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Antibodies: Immunoconjugates and autologous cellular therapy in acute lymphoblastic leukemia

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A B S T R A C T

Using a case study of a 57-year-old man with relapsed/refractory precursor-B (pre-B) acute lymphoblastic leukemia (ALL), this review discusses treatment with immunoconjugates and autologous therapy in acute ALL. Three therapies—blinatumomab, inotuzumab, and CAR T cells—are considered here, each with advantages in specific clinical situations. These therapies represent some of the exciting advances that have been made in the treatment of ALL over the last several years.

Introduction

The incidence of relapse in adults with acute lymphoblastic leukemia (ALL) remains high. At the time of relapse, the prognosis is dismal [1], and novel therapies are clearly needed. In this review, we will focus on three antibody-based therapies currently being evaluated in ALL: blinatumomab, inotuzumab, and chimeric antigen receptor (CAR) T cells.

This review begins with a patient case that will help highlight some of the key aspects of these therapies. Mr W is a 57-year-old gentleman with relapsed/refractory precursor-B (pre-B) ALL who was referred to my clinic for participation on clinical trial S1312: a phase 1 trial of inotuzumab in combination with CVP (cytoxan, vincristine, prednisone). Initially, he had been diagnosed as having an aggressive B-cell lymphoma and received treatment with rituximab-EPOCH (etoposide, prednisone, vincristine, cytoxan, doxorubicin) followed by sacral irradiation. At the time of relapse, it was noted that he had pre-B ALL and he was treated with part B of hyperCVAD (high-dose methotrexate, high-

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dose cytarabine) and then the C10403 induction regimen [2]. Unfortunately, a follow-up bone marrow demonstrated a hypocellular marrow (<10% cellular) with 66% blasts (CD19+, CD22+). His cytogenetics were complex. He was not eligible for the clinical trial because he had Grade 2 peripheral neuropathy. Around the time that I saw him, blinatumomab was FDA approved, and we decided to proceed with this therapy.

Blinatumomab

Blinatumomab is a BiTE (bispecific T-cell engaging) antibody [3]. It has two arms. The one arm (anti-CD3) engages the cytotoxic T cell while the other arm (anti-CD19) engages the lymphoblast (Fig. 1). This in turn leads to activation and proliferation of the cytotoxic T cells and redirected cell lysis and apoptosis of the B-lymphoblasts [4]. Because of its mechanism of action, the drug does lead to significant lymphopenia [4]. However, it does not tend to cause significant myelosuppression. In our patient's case, this was an advantage since he had been heavily pre-treated and had a hypocellular marrow.

A large phase 2 multi-center study of blinatumomab in relapsed/refractory Philadelphia chromosome (Ph chromosome)-negative pre-B ALL was published at the beginning of 2015 [5]. This trial enrolled 189 patients with relapsed/refractory ALL. The median age was 39 years. Approximately one-third of patients had undergone prior allogeneic hematopoietic stem cell transplant (AHSCT) and 39% of the patients were salvage 2 or higher (Table 1). All patients in first relapse had relapsed within 12 months of their initial remission. Sixty-nine percent of patients had a bone marrow blast count ≥50%. The most common adverse events in this trial were fever (60%) and headache (34%) (Table 2). Febrile neutropenia, neutropenia, and anemia were the most common Grade 3–4 toxicities. Two percent of

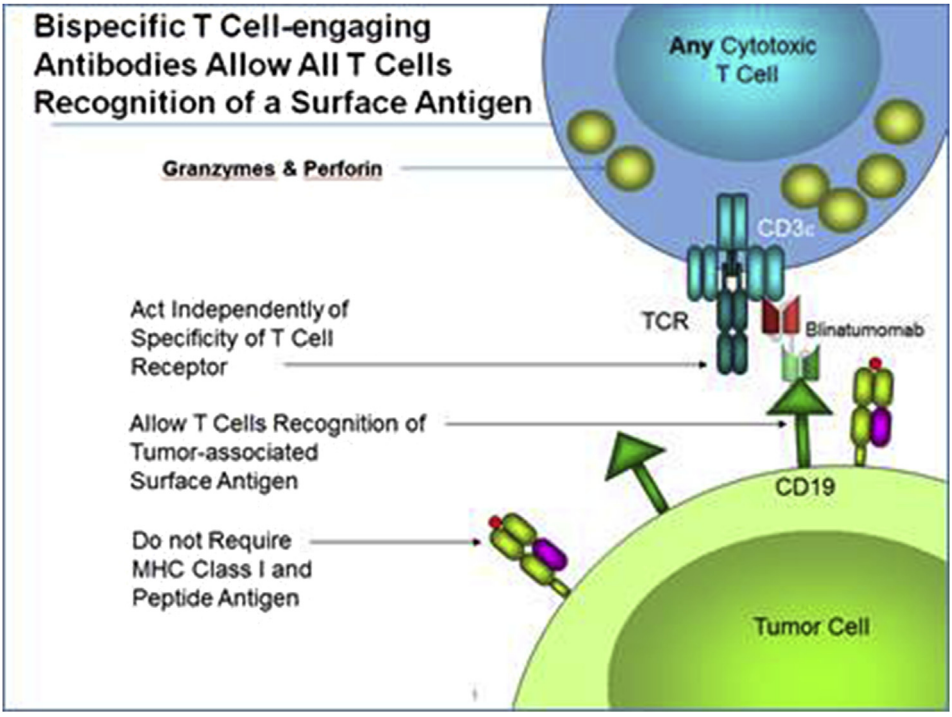

Fig. 1. Mechanism of action of BiTE antibodies. The bispecific T-cell engaging antibody has two arms. One arm (anti-CD3) engages the cytotoxic T cell while the other arm (anti-CD19) engages the lymphoblast. This in turn leads to activation and proliferation of the cytotoxic T cells and redirected cell lysis and apoptosis of the B-lymphoblasts. Figure reproduced with permission of Amgen, Inc.