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Experience of brentuximab vedotin in relapsed/refractory Hodgkin lymphoma and relapsed/refractory systemic anaplastic large-cell lymphoma in the Named Patient Program: Review of the literature

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Contents

Abstract

Brentuximab vedotin was made available via a Named Patient Program (NPP) to non-US/Canadian patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL) or systemic anaplastic large-cell lymphoma (sALCL) until approval in their respective countries. We re-evaluated the efficacy and safety NPP data in a pooled analysis. Through a systematic literature review, 21 NPP publications were identified describing 14 cohorts ($N = 245$). Among patients with a specified diagnosis, 207 had HL, 28 had ALCL, and one had CD30+ T-cell lymphoma (not specified). In cohorts reporting response, overall response and complete remission rates were 67% and 26%, respectively, in R/R HL, and 75% and 74%, respectively, in R/R ALCL. Incidences of grade 3/4 neurologic and hematologic toxicities were 6% and 12%, respectively; 5% of patients discontinued because of toxicity. In real-world practice, response rates and tolerability to brentuximab vedotin are similar to those reported in the two pivotal phase 2 trials in these settings.

Keywords: Anaplastic large cell lymphoma; Antibody–drug conjugate; Brentuximab vedotin; CD30; Hodgkin lymphoma; Named Patient Program

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1. Introduction

Brentuximab vedotin (ADCETRIS®; Seattle Genetics, Inc., Bothell, WA, USA, and Takeda Pharmaceuticals International Co., Cambridge, MA, USA), a CD30-targeted antibody–drug conjugate, comprises three components: the anti-CD30 antibody cAC10 [1,2]; the microtubule-disrupting agent monomethyl auristatin E (MMAE) [1,3]; and a protease-cleavable linker that covalently attaches MMAE to cAC10 [1,3,4]. In August 2011, brentuximab vedotin received accelerated approval by the US Food and Drug Administration (FDA) for the treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and for the treatment of patients with systemic anaplastic large-cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen [5]. Approval was based on demonstration of efficacy and safety in relapsed or refractory (R/R) HL post-ASCT and R/R sALCL in two pivotal phase 2 studies (HL: SG035-0003, NCT 00848926; sALCL: SG035-0004, NCT 00866047) [6,7].

The Named Patient Program (NPP; Takeda Pharmaceuticals International Co., Cambridge, MA, USA) made brentuximab vedotin available for compassionate use in patients meeting the US label criteria, in approximately 60 countries outside of the US or Canada, until the drug was approved in their respective countries. Subsequently, in 2012, the European Commission granted brentuximab vedotin conditional marketing authorization for the treatment of adult patients with R/R CD30-positive HL following ASCT or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option, and for the treatment of adult patients with R/R sALCL [8].

The aim of this review was to summarize the available published reports of NPP outcomes with brentuximab vedotin in order to examine the effectiveness and safety of brentuximab vedotin in routine practice in the context of the published phase 2 data.

2. Systematic literature review methodology

To identify NPP publications, a systematic literature review (data cut-off: December 12, 2013) was conducted (search terms: brentuximab vedotin, SGN-35, ADCETRIS) using PubMed and the 2012/13 editions of the following pre-specified congress abstract books: American Association for Cancer Research (AACR); American Society of Clinical Oncology (ASCO); American Society of Hematology (ASH); European Group for Blood and Marrow Transplantation (EBMT); European Hematology Association (EHA); European Society of Medical Oncology (ESMO); International Conference on Malignant Lymphoma (ICML); and International Symposium on Hodgkin Lymphoma (ISHL). References were reviewed manually. Case reports describing brentuximab vedotin application under compassionate use outside of the NPP were excluded.

Patient demographics, treatment histories, response, duration of response (DOR), overall survival (OS), progression-free survival (PFS), and safety data were reviewed. Objective response rates (ORR) and complete remission (CR) rates were pooled and summed by indication, i.e. HL and ALCL, for all unique NPP cohorts reporting data and for all cohorts excluding patient case studies (i.e. cohorts where $n > 1$) to minimize potential selection bias. Adverse-event (AE), dose-reduction, and treatment-discontinuation rates were calculated as a proportion of the total number of patients within the NPP cohorts reporting the specific event.

3. Analysis of NPP efficacy and safety data

3.1. Studies identified

At the data cut-off, 124 manuscripts and 115 abstracts were retrieved. Twenty-one NPP publications were identified [9–28], describing 245 patients (224 of whom were treated with brentuximab vedotin in the NPP and 21 in protocols) in 14 unique cohorts treated in seven countries (Table 1).

3.2. Patient characteristics

Among the 236 patients with a specified diagnosis, 207 had R/R HL [9,11–14,16,19–21,23,25,26,28], 28 had R/R ALCL (identified in the respective publications as ALCL, $n = 23$; sALCL, $n = 4$; cutaneous ALCL [cALCL], $n = 1$) [15,19,23,25–27], and one had R/R CD30-positive T-cell lymphoma (not specified) [19]; 10 of the patients received brentuximab vedotin outside of the NPP (Table 1).

NPP patients with R/R HL had most commonly received a median of four prior therapies. The two NPP cohorts comprising only R/R ALCL patients ($n = 3$) reported medians of 3.5 [27] and 4 [15] prior therapies. The median number of prior therapies, the frontline chemotherapies received, and the percentage of patients with primary refractory disease or who were unresponsive to their last prior therapy are presented in Table 1 for each NPP cohort where published.

Across the NPP cohorts reporting prior transplant information, 73% of patients had received ASCT or allogeneic SCT before brentuximab vedotin treatment (Table 1) [9–11,13,14,16,21,22,25,26,28]. Sixty-five percent of 187 patients (13 cohorts) had received prior ASCT [9–11,13–16,20,21,23,25–28], and 13% of 125 patients (four cohorts, all R/R HL) had undergone allogeneic SCT [9,13,26,28]. Across the R/R HL cohorts, 71% of 149 patients had received prior ASCT [9,13,14,16,20,21,23,26,28]. These data exclude 39 R/R HL patients with prior ASCT and/or allogeneic SCT, as reported by Rothe et al. [11], as further details were not published. Among R/R ALCL NPP cohorts reporting prior transplant information, no patients (two cohorts,