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Fast Cars and No Brakes: Autologous Stem Cell Transplantation as a Platform for Novel Immunotherapies

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A B S T R A C T

Autologous stem cell transplantation (ASCT) is indicated in a number of hematologic malignancies, including multiple myeloma, non-Hodgkin lymphoma, and Hodgkin lymphoma. Relapse, however, remains 1 of the main causes of post-ASCT failure, and several strategies are being investigated to decrease the risk of relapse of progression. Recent advances in the treatment of hematological malignancies have included adoptive transfer of genetically modified T cells that express chimeric antigen receptors or T cell receptors, as well the use of checkpoint inhibitors. Early clinical results in nontransplantation patients have been very promising. This review will focus on the use of gene-modified T cells and checkpoint inhibitors in stem cell transplantation.

INTRODUCTION

Autologous stem cell transplantation (ASCT) is indicated in a number of hematologic malignancies, including multiple myeloma (MM), non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL) [1-6]. Relapse, however, remains 1 of the main causes of post-ASCT failure and several strategies are being investigated to decrease the risk of relapse of progression. Furthermore, some patients may not be candidates for ASCT because of inadequate response to salvage therapy. Although the ongoing development of novel targeted therapies impacts the actual indications for ASCT, there remains a significant unmet need for novel approaches to improve disease control in the setting of ASCT. The benefits of increasing regimen intensity, for example, need to be weighed against the risk of increased toxicity and may differ for various histologies [7]. The use of post-transplantation maintenance or consolidation has been validated in several indications and has been previously reviewed in this journal [8]. More recently, significant advances in the treatment of hematological malignancies have been made in the field of immunotherapy [9-14]. This includes adoptive transfer of genetically modified T cells that express chimeric antigen receptors (CAR) or T cell receptors (TCR) [9-11], as well as the growing use of antibody-based approaches with checkpoint inhibitors [12,13]. In this review, we will focus on these approaches in the context of hematopoietic stem cell transplantation (HCT).

PAVING THE ROAD FOR CARS: CAR-MODIFIED T CELLS DIRECTED AGAINST CD19 AFTER HIGH-DOSE THERAPY AND AUTOLOGOUS TRANSPLANTATION

The cluster of differentiation antigen 19 (CD19) is a 95 kD transmembrane glycoprotein ubiquitously expressed on B cells from pro-B to mature B cell phenotypes, including all B cell NHL (B-NHL)/chronic lymphocytic leukemia/small lymphocytic lymphoma, and B cell acute lymphoblastic leukemia (B-ALL). CD19 is not expressed on other hematopoietic or organ cell populations. Although targeting CD19 can hypothetically result in B cell aplasia, the clinical experience with the anti-CD20 monoclonal antibody rituximab has shown that this does not result in severe consequences. Thus, CD19 serves as an acceptable tumor antigen to target for cellular therapy. Genetically engineered recombinant TCR directed against a specific tumor antigen (CARs) can recognize and lyse tumor targets. Although most of the clinical experience of targeting CD19 with CAR-modified T cells (19-CAR-T) to date has been reported in patients with acute lymphoblastic leukemia [15-20], the present section will

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focus on the use of 19-CAR-T for B-NHL, excluding chronic lymphocytic leukemia/small lymphocytic lymphoma.

The initial CAR constructs consisted of an antigen recognizing single chain variable fragment extracellular domain from an antibody with a transmembrane link to a functional CD3ζ intracellular signaling domain [21]. Although this initial design demonstrated T cell effector function, proliferation and expansion were not achieved until second-signal transmembrane costimulatory domains were constructed in later generation design [22]. This translated into improved antitumor efficacy in early animal models compared with first generation constructs [23]. The clinical experience of 19-CAR-T for B-NHL reviewed in this manuscript will largely focus on second-generation 19-CAR-T constructs with TCR/CD3 signal 1 coupled to signal 2 with either CD28, or 4-1BB.

Clinical Studies: 19-CAR-T for B-NHL

The first clinical experience in 19-CAR-T for patients with follicular lymphoma (FL, n = 2) and diffuse large B cell lymphoma (DLBCL, n = 2) was from the City of Hope with a first-generation construct [24]. Both DLBCL patients received 19-CAR-T 1 month after high-dose therapy and ASCT and 1 of 2 remained free of progression at the time of publication. The 2 patients with FL progressed after therapy. Significant toxicity was not observed and 19-CAR-T failed to persist, with only 1 of 4 patients demonstrating peripheral 19-CAR-T persistence at 1 week with this first-generation construct, despite IL-2 being exogenously administered in the 2 FL patients.

The first case report of a second-generation 19-CAR-T incorporating a CD28 costimulatory domain was of a patient with FL treated along with exogenous IL-2 at the National Cancer Institute (NCI) [25]. The patient experienced a partial remission (PR) lasting approximately 10 months and 19-CAR-T persistence for > 6 months. More recently, the NCI group updated its prospective experience of 19-CAR-T with CD28 costimulation for refractory B-NHL preceded by lymphodepleting chemotherapy consisting of cyclophosphamide 60 mg/kg to 120 mg/kg and fludarabine at a total dose of 125 mg/m^2 [26]. Six of 7 patients with DLBCL responded with either a complete remission (CR) or PR and all 6 patients with indolent B-NHL responded (PR or CR). The longest responses were 1 and 2 years for DLBCL and indolent B-NHL, respectively. The 19-CAR-T expansion peaked from 7 to 17 days. The investigators lowered the dose of 19-CAR-T from 5×10^6/kg to 1×10^6/kg because of toxicity, most notably cytokine release syndrome (CRS). Thirteen of 15 patients experienced ≥ grade 3 toxicity, predominately with manifestations of CRS. In a sequential study presented at the American Society of Hematology meeting in 2014, the NCI investigators studied lower dose chemotherapy (cyclophosphamide 900 mg/m^2 and fludarabine 90 mg/m^2) and noted less toxicity related to severe CRS, but there were too few patients to assess its impact on disease efficacy [27].

A group from the University of Pennsylvania recently presented interim results of their phase 2a study treating chemorefractory FL, mantle cell lymphoma (MCL), and DLBCL patients with 19-CAR-T at the 2015 American Society of Clinical Oncology (ASCO) meeting [28]. The construct of their second-generation 19-CAR-T incorporates a 4-1BB costimulatory transmembrane domain. Patients were treated with variable lymphodepleting chemotherapy before administration of 19-CAR-T on study. Of 12 evaluable treated patients with DLBCL, 2 patients had a CR and 4 had a PR to 19-CAR-T for an overall response rate of 50%. The longest responder is in continued remission > 1 year after 19-CAR-T. All 7 patients with FL responded, with the longest remission being > 1 year after treatment, whereas 1 of 2 patients with MCL experienced a response with < 2 months of follow-up. The investigators observed 12 nonhematologic toxic events ≥ grade 3, with 4 of these events related to CRS or neurotoxicity.

The Fred Hutchinson Cancer Research Center group recently presented an update at ASCO 2015 of 19-CAR-T with 4-1BB costimulation for refractory B cell malignancies [29]. Their study is unique in that the 19-CAR-T were composed of a fixed 1:1 ratio of CD8$^+$ T central memory cells to CD4$^+$ T cells based on encouraging preclinical data [30]. Seven of 13 B-NHL patients responded (CR, n = 1; PR n = 6) with no episodes of severe CRS observed. Clinical responses correlated to peak and persistence of 19-CAR-T in this interim analysis.

Lastly, investigators from Memorial Sloan Kettering Cancer Center are currently testing 19-CAR-T in consolidation for high-risk relapsed/refractory DLBCL/aggressive histology B-NHL in partial chemosensitive remission after a high-dose therapy ASCT (NCT01840566) [31]. The rationale for this study is administering the cellular immune therapy in a lymphoablative setting immediately after high-dose therapy ASCT (2 and 3 days after stem cell reinfusion) for potential optimization of 19-CAR-T expansion and efficacy. The 19-CAR-T utilized by this group includes a CD28 costimulatory molecule. An interim update presented at the 2015 ASCO meeting revealed 4 of 10 evaluable patients in continuous remission at a median of 14 months after study treatment and up to nearly 2 years in 2 patients [31]. Although this group has previously reported peak C-reactive protein to correlate with CRS, this correlation was not observed in the first 11 patients. All but 1 patient developed fevers, as expected, in neutropenic nadir. The most common ≥ grade 3 toxicity was reversible neurotoxicity in 7 of 11 patients, which the investigators attributed to CRS. The study is ongoing and expanding at the first dose level of 5×10^6/kg 19-CAR-T.

Limitations and Future Directions

Despite encouraging data, 19-CAR-T therapy for B-NHL has not matched the extremely impressive activity of this modality in B-ALL, wherein the vast majority of patients achieve CR [15,18]. Whether this is due to microenvironmental phenotypic differences (marrow versus nodal-based disease) or other factors between B-ALL and B-NHL remains highly speculative. As outlined above, the 2 major toxicities of 19-CAR-T therapy include CRS and neurologic manifestations including but not limited to seizures, seizure-like activity, focal motor deficits, aphasia, and global encephalopathy [32]. Strategies being developed to circumnavigate or treat these toxicities include the use of anti-IL-6 receptor blockade [15] and engineering suicide genetic elements to “turn-off” the activated cellular product when toxicity is observed [33]. The goal will be to abrogate toxicity without ablation of the cellular therapy, for which corticosteroids currently serve in severe and recalcitrant toxicity. Future investigation toward improvement in 19-CAR-T efficacy for B-NHL may involve further costimulatory elements and/or lymphoproliferative cytokine genes engineered into the 19-CAR-T product [34]. Additionally, combinatorial antigen specificity warrants clinical investigation [35]. Lastly, the potential for immune