preexisting in the patient against tumor cells. Blinatumomab is activating T cells at low pico- to femtomolar concentrations, indicating that the bispecifc antibody is remarkably well mimicking a natural MHC class I/peptide interaction with the T cell receptor. Of note, T cells are only activated by blinatumomab and other BiTE antibodies when a target cell is presenting the BiTE antibody to T cells [8].

The mode of BiTE action is depicted in Fig. 2. Blinatumomab and other BiTE antibodies transiently induce a cytolytic synapse between a cytotoxic T cell and the cancer target cell. As a consequence, granules containing granzymes and the pore-forming protein perforin fuse with the T cell membrane and discharge their toxic content. Released perforin forms pores in the presence of extracellular calcium that insert into the cancer cell membrane. They can then serve as entry sites for granzymes and are responsible for release of cytosolic content. Several assays for determining the activity and potency of BiTE antibodies rely on the uptake or release of indicator dyes from target cells.

The same time cancer cells are perforated by perforin, apoptosis is induced primarily by granzmye B, which can cleave pro-caspases in cancer cells but can itself act as a caspase by sharing substrate proteins with activated caspases. Target cells hit by BiTE-activated T cells show all hallmarks of apoptosis including membrane blebbing and DNA fragmentation. The same time the target cell is disintegrating, the killing T cell is potently activated. T cell activation markers CD69 and CD25 and cell adhesion molecules appear on its cell surface [8]. BiTE-activated T cells transiently release inflammatory cytokines and produce new granzymes and perforin in order to fill up granules as a basis for serial lysis of cancer cells. Importantly, BiTE-activated T cells are kicked into cell cycle, which will locally increase their number within target tissue.

In this scenario, BiTE antibodies functionally replace the MHC class I/peptide/T cell receptor complex in terms of size and functionality. This relates to (i) their capacity of forming a properly structured cytolytic synapse, (ii) their potent stimulation of T cells to perform serial lysis of target cells, and (iii) their induction of proliferation, which will locally and systemically increase the number of T cells. Of all T cell populations in the organisms, both