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Phase I dose escalation study of the anti-CD2 monoclonal antibody, siplizumab, with DA-EPOCH-R in aggressive peripheral T-cell lymphomas

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Mature T- and natural killer (NK)-cell neoplasms are a heterogeneous group of diseases, accounting for roughly 10% of non-Hodgkin lymphomas in the United States management. Compared to mature, aggressive B-cell lymphomas, most T- and NK-cell neoplasms have inferior overall survival (OS) and progression-free survival (PFS) with anthracycline-based regimens [1]. In a retrospective analysis of T- and NK-cell lymphomas treated between 2000 and 2010 with predominantly cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based regimens (70% of patients), there was a three-year PFS and OS of 32 and 52%, respectively. This is compared to matched cohort of diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP where five-year OS was 70% [2]. This disparity in outcomes is partially explained by the incorporation of rituximab into CHOP-based regimens for DLBCL, which has increased OS [3,4]. Recommended first-line therapy for most peripheral T-cell lymphomas (PTCLs) is CHOP-based chemotherapy, and with exception of anaplastic large cell lymphoma (ALCL), this results in an unsatisfactory rate of relapse-free and OS.

Siplizumab (MEDI-507) is a humanized IgG1 κ class monoclonal antibody that binds to the CD2 receptor found on T-lymphocytes, natural killer cells, and thymocytes. Siplizumab interferes with T-cell activation and expansion, and leads to depletion of NK and T cells. Siplizumab monotherapy showed efficacy in a phase I trial of T-cell lymphoproliferative neoplasms, over half of which had adult T-cell leukemia/lymphoma (ATL). Out of 22 patients, nine responses were seen, seven partial, and two complete. The most common toxicity was grade 1/2 infusion reactions, but there was an associated 13% incidence of

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EBV-related lymphoproliferative disorder (LPD) [5]. We hypothesized that a regimen augmented with siplizumab could be safely administered and improve cure rates in frontline therapy of PTCLs, including rare histologies such as ATL. To ameliorate the potential for EBV-related LPD from siplizumab, our study regimen included rituximab. We performed a single-center phase I study of siplizumab with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-RS) in patients with untreated PTCLs.

This study enrolled patients (≥ 18 years) with untreated, mature T- and NK-cell lymphomas expressing CD2 in at least 30% of malignant cells. All cases had confirmed histopathologic diagnosis by Laboratory of Pathology, NCI. Patients with ALK-positive ALCL and T-cell precursor disease were ineligible. Further eligibility criteria included normal organ function unless the organ injury was from tumor involvement. The study was approved by the investigational review board of NIH, all patients provided written informed consent, and the study was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01445535).

Siplizumab was administered in four escalating dose cohorts at intravenous doses of 3.4 mg/kg, 4.8 mg/kg, 8.5 mg/kg, and 15 mg/kg. A classic (3 + 3) dose-escalation design was used. Siplizumab was given day 1 of each cycle followed by dose-adjusted EPOCH-R on days 1–5 for a 21-day cycle. Dose-adjusted EPOCH-R was administered as previously described [6]. Patients at risk of CNS disease, defined as two or more extranodal sites of disease with elevated LDH or bone marrow involvement, received intrathecal methotrexate once per cycles 3–6. Patients with active CNS disease were treated per protocol. Prophylaxis was given for pneumocystis jirovecii, herpes simplex virus, and fungal infections. Six cycles of therapy were administered, unless progressive disease or excessive toxicity occurred.

The primary objective was to assess the feasibility and safety of administering dose-adjusted EPOCH-RS. For safety evaluations, adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 3.0. Dose-limiting toxicity (DLT) for siplizumab was defined as infusional grade 3 non-hematologic toxicity lasting longer than 6 hours after the infusion, any grade 4 non-hematologic toxicity, or the development of an EBV-related LPD. Expected toxicities of dose-adjusted EPOCH-R and grade 3 laboratory AEs would not be considered DLTs. EBV viral loads were assessed each cycle and a rise in EBV viral loads would trigger an evaluation for EBV-related LPD. Secondary objectives included assessments of best response per International Working Group Criteria, PFS, and OS [7]. Responses were assessed by CT scans after the fourth and sixth cycles of therapy. At completion of therapy, patients were monitored with CT scans every three months for the first year, every four months for the second year, every six months for years 3–5, and annually thereafter.

OS was determined from the on-study date until date of death or last follow-up. PFS was determined from the on-study date until date of progression or last follow-up; for this endpoint, patients who died without progression were also considered to have had an event at date of death. The probability of OS and PFS as a function of time was estimated by the Kaplan–Meier method.

A total of 15 patients with untreated, aggressive T-cell neoplasms were enrolled from March 2009 to November 2011 (Table 1). The median age of patients treated was 49 years. Patients with high–intermediate or high-risk IPI represented 64% of patients. One patient enrolled and was unable to receive therapy secondary to sipilizumab availability. Another patient withdrew from treatment after two cycles secondary to functional decline from lymphoma. Of 13 evaluable patients, 62% (8 of 13) achieved complete response (CR), 23% (3 of 13) achieved partial response (PR), and 15% (2 of 13) had progressive disease. With median follow-up of 86 months, median OS was 12.1 months, (95%CI: 6.7–30.7 months) and the median PFS was 6.8 months (95%CI: 2.9–27.1 months) (Figure 1).

Toxicity was assessed in all 14 treated patients and in each of 75 cycles of dose-adjusted EPOCH-RS administered. The most common treatment-related AEs of all grades were hematologic. The toxicity profile of EPOCH-RS was similar to that reported previously with EPOCH-R [6], and there were no unanticipated toxicities. There were four grade 3 and one grade 4 serious infections, and there was one patient death related to gram-positive sepsis. The average pre-therapy peripheral blood EBV PCR was 2790 genome equivalents per million mononuclear cells and all patients had undetectable EBV PCR levels at end of therapy. There were no DLTs or development of EBV-related LPD.

This report described results from a dose-escalation phase I study of dose-adjusted EPOCH-RS for untreated aggressive T-cell lymphomas. The study regimen was safely given and there were no DLTs observed. This regimen had overall response rate (ORR) of 84.5% with 62% of patients achieving CR. However, majority of patients achieving response relapsed and did not have long-term disease-free survival. Over 50% of patients on study had ATL, which may be related to low rates of PFS. The ORR is similar to other chemo-immunotherapy trials in the upfront treatment of PTCL, such as the phase I/II study of alemtuzumab with CHOP where a 75% ORR was achieved [8]. However, infectious complications of that trial were significant, including 1 case of JC virus encephalopathy and 9% CMV reactivation rate per cycle. In our trial, there was one death related to gram-positive sepsis and five cases of grade 3 or 4 infectious complications. Rituximab was effective in preventing the development of EBV-related LPD.

The frontline treatment of PTCL is suboptimal. CHOP is standard of care, and addition of etoposide as in dose-adjusted EPOCH is generally recommended for younger patients. In a phase III trial evaluating more intensive chemotherapy, VIP-reinforced-ABVD (alternating cycles of etoposide, ifosfamide, cisplatin with doxorubicin, bleomycin, vinblastine, dacarbazine) was not superior to CHOP, showing a median OS of 42 months in both arms [9]. Efforts to improve upon CHOP with the addition of bortezomib [10], denileukin diftitox [11], alemtuzumab [8], or everolimus [12] have not led to improved OS, despite having higher initial ORR/CR rates than CHOP. At this time, improving the frontline therapy of PTCL may not lead to gains in disease-free and OS without expanding upon consolidation or maintenance therapies.

The role of autologous stem cell transplantation (ASCT) in the consolidation of PTCL therapy remains unsettled. There are no randomized controlled trials to evaluate the benefit of consolidation ASCT for patients in first remission. The largest non-randomized study

evaluated high-dose chemotherapy in patients achieving remission following six cycles of initial CHOP-based chemotherapy. In the intention-to-treat population, the five-year OS and PFS were 51 and 44%, respectively. Patients with ALK-negative ALCL, which comprised about 20% of all patients, had the best outcomes with five-year OS and PFS of 70 and 61%, respectively [13]. A phase II study of dose-adjusted EPOCH in ALCL showed that ALK-negative ALCL patients have excellent outcomes with chemotherapy alone, with event-free survival of 62.5% and OS of 87.5% at median follow-up of 14 years; thus, inclusion of ALCL patients on ASCT trials may overstate potential benefits [14].

To better define which patients may benefit from high-dose chemotherapy consolidation or maintenance strategies, the development of predictive biomarkers is essential. In DLBCL, use of ctDNA was prognostic and predictive of future relapse [15]. A similar platform for PTCLs could be used in design of further trials to assess the role of risk-adapted therapies, such as ASCT or maintenance strategies with chemotherapy and/or novel agents.

In conclusion, we found that dose-adjusted EPOCH-RS is well-tolerated and had an ORR of 84.5% in untreated patients with PTCL. However, this did not result in long-term PFS. The addition of rituximab ameliorated the risk of EBV-related LPD. Given the low rates of PFS with CHOP-based regimens, the development of predictive biomarkers to aid in the design of further trials is necessary.

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Figure 1.

Kaplan–Meier curves for progression-free survival and overall survival. The OS (top panel) for patients treated with DA-EPOCH-RS was 50.0% (95%CI: 22.9–72.2%) at 12 months and 35.7% (95%CI: 13.0–59.4%) at 24 months. The PFS (bottom panel) for treated patients was 35.7% (95%CI: 13.0–59.4%) at 12 months and 28.6% (95%CI: 8.9–52.4%) at 24 months.

Table 1.

Patient characteristics and response.

Study number	Gender/ Age (y)	Disease	Stage	IPI	Siplizumab dose	No. of cycles completed	Response
01	F/49	ATL	IV	2	3.4 mg/kg	4	PD
02	F/43	ATL	IV	4	3.4 mg/kg	6	PR
03	F/19	PTCL, NOS	IV	3	3.4 mg/kg	6	CR
04	M/33	PTCL, NOS	IV	2	4.8 mg/kg	6	CR
05	M/39	PTCL, NOS	IV	1	4.8 mg/kg	6	PR
06	M/53	ATL	IV	3	4.8 mg/kg	6	CR
07	M/77	PTCL, NOS	IV	4	8.5 mg/kg	6	CR
08	M/67	ATL	IV	4	8.5 mg/kg	6	PR
09	F/65	ATL	IV	4	8.5 mg/kg	3	PD
10	F/68	ATL	IV	4	15 mg/kg	6	CR
11	F/65	EATL	IV	5	15 mg/kg	2	NE
12	F/36	ATL	II	0	15 mg/kg	6	CR
13	M/33	PTCL, NOS	IV	3	15 mg/kg	6	CR
14	F/35	ATL	IV	3	15 mg/kg	6	CR
15	F/31	CGDTCL	IVB	3	15 mg/kg	0	NE

ATL: adult T-cell leukemia/lymphoma; PTCL-NOS: peripheral T-cell lymphoma not otherwise specified; EATL: enteropathy-associated T-cell lymphoma; CGDTCL: cutaneous gamma/delta T-cell lymphoma; PD: progressive disease; CR: complete remission; PR: partial remission; NE: not evaluable for response.