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Characterization of the peripheral neuropathy associated with brentuximab vedotin treatment of Mycosis Fungoides and Sézary Syndrome

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is common, frequently limits chemotherapy dosing, and negatively impacts quality of life. The National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0, and the Total Neuropathy Score clinical version (TNSc) are both validated scores to quantify peripheral neuropathy (PN), with the TNSc being more sensitive to clinical changes. Mycosis fungoides and Sézary syndrome (MF/SS) are characterized by a chronic course, where current therapies are generally non-curative and treatment toxicities have the potential for significant lasting effects. Brentuximab vedotin (BV) is an antibody-drug-conjugate composed of an anti-CD30 monoclonal antibody linked to the microtubule-disrupting agent, monomethyl auristatin E, with a known associated CIPN. In our phase II clinical trial of BV in MF/SS, 25 (69%) of 36 patients developed PN, with 18 (50%) developing Clinically Significant PN, CTCAE v4.0 grade 2 or higher. The median time to grade 2 PN was 15 weeks (range 0.4–48) after the initial dose. By Kaplan–Meier calculation, the median time to improvement from Clinically Significant PN was 30 weeks from the last BV dose. Seventy-four percent had improvement by 24 months. We found that TNSc scores significantly correlated with CTCAE grade, with Spearman correlation coefficient 0.68 ($p < 0.001$). By logistic

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Compliance with ethical standards

Conflict of interest

Author Y Kim has received research grants from Seattle Genetics. All remaining authors declare they have no conflict of interest to report.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

regression, for each 100 mg increase in BV total dose, the likelihood of developing Clinically Significant PN increased by 23% (95% CI 4–46%). Improved monitoring of CIPN associated with BV is of paramount importance in the MF/SS population.

Keywords

Brentuximab vedotin; Neuropathy; Chemotherapy-induced peripheral neuropathy; Mycosis fungoides; Sézary syndrome; Total neuropathy score

Introduction

Peripheral neuropathy (PN) is a common side effect of chemotherapies and may result in modification of treatment plans, incomplete treatment courses, and negative impacts on quality of life [1]. Chemotherapy-induced peripheral neuropathy (CIPN) is well described in patients receiving microtubule disrupting agents, like taxanes, and DNA cross-linking drugs, like the platinum agents [2]. In a subset of patients affected by CIPN, the symptoms persist after treatment stops, and, in platinum compounds, may even worsen for up to 6 months after the last dose [2]. The magnitude of CIPN has prompted the American Society of Clinical Oncology to issue clinical practice guidelines that describe the need for a reliable tool to define end points for future clinical trials [3]. The Total Neuropathy Score, which incorporates nerve conduction studies, was developed for a study of patients receiving a combination of paclitaxel and cisplatin [4]. In this cohort, 95% of patients developed signs of CIPN, 76% developed symptoms, and CIPN was noted to be a significant dose-limiting side effect [4]. The Score was then validated in a cohort of patients with diabetic polyneuropathy [5]. A streamlined version without nerve conduction studies, the Total Neuropathy Score clinical version (TNSc), was introduced as a way to employ the score in a cancer center without specialized instruments [6]. The TNSc itself was later correlated with a prior version of the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) and proved more sensitive to changes in CIPN [6, 7]. It has since been validated as a clinical measure of CIPN [8].

Mycosis fungoides (MF) and its leukemic variant, Sézary syndrome (SS), are the most common subtypes of cutaneous T cell lymphoma (CTCL) [9]. Although advanced stage MF/SS can be life-threatening, most early stage disease remains indolent and rarely progresses beyond skin involvement [10]. Current available therapies are largely non-curative, thus accumulated treatment toxicities have major impacts on patients' quality of life. This dynamic creates a need to focus on potential harmful effects of treatment in a chronic disease state and to explore more appropriate dosing strategies to minimize irreversible toxicities.

Brentuximab vedotin (BV) is an antibody-drug conjugate linking a CD30 antibody to four molecules of the microtubule inhibitor monomethyl auristatin E (MMAE), which has multiple proposed mechanisms of action [11, 12]. BV is FDA-approved for relapsed Hodgkin's lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL) [13]. The agent is currently in the NCCN non-Hodgkin's lymphoma practice guidelines for the treatment of advanced-stage MF/SS. Furthermore, BV is being explored in a phase 3 clinical

trial in MF and cutaneous ALCL for submission for FDA review (NCT01578499). In HL and sALCL, CIPN was the most common non-hematological adverse event, affecting 36–55% of study subjects [14–16]. Sixty-three to 81% of patients with CIPN showed improvement or resolution, with reported median times to improvement of 9.9–13.2 weeks [15, 16].

The results of a phase II trial of BV in CD30 positive cutaneous T cell lymphoma and lymphomatoid papulosis, as well as the recent phase II report including most of our cohort with MF/SS, indicate higher rates of CIPN after BV than in prior studies, with rates of 67 and 66%, respectively [17, 18]. Resolution of PN in the first trial occurred in 45% of patients, with a median time of 41.5 weeks (range 2–66 weeks) [17]. In the report with most of our cohort, improvement or resolution was reported in 86% of patients by 24 months, and the median time to improvement by Kaplan–Meier calculation was 49.0 weeks (95% CI 20.4–70.1 weeks) [17, 18]. We feel these data underscore the need to better describe the CIPN associated with BV in this patient population. In this context, the aims of the current study were to detail the frequency, severity, and chronicity of CIPN in all patients with MF/SS enrolled in our phase II clinical trial of BV. We also used the TNSc as an adjunctive tool to evaluate and monitor CIPN in this population.

Patients and methodology

Patients and study design

Thirty-six patients were enrolled in a phase II, investigator-initiated study at Stanford exploring the clinical activity and safety of BV in MF/SS, stage IB–IVB, who failed at least one systemic therapy. Thirty-two of the 36 patients were recently reported, but this paper includes four additional patients not previously described [18]. The patients were 18 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients were treated with BV (1.8 mg/kg, or dose reduced to 1.2 mg/kg), administered every 3 weeks for up to eight cycles. The patients with continued clinical improvement were allowed up to a maximum of eight additional cycles, and those with a complete response were allowed 2 further cycles.

Assessment of peripheral neuropathy

PN was assessed prior to each BV treatment and graded according to the CTCAE, version 4.0. During the course of the study, we began to use the TNSc in addition to CTCAE grading to monitor PN. The TNSc values were consecutively obtained thereafter. The two scales were recorded independently of each other, and there was no interconversion. The TNSc involves a structured history and physical. For the history, the extent and location of any sensory and motor symptoms are recorded, and the presence of autonomic symptoms is assessed, including syncope, diarrhea, constipation, or bowel or bladder incontinence. Regarding the exam, any abnormality of pinprick or vibration sensation is documented, and the extent and location of any decrement of reflexes is recorded. We developed a TNSc template to prompt the examining clinician with these requirements. This template, which we have included in the supplementary data, allowed non-neurologists to be efficient examiners.

Given the neurotoxicity of BV observed initially, beginning halfway through the study, all patients were formally evaluated by a neurologist at screening, every seven cycles on trial, and at the end of trial. During the trial period, a neurological exam was done at every visit by a member of the clinical team. Additionally, patients with grade 2 PN were followed by a neurologist every two cycles. After the end of trial visit, patients with a residual grade 1 PN were evaluated every 6 months until the last clinical assessment, and patients with a residual grade 2 PN were seen every 2 months until improvement or resolution.

Several patients underwent clinically indicated electromyography and nerve conduction studies (EMG/NCS), but these studies were not a protocol requirement.

Per the trial protocol, grade 2 PN prompted dose modification, including dose delay until improvement of PN to grade 1 or better, followed by a dose reduction to 1.2 mg/kg. With the development of grade 3 PN, BV was discontinued.

One patient on study had a nerve biopsy to assist in the diagnosis of neuropathy. Immunohistochemical analysis of CD30 expression was performed on the tissue with quantitative tissue immunohistochemistry using the Nuance system (PerkinElmer, Waltham, MA), as described previously [18, 19].

Statistical analysis

The time to improvement or resolution of PN was analyzed by the Kaplan–Meier method. The association between the development of PN and (a) the cumulative dose of BV, and (b) whether the patient had treatments within the previous year, was evaluated by logistic regression, and odds ratios are reported. A Spearman correlation was used to test the relationship between CTCAE and TNSc scores. All statistical analyses were conducted using the SAS statistical software package, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Patient characteristics

Table 1 shows baseline clinical characteristics of the 36 patients enrolled in the study. The median age was 64.5 (range 20–87), with 23 (64%) males. Most patients (75%) had no baseline PN prior to the trial. Of the nine patients with baseline PN, five were documented with diabetes, three of whom had prior treatments within 1 year, including interferon, methotrexate, and pralatrexate. Two of the patients with baseline PN without diabetes had prior treatment with methotrexate within the past year. Seven of the patients with baseline PN developed worsening PN to grade 2 during treatment, and three of the seven had subsequent improvement to grade 1.

Clinical presentation of neuropathy

Patients generally reported distal numbness, though the symptoms were often subtle. Functional complaints, including tactile changes in the hands and changes to gait, were usually more prominent. Distal vibratory sensory loss was almost always the most prominent finding on physical examination.

Time course of peripheral neuropathy

We found that patients with grade 1 or no PN described symptoms and impairments that were generally mild, which we labeled “Not Clinically Significant.” Patients with grade 2 or higher PN described impairments of function that were notable, which we labeled “Clinically Significant.”

Twenty-five (69%) of 36 patients developed worsening PN with 7 (28%) grade 1, 17 (68%) grade 2, and 1 (4%) grade 4 (Fig. 1a). Median time-to-onset for any PN was 15 weeks (range 0.4–48) after the first dose, and the median time to onset of grade 2 PN was 20.8 weeks (range 6–48). Twelve of the 18 patients who developed Clinically Significant PN worsened after the last BV dose. One patient had grade 4 PN, thought to be an acute onset of axonal neuropathy by Wallerian degeneration. This patient ultimately died of pneumonia after declining aggressive therapy for pneumonia and relapsed MF. Per the trial protocol, 12 patients had dose reduction or delay because of grade 2 PN, and seven patients had end of treatment because of PN.

Thirteen (52%) of 25 patients showed overall improvement or resolution of PN by the end of follow-up period (Fig. 1a). By Kaplan–Meier calculation, the median time to improvement or resolution of any grade of PN was 53 weeks from the last BV dose (Fig. 1b). At 12 months, 47% of these patients had improvement, and at 24 months, 66% had improvement. For patients who developed Clinically Significant PN, the median time to improvement or resolution by Kaplan–Meier calculation was 30 weeks (Fig. 1c). At 12 months, 51% of these patients had improvement, and at 24 months, 74% had improvement. Three patients with Clinically Significant PN had resolution prior to their last dose.

Using the total neuropathy score clinical version

The TNSc values significantly correlated with CTCAE grade, with a Spearman correlation coefficient of 0.68 ($p < 0.001$) (Fig. 2a). Eleven patients were monitored with both CTCAE grade and the TNSc from the start of treatment (Fig. 2b). There was an overall gradual increase in CTCAE grade and TNSc with cumulative doses of BV, with grade 2 PN occurring around a TNSc of 6–12.

Factors with increased likelihood of clinically significant PN

As shown in Table 2, factors including age, sex, and clinical stage were not significantly different between patients with Clinically Significant and Not Clinically Significant PN. Interestingly, the total dose of BV and whether the patient had treatments within the previous year varied significantly between the two groups. By logistic regression, for each 100 mg increase in BV total dose, the likelihood of developing Clinically Significant PN increased by 23% (95% CI 4–46%). A similar analysis showed that, for patients with treatments in the prior year, the likelihood of developing Clinically Significant PN increased 13-fold (95% CI 2.59–65.20).

Electromyography and nerve conduction studies

A review of 5 EMG/NCS obtained to evaluate symptoms in four patients demonstrates a general pattern of axonal damage. The first patient was evaluated for rapid onset of

numbness and weakness and had grade 4 PN. EMG/NCS was consistent with a severe, length-dependent axonopathy. Two EMG/NCS separated in time were performed on a second patient with grade 2 PN and numbness of the bilateral feet. The results demonstrated a progressive, diffuse demyelinating neuropathy, and we speculate about a possible underlying hereditary neuropathy. A third patient, with grade 1 PN, underwent EMG/NCS for buttock and shoulder pain, which revealed patchy axonal findings. The fourth patient had foot drop and EMG/NCS showed a length-dependent, axonal pattern, similar to the first patient's.

Nerve biopsy for CD30 staining

The patient with grade 4 PN underwent a nerve biopsy with negative CD30 staining, as shown in Fig. 3. Quantitative tissue immunohistochemistry did not highlight any cells within the nerve expressing CD30.

Discussion

Our data support the finding that CIPN reported after BV treatment in our relapsed/refractory MF/SS subset is more common than that reported in HL and sALCL patients. In our cohort, 69% of patients treated with BV for MF/SS developed PN. As previously noted, in a similar trial of BV in patients with CD30 + cutaneous T cell lymphoma and lymphomatoid papulosis, 67% of patients developed PN [17]. Because BV and other current available therapies for MF/SS are non-curative, characterizing such toxicities in this population is of particular importance.

The literature on long-term outcomes of CIPN is limited in that cohorts are frequently not followed to resolution. Accurate descriptions of long-term outcomes remain an important area for future study [20]. Platinum-induced CIPN is thought to improve or resolve by 1 year, and CIPN associated with taxanes is reported to generally resolve within 3 months [20]. The median duration of CIPN following cessation of vincristine has been reported as 3–5 months [21]. As discussed earlier, patients with CIPN attributed to BV for HL and sALCL had median times to improvement ranging from 9.9–13.2 weeks [15, 16].

CIPN following BV treatment for MF/SS appears to have a longer course. For patients in our cohort, the median time to improvement or resolution by Kaplan–Meier calculation of PN was 53 weeks from the last BV dose. The similar, concurrent protocol of BV in CD30 + cutaneous T cell lymphoma and lymphomatoid papulosis found a median time to resolution of 41.5 weeks [17]. The distinct statistical methods between these calculations likely accounts for much of the difference between the results. For patients with Clinically Significant PN in our cohort, the median time to improvement by Kaplan–Meier calculation was not increased, measured at 30 weeks. Sixty-six percent of our patients with any grade of PN showed improvement by 24 months, and 74% of patients with Clinically Significant PN had improvement over the same time period. This experience is consistent with a report of patients treated with a combination of platinum and taxane, in which almost a quarter of patients had residual CIPN, with a median follow-up of 48 months [22].

Given the increased incidence and prolonged CIPN duration detailed above for BV in MF/SS, classic PN comorbidities, including alcohol consumption and diabetes mellitus, should be more thoroughly evaluated in future studies within this population. Patients with MF/SS have a higher median age and a more chronic disease course than other groups in which BV has been previously studied. With the higher likelihood of classic PN comorbidities, we speculate about a significant contribution to the burden of CIPN from these potential factors.

The etiology of BV-related CIPN remains unclear. Its clinical presentation is that of a large fiber, sensory predominant syndrome. Our data demonstrate that Clinically Significant PN was more likely with higher BV doses, with the likelihood of Clinically Significant PN increasing by 23% (95% CI 4–46%) for each 100 mg increase in total dose. The close clinical relationship to cumulative dose, significant component of vibratory loss, and associated gait changes raises the possibility of a pathogenesis in the dorsal root ganglion akin to platinum-based agents [2]. Some evidence from EMG/NCS implies an axonal pathology, similar to that proposed for vincristine and taxanes [2]. A nerve biopsy in the most severely affected patient did not reveal a CD30-mediated mechanism of injury, but BV may have an axonal pathology mediated by free MMAE. Bystander killing of tumor cells by free MMAE is a known additional mechanism of action of the drug [12].

In our experience, the CTCAE grading system for CIPN lacks granularity, relies heavily on patient report, and often over-emphasizes “positive symptoms,” such as tingling and pain, while missing “negative” symptoms, including loss of sensation or balance trouble. We adopted the TNSc as a more sensitive instrument to capture the development of PN. The most prominent clinical exam finding in this study was almost always vibratory sensory loss, which is captured in this score and often missed otherwise. The TNSc significantly correlated with CTCAE grades, and a TNSc approaching 6–12 translated to grade 2 PN. Of note, neither of these scores is linear, and important components of both include subjective patient reporting.

The relationship between the TNSc and CTCAE should be further explored. One method would be to include both scores in a prospectively designed trial, such that one arm incorporated the TNSc for dose modification and the other used the CTCAE grade. An initial TNSc threshold might be considered at a score of 6–9. For the significant subset of MF/SS patients who have a poor prognosis, the additional resolution from the TNSc may improve risk-stratification for treatment decisions. Moreover, the optimal role and use of BV remains to be established in the CTCL population, as greater dose exposure (longer therapy) has not been shown to correlate with improved clinical outcome. Thus, modifications to the treatment schedule should also be considered, such as comparing continuous therapy to short bursts of therapy.

The TNSc has already been demonstrated more sensitive to changes in CIPN severity [7]. It follows that any such improvements provided by the TNSc may allow earlier detection of CIPN from BV before it becomes Clinically Significant by facilitating timely dose reductions or treatment changes. These refined methods may aid in establishing the optimal

use of BV that carefully balances the risk and benefit profiles in the MF/SS or other CTCL population, currently under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Development and resolution of PN. **a** Swimmer's plot illustrating the time course of the 25 patients who developed PN. Kaplan-Meier illustrations of the resolution or improvement of **b** any PN, and **c** clinically significant (Gr 2) PN

Fig. 2.

Comparison of CTCAE grade with TNSc. **a** The correlation between CTCAE grade and TNSc is statistically significant, the Spearman correlation coefficient is 0.68 ($p < 0.001$). **b** Time course of peripheral neuropathy in 11 patients from the start of trial by TNSc and CTCAE grade

Fig. 3.

a Photomicrograph of sural nerve in longitudinal section demonstrating a mild loss of myelinated fibers and no inflammatory infiltrate. Hematoxylin and eosin. *Bar* 100 microns.

b Anti-CD30 immunohistochemistry shows no positivity. *Bar* 100 microns

Table 1

Patient baseline demographics and clinical characteristics, n = 36

Median age, years (range)	64.5 (20–87)
Gender, n (%)	
Men	23 (64)
Women	13 (36)
Clinical stage	
IB	5 (14)
IIB	20 (56)
IV/SS	11 (31)
Baseline PN, n (%)	9 (25)
Unknown	2 (6)
Grade 0	27 (75)
Grade 1	6 (17)
Grade 2	1 (3)
Grade 3	0 (0)
Grade 4	0 (0)

PN peripheral neuropathy, *SS* Sézary syndrome

Table 2

Patient characteristic variation with clinical significance of peripheral neuropathy

	Not clinically significant	Clinically significant	p value
Median age, years (range)	64.5 (20–87)	62.5 (38–82)	0.4961
Gender, n			
Men	9	14	0.1642
Clinical stage			0.3495
IB	1	4	
IIB	10	10	
IV	7	4	
SS	2	2	
Treatment within the prior year	3	13	0.002
Median total dose, mg (range)	540 (84–1904)	1127 (298–1581)	0.0048

PN peripheral neuropathyNot clinically significant = no or CTCAE grade 1 *PN*, clinically significant = CTCAE grade 2 *PN* or higher