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ABSTRACT

Background: Brentuximab vedotin (BV) has been approved for CD30-expressing cutaneous T-cell lymphoma (CTCL) after at least one previous systemic treatment. However, real clinical practice is still limited.

Objectives: To evaluate the response and tolerance of BV in a cohort of patients with CTCL.

Methods: We analyzed CTCL patients treated with BV from the Spanish Primary Cutaneous Lymphoma Registry (RELCP).

Results: Sixty-seven patients were included. There were 26 females and the mean age at diagnosis was 59 years. Forty-eight were mycosis fungoides (MF), 7 Sézary syndrome (SS)and 12 CD30+ lymphoproliferative disorders (CD30 LPD). Mean follow-up was 18 months. Thirty patients (45%) showed at least 10% of CD30+ cells among the total lymphocytic infiltrate. The median number of BV infusions received was 7. The overall response rate (ORR) was 67% (63% in MF, 71% in SS and 84% in CD30 LPD). Ten of 14 patients with folliculotropic MF (FMF) achieved complete or partial response (ORR 71%). The median time to response was 2.8 months. During follow-up, 36 cases (54%) experienced cutaneous relapse or progression. The median progression free survival (PFS) was 10.3 months. The most frequent adverse event was peripheral neuropathy (PN) (57%), in most patients (85%), grade 1 or 2.

Conclusions: These results confirm the efficacy and safety of BV in patients with advanced-stage MF, and CD30 LPD. In addition, patients with FMF and SS also showed a favorable response. Our data suggest that BV retreatment is effective in a proportion of cases.

INTRODUCTION

Brentuximab vedotin (BV), a humanized anti-CD30 antibody conjugated with the antimitotic agent monomethyl-auristatin E, has recently been approved for the treatment of CD30 expressing cutaneous T-cell lymphomas (CTCL), after a previous systemic therapy[1-3]. Due to the low frequency of these lymphomas, there is limited real clinical practice on the use of BV in this setting. In fact, there are still important issues to be addressed, as its efficacy in the mycosis fungoides (MF) variants and Sézary syndrome (SS), its effectiveness in retreatment and the management of the peripheral neuropathy frequently associated with its use.

The aim of this study is to evaluate the clinical response and tolerance of BV in a cohort of patients with CTCL from the Spanish Primary Cutaneous Lymphoma Registry (RELCP).

MATERIALS AND METHODS

Patient selection

The RELCP is an ongoing prospective registry of patients with primary cutaneous lymphoma (PCL) in Spain. Participating centers prospectively collected data from all consecutive patients with PCL, including diagnosis, therapies, and updated status. For this study, we analyzed all patients with CTCL treated with BV from 01/10/2018 to 02/10/2021. One cycle of BV typically involves 1.8mg/Kg being administered intravenously once every 3 weeks. The study was approved by the Ethics Committee (Hospital Universitari Bellvitge, in Barcelona, LIN-BRE-2021-01).

Patients were classified according to the World Health Organization (WHO)-European Organization of Research and Treatment of Cancer (EORTC) classification criteria[4]. TNM stage was defined according to the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the EORTC[5,6].

Response criteria and end points

Response to treatment was evaluated according to the following standard definitions: complete remission (CR) is defined as no clinical lymphoma lesions; partial remission (PR), clearance of at least 50% of skin lesions from baseline; stable disease (SD), from

25% to <50% decrease of skin lesions; and progressive disease (PD), ≥25% increase in skin disease from baseline or detection of new lesions after CR is achieved. In SS cases, blood and global responses were evaluated following the criteria proposed by ISCL/EORTC[7].

The endpoints were considered as follow[7]: overall response rate (ORR), percentage of patients achieving CR or PR; progression free survival (PFS), was defined as the time elapsed from first objective response to the relapse/progression or death because of any cause (in patients with disease progression) or until last control (in patients without relapse/progression).

Safety

Patients were monitored for adverse events (AEs) per routine clinical practice. Peripheral neuropathy (PN) was graded as follows according to the WHO rating scale: grade 1 (mild paresthesia and/or decreased tendon reflexes), grade 2 (moderate paresthesia and/or mild weakness), grade 3 (severe paresthesia limiting daily life common activities), grade 4 (life-threatening consequences, urgent intervention indicated).

Statistical analysis

We performed a descriptive analysis presenting medians or means and associated distribution measures, depending on distribution symmetry. Categorical variables were expressed as absolute numbers and percentages. Differences between main parameters and type of lymphoma were compared using parametric or non-parametric hypothesis tests as appropriate.

RESULTS

Sixty-seven patients were included. The patient's characteristics, clinical responses and adverse events are summarized in Table 1. There were 26 females and the mean age at diagnosis was 59 years [range, 24-92]. Forty-eight were MF (14 of them folliculotropic MF (FMF), 7 SS and 12 CD30+ lymphoproliferative disorders (CD30 LPD), including 10 primary cutaneous anaplastic large-cell lymphomas (pcALCL) and 2 lymphomatoid papulosis (LyP). The mean follow-up was 18 months. The mean time

between diagnosis and BV therapy was 5.7 years with a mean number of previous systemic treatments of 4 [range, 1-11]. Thirty patients (45%) showed at least 10% of CD30 positive cells among the total lymphocytic infiltrate in skin biopsies. The median number of BV infusions received was 7 [range, 1-20].

Considering the whole group, ORR was 67% (63% in MF, 71% in SS and 84% in CD30 LPD). Twenty-five patients (37%) achieved a CR, 20 (30%) showed a PR, 15 (22%) a SD and 7 (11%) had PD. ORR according to stages were as follow: in the group of MF/SS; stage IIB, 26/35 (74%), stage III, 0/5 (0%) and stage IV, 9/15 (60%); In SS patients 2/7 had CR in skin and blood and 3/7 showed PR in skin and blood. In the group of CD30 LPD; stage T1, 1/1 (100%), T2, 3/4 (75%), T3, 6/7 (86%). According to CD30 expression, ORR was 58% in patients with < 10% and 70% in those with > 10%. In patients with FMF, ORR was 71% with 50% (7/14) achieving CR.

The median time to response was 2.8 months (p25:2.0, p75:4.8) and the median number of BV cycles to achieve the maximum response was 7 (p25:4, p75:12). The median PFS for the whole group was 10.3 months and for the CD30 LPD group was 23.2 months. This difference did not reach statistical significance. (Fig 1). Median PFS in patients with < 10% of CD30 expression was 8.2 months and 10.3 months for those with > 10% CD30 expression. During follow-up, 36cases (54%) experienced cutaneous relapse or progression. Thirteen of them were treated again with BV, with a median of 3 additional infusions. The ORR to retreatment was 54% (23% achieved CR). Eight patients (5MF, 2SS and 1 CD30 LPD) received a hematopoietic stem cell transplantation (HSCT) after treatment with BV. Five of them remained in CR at the end of follow-up. In 3 patients a relapse of the disease was observed. One of these patients responded again to BV treatment. One patient died because of disease progression.

The most frequent adverse event was PN, observed in 38/67 patients (57%) with 34 cases showing grade 1-2 and 4 cases having grade 3 neuropathy. The median number of BV infusions before the first symptom of PN appeared was 4. Patients developing PN received a significantly higher number of BV infusions (mean 9.6) when compared with those without neuropathic symptoms (mean 5.9) ($p=0.003$, t-test). Dose adjustment was needed in 12 patients and 4 discontinued BV due to

PN. There was no association between PN and type of lymphoma (p=0.83, Fisher) or percentage of CD30 expression (p=0.37, Fisher).

In 27 patients (40%) other adverse events were observed during the treatment with BV. Thirteen of them were considered as serious adverse events and are summarized in Table 1. One patient died due to sepsis.

After a median follow-up of 18 months, 16 (24%) patients were free of cutaneous lymphoma lesions and 37 (55%) cases showed active disease. Eleven (16%) patients died due to disease progression.

DISCUSSION

CTCL are a heterogeneous group of extranodal non-Hodgkin lymphomas with different clinical presentation and prognosis. MF, SS and CD30 LPD are the most common types, accounting for more than 70% of cases[4]. Initial stages of MF are usually well controlled with skin-directed therapies for years or decades, but advanced MF and SS are aggressive diseases with no curative treatment so far. These patients use to suffer severe pruritus, low quality of life and reduced survival due to disease progression, immunosuppression and side effects related to multiple lines of therapy.

Recently BV has been approved for the treatment of CD30-expressing CTCL patients[1-3]. In the ALCANZA study, a phase III randomized, controlled, multicentric clinical trial, BV showed a superior objective response rate when compared with physician´s choice (bexarotene or methotrexate) in patients with CD30-expressing MF or pcALCL. Moreover, a significant improvement in PFS with BV (median 16.7 months) with respect to the group with conventional therapy (3.5 months) was observed[1].

In this paper we describe the results in a series of 67 CTCL cases treated with BV from the RELCP in Spain[8]. RELPC is a prospective database including uniform information about diagnosis, treatments, and outcomes so we believe these results to represent the real practice in our country.

Considering the whole group, our results showed an ORR of 67% and a median PFS of 10.3 months. This is in contrast with the results in the ALCANZA trial showing a

223 global PFS of 16.7 months. We believe that the lower PFS could be explained by the
224 fact that whereas in the ALCANZA, a proportion of MF cases had IA-IB initial stages, in
225 our cohort all MF patients had advanced stages (IIB-IVA2). As the ORR in these cases
226 was 63%, our data strength the notion that BV is an effective treatment in patients
227 with tumoral or more advanced stages of MF[1].

228 In our hands, the clinical response does not seem to be influenced by the level of CD30
229 expression by the lymphoma cells. These data are consistent with recent studies and
230 suggests that BV may be a therapeutic option even in those cases with low or even
231 no expression of CD30[1,9-12]. However, median PFS was slightly longer in patients with
232 higher expression of CD30. This observation agrees with the results coming from
233 Gosmann et al. and suggests that duration of response can be longer in patients with
234 high CD 30 expression[13].

235 In addition, we observed a high rate of CR in patients with FMF (Fig. 2a-d), a variant of
236 MF that due to the deep location of the infiltrate, is considered particularly resistant to
237 skin-directed therapies. Although in the ALCANZA trial no specific information about
238 this MF variant was given[1], our results agree with recent observations and suggest that
239 BV may be an effective option in FMF[9,14].

240 Looking at the CD30 LPD, in this study we included 10 pcALCL and
241 2 LyP. Eight of the 10 pcALCL patients had advanced stages with extracutaneous
242 involvement. The ORR in this setting was 84% with a 42% of CR rate. Most patients in
243 this group showed a quick and durable response to BV with a median PFS of 23.2
244 months. Although not statistically significant, the differences in PFS in the CD30 LPD
245 group in comparison with the total group are striking and may reflect the better
246 behavior and clinical prognosis of this group of lymphomas. Although only two cases
247 of LyP were included, both cases experimented CR to BV. In a phase II open-label
248 study, Lewis et al reported an ORR of 100% and a CR rate of 75% in patients
249 with LyP treated with BV[15]. These authors suggested that BV could be
250 an alternative treatment for patients with severe forms, resistant to conventional
251 therapy. We believe that more studies are needed to determine
252 the right BV regime in LyP, a process characterized by a chronic and indolent
253 course, with the aim of minimizing the risks of PN.

Regarding the SS, there were 7 patients in our study showing an ORR of 71%, including 2 CR. Given that patients with SS were not included in the ALCANZA study, the indication of BV in this form of CTCL has been a matter of discussion[1]. In a recent series of 13 SS patients, an ORR of 38% was observed after 6 cycles of BV. The authors concluded that there appear to be no advantages over other forms of conventional treatment and suggested that this may be due to the lower expression of CD30 in SS[16]. These data are in contrast with those recently published by Papadavid et al. showing no differences in ORR or PFS between patients with SS and MF[9]. Although more studies focusing SS are necessary, we believe that our results agree with those of Papadavid et al. and suggest that BV may be an effective option in patients with SS.

Eight patients achieving CR after BV, underwent successful HSCT. Therefore, in selected cases BV may facilitate bridging to a successful HSCT[17,18].

Regarding BV retreatment, there is limited information so far. Engelina et al. reported a second course of BV in 2 patients with 1 PR after 2 cycles and 1 SD after 10 cycles[19]. Papadavid et al. reported 3 cases retreated with BV but information about clinical response was not given[9]. André et al. described a clinical response to BV retreatment in 2 patients with transformed MF relapsing after HSCT[18]. In our series, 13 patients received a second course of therapy showing an ORR of 54%. Although further studies are needed, our results suggest that a significant proportion of patients may achieve clinical benefits after BV retreatment.

In general, BV was well tolerated. As expected, PN was the most frequently observed AEs in our patients, affecting 57% of them. In agreement with data from the phase II and phase III clinical trials, most patients had mild to moderate symptoms and only a minority of them needed dose adjustment or treatment discontinuation[1-3]. In our series, PN was clearly related to the accumulative dose with most patients initiating symptoms after 5-6 BV infusions. Also, in agreement with recently published data from ALCANZA subanalysis, in our series no association between the PN and the type of lymphoma or level of CD30 expression was found[20]. At the end of follow-up, 2 patients presented complete resolution of PN, 2 patients had PN grade 3 and the rest of the cases continued with mild or moderate symptoms (grade 1 or 2).

In conclusion, this study represents the second largest series of CTCL patients treated with BV in real clinical practice published to date. Our results confirm the data reported in ALCANZA and previous real world published data. In addition, this study adds new information supporting the role of BV in the treatment of the advanced forms of MF, FMF, and SS. Data coming from our patients also suggests that a BV retreatment could be effective. A limitation of this study is the low number of patients in some subgroups.

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Figure legend

Figure 1. Kaplan-Meier curve for progression free survival in patients with mycosis fungoides, Sézary syndrome and CD30+ lymphoproliferative disorders treated with Brentuximab Vedotin.

Figure 2. Patients with folliculotropic mycosis fungoides treated with Brentuximab Vedotin.

Figure 2 (a). A 70-year-old patient presented with infiltrated erythematous plaques and tumors in the face,

Figure 2 (b). The patient achieved complete remission after 6 cycles of Brentuximab Vedotin.

Figure 2 (c). A 92-year-old patient presented with rapidly growing ulcerated tumor lesions in the face.

Figure 2(d). The picture shows complete response after 7 cycles of treatment.

Table legend

Table 1. Clinical characteristics, responses, and adverse events in cutaneous T-cell lymphoma patients treated with Brentuximab Vedotin.

Eliminado:
Eliminado: facial area
Eliminado: on
Eliminado: responses
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