CAR T-Cell Therapy Shows High Levels of Durable Response in Refractory Large B-Cell Lymphoma

Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531–44.

STUDY OVERVIEW

Objective. To evaluate the efficacy and safety of the anti-CD19 chimeric antigen receptor (CAR) T-cell, axicabtagene ciloleucel (axi-cel), in patients with refractory large B-cell lymphoma.

Design. The ZUMA-1 trial was a phase 1-2 multicenter study. The results of the primary analysis and updated analysis with 1-year follow up of the phase 2 portion of ZUMA-1 are reported here.

Setting and participants. The phase 2 portion of the ZUMA-1 trial enrolled 111 patients from 22 centers in the United States (21) and Israel (1) from November 2015 through September 2016. Eligible patients included those with histologically confirmed large B-cell lymphoma, primary mediastinal B-cell lymphoma or transformed follicular lymphoma. Patients were required to have refractory disease, defined as disease progression or stable disease as the best response to chemotherapy or disease progression within 12 months following autologous stem cell transplantation. All patients were required to have adequate organ function, an absolute neutrophil count > 1000, absolute lymphocyte count > 100 and platelet count > 75,000.

Intervention. Patients first underwent leukapheresis and CAR T-cell manufacturing. Following this patients were admitted to the hospital and received a low-dose conditioning regimen consisting of fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2 given on days –5, –4 and –3. On day 0 the patient was infused with their manufactured CAR T-cell product at a target dose of 2 x10^6 CAR T cells per kilogram of body weight. Patients could not receive "bridging chemotherapy" between leukapheresis and infusion of axi-cel product. Patients could be retreated with axi-cel if they experienced disease progression at least 3 months after their first dose.

Main outcome measures. The primary endpoint of this study was objective response rate, which was defined as the combined rate of complete response (CR) and partial response (PR). The secondary endpoints were duration of response, progression-free survival (PFS), overall survival (OS), and adverse events. Blood levels of CAR T cells and serum cytokine levels were followed.

Main results. A total of 111 patients were enrolled. Axicel was administered to 101 patients included in the intention to treat analysis. Of these, 77 had diffuse large B-cell lymphoma and 24 had primary mediastinal B-cell lymphoma or transformed follicular lymphoma. The median follow-up was 8.7 months for the primary analysis and updated analysis median follow-up was 15.4 months. The median time from leukapheresis to delivery of the product was 17 days. Only 1 patient had unsuccessful manufacturing. The median age of the treated patients was 58 years. Most of the patients (77%) had disease resistant to second-line or later therapy and 21% had disease relapse after autologous stem cell transplant.

Primary analysis results. The objective response rate was 82% with a 54% CR rate. The median time to response was 1 month and median duration of response was 8.1 months. The response rates were consistent across all subgroups including age, disease stage, IPI score, presence or absence of bulky disease, cell-of-origin subtype, and the use of tocilizumab or glucocorticoids. High response rates were maintained in those with primary refractory disease (response rate 88%) and those with prior autologous stem cell transplant (response rate 76%). The response rate was not influenced by CD19 expression. At the time of the primary analysis 52 patients died from disease progression and 3 died from adverse events during treatment. Forty-four patients remained in remission, 39 of whom maintained a CR.

Updated analysis results. At the time of the updated analysis 108 patients in the phase 1 and phase 2 portions had been followed for at least 12 months. The objective response rate was 82% with a CR rate of 58%. At the data cut-off, 42% remained in response with 40% maintaining a CR. Again, response rates were consistent across all previously mentioned subgroups. The median duration of response was 11.1 months. The median PFS was 5.8 months with PFS rate of 41% at 15 months. The median OS was not reached. A total of 56% of patients remained alive at the time of this analysis.

Safety. During treatment 100% of patients had adverse events (AEs), which were grade 3 or higher in 95%. Fevers (85%), neutropenia (84%) and anemia (66%) were the most common AEs. Myelosuppression was the most common grade 3 or higher AE. Cytokine release syndrome occurred in 93% of patients of which 13% were grade 3 or higher (9% grade 3, 3% grade 4 and 1% grade 5). 17% of patients required vasopressor support. The median time from infusion to the onset of cytokine release syndrome was 2 days (range, 1–12). The median time to resolution was 8 days. One grade 5 event of hemophagocytic lymphohistiocytosis and one grade 5 cardiac arrest occurred. Grade 3 or higher neurological events occurred in 28% of patients, with encephalopathy occurring in 21%. Neurological events occurred at a median of 5 days after infusion and lasted for a median of 17 days after infusion. Forty-three percent of patients received tocilizumab and 27% received glucocorticoids.

Biomarkers. CAR T levels peaked within 14 days after infusion. Three patients with a CR at 24 months still had detectable levels in the blood. CAR T cell expansion as significantly associated with disease response. Interleukin -6, -10, -15 and -2Ra levels were significantly associated with neurological events and cytokine release syndrome of grade 3 or higher. Anti-CAR antibodies were not detected in any patient.

Commentary

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma with 5-year survival rates of ~60% following conventional chemoimmunotherapy in the first-line setting. Following relapse, salvage therapy followed by high-dose chemotherapy with autologous stem-cell transplantation can result in long-term remissions; however, those who relapse have a poor prognosis. The recently published SCHOLAR-1 study retrospectively analyzed the outcomes of patients with relapsed or refractory DLBCL and found that for patients with refractory disease the objective response to salvage therapy was only 26% (7% CR) with a median OS of 6.3 months [1]. CAR-engineered T cells offer a novel and revolutionary therapy for these patients, whom otherwise have very poor outcomes.

Early CAR T-cell trials by Bretjens and colleagues first documented a CR in a subset of patients with refractory

hematologic malignancies [2]. Since that time there has been tremendous advancement in CAR T development and clinical application. In the December 2017 issue of the *New England Journal of Medicine* there were 2 studies published validating the efficacy of CD19-targeted CAR T-cell therapy in relapsed/refractory lymphoma, the current ZUMA-1 study as well as another small case-series by Schuster and colleagues. Schuster et al evaluated the CD19-directed CAR, CTL019, in 28 patients with relapsed/refractory DLBCL or follicular lymphoma. The ORR noted in this study was 64% with a CR rate of 57% [3]. Similarly, in the current ZUMA-1 study the CR rate was 54% in 101 patients with relapsed and refractory large B-cell lymphomas. In addition, with a median follow-up of 15.4 months responses were ongoing in 42% of patients including 40% who had a CR. The durability of such responses has been demonstrated in 3 of 7 patients from the phase 1 portion of this study at 24 months. Durable responses have also been reported with anti-CD19 CAR T-cell therapy in 4 of 5 patients who had a CR and remain in remission after 3-4 years of follow-up [4]. While promising, the durability of responses remains unclear. While CAR therapy represents an exciting therapeutic strategy, it should be noted that in this study approximately 50% of patients will not achieve a durable response and the reason for this is not completely understood.

One of the most discussed aspects of CAR therapy has been the unique toxicity profile, which was again noted in the ZUMA-1 study. As noted, 95% of patients in this study experienced a grade 3 or higher AE. Of interest, cytokine release syndrome occurred in 93% of patients with 13% being grade 3 or higher. There were 2 deaths attributed to such. Neurological toxicity was also noted in 64% of patients in this trial. While the vast majority of these AEs were reversible, they clearly represent high treatment-related morbidity.

The results of the ZUMA-1 study lead to the FDA approval of anti-CD19 CAR T-cell therapy for relapsed or refractory large B-cell lymphoma in October 2017 and represents a pivotal advancement in the management of these patients with otherwise limited treatment options and overall poor outcomes. The ZUMA-1 trial not only demonstrates the efficacy of such agents but also demonstrates the feasibility of incorporating them into clinical practice with a 99% manufacturing success rate and short (median 17 days) product delivery time. The economic burden of such therapies warrant particular consideration as the indications for CAR therapy will continue to expand, driving the cost of care higher. Nevertheless, this represents an exciting step forward in personalized medicine.

Applications for Clinical Practice

CAR T-cell therapy with the CD-19 targeted CAR axicabtagene ciloleucel (axi-cel) results in a high rate of objective and durable responses in patients with relapsed or refractory large B-cell lymphomas. While such treatment does carry a high rate of toxicity in regards to cytokine release and neurological complications, this represents an important treatment option in patients with refractory disease with a historically poor prognosis. However, there will be a need to develop policies to address the economic challenges associated with such treatments.

—Daniel Isaac, DO, MS

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Low-Intensity PSA-Based Screening Did Not Reduce Prostate Cancer Mortality

Martin RM, Donovan JL, Turner EL, et al; CAP Trial Group. Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. JAMA 2018;319:883–95.

STUDY OVERVIEW

Objective. To determine the effect of a single prostate-specific antigen (PSA) screening and standardized diagnostic pathway on prostate cancer–specific mortality when compared with no screening.

Design. Cluster randomized controlled trial.

Setting and participants. The study was conducted at 573 primary care clinics in the United Kingdom. 419,582 men, 50 to 69 years of age, were recruited between 2001 and 2009 and follow-up ended in 2016. Primary care clinics were randomized to intervention or control. Men in intervention group primary care clinics received an invitation to a single PSA test followed by standardized prostate biopsy in men with PSA levels of 3 ng/mL or greater. A trial that compared radical prostatectomy, radiotherapy, and androgen deprivation therapy and active monitoring was embedded within the screening trial [1]. The control group practices provided standard treatment and PSA testing was provided only to men who requested it. The majority of primary practices were in urban areas (88%–90%) and with multiple partners within the practice (88%–89%). Cases of prostate cancer that were detected in the intervention or control groups during the course of the study were managed by the same clinicians.

Main outcome measures. Main study outcome measures were definite, probable, or intervention-related prostate cancer mortality at a median follow-up of 10 years. An independent cause of death evaluation committee that was blinded to group assignment determined the cause of death in each case. The secondary outcomes included all-cause mortality and prostate cancer stage and Gleason grade at cancer diagnosis. The analysis was an intention-to-screen analysis. Survival analysis using Kaplan-Meier plots were done to demonstrate cumulative incidence of outcomes discussed above. Mixed effects Poisson regression models were used to compare prostate cancer incidence and mortality in intervention vs. control practices accounting for clustering.

Main results. A total of 189,386 men were in the intervention group, 40% attended the PSA testing clinic, and 67,313 (36%) had a blood sample taken for PSA testing, resulting in 64,436 valid PSA test result. 6857 (11%) had elevated PSA levels, of which 85% had a prostate biopsy. In the control group, it was estimated that contamination (PSA testing in the control group) occurred at a rate of approximately 10%–15% over 10 years. After a median follow-up of 10 years, 549 men died of prostate cancer–related causes in the intervention group, at a rate of 0.3 per 1000 person-years, and 647 men died of prostate cancer–related causes in the control group, at a rate of 0.31 per 1000 person-years. The rate difference was 0.013 per 1000 person-years with a risk ratio (RR) of 0.96 (95% confidence interval [CI], 0.85–1.08), $P = 0.50$), which was not statistically significant. The number of men diagnosed with prostate cancer was higher in the intervention group than in the control group (4.3% vs. 3.6%, RR 1.19 (95% CI 1.14–1.25), $P < 0.001$). The incidence rate was 4.45 per 1000 person-years in the intervention group and 3.80 per 1000 person-years in the control group. The prostate cancer tumors in the intervention group were less likely to be high grade or advanced stage when compared to the control group. There were 25,459 deaths in the intervention group and 28,306 deaths in the control group. There was no significant difference in the rates of all-cause mortality between the two groups.

Conclusion. The study found that a single PSA screening among men aged 50–69 did not reduce prostate cancer mortality at 10 years follow-up, but led to the increase in the detection of low-risk prostate cancer cases. This result does not support the screening strategy of a single PSA testing for population-based screening for prostate cancer.

Commentary

The use of a PSA test for population-based screening for prostate cancer is controversial; the United States Preventive Services Task Force (USPSTF) recommended against the routine use of PSA test for screening for prostate cancer because the evidence of its benefit is weak and because of the potential risks of unintended consequences of PSA screening [2]. This study is the largest study to date on PSA screening and it found that a low-intensity screening approach—a single PSA test—was not effective in reducing prostate cancer deaths, but rather identified early-stage prostate cancer cases. This result contrasts with previous large scale studies that found that screening led to an increased rate of prostate cancer diagnosis and reduced prostate cancer mortality in one trial [3] and no effect on diagnosis or mortality in another [4].

The rationale for USPSTF recommendation has a lot to do with the unintended consequences of PSA screening; PSA is a rather nonspecific test and elevated levels can be caused by a number of different prostate pathologies. Screening can often lead to procedures and treatments that cause harm to individuals who may not have prostate cancer to begin with or have slow-growing cancer that would otherwise not impact their overall health status over time [5]. This is particularly relevant for older adults that may have other comorbid diseases that impact their health. The selection of a single PSA test as the screening strategy in this study is an attempt to reduce the potential burden of repeated testing and thereby reduce risk of unintended harms. The tradeoff is that it is less effective in identifying prostate cancer over time and may partly explain why this study's result contrasts with prior studies.

Applications for Clinical Practice

PSA test as a diagnostic tool for prostate cancer has significant drawbacks, and population screening strategies using this test will need to grapple with issues of misdiagnosis, overdiagnosis, and treatment that can have potential harmful consequences. The alternative of not screening is that prostate cancer may be diagnosed at later stages and more men may suffer morbidity and mortality from the disease. A better test and screening strategy are needed to balance the benefits and harms of screening so that older men may benefit from early diagnosis of prostate cancer.

—William W. Hung, MD, MPH

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