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Antileukemic effect of daclizumab in CD25 high-expressing leukemias and impact of tumor burden on antibody dosing

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Abstract

Humanized anti-CD25 antibody, daclizumab, was applied in a pilot study of 10 patients with CD25(+) leukemias and pharmacokinetic/pharmacodynamic properties were characterized. Two widely held concepts – tumor sink accelerating pharmacokinetics and higher antigen expression correlating with target cell clearance – were supported by this first systematic evaluation of these questions with actual human clinical data. A flexi-dosing regimen was validated for maintaining target drug levels in vivo with a wide range of tumor burdens. Daclizumab induced clearance of peripheral leukemic cells when highly positive for CD25, but durable responses were not obtained. If daclizumab will have a role in antileukemic therapy, it may be in minimal disease settings or as a component of a combination regimen, but only when CD25 expression is high.
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1. Introduction

CD25 or T-cell activation antigen ("Tac") is the 55 kDa alpha chain of the interleukin 2 (IL2) receptor (IL2Rα). CD25 is not expressed on resting T cells but appears at high levels on activated T cells. There, it cooperates with the 75 kDa beta chain and the 65 kDa gamma chain of the IL2 receptor to form a high affinity complex that augments the activated cell's response to IL2. Similarly, CD25 is up-regulated on activated T lymphocytes in select autoimmune diseases and in individuals with allograft rejection or graft-versus-host responses [1]. CD25 is aberrantly expressed on a number of hematologic malignancies including HTLV(+) adult T-cell leukemias, the Reed–Sternberg cell of Hodgkin's disease, B-cell hairy cell leukemias and the true histiocytic lymphomas. Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome) and non-Hodgkin lymphomas may also express CD25, as well as a portion of chronic and acute leukemias.

Daclizumab (humanized anti-Tac, "HAT", Zenapax [Roche, Nutley, NJ]) is a humanized IgG1 antibody directed against CD25 that is based on the murine antibody, anti-Tac ("MAT") [2,3]. Although MAT is inactive in antibody-dependent cellular cytotoxicity (ADCC) assays, it was used with modest effect in adult T-cell leukemia (ATL), with

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ALL, acute lymphocytic leukemia; AML, acute myleogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myleogenous leukemia; HAHA, human anti-humanized antibody; HAMA, human anti-mouse antibody; HAT, humanized anti-Tac; MAT, murine anti-Tac; MFI, mean fluorescence intensity; MMPS, monocyte–macrophage phagocytic system (reticuloendothelial system); PE, phycoerythrin; Tac, T-cell activation antigen (CD25)

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responses of 1 month to >10 years in 7 of 18 patients (including 1 mixed response) [4–6], for a CR + PR + MR rate of 39% (15–66%, 95% confidence limit). MAT was applied in renal allograft patients to suppress activated T cells, with significant reduction of acute rejection episodes (5/40 patients versus 21/40 patients in controls; $p < 0.001$) and delay of time to first rejection (12.5 days versus 7.6 days in controls; $p < 0.05$). A high incidence of human anti-mouse Ig antibodies (HAMAs) abrogated a more prolonged therapeutic utility [7].

Daclizumab was designed with human constant and variable framework domains to enhance the murine antibody's ability to induce ADCC and to reduce its immunogenicity. Additionally, the presence of human Fc prolonged the half-life of the antibody from 3 days to an average of 20 days, as typical of human IgG, for extended efficacy after dosing. Daclizumab was the second humanized (or "hyperchimeric") antibody to be produced against a human antigen [2,3] and the first to receive clinical approval status in the United States, for the indication of prophylaxis against acute allograft rejection [8].

The limited expression of CD25 on normal tissue and its increased expression on subsets of acute lymphocytic leukaemia (ALL), acute myleogenous leukaemia (AML), chronic lymphocytic leukaemia (CLL) and chronic myleogenous leukaemia (CML) make it a plausible target for immune-based therapy. We initiated a Phase Ib/II trial to test the efficacy of daclizumab therapy in CD25(+) leukemias. We assessed drug pharmacokinetics and pharmacodynamics, and we attempted to determine mechanisms of response and non-response. These evaluations provide key clinical data to support the intuitive concepts of higher whole body tumor antigen burden causing accelerated plasma antibody clearance, and of higher surface antigen expression leading to more efficient leukemic cell clearance.

2. Patients and methods

2.1. Patients

Patients with CD25(+) AML, ALL, CLL and CML were studied at New England Deaconess Hospital and the Beth Israel Deaconess Medical Center, Boston, MA, between 1996 and 2000. Eligibility required that >30% of malignant cells react with anti-CD25 antibody as determined by flow cytometry. Patients had to be ≥18 years with a life expectancy of >2 months and free of other serious medical conditions. Patients with AML and ALL had to have failed at least one attempt at curative therapy. Except as noted, patients were off of cytotoxic therapy for at least 4 weeks prior to study entry. All patients provided written informed consent.

2.2. Drug

Daclizumab (Zenapax [Roche]) was supplied in vials at 25 mg/5 ml. MX-daclizumab (1 mg) was labeled with 5 mCi ^{111}In as previously described [9] and mixed with the first dose of daclizumab for co-administration.

2.3. Study design

The dosing rationale was to provide for 98–99% antigen saturation with complete blockade of potential IL2-dependent proliferation through the IL2Rα [3]. This was to be accomplished by a dose of 1 mg/kg of daclizumab administered on day 1, followed by 0.5 mg/kg every half-life, projected to maintain serum trough levels >2.5 μg/ml with >98% saturation of the CD25 sites [3]. Although tissue levels would initially be lower, with repeat dosing and sustained plasma concentrations, there would be a gradual equalization between tissue and plasma concentrations over time (e.g., Fig. 5a). Hence, it was expected that this dosing plan would ultimately lead to CD25 saturation in tissue as well as blood.

Initial doses of daclizumab contained ^{111}In-labeled daclizumab (range: 1.7–6.3 mCi) for determination of biologic half-life and tissue distribution. This employs the ^{111}In-MX daclizumab chelate previously employed for ^{111}In imaging and ^{90}Y therapy in ATL patients [5,10]. Using "flexi-dosing", timing of doses was individualized to each patient. Second and subsequent doses were administered at intervals equivalent to the half-life of the antibody in each patient, as determined by serial measurement of the plasma radioactivity of ^{111}In-labeled antibody. Treatment was to continue until patients had complete response, non-response at 1 month, progression of disease at any time or development of neutralizing anti-globulin antibodies (HAHAs; see Methods in Appendix A).

For other Materials and Methods, see Supplemental Materials (Appendix A).

3. Results

3.1. Patient and disease characteristics

Ten leukemia patients were treated with daclizumab with a median age of 52 years (range, 28–79 years) (Table 1). The patients were six men and four women; nine were Caucasian and one was African-American. Four patients had CLL, three had AML, two had CML and one had ALL. All patients had previous chemotherapy. Disease characteristics are listed in Table 2.

3.2. Antileukemic effects

Complete response criteria for leukemia require the absence of blasts in the peripheral blood and normal hematopoesis by bone marrow aspirate 4 weeks after the treatment. Although no patients treated achieved normal hematopoiesis, daclizumab did reduce leukemic cell counts in some patients.

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