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- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

1.0 ABSTRACT

Study Title

Brentuximab vedotin administration registry and outcomes study in Polish CTCL patients.

Keywords

Brentuximab vedotin, CTCL, neuropathy, sORR4 (objective skin response lasting 4 months or longer), progression-free survival (PFS).

Background and Rationale

CTCL, with the major and most common subtypes: mycosis fungoides and primary cutaneous anaplastic large cell lymphoma (pcALCL) can be associated with a high symptom burden. Prognosis is extremely variable depending on the subtype and the stage of disease. Treatment patterns are variable, with some agents not being reimbursed and others used by selected specialists only. Furthermore, patients with advanced stages of CTCL might be either refractory or intolerant to treatment with methotrexate, interferon or bexarotene.

At the time of designing the study, it was believed that brentuximab vedotin might significantly modify the CTCL management paradigm in Poland. The drug was available for the treatment of mycosis fungoides and pcALCL in the scope of a Drug Program, for a precisely defined group of patients.

The aim of the study was to assess brentuximab vedotin effectiveness and safety, as well as to describe characteristics of patients with mycosis fungoides and pcALCL who were treated in the scope of the Drug Program. Furthermore, treatment patterns were investigated.

Research Question(s) and Objective(s)

Primary objectives

1. To determine the objective skin response (measured by mSWAT) which lasted 4 months or longer (sORR4)
2. To measure best overall skin response rate, (BsORR) measured by mSWAT

Secondary objectives

1. To determine PFS according to the progression confirmed by the physician
2. Clinical and demographic characteristics of CTCL patients (disease subtypes – MF, pcALCL; skin symptoms, time from symptoms presentation to diagnosis)
3. To determine duration of response (DOR) in patients who completed treatment. Duration was measured 6 months after end of the treatment in patients who achieved objective response (OR)

Study Design

The study was a prospective, non-interventional, single arm, open label, multi-center study with consecutive patients aged ≥ 18 with cutaneous T-cell lymphoma meeting inclusion criteria to the Drug Program, enrolled between October 2020 and April 2024.

Setting

During the treatment period, 9 visits were scheduled in line with the Drug Program visits (week 0, week 6, week 12, week 18, week 24, week 30, week 36, week 42 and week 48). Additionally, one

follow-up visit, 6 months post treatment cessation was scheduled. Follow-up was conducted in patients who completed all 16 cycles of treatment with response/remission or patients who achieved response/remission; however, their treatment was stopped due to intolerance.

Study Population: Subjects and Study Size, Including Dropouts

Study subjects were patients with mycosis fungoides or primary cutaneous anaplastic large cell, with the presence of the CD30+ antigen in the lymphoma tissue. Eligible patients were male or female subjects, aged ≥ 18 years, included in the CTCL Drug Program between October 2020 and April 2024 who received treatment according to the Adcetris (brentuximab vedotin) SmPC. There was no predefined sample size, and all data entered in the study database were considered for the analysis.

Data Sources and Data Collection

Patients' data were collected during routine clinical care. Patients' medical records were the source of all data recorded in the eCRFs. Therefore, only data available and already existing in patients' files were recorded.

Data Analysis

Variables (Exposures, Outcomes and/or Endpoints)

The main outcomes of the study were:

1. Proportion of subjects with objective skin response (measured by mSWAT) which lasted 4 months or longer (ORR4) as determined by the physician. Objective response was defined as either Complete or Partial response
2. Proportion of subjects with either: Complete Response (CR), Partial response (PR), Stable disease (SD) or Progressive disease (PD) as best response at any time between initiation and cessation of the treatment as determined by the physician (Best Overall Skin Response, measured by mSWAT - BsORR).
3. Incidence rate of adverse events and serious adverse events reported from the date of first use of brentuximab vedotin (treatment emergent adverse events; TEAE).

Secondary outcomes included:

1. Progression free survival - defined as the time from the first use of brentuximab vedotin until progressive disease (as determined by the physician, based on mSWAT assessment) or death from any cause
2. Duration of response - defined as the time between the first response (either CR or PR) and progressive disease (or death from any cause) after completing the treatment in the Drug Program.

Results (Data Analysis)

In total, 38 patients were assessed for eligibility, of whom 37 subjects were enrolled. 18 (48.5%) subjects completed the study. The reasons for early termination included no response to treatment in 8 (38.1%) patients and adverse events in 5 (23.8%) of patients. The overall median age of study subjects was 59.5 (range: 28.0 - 81.0) years in patients with mycosis fungoides and 71.0 (range: 40.0 - 73.0) years in the pcALCL cohort. 22 (59.5%) patients were males, 15 (40.5%) patients were females. According to the EORTC TNMB classification, the majority of mycosis fungoides patients were diagnosed in Stage IIB (47.1%, N = 16) or higher (IIIA: 11.8%, N = 4; IIIB and

IVA1: 5.9%, N = 2 each; IVA2: 11.8%, N = 4; IVB: 2.9%, N = 1). Only 5.9% (N = 2) and 8.8% (N = 3) of patients were in stage IIA and IB, respectively. pcALCL patients were diagnosed in Stage IIIA or higher (IIIB and IVA2), 33.3% (N = 1) each. According to the ECOG scale, 58.8% (N = 20) of mycosis fungoides patients were in Grade 1 or Grade 2 (11.8%, N = 4), the remaining subjects (29.4%, N = 10) were in Grade 0. Of pcALCL patients, 2 (66.7%) were in Grade 1, 1 patient (33.3%) was in Grade 0. Median baseline mSWAT score of study subjects was 81.0 (range 17.0 - 266.0) in patients with mycosis fungoides and 49.0 (range 24.0 - 94.0) in patients with pcALCL. Skin manifestations and subjective symptoms at baseline in patients with mycosis fungoides included mostly pruritus (79.%, N = 27), pain (41.2%, N = 14), skin coloring (41.2%, N = 14), erosion (35.3%, N = 12), erythroderma (35.3%, N = 12), baldness (32.4%, N = 11), ulcerations (29.4%, N = 10), hyperkeratosis of hands and feet (26.5%, N = 9 each), nail dystrophy (23.5%, N = 8), discoloration (14.7%, N = 5); of 3 pcALCL patients enrolled, all (100.0%) experienced pruritus, 2 patients (66.7%) experienced: pain, baldness, erosion, skin coloring and discoloration, one patient (33.3%) experienced ulcerations. The median time from diagnosis to inclusion in the study reached 4.3 (range: 0.1 - 19.2) years in mycosis fungoides and 0.5 (0.5 - 2.9) years in pcALCL. The median time from progression to inclusion in the study in mycosis fungoides and pcALCL was 0.2 (range 0.0 - 1.9) years and 0.1 (0.0 - 0.1) years, respectively. In patients with mycosis fungoides, the median no. of therapy lines prior to study enrollment was 3.0 (range: 1.0 - 11.0), with half of patients treated with 3 or 4 previous therapy lines (31.2%, N = 10 and 25.0%, N = 8, respectively). The treatment modalities included systemic therapy (85.3%, N = 29), skin-directed therapy (61.8%, N = 21) and radiotherapy (32.4%, N = 11). In pcALCL, the median no. of previous therapies was 3.0 (range: 1.0 - 4.0); in all 3 (100.0%) patients, systemic therapy was applied, skin-directed and radiotherapy were applied in 1 (33.3%) patient each.

The median number of brentuximab vedotin infusions per patient was 13.0 (range 1.0 - 17.0), subjects with mycosis fungoides received a slightly higher median of 13.5 (range 1.0 - 17.0) infusions than pcALCL patients (8.0, range (6.0 - 11.0). Most patients received their first infusion in a hospital (73.0%, N = 27), with the remaining doses administered in an ambulatory setting (27.0%, N = 10). Over the course of the study, the proportion of hospital-based infusions gradually decreased, while one-day care infusions became more frequent.

Overall, skin response to brentuximab vedotin was recorded in 55.9% (95% CI: 38.1%; 72.4%, N = 19) patients with mycosis fungoides and all 3 (100%) patients with pcALCL. Complete response was achieved in 5.9% (95% CI: 1.0%; 21.1%) patients, all with mycosis fungoides. 50% (N = 17) of patients with mycosis fungoides and all (N = 3) patients with pcALCL achieved partial response. The median time to achieve the first response reached 130.0 (range: 22.0 - 519.0) days in mycosis fungoides and 50.0 (range: 40.0 - 54.0) days in pcALCL. The objective skin response lasting at least 4 months (ORR4) was observed in 38.2% (95% CI: 22.7%; 56.4%, N = 13) patients with mycosis fungoides and 66.7% (95% CI: 12.5%; 98.2%, N = 2) patients with pcALCL.

In mycosis fungoides patients who achieved the objective (i.e. either complete or partial) response to brentuximab vedotin and completed the treatment in the scope of the Drug Program, the median duration of response in the Kaplan-Meier estimation reached 434 [95% CI: 434; NA] days. In 3 pcALCL patients, the median duration of response reached 176 [95% CI: 122; NA] days. Progression-free survival, analyzed in mycosis fungoides only, in the Kaplan-Meier estimation reached 518 (95% CI: 330; NA) days.

The most frequent adverse events were 22 incidents (20.6% of all adverse events) of neuropathy in 19 (51.4% of all) patients. Of these, 21 incidents were considered related to brentuximab vedotin use (28.4% of all events attributed to the drug). 14 neuropathy incidents recorded in 12 (32.4% of

all) patients were considered serious (22.6% of all adverse events), of these, all 14 were considered related to brentuximab vedotin (26.9% of all serious adverse events attributed to the drug). The median time to first neuropathy occurrence was 141.0 (range 63.0 - 305.0) days. In 21.1% of patients who experienced neuropathy, resolution of neuropathy was observed within the median of 15.5 weeks; in 10.5% of patients who experienced neuropathy, an improvement in the severity by ≥1 grade was recorded. Grade 1 or 2 neuropathy was recorded at the end of the study in 31.6% and 21.1%, respectively, of all patients who experienced neuropathy. Grade 3 or 4 neuropathy was recorded at the end of the study in 15.8% and 10.5% of patients who experienced neuropathy, respectively. Other frequent adverse events included 8 (7.5% of all adverse events) incidents of neutropenia, reported in 3 (8.1% of all) patients. Of these, 7 (9.5%) of the incidents of neutropenia were attributed to brentuximab vedotin (9.5% of all adverse events attributed to the drug). 7 (13.5%) incidents of neutropenia in 2 (5.4%) patients were assessed as serious (11.3% of all serious adverse events).

Discussion

Prolonged overall response and progression-free survival are meaningful primary end points for all patients with mycosis fungoides. Only a handful of trials employed ORR4 as the study endpoint. The proportion of patients achieving ORR4 in the study reached 40.5%, with 38.5% of patients with mycosis fungoides and 66.7% in pcALCL. Available literature presents distinct data ranging from 42% to 56.3% regarding the results of skin response as measured by the reduction of mSWAT score. The direct comparison across studies is problematic due to non-homogenous study populations which included variable cohorts of patients with mycosis fungoides, Sézary syndrome and pcALCL. Additionally, due to the low incidence of CTCL, real-world clinical data on brentuximab vedotin are limited, with small groups of patients enrolled in the studies. There are substantial differences in the study population characteristics which need to be taken into account when addressing the observations in the current study and the literature data on brentuximab vedotin efficacy in CTCL. The differences between the ORR4 results in the current study and ALCANZA study, as well as other studies are partially explained by the disease stage. In a retrospective multicentric study including nine EORTC centers that specialized in CTCL in eight countries ORR4 presented a significant association with the disease stage; more responders/ORR4 belonged to stages IIB, IIIA and IIIB, whereas the benefit of brentuximab vedotin in terms of ORR4 in ALCANZA study was observed across all stages of mycosis fungoides. In the current study, the ORR4 results were not stratified by the disease stage. Similarly, in a Phase II clinical trial the ORRs were 54%, 79%, and 100% in the low, medium, and high CD30 expression groups, whereas in another study, the ORRs among mycosis fungoides/Sézary syndrome patients with low (< 10%), medium (10%–50%), and high (> 50%) CD30 expression showed no significant

differences (50%, 58%, and 50%, respectively). In the current study, patients were not stratified by CD30 expression, the only condition of the Drug Program was the presence of CD30 antigen.

It might be hypothesized that the differences in the response rates between the pcALCL and mycosis fungoides/Sézary syndrome groups observed in the current study and the literature might potentially reflect the better clinical behavior and prognosis of pcALCL, as well as the superior efficacy of brentuximab vedotin in this type of lymphoma. According to the literature, pcALCL patients respond more quickly to treatment with brentuximab vedotin. However, the number of patients with pcALCL in the study was small (only 3 patients), therefore any such observation needs to be considered with caution, its confirmation warrants further studies with bigger pcALCL cohorts.

The median duration of response (DOR) in the 6-month follow-up in patients who completed the treatment reached 434 days in mycosis fungoides and 176 days in pcALCL. Progression-free survival (PFS) according to the Kaplan-Meier in mycosis fungoides reached 518 days. Similarly to the response rates, the available literature data shows variable response duration and PFS. In ALCANZA study, with a median follow-up of 36.8 months, the median PFS per IRF calculated with Kaplan-Meier method in the brentuximab vedotin arm was 16.7 months. In patients with mycosis fungoides, median PFS per IRF was 16.1 months, whereas in pcALCL patients it was 27.5 months. In the retrospective multicentric study involving sites - members of the EORTC Cutaneous Lymphomas Task Force, the median PFS in mycosis fungoides patients reached 8.4 months, it was longer in stages IIB, IIIA and IIIB (median 10.0 months) than in stages IVA1, IVA2 and IVB (median 3.0 months). According to the prognostic model for advanced mycosis fungoides/Sézary syndrome, Stage IV is an independent prognostic indicator associated with poorer survival.

Irrespective of the differences in the response to brentuximab vedotin in CTCL in the studies, the ORR4, duration of response and progression-free survival of several months in the current study are the important observations for patients with advanced disease as they reinforce the available data on the efficacy of brentuximab vedotin in CTCL, especially taking into account the differences in ORR4 and PFS in the brentuximab vedotin and bexarotene or methotrexate cohorts in ALCANZA study. Since the sequential use of systemic agents in the management of patients with advanced-stage disease is usually required, these several months in patients who responded to the treatment and showed the clinically meaningful reduction in skin symptoms may prolong the time to further lines of the toxic therapy. The real-world observations of the prolonged PFS, as well as high response rates in CTCL patients in whom brentuximab vedotin was used already as 2nd line of therapy in patients with mycosis fungoides and pcALCL in the real-world retrospective, physician panel–based chart review give rise to considering early introduction of brentuximab vedotin as the viable option in the CTCL therapy sequence. Possible future studies with the use of brentuximab vedotin in the earlier lines of the CTCL treatment may aid in understanding the impact of the treatment sequence on the clinical outcomes in CTCL.

Neuropathy was reported in 51.4% of patients in the study, the median time to first neuropathy occurrence was 141 days which, given the dosing frequency, translates to 6-7 infusions. Resolution of neuropathy was observed in 21% of patients within the median of 15.5 weeks. In 10% of patients, an improvement in the neuropathy severity by ≥1 grade was recorded. Half of patients continued with grade 1 or 2 neuropathy symptoms. In ALCANZA study, 67% of patients in the brentuximab vedotin arm developed neuropathy. In most patients, the maximum grade of neuropathy was grade 1 (41%) or 2 (45%). By the final data cutoff, 86% of patients with any grade peripheral neuropathy had complete resolution (59%) or improvement to grade 1 or 2 (27%), the

median time to neuropathy improvement was 15 weeks, to resolution 33 weeks. An association between development of neuropathy and number of brentuximab vedotin infusions and cumulative dose was reported. Taking into account the results of the study in patients with mycosis fungoides treated with the reduced dose of brentuximab vedotin (0.9 mg/kg), in which a lower rate of grade ≥2 neuropathy than reported with full dose therapy in ALCANZA study was reported, future studies with larger cohorts (in this study, only 19 patients were enrolled) in CTCL may be needed to investigate the balance of efficacy and safety of brentuximab vedotin in CTCL administered at the reduced dose.

The rate of fatal events in the current study did not differ from the data available in the literature. It reached 24% of patients with most of the deaths related to disease progression. In ALCANZA study, 24% death rate in the brentuximab vedotin group was observed.

The results of the current study corroborate the available data on brentuximab vedotin efficacy in the treatment of CTCL in CD30-positive patients in the real-world setting. Despite the occurrence of well-known and common brentuximab vedotin toxicity - peripheral neuropathy, the study results indicate that it is well tolerated in clinical applications. Future research should involve larger cohorts and extended follow-up to better assess the long-term efficacy and safety of brentuximab vedotin in CTCL.

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