Tisagenlecleucel in relapsed/refractory diffuse large B-cell lymphoma patients without measurable disease at infusion

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Key Points

- Tisagenlecleucel expanded in vivo and provided clinical benefit in r/r DLBCL patients in CR after bridging therapy.

- Tisagenlecleucel produced durable responses in r/r DLBCL patients without detectable disease before infusion.

Tisagenlecleucel demonstrated high rates of durable responses in adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) in the JULIET trial. Most patients (92%) received bridging therapies to control disease after study entry and before tisagenlecleucel infusion. Here, we examine the efficacy and safety of tisagenlecleucel in the subset of 7 patients who achieved complete response (CR) after bridging therapy and before tisagenlecleucel infusion. Tisagenlecleucel rapidly expanded in all 7 patients, and the transgene levels were measurable for up to 2 years after infusion. After infusion, all 7 patients were still in CR at the month 3 evaluation, and 5 of 7 patients remained progression-free >12 months. Adverse events were similar to the overall JULIET population. Cytokine release syndrome (CRS) was reported in 4 of 7 patients (grade 2 = 2 and grade 3 = 2 using the Penn grading scale), and 1 patient experienced grade 1 neurotoxicity. No patient required tocilizumab or steroids for CRS management. These data provide preliminary evidence of tisagenlecleucel efficacy in patients with r/r DLBCL without detectable disease after bridging or salvage therapies and warrant further investigation of tisagenlecleucel as consolidative therapy in future trials. This trial was registered at www.clinicaltrials.gov as #NCT02445248.

Introduction

Relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) has a poor prognosis.[1] Results from the SCHOLAR-1 and Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) studies suggest that response rates to available rituximab-based salvage regimens for r/r DLBCL remain dismal and are unlikely to be durable.[1-3] In SCHOLAR-1, the objective response rate was 26% with a 7% complete response (CR) rate and a median overall survival (OS) of 6.3 months.[2]

Tisagenlecleucel, an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, results in high rates of durable responses in patients with r/r DLBCL.[4,5] Results from JULIET (NCT02445248), a single-arm, open-label, multicenter, global phase 2 trial of tisagenlecleucel in adults with r/r DLBCL, demonstrated an objective response rate of 52%, with CR and partial response (PR) rates of 40% and

12%, respectively.[5] Long-term follow-up in JULIET demonstrated durable responses with a consistent safety profile and improved OS compared with historical treatment options.[6]

Among the 111 patients who received tisagenlecleucel in JULIET, most patients (92%) received various bridging therapies, including conventional combination chemotherapy to control disease during the period between enrollment and start of lymphodepleting chemotherapy.[5] However, a subset of 7 patients had no evidence of active disease after bridging therapy and received tisagenlecleucel infusion per protocol. Data from these patients were excluded from the efficacy table in the US package insert[7] for the DLBCL indication with the US Food and Drug Administration.

Because tisagenlecleucel targets CD19^{+} B cells and the study required measurable disease at enrollment, it was unknown whether tisagenlecleucel would expand and provide clinical benefit in patients without measurable disease before infusion. This post hoc exploratory analysis reports on expansion, safety, and outcomes of tisagenlecleucel therapy in the subset of patients with r/r DLBCL who had no measurable disease after bridging therapy and before receiving tisagenlecleucel infusion.

Study design

Study design and patients

Details of JULIET were described previously.[5] Briefly, patients were ≥18 years of age at entry and had ≥2 prior lines of therapy including rituximab and an anthracycline. Key eligibility criteria included progressive disease (PD) after, or ineligibility for, autologous stem cell transplantation. Eligible patients underwent leukapheresis and cryopreserved material was shipped to a central manufacturing facility. Patients could receive bridging therapy if deemed necessary by their treating physician. An independent review committee assessed disease status and response using the positron emission tomography (PET) 5-point Deauville scale (Lugano classification).[8] A restaging PET–computed tomography scan before lymphodepletion was added as a protocol amendment, but was not completed for all patients. Thus, it is possible that additional patients may have been treated without measurable disease, due to lack of imaging after bridging therapy. Most patients (n = 103) underwent lymphodepleting chemotherapy with fludarabine and cyclophosphamide or bendamustine before tisagenlecleucel infusion; patients with white blood cell counts <1 × 10^9/L within 1 week of infusion could omit lymphodepleting chemotherapy per protocol. Patients received a single infusion of tisagenlecleucel with a target dose of 5 × 10^8 viable CAR^{+} T cells.

Efficacy and safety end points

End points for this analysis included tisagenlecleucel cellular kinetics, response type and duration, survival status, and safety in this patient subset of JULIET. Adverse events were reported using the Medical Dictionary for Regulatory Activities, version 20.1, and Common Terminology Criteria for Adverse Events, version 4.03.[5] Cytokine release syndrome (CRS) was graded using the University of Pennsylvania grading scale and was managed by a protocol-specific algorithm.[5,9,10] A retrospective analysis of CRS severity using the Lee grading scale[11] was also conducted.

Tisagenlecleucel and cellular kinetics

Tisagenlecleucel expansion and persistence were characterized using time course of transgene levels (in copies per microgram of genomic DNA) in peripheral blood, measured as previously described using a TaqMan-based quantitative polymerase chain reaction assay.[5,12]

Results and discussion

As of 8 December 2017, 111 patients had received tisagenlecleucel in the JULIET trial. Among these patients, 7 had no evidence of active disease after bridging therapies and before tisagenlecleucel infusion.

Demographics and baseline disease characteristics of the 7 patients are shown in Table 1 and were similar to the overall JULIET patient population.[5] All 7 patients received both bridging therapy and lymphodepleting chemotherapy. The mean absolute lymphocyte counts before lymphodepleting chemotherapy were similar between the 7 patients and overall population, and the mean absolute lymphocyte counts after lymphodepleting chemotherapy were similar between the 7 patients and the overall JULIET population (data not shown).

Tisagenlecleucel rapidly expanded during the first 28 days after infusion in all 7 patients, and CAR transgene levels were measurable at a maximum of ~2 years (Figure 1A). Median time to last quantifiable transgene level was 351 days (range, 190-693 days) and is expected to increase with longer follow-up. Mean transgene levels at peak expansion (maximum concentration [Cmax]) in the 7-patient subset (geometric mean Cmax [percentage of coefficient variation]: 5760 copies per microgram [112%]) were comparable with those of the rest of the patients in the JULIET trial with reliable parameter estimates (n = 94; geometric mean Cmax [percentage of coefficient variation]: 5790 copies per microgram [291%]) (Figure 1B). In the JULIET trial population, the mean expansion was similar between responders and nonresponders.[5] Additionally, median time to peak expansion of 9 days from the 7-patient subset was similar to that observed in the rest of the patients in the JULIET population.

With a median follow-up of 14.5 months, all 7 patients maintained CR at the initial assessment 28 days after infusion and at the month 3 assessment (Table 1); 5 patients (1, 2, 3, 4, and 7) remained progression-free for >12 months at the data cutoff of 8 December 2017. Patient 7 declined all scans beyond the month 3 visit but continues in follow-up with no sign of disease progression >2 years after tisagenlecleucel infusion. Patient 5 experienced PD on day 274, began new anticancer therapy, and died on day 544 of PD. Patient 6 experienced PD on day 196 and withdrew consent to further follow-up (Table 1). Median time from last bridging therapy to the start of lymphodepleting chemotherapy was 44 days in the 7 patients and 24 days for the overall infused population.

Adverse events of special interest in this subset (Table 1) were similar to those in the overall JULIET population. Four of 7 patients experienced CRS (grade 2 = 2 and grade 3 = 2, using the Penn scale[9]) with a median duration of 5 days. None of these 4 patients required tocilizumab or steroids for CRS management. Only 1 patient experienced grade 1 neurologic events.[13] No deaths were observed due to tisagenlecleucel, CRS, or cerebral edema/neurotoxicity. Retrospective analysis of CRS severity using the Lee grading scale[11] found that all 4 patients had grade 2 CRS.[14]

Table 1. Patient demographics, baseline disease characteristics, efficacy, and safety outcomes

Patient	Age, y	Sex	Prior lines of therapy for DLBCL	Stage at study entry	IPI at study entry	Disease status	Bridging therapy	Duration of bridging therapy, d*	LD chemo	BOR	Response at last follow-up	DOR, d†	DOR censoring event	Survival status	CRS	CRS duration, d	NT
1	54	F	1. R-CHOP with CR for ~6 mo 2. R-ICE → R-GDP → BEAM → HSCT with relapse 3 mo after transplant	III	≥2	Relapsed to last line	1. Rituximab + cisplatin + gemcitabine 2. Rituximab + bendamustine	129	FluCy	CR	CR	384	Ongoing without event	Alive	No	—	No
2	62	F	1. R-EPOCH with CR for ~4 mo 2. R-DHAP → azacitidine + vorinostat + busulfan + gemcitabine + melphalan (conditioning) → HSCT with CR for ~2 y	IV	≥2	Relapsed to last line	1. Cyclophosphamide + rituximab	3	FluCy	CR	CR	351	Ongoing without event	Alive	Grade 2	4	No
3	68	M	1. CHOP with CR for ~15 y 2. R-CHOP with CR for ~3 y 3. R-ICE with PR for ~3 y	I	<2	Relapsed to last line	1. Rituximab + bendamustine	2	FluCy	CR	CR	340	Ongoing without event	Alive	Grade 3	7	No
4	58	F	1. R-CHOP with CR for ~4 y 2. R-DHAP → ofatumumab + ICE → BEAM → HSCT with CR for ~2 y	I	<2	Relapsed to last line	1. Trofosfamide 2. Ofatumumab + gemcitabine + liposomal doxorubicin + vinorelbine	60	FluCy	CR	CR	324	Ongoing without event	Alive	No	—	No
5	68	F	1. R-CHOP with CR for ~1.5 y 2. Rituximab + methotrexate + etoposide + ifosfamide with CR for ~11 mo	I	<2	Relapsed to last line	1. Rituximab + bendamustine	2	FluCy	CR	PD at day 274	246	New anticancer therapy other than HSCT	Died day 544, DLBCL	Grade 3	5	Dysphagia grade 1

All 7 patients had DLBCL except 1 patient with transformed follicular lymphoma. In JULIET, 79% had DLBCL and 19% had transformed follicular lymphoma.

—, not applicable; BEAM, carmustine, etoposide, cytarabine, melphalan; BOR, best overall response; chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; F, female; FluCy, fludarabine plus cyclophosphamide; HSCT, hematopoietic stem-cell transplantation; ICE, ifosfamide, carboplatin, etoposide; IPI, International Prognostic Index; LD chemo, lymphodepleting chemotherapy; M, male; NT, neurotoxicity; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone; R-DHAP, rituximab plus dexamethasone, cytarabine, cisplatin; R-EPOCH, rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; R-GDP, rituximab plus gemcitabine, dexamethasone, and cisplatin; SD, standard deviation; WBC, white blood cell.

*Duration of bridging therapies is calculated from the first dose of bridging therapy to the last dose of bridging therapy. Dexamethasone was not included in the calculation of duration of bridging therapy.

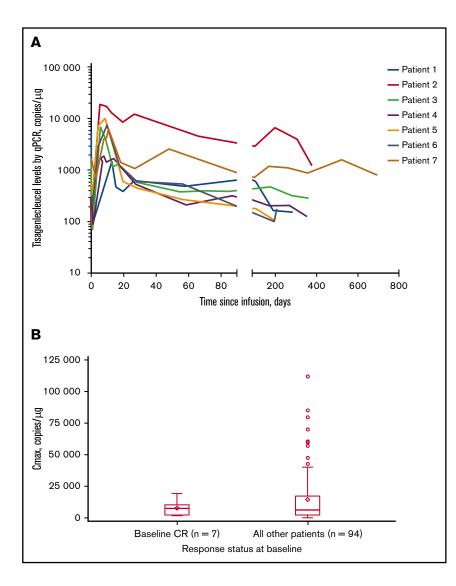†DOR was measured from date of BOR until disease relapse or death.

Table 1. (continued)

Patient	Age, y	Sex	Prior lines of therapy for DLBCL	Stage at study entry	IPI at study entry	Disease status	Bridging therapy	Duration of bridging therapy, d*	LD chemo	BOR	Response at last follow-up	DOR, d†	DOR censoring event	Survival status	CRS	CRS duration, d	NT
6	64	F	1. R-CHOP + methotrexate with CR for ~4 mo; 2. R-ICE with SD for ~1 mo; 3. Rituximab + methotrexate + cytarabine + methylprednisolone → busulfan + etoposide + cyclophosphamide (conditioning) → HSCT with CR for 4 mo	IV	≥2	Relapsed to last line	1. Rituximab + methotrexate + cytarabine	71	FluCy	CR	PD at day 196	165	Withdrew consent	Lost to follow-up	No	—	No
7	71	F	1. R-EPOCH with CR for ~7 mo; 2. R-GDP with PR for ~3 mo	III	≥2	Relapsed to last line	1. Ifosfamide + carboplatin + etoposide	24	FluCy	CR	CR	65	Adequate assessment no longer available	Alive	Grade 2	12	No
Overall JULIET population[5]	56	35.5% F 64.5% M	1: 5% 2: 44% 3: 31% 4-6: 21%	I: 7% II: 17% III: 20% IV: 56%	<2 risk factors: 27.9% ≥2 risk factors: 72.1%	Relapse: 45% Refractory: 55%	92%	56	93% (FluCy: 73%; bendamustine: 20%)	40% CR 12% PR	—	—	—	90% OS rate at 12 mo in patients with CR	22% grade 3/4	—	12% grade 3/4

All 7 patients had DLBCL except 1 patient with transformed follicular lymphoma. In JULIET, 79% had DLBCL and 19% had transformed follicular lymphoma.

—, not applicable; BEAM, carmustine, etoposide, cytarabine, melphalan; BOR, best overall response; chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DOR, duration of response; F, female; FluCy, fludarabine plus cyclophosphamide; HSCT, hematopoietic stem-cell transplantation; ICE, ifosfamide, carboplatin, etoposide; IPI, International Prognostic Index; LD chemo, lymphodepleting chemotherapy; M, male; NT, neurotoxicity; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone; R-DHAP, rituximab plus dexamethasone, cytarabine, cisplatin; R-EPOCH, rituximab plus etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; R-GDP, rituximab plus gemcitabine, dexamethasone, and cisplatin; SD, standard deviation; WBC, white blood cell.

*Duration of bridging therapies is calculated from the first dose of bridging therapy to the last dose of bridging therapy. Dexamethasone was not included in the calculation of duration of bridging therapy.

†DOR was measured from date of BOR until disease relapse or death.

In summary, tisagenlecleucel expansion occurred in all 7 patients with no measurable disease after bridging therapy, and mean expansion was similar to the JULIET trial. More than one-half of the patients (5 of 7) remained progression free >12 months after infusion, which is longer than would be expected with bridging therapy alone. One hypothesis to explain these observations is that CAR T cells can expand in response to residual disease undetected by PET imaging. These findings are novel because data from these 7 patients were excluded from the DLBCL efficacy table in the Kymriah (tisagenlecleucel) US package insert,[7] and, in the commercial setting for axicabtagene ciloleucel therapy,[15] patients who attained CR after bridging therapy did not receive their CAR T-cell infusion.

In conclusion, these results provide preliminary evidence of tisagenlecleucel efficacy in patients with r/r DLBCL without detectable disease after bridging or salvage therapies. Additionally, these 7 patients experienced low rates of CRS and neurotoxicity. These data warrant further exploration in clinical trials of tisagenlecleucel as consolidative therapy for patients with relapsed and high-risk DLBCL in CR.

Authorship

Contribution: M.R.B., R.T.M., E.K.W., U.J., J.R.W., J.P.M., I.F., H.H., P.B., and S.J.S. enrolled patients, performed research, and contributed to data collection and interpretation; C.d.C., R.T., Ö.A., R.A., L.P., and V.V.R. performed cellular kinetic and/or statistical analyses and/or contributed to data interpretation; M.R.B. and S.J.S. wrote the first draft; and all authors were involved in revising the manuscript and approved the final version.

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