SHORT REPORT OPEN ACCESS

Assessment of the Tolerability and Optimal Dosing of the Combination of Brentuximab Vedotin and Lenalidomide in Patients With Relapsed or Refractory T-cell Lymphoma: Results of a Single-centre Phase 1 Dose-escalation Study

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Keywords: brentuximab vedotin | cutaneous T cell lymphoma | peripheral T cell lymphoma | T cell lymphoma

ABSTRACT

Objective: We report the results of a pilot study investigating the combination of brentuximab vedotin (BV) and lenalidomide in patients with relapsed/ refractory T-cell lymphoma.

Methods: A dose escalation study design was utilized. Primary and secondary endpoints included maximum tolerated dose (MTD), adverse events, and response rates.

Results: Six patients were treated with BV and two dose levels of lenalidomide, in 21-day cycles. The protocol-determined MTD was BV 1.8 mg/kg and lenalidomide 25 mg, however, all patients required subsequent dose reductions with ongoing treatment. The most common adverse event was peripheral neuropathy in four of six patients. Two patients achieved complete responses and three achieved partial responses.

Discussion:: The combination is deliverable with dose attenuation. Further study is needed to define clinical benefit.

Clinical Trial Registration: This trial was registered on ClinicalTrials.gov (NCT number 03302728).

1 | Introduction

T-cell lymphoma comprises a diverse group of uncommon haematologic malignancies, most of which carry an adverse prognosis, particularly when relapsed or refractory. This remains an area of high unmet need. For patients with relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL), the median overall survival (OS) from the time of first relapse or failure of first-line therapy is 5.8 months [1]. Patients with advanced cutaneous T-cell lymphoma (CTCL) have a slightly better median OS from the time of diagnosis, but almost always require sequential treatments to maintain disease control, often without achieving lengthy remissions [2].

Brentuximab vedotin (BV) is an antibody-drug conjugate combining a CD30-specific monoclonal antibody with the antimitotic agent monomethylauristatin E and is used predominantly in R/R Hodgkin lymphoma and T-cell lymphoma. In PTCL, BV has demonstrable benefits in patients with R/R systemic anaplastic large cell lymphoma (sALCL), with an overall response rate

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(ORR) and median progression-free survival (PFS) of 86% and 13.3 months respectively in a phase 2 study [3]. The utility of BV in other PTCL subtypes, however, is not as favorable, with ORR of 41% and complete response rate (CRR) of 24% in a phase 2 study in R/R disease. For PTCL-not otherwise specified (PTCL-NOS), median PFS was only 2.6 months, and 1.6 months [4].

In CTCL, the phase 3 ALCANZA trial demonstrated an ORR of 67% with PFS of 16.7 months in BV-treated patients with either R/R mycosis fungoides (MF) or primary cutaneous ALCL (pcALCL). CRR was 10% [5].

Phase 2 data for the immunomodulatory drug lenalidomide as monotherapy for R/R T-cell lymphoma demonstrated limited benefit, with ORR of 22%–26% for PTCL [6, 7], and ORR of 28% for CTCL [8]. PFS was short in both groups: 2.5 months for PTCL and 8 months for CTCL.

We postulated that the combination of BV and lenalidomide may be more efficacious than monotherapy for either agent, not least given the evolving understanding of the role of BV in enhancing T-cell activation and maturation, and priming and migration of antigen-presenting dendritic cells into the tumor [9, 10], suggesting a potential benefit from the immunomodulatory effects of lenalidomide.

2 | Methods

We designed a phase 1, dose-escalation study with a 3×3 design to investigate the maximum tolerated dose (MTD) and dose-limiting toxicities of BV in combination with lenalidomide.

Patients aged 18 years or over were eligible if they had a diagnosis of R/R PTCL or CTCL, with at least one prior line of systemic therapy. For patients with PTCL to be eligible, immunohistochemical CD30 expression was mandated at 10% or higher, in line with existing phase 2 data. Patients with CTCL were eligible at any CD30 level, given data suggesting that patients with even low CD30 expression derived clinical benefit from BV [5].

All patients were planned to receive the standard BV dose of 1.8 mg/kg delivered every 21 days, in combination with either lenalidomide 15 mg (dose level 1) or 25 mg (dose level 2), on days 1–14 of the 21-day cycle. The protocol also considered dose levels 1 and 2 with de-escalation for BV and lenalidomide if dose level 1 was not safe. Up to 16 cycles of treatment were permitted. A planned expansion cohort at the MTD of up to 20 patients was incorporated in the initial study design. Dose de-escalation levels for BV and lenalidomide were included for toxicity. Follow-up for disease response, commencement of subsequent therapies, and survival were continued 6 months after the conclusion of trial participation.

The primary endpoints were to determine the MTD and dose-limiting toxicities of the combination. Secondary outcomes were to establish the combination's safety profile, describe treatment intensity, establish the ORR, and describe event-free survival and overall survival. The response was assessed radiologically using RECIST v 1.1. criteria for patients with PTCL, and using clinical and radiologic assessment of response according to Olsen et al. for patients with CTCL [11]. Toxicities were measured according to CTCAE version 4.03.

Statistical analysis was limited to tabulation, patient listings, and swimmer plots given the small cohort.

3 | Results

Six patients were enrolled between September 2018 and June 2020. The study was not expanded due to slow recruitment and closed in 2021 after meeting the primary endpoint, the determination of MTD. The study population included two patients with PTCL (histologic subtypes sALCL and PTCL-NOS) and four with CTCL (three with MF and one with multifocal pcALCL). The median age was 63 years (range 25–82). Median number of lines of prior systemic therapy was three (range 1–6). Baseline patient characteristics are shown in Table S1.

Time on therapy ranged from two to 16 cycles. No patients experienced dose-limiting toxicities within the first cycle (DLT assessment period). Therefore, BV 1.8 mg/kg and lenalidomide 25 mg was considered the MTD.

Four patients required a dose reduction of BV to 1.2 mg/kg or lenalidomide to 10 or 15 mg due to emergent adverse events (AEs). Treatment intensity and dosing are summarized in Table 1. No patient received the combination in all 16 cycles, with lenalidomide or BV being omitted in some cycles due to AEs. The maximum duration of combination therapy was 14 cycles. Three patients ceased treatment due to AEs, and one patient ceased treatment due to disease progression. Graphical representation of dosing, including treatment hiatuses due to side effects, duration of therapy, and best response is depicted in Figure 1.

The best responses were complete response (CR) in two patients, partial responses in three patients, and stable disease in one patient. Two of the patients had multiply refractory disease, having received four and six prior therapy lines respectively, with the latter patient having experienced mixed response followed by progressive disease to his four most recent treatments. On trial, he achieved a marked reduction in tumor bulk to near radiologic CR, which was sustained for 8 months before developing low-volume progression.

All patients were alive at three and 6 months follow-up. Four patients had not received any subsequent anticancer therapy.

Most AEs were as anticipated from the use of BV and lenalidomide as monotherapy. Four of six patients experienced either grade 1 or 2 peripheral neuropathy, leading to BV dose reduction in all patients, and eventual discontinuation of this agent in two patients. Time to improvement or resolution of peripheral neuropathy was not formally assessed, however, no patient reported complete resolution of their symptoms by the time of conclusion of the study treatment. Cytopenias were observed in four of six patients but were mostly manageable with dose reductions and prophylactic filgrastim use.

Grade 3 or 4 AEs were observed in four patients: nausea/fatigue, neutropenia, anaphylaxis, and febrile neutropenia

TABLE 1 | Summary of treatment course for cohort.

Last cycle (any treatment)	BV cycles taken	BV dose reduction	Len cycles dispensed	Len dispensed dose taken (%)	Len dose reduction	Reason ceased all treatment	DLT
16	15	Yes	14	88.8	Yes	Received 16 cycles	No
16	9[a]	Yes	16	100.0	Yes	Received 16 cycles	No
2	2	No	2	89.3	No	Adverse event[b]	No
3	3	No	3	100.0	Yes	Adverse event[c]	Yes
7	7	Yes	3[d]	83.3	Yes	Adverse event[e]	Yes
9	9	Yes	9	100.0	No	Disease progression	No

Abbreviations: BV, brentuximab vedotin; Len, lenalidomide.

[a]Permanently withdrawn from brentuximab vedotin due to grade 2 peripheral sensory neuropathy.

[b]Grade 3 nausea, grade 2 fatigue, and grade 1 paraesthesia.

[c]Grade 3 anaphylaxis.

[d]Permanently withdrawn from lenalidomide due to grade 1 sensory neuropathy and grade 4 neutrophil count decrease.

[e]Grade 2 peripheral sensory neuropathy.

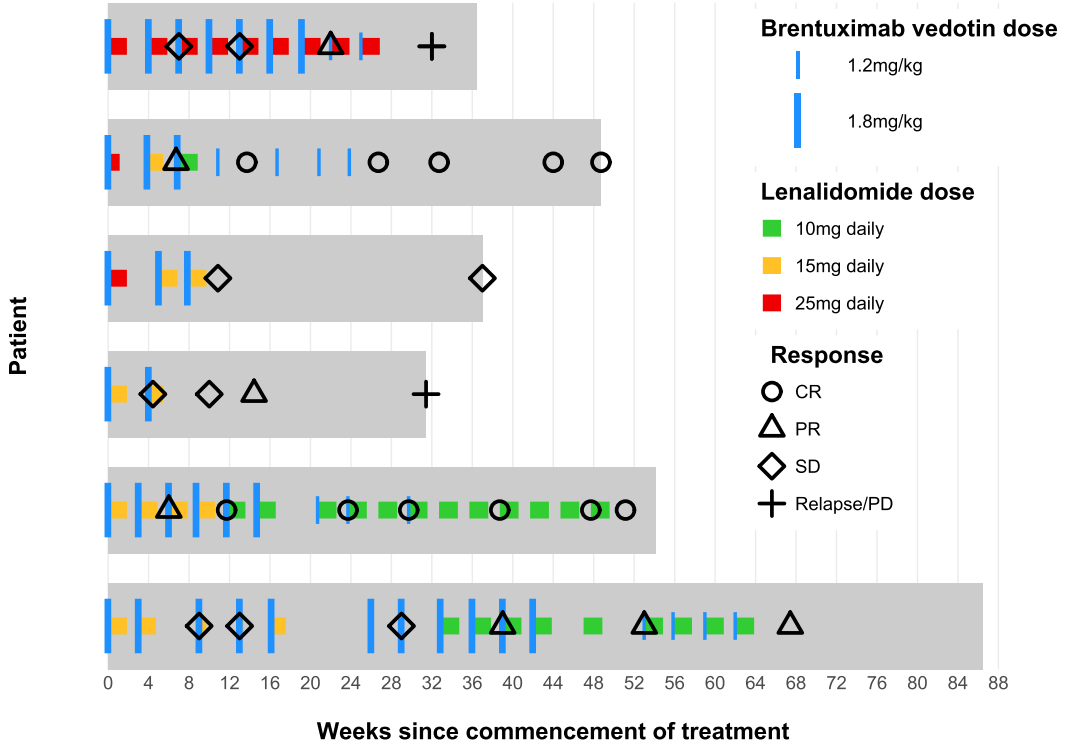

FIGURE 1 | Swimmers plot representing the treatment trajectory of each individual patient. This figure incorporates time on treatment, exposure to each therapy, treatment intensity of both agents and clinical response over time.

due to cytomegalovirus (CMV) reactivation. CMV reactivation was possibly attributable to BV but potentially to the use of protocol-permitted corticosteroids to manage tumor flare. This patient continued on study after the institution of valganciclovir. One patient experienced grade 4 febrile neutropenia with recurrent neutropenic episodes despite filgrastim use and treatment delay, leading to treatment cessation. One patient experienced anaphylaxis, initially presenting as salbutamol-responsive bronchospasm during her second BV dose. Given her baseline asthma history with possible intercurrent viral symptoms at the time of her initial bronchospastic episode, she received a third dose of BV. She developed recurrent

anaphylactoid symptoms with rechallenge and ceased study treatment.

4 | Discussion

This is the second report globally on the combination of BV and lenalidomide in patients with R/R T-cell lymphoma [12]. The combination of BV and lenalidomide was deliverable in our cohort, and the toxicity profile aligned with that reported by William et al. Most patients who received two or more cycles required treatment dose reductions, such that routine dosing in our cohort parallelled the doses of BV 1.2 mg/kg and lenalidomide 10 mg in the previously reported study. We also note the results of the phase 1 study of BV/lenalidomide in patients with R/R diffuse large B-cell lymphoma which reported an MTD of BV 1.2 mg/kg every 21 days and lenalidomide 20 mg delivered continuously [13], analogous to the dose attenuations we observed.

AEs were mostly as predicted in study development. Importantly, no grade 3 or 4 peripheral neuropathy was observed. Additionally, grade 3 or 4 neutropenia was uncommon, likely reflecting the use of prophylactic filgrastim after any grade of neutropenia.

Emergent side effects included CMV reactivation and anaphylaxis to BV. Both have been reported previously [14, 15] and are unlikely to represent toxicity specifically attributable to the combination. Importantly, CMV reactivation did not represent a treatment-limiting event in our patient. Although these side effects are uncommonly observed, these observations serve as an important reminder to clinicians routinely prescribing BV.

Despite the high ORR, the cohort size is too small to permit robust interrogation of clinical benefit, let alone direct comparison to BV monotherapy. We note the analogous results from William et al. reporting a lower ORR of 33% in their cohort of 17 T-cell lymphoma patients, and also note the more durable clinical benefit observed in our cohort. We postulate that the phase 3 ALCANZA data – published after the genesis of this study – may make this combination less attractive to patients with CTCL who may achieve meaningful disease control with BV monotherapy. However, the responses observed in our PTCL patients are anecdotal but intriguing, not least given the significant clinical benefit achieved by one patient with multiply refractory disease.

5 | Conclusion

In patients with R/R T-cell lymphoma, the combination of BV and lenalidomide was deliverable and tolerable with dose attenuation. The viability of this strategy remains unclear and requires further study.

Author Contributions

Carrie van der Weyden and **Michael Dickinson** designed the research study and performed the research, with expert input from **Henry Miles Prince** in the research design phase. **Michael Dickinson** was the Principal Investigator for this study. **Carrie van der Weyden**, **Mathias Bressel**, and **Amit Khot** participated in the research review and determination of safety and maximum tolerated dose. **Mathias Bressel** and **Carrie van der Weyden** contributed to the analysis of the data. **Carrie van der Weyden** wrote the paper with collaborative editorial input from all co-authors.

Ethics Statement

This study and the publication of subsequent results were approved by the Peter MacCallum Cancer Centre Institutional Review Board (HREC approval number 15/17).

Consent

All patients provided written consent.

Conflicts of Interest

Carrie van der Weyden has participated in Advisory boards for Kyowa Kirin. Amit Khot has participated in advisory boards for Kyowa Kirin, Mundipharma, and Celgene/BMS. He has been the recipient of travel grants from Celgene/BMS. Henry Miles Prince has participated in advisory boards for BMS. Michael Dickinson has been the recipient of research funding for this study from BMS/Takeda, participated in Advisory boards for BMS, MSD, GenMab, Roche, and Abbvie, and has been the recipient of research funding from GenMab, Roche, Abbvie, and BMS. Mathias Bressel declares no conflicts of interest.

Data Availability Statement

De-identified additional data may be made available from the corresponding author on request for approved purposes.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.