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Extended Abstract

# Translational Medicine 2015: Treatment of CD20-directed chimeric antigen receptor-modified T cells in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: An early phase IIa trial report - Wei-Dong Han - Chinese PLA General Hospital

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## ABSTRACT

Patients with relapsed or refractory Non-Hodgkin lymphoma (NHL) make sure a dismal prediction. Chimeric antigen receptor (CAR) modified T cells targeting CD20 have shown activity in clinical test phase I clinical trial for patients with advanced B-cell lymphomas. We performed a phase IIa trial to further assess the security and efficacy of administering autologous anti-CD20 CAR T (CART-20) cells to patients with refractory or relapsed CD20+ B-cell lymphoma. Eleven (11) patients comprising one with previous auto-HSCT and one primary cutaneous B-cell lymphomas were enrolled. Seven (7) patients experienced cytoreductive chemotherapy for tumor debulking and lymphocyte depletion before T cell potions. CART-20 cells were infused into patients at doses of 2.8 to 14.6×106 cells/kg. The general objective response rate was 9 of 11 (81%), with six complete remissions (CR) and three partial remissions (PR); no severe toxicity was observed. The median PFS had lasted for quite 10 months with one maintaining for 25-month continuous CR. a big inverse correlation between the molecule levels of the CAR gene and disease recurrence or progression was observed. Additionally, it had been deservered to be addressed clinically that the lesions in some special sites like in spleen and testicle were refractory to CART-20 treatment.

**Keywords:** T cells; Non-Hodgkin lymphoma; Chimeric antigen receptor.

## INTRODUCTION

Non-Hodgkin lymphoma (NHL) may be a hematological malignancy with high mortality and a poor prognosis. The expected 5-year and 10-year overall survival rates for subjects treated with standard chemotherapy are 58% and 43.5%, respectively. However, for relapsed and refractory NHL, the response rates to conventional salvage chemotherapy are approximately 40-50%. Patients previously treated with rituximab had a significantly worse progression-free survival (PFS) rate than patients who were rituximab-naive (29% vs. 44%, respectively). In diffuse large B-cell lymphoma (DLBCL), an autologous hematopoietic somatic cell transplant has become the standard of care for patients in their first relapse. However, the treatment-related mortality with allogeneic transplantation can reach up to 25%, and the fatalities from the autologous hematopoietic somatic cell transplant procedure are even higher. Therefore, the look for novel therapeutic modalities which will yield improved and sustained outcomes in such patients is constant. Adoptive cell transfer, typically represented by tumor-specific Chimeric Antigen Receptor-modified T (CART) cells, holds great promise as a tumor therapy. The CD20 antigen on the surface of B-NHL cells may be a well-established immunotherapy target for lymphoma. For indolent B-cell and mantle cell lymphomas, the efficacy and safety of CART-20 has been confirmed. Based on the results from our prior study, we revised the eligibility criteria for the patients within the Phase IIa study to scale back toxicity and evaluated the efficacy and in vivo persistence of CART-20 cells in subjects with high-risk relapsed or refractory B-cell NHL.

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In this report, we enrolled 11 patients with relapsed or chemotherapy refractory B-cell NHL, including one with a previous autologous hematopoietic somatic cell transplant treatment and one with a primary cutaneous B-cell lymphoma.

Together with the previous results of clinical test phase I clinical trial, our study provides further support for the use of CART-20 as a clinical treatment for patients with NHL and raises the likelihood of using CART-20 in an early disease stage.

Materials and Methods: A. Study design: This single institution, open-label, Phase IIa escalation study (ClinicalTrials.gov identifier: NCT01735604) was performed within the Department of Bio-therapeutics of the Chinese PLA General Hospital. The study protocol was approved by the ethics panel of the Chinese PLA General Hospital. All patients provided consent upon enrollment in accordance with the Declaration of Helsinki Principles. No commercial sponsor was involved contained by the study. The patients go through cytoreductive chemotherapy for tumor debulkingand lymphocyte depletion between days − 7and− 3 before T-cell fermentation. Though, dependable with the judgment of surgeons, if patients had a small tumor burden (maximum diameter of 5cm or number of lesions⩽3) and a lymphocyte deficiency (absolute lymphocyte of 0.3×109l− 1, regard less of the presence of regulatory T cells, T lymphocytes or B lymphocytes). Taking into account the requirements of reducing lymphocytes, excluding the interference of precondition and minimizing the damages to patient's bone marrow and system, we selected the shortest chemotherapeutic regimens include cyclophosphamide that were capable of inducing a reaction of tumor within the short term as precondition regimen during this trail. The patients received escalating doses of CART-20 cells split into 3-5 doses on consecutive days beginning on day zero. B. Patients: All 11 patients had histologically confirmed relapsed or refractory CD20+NHL and were enrolled during this study between May 2014 and June 2015. The clinical data set cut off time point is at the top of November of 2015. We defined refractory lymphoma as progression or incomplete remission at four weeks after the top of the foremost recent chemotherapy or anti-CD20 therapy. Other inclusion criteria were: age ⩾18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0-3, and anticipation of at least three months, adequate hematological and renal function (absolute neutrophil count ⩾1.5×109l- 1, platelet count ⩾100×109l- 1, bilirubin ⩽1.5×the upper limit of the traditional range). Treatment with prior cytotoxic or biologic therapies must have ended a minimum of four weeks previously. Patients were excluded if that they had evidence of involvement of the lung or alimentary tract , uncontrolled bulky lymphoma (maximum diameter ⩾5cm or number of lesions 43) after debulking treatments, an uncontrolled infection requiring antibiotics, class III or IV cardiac disease or other specified cardiac conditions, or uncontrolled diabetes. Response criteria, staging and follow-up Clinical responses were assessed consistent with the recommendations of the International Workshop NHL Response Criteria. The toxicity and adverse events were graded using the National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0. The top of the follow-up period was 1st November 2015, and the median follow-up period was eight months. Disease staging using computed tomography (CT) and wholebody 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scans was performed at the time of study entry. The CT was repeated during follow-up every two months (first year), every six months (years 2-3) and annually thereafter. An FDG-PET study was performed at 4-6 weeks after treatment in all patients. Extensive laboratory tests, including the evaluation of lymphocyte subpopulations, and a bone marrow biopsy were performed at baseline and repeated at regular intervals during the study period and during followup. Results: Overall clinical responses all patients were assessed for responses 4-6 weeks after the CART-20 cell infusion. The therapeutic outcomes are summarized in. Seven patients received cytoreductive chemotherapy, including cyclophosphamide for debulking and lymphocyte depletion, before the infusion, whereas the opposite four patients were not treated on the idea of a smaller tumor burden and a lower level of lymphocytes. The general response rate was 81.8%, with 54.5% of the patients (6/11) achieving a CR and 27.3% (3/11) achieving partial remissions (PRs). The opposite two patients had stable disease. The median PFS was six months, with a median follow-up of eight months (range: 5-27 months). Two (2) of the three patients with indolent B-cell malignancies achieved CR and one had stable disease. Patient UPN02 demonstrated an asymptomatic exudative inflammation of the lung at ~ 60 days after infusion without a significant elevation within the cytokines. Only a ground-glasslike change of the lower lung lobes detected with a CT scan and mildly elevated levels of interleukin-6 and tumor necrosis factor-α were observed. He was given dexamethasone by inhalation for one week. After the treatment, a repeat CT scan didn't show the ground-glass changes. Most patients were administered intravenous immune globulin monthly to stop hypogammaglobulinemia. The cytopenias, including neutropenia, thrombocytopenia and anemia, associated with cytoreductive chemotherapy aren't listed. Discussion: CD20 is a perfect target antigen for NHL immunotherapy because it is nearly universally expressed with high copy numbers on the surface of B-cell lymphomas and is minimally modulated. This study, which followed our prior clinical test phase I clinical trial, tested the clinical efficacy of autologous CART-20 cell infusion and evaluated the related toxicities. The results showed that nine of the 11 NHL patients achieved different degrees of clinical remission without serious toxicity. Our results provided further support for the promising applicability of CART-20 in CD20cell malignant diseases, even at an early stage of the diseases. The data from several early clinical trials suggested that high doses of CART cells are related to increased responses but are amid greater toxicity. Subsequent, studies showed that the infused total dose correlated poorly with the steady-state number of cells that engrafted or the persistence of the CART cells. No direct correlation has been found between the T-cell dose and therefore the clinical responses across multiple clinical trials in various settings. Bentsen's et al., 18 reported that T cells could exhibit optimal persistence and antitumor efficacy dose of 1×10719–28ζ T cells per kg, compared with the initial dose of 3×10719–28ζ T cells per kg. We speculated that the CART cells had a high replicative potential and would expand in the host. In our study, we also found that the height number of circulating CART cells didn't correlate with the dose of the infused CART cells or with the share of central or effector memory T cells within the T-cell products within the range of 0.41×107–1.46×107kg-1. This difference could also be due to the better immune status of patients with lymphoma than patients with leukemia. Relapse following CART cell therapy remains a challenge. All of the disease relapses observed in our patients were demonstrated to be CD20-positive. B-cell aplasia continues to result from CART cell

persistence. Shannon et al. that relapse of acute lymphocytic leukemia cells that retain surface CD19expression results from the rapid disappearance of CARmodified T cells or decreased function of these T cells. In our study, we also observed a direct correlation between the CD20 cell a plasia and copies of the genes indicating the CART cells. Therefore, increasing the persistence of the CART cells in vivo is an essential prerequisite to avoid tumor relapse. Various measures can prolong T-cell persistence to stop a number of these relapses, including optimization of the CAR designs, manufacturing technologies or T-cell subset ratios. However, repeated infusions appear to be more feasible supported the management of the event of toxicity. Relapse is heralded by recovery of the traditional B cells, suggesting that monitoring the return of normal B cells is important to spot patients at the very best risk for relapse, which could potentially provide a window for repeat infusion. Conclusion:In conclusion, our study confirmed that adoptive immune therapy with CD20-directed CART cells may be a feasible and possibly effective treatment modality for CD20+NHL patients. Debulking regimens combined with a lymphocyte-depleting conditioning strategy prior to CART cell infusions may improve clinical responses and reduce severe toxicity. Finally, combining the CART treatment with local radio -therapy can enhance the therapeutic effects of CART cells at tumor sites, especially in spleens where there the antigen expression is low.