blood advances

TO THE EDITOR:

Long-term safety for patients with tisagenlecleucel-treated relapsed/refractory diffuse large B-cell lymphoma

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Chimeric antigen receptor (CAR) T-cell therapy has promising outcomes in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). The incidence, grading, and management of acute adverse events (AEs) have been described for CAR T-cell therapies.[1-5] Reports of long-term (LT) AEs being treated with CAR T-cell therapy are emerging,[2,6-8] and new management practices are being established.[9,10] In the pivotal, global, single-arm, phase 2 JULIET trial, tisagenlecleucel demonstrated efficacy and manageable safety in adult patients with R/R DLBCL[5] and ongoing durable efficacy at a median of 40.3 months of follow-up.[11] Here, we report the LT safety profile of tisagenlecleucel from the JULIET trial.

Eligibility and end points for the JULIET trial (NCT02445248) were described previously.[5] Patients (age 18 years or older) with aggressive B-cell lymphomas who received ≥2 previous lines of therapy were eligible.[5] All AEs were summarized by using the maximum grade recorded. Responders were defined as patients with best overall response of either complete or partial response. Efficacy and short-term AEs have also been described previously.[5] The type, frequency, and severity of LT AEs (ie, those that occurred or persisted beyond 90 days or occurred beyond 2 years after infusion) were recorded using Common Terminology Criteria for Adverse Events v4.03. Cytopenia grade was determined by measuring

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Novartis Pharmaceuticals is committed to sharing data with qualified external researchers, so they provide access to patient-level data and supporting clinical documents from eligible studies upon request. Requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Trial data are made available according to the criteria and process described on www.clinicalstudydatarequest.com.

The full-text version of this article contains a data supplement.

Table 1. Occurrence and resolution of LT cytopenias

	Anemia	Thrombocytopenia	Lymphocytopenia	Neutropenia
All patients (N = 115), n (%)				
Cytopenias resolved to grade ≤2 by 90 days	49 (43)	43 (37)	44 (38)	43 (37)
LT cytopenias	3 (3)	9 (8)	8 (7)	9 (8)
Responders (n = 60)				
Cytopenias resolved to grade ≤2 by 90 days	45 (75)	39 (65)	40 (67)	38 (63)
LT cytopenias	2 (3)	8 (13)	7 (12)	9 (15)
Probability of grade 3 to 4 cytopenias not resolved to grade ≤2, % (95% CI)				
Month 3	100	100	83 (27.3-97.5)	100
Month 6	0	50 (15.2-77.5)	42 (5.6-76.7)	44 (13.6-71.9)
Month 9	0	25 (3.7-55.8)	42 (5.6-76.7)	22 (3.4-51.3)
Month 12	0	NE	21 (0.9-59.5)	NE

LT cytopenias were defined as grade ≥3 occurring at or persisting beyond 90 days after infusion.
NE, not estimable.

lymphocytes, neutrophils, hemoglobin, and platelets. LT cytopenias occurred or persisted beyond 90 days.

Hypogammaglobulinemia was defined as immunoglobulin G (IgG) <4 g/L and B-cell aplasia was defined as <0.2 $CD19^+$ cells per microliter. Data regarding CD4 count are not available for this patient population but can be investigated in future studies. Administration of intravenous immunoglobulin (IVIg) was at the physician's discretion. IgG, IgM, and IgA levels were evaluated at baseline, on days 14 and 28, at months 3, 6, 9, and 12, and at the end of follow-up (5 years), together with the use of IVIg and clinical outcomes. Baseline measurements were defined as the last measurements before infusion. Infections after 12 months were recorded if they required anti-infective treatment or led to significant disability, hospitalization, and/or surgery. Categorical data (eg, sex) were summarized as frequency counts and percentages, and continuous data (eg, age) were summarized by descriptive statistics (eg, mean).

Resolution of grade 3 to 4 cytopenias to grade ≤2 and onset of remission to B-cell recovery (≥1% B cells in white blood cells or ≥3% B cells in lymphocytes) was analyzed via the Kaplan-Meier method and was reported from infusion until disease progression, at initiation of new anticancer treatment, or at last available follow-up or death, whichever came first. All 95% confidence intervals (CIs) for Kaplan-Meier estimates were calculated using log-log transformation within PROC LIFETEST (SAS v9.3).

The JULIET trial was designed and sponsored by Novartis Pharmaceuticals, was approved by the institutional review board at each participating institution, and was conducted according to the Declaration of Helsinki. Data were analyzed and interpreted by the sponsor and the authors. The authors ensured adherence of the study to the protocol, which is available in the supplemental Data. The safety analysis included 115 patients who received infusions of tisagenlecleucel. As of 1 July 2019, median follow-up was 32.6 months (maximum, 44.9 months), and 60 patients (52%) had a response. Baseline characteristics of patients have previously been described.[5]

Of the responders, 16 (27%) of 60 had LT cytopenia (ie, grade ≥3), including 2 (3%) with anemia, 8 (13%) with thrombocytopenia, 7 (12%) with lymphopenia, and 9 (15%) with neutropenia (Table 1). Among responders with LT cytopenias, 14 (88%) of 16 received 2 to 4 (range, 1-6) previous lines of therapy, similar to the 31 responders without LT cytopenias. Eleven responders (69%) with LT cytopenias received red blood cell and/or platelet transfusions after treatment with tisagenlecleucel, of which 4 (25%) received transfusions and granulocyte colony-stimulating factor after 90 days.

Table 2. Infections in responders with and without LT cytopenia

No. of infections in responders at time after infusion with tisagenlecleucel	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
		With LT cytopenia (n = 15)			Without LT cytopenia (n = 28)	
≤8 weeks	5 (33.3)	1 (6.7)	0	9 (32.1)	5 (17.9)	0
		With prolonged cytopenia (n = 15)			Without prolonged cytopenia (n = 28)	
>8 weeks to ≤1 year	9 (60.0)	3 (20.0)	0	19 (67.9)	7 (25.0)	1 (3.6)
		(n = 13)			(n = 25)	
>1 y	6 (46.2)	1 (7.7)	0	11 (44.0)	4 (16.0)	1 (4.0)

All data are n (%).

For responders, median time to resolution of cytopenia to grade ≤2 was 3.5 months (95% CI, 3.19 months to not estimable [NE]) for anemia, 6 months (95% CI, 3.1-11.9 months) for thrombocytopenia, 4 months (95% CI, 3.0 months to NE) for lymphopenia, and 4 months (95% CI, 3.1-10.2 months) for neutropenia. Most cytopenias resolved by month 12 after infusion, except for 21% of patients who had LT lymphopenia (Table 1). Three nonresponders from a total of 55 patients had LT cytopenias, including 1 (2%) with anemia, 1 (2%) with thrombocytopenia, and 1 (2%) with lymphopenia; no resolution was observed. In all, 74% of patients (85 of 115) and 73% of responders (44 of 60) had B-cell aplasia before infusion (supplemental Table 1). For responders, median time to B-cell recovery was 11 months (95% CI, 5.3-16.9 months; supplemental Figure 1), and 30 responders had B-cell recovery.

Hypogammaglobulinemia occurred in 62 patients (54%) (35 responders, 27 nonresponders), 29 had baseline IgG levels ≥4 g/L, and 27 (43.5%) received IVIg. Sixteen responders (46%) did not have hypogammaglobulinemia before infusion. Among responders, the median duration of hypogammaglobulinemia was 742 days (range, 0-1132 days); 20 patients (57%) received IVIg after infusion. Doses of IVIg were heterogeneous and followed local guidelines (supplemental Table 2). Infections occurred in 21% of patients (24 of 115), and 30% of patients (34 of 115) did not have hypogammaglobulinemia.

Grade 3 to 4 infections occurred in 17% of responders (10 of 60) ≤8 weeks, in 21% of responders (12 of 58) between 8 and 52 weeks, and in 14% of responders (6 of 42) >1 year after infusion. In 60 patients with grade 3 to 4 infections after infusion, 6 (10%) had pneumonia, 3 (5%) had urinary tract infections, and 3 (5%) had general infections. Infections were predominantly bacterial and viral; 1 patient had cytomegalovirus and 2 patients had herpes simplex virus.

Among responders with LT cytopenias, grade 3 infections occurred in 1 patient (7%) at ≤8 weeks, in 3 patients (20%) between 8 and 52 weeks, and in 1 patient (8%) >1 year after infusion. Among responders without LT cytopenias, grade 3 infections occurred in 5 patients (18%) at ≤8 weeks, and grade 3 to 4 infections occurred in 8 patients (29%) between 8 and 52 weeks and in 5 patients (20%) >1 year after infusion (Table 2). Grade 3 infections occurred among 29 patients with LT neutropenia: for responders, 1 patient (17%) at ≤8 weeks, 0 patients between 8 and 52 weeks, and 0 patients >1 year after infusion; for nonresponders, 6 patients (26%) at ≤8 weeks, 2 patients (12.5%) between 8 and 52 weeks, and 0 patients >1 year after infusion.

Of patients who received an infusion, 8% percent (9 of 115) reported secondary malignancies (SMs), including 1 patient with myelodysplastic syndrome (MDS) and 1 with acute myeloid leukemia (AML). Among SMs, 78% were grade ≥3 (non–life-threatening to acute life-threatening) and ∼50% occurred >1 year (range, 1.1-1.6 years) after infusion. The estimate for cumulative incidence at 42 months was 7.7% (95% CI, 3.6%-13.9%) for SMs and 58.6% (95% CI, 48.4%-67.4%) for death as a result of any cause. Considering only the patients who achieved a complete or partial response, 13% (8 of 60) developed SMs. This apparently higher incidence in responding patients can be explained by the prolonged survival and the cumulative toxicity of previous therapies in this subgroup compared with nonresponders. All patients with an SM had received at least 1 and up to 5 lines of previous therapies, including 4 patients who received autologous stem cell transplantation (ASCT) before infusion with tisagenlecleucel (supplemental Table 3).

Patients with R/R DLBCL treated with tisagenlecleucel had manageable LT AEs. Sixteen responders (14%) of a total of 115 patients had LT cytopenias lasting ≥90 days. Although mechanisms underlying LT cytopenias are unknown, most LT cytopenias resolved by 12 months. Patients with DLBCL who receive rituximab[12] are at risk for de novo hypogammaglobulinemia and exacerbated baseline hypogammaglobulinemia.[13] In the JULIET trial, 98% of the patients received previous treatment with rituximab,[14] and 53% had hypogammaglobinemia before they received an infusion of tisagenlecleucel. Consistent with other studies,[2,6,7] we observed low rates of severe or opportunistic late infections; few responders had LT infections. Given the variability in management and the small number of patients, it is difficult to draw conclusions regarding any correlation between infections and cytopenias or hypogammaglobulinemia and use of IVIg. However, the low infection rate suggests that treatment centers are appropriately managing hypogammaglobulinemia, cytopenias, and infections.

Data from the California Cancer Registry showed that patients diagnosed with DLBCL between 2001 and 2012 had a 5-year cumulative incidence of ∼5% for SMs.[15] The 15-year cumulative incidence of patients developing SMs after ASCT was ∼10%.[16,17] Here, SMs occurred in 8 patients (7%) who had received an infusion, similar to a previous tisagenlecleucel pilot trial with 5 years of follow-up.[8] MDS and AML could be related to the number and type of previous therapies (eg, ASCT).[6] Over a 3.74-year follow-up period in the JULIET trial, prostate cancer was diagnosed in 3 of 115 males (0.8% annual incidence) and breast cancer was diagnosed in 1 of 115 females (0.2% annual incidence). These incidence rates are lower than the annual incidence of prostate cancer (7.3%) and breast cancer (11.7%) in an age-matched population.[18] Risk of SMs and LT AEs after CAR T-cell therapy needs further elucidation with longer follow-up from clinical trials like the JULIET trial.

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