Italian real-life experience with brentuximab vedotin: results of a large observational study of 40 cases of relapsed/refractory systemic anaplastic large cell lymphoma

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ABSTRACT

Between November 2012 and July 2014, in accordance with national law 648/96, brentuximab vedotin was available in Italy for patients with relapsed systemic anaplastic large cell lymphoma outside a clinical trial context. A large Italian observational retrospective study was conducted on the use of brentuximab vedotin in everyday clinical practice to check whether clinical trial results are confirmed in a real-life context. The primary endpoint of this study was best response; secondary endpoints were the overall response rate at the end of the treatment, duration of response, survival and safety profile. A total of 40 heavily pretreated patients were enrolled. Best response was observed after a median of four cycles in 77.5%; globally, 47.5% patients obtained a complete response, 64.2% in the elderly subset. The overall response rate was 62.5%. At the latest follow up, 15/18 patients are still in complete remission (3 with consolidation). The progression-free survival rate at 24 months was 39.1% and the disease-free survival rate at the same time...
was 54% (median not reached). All the long-term responders were aged <30 years at first infusion. The treatment was well tolerated even in this real-life context and no deaths were linked to drug toxicity. Brentuximab vedotin induces clinical responses quite rapidly, i.e. within the first four cycles of treatment in most responders, thus enabling timely use of transplantation. For patients ineligible for transplant or for those in whom a transplant procedure failed, brentuximab vedotin may represent a feasible effective therapeutic option in everyday clinical practice.

Introduction

Approximately 40% to 65% of patients with systemic anaplastic large-cell lymphoma (ALCL) develop recurrent disease after front-line therapy.1 Historically, at relapse the disease is resistant to conventional multiagent chemotherapy regimens and there is no established standard of care. High-dose therapy and autologous stem cell transplantation (SCT) may result in long-term remission in 30% to 40% of patients, but the benefit is limited to patients with chemotherapy-sensitive disease.2-6

Given that most patients with relapsed or refractory (R/R) systemic ALCL are scheduled to undergo a highly toxic high-dose chemotherapy regimen, any strategy aimed at achieving minimal residual disease, specifically a positron emission tomography-negative status before autologous SCT, without severe toxicity would represent a major advance in the overall management of these patients. Furthermore, despite the role of autologous SCT, the outcomes remain poor in patients with primary chemorefractory disease, in whom long-term survival rarely exceeds 15-17%.1 In fact, disease recurrence still remains the principal cause of failure of autologous SCT, and early disease progression after transplantation, i.e. within 6 months of high-dose conditioning, emerges as the most important predictor of an unfavorable outcome. No standard treatment options exist for patients whose disease relapses after autologous SCT or for patients not eligible for autologous SCT. In fact, while autologous SCT may induce long-term progression-free survival in a fraction of patients, only a few are candidates for this procedure, mainly because of unsatisfactory pre-transplant cytoreduction and the substantial risk of morbidity due to the heavy load of previous therapies. In this light, optimization of the outcomes obtained with high-dose regimens and autologous SCT still remains a strategic priority, in order to offer the best chance of cure for the largest fraction of patients with R/R disease.

Brentuximab vedotin (BV) is an antibody-drug conjugate targeting CD30 which may be an excellent candidate among the newly developed agents for the treatment of R/R systemic ALCL.7 In fact, systemic ALCL is characterized by the expression of CD30. In the initial phase 1 study of BV in patients with CD30+ lymphoid diseases, the two patients with systemic ALCL both achieved a complete response.7 The favorable activity of this agent in R/R systemic ALCL was clearly documented by Pro et al. in a phase 2 study involving 58 patients: 86% obtained a response, which was a complete response in 57% of cases.9 The median progression-free survival of these patients was 13.3 months, and the median overall survival was not reached (estimated 64% at 4 years). The same relevant proportion of complete responses in this subset of patients also emerged from the data collected by Zinzani et al. regarding the BV Named Patient Program experiences across Europe.10

A high response rate is important not only in pretreated patients with a poor prognosis, but also in first-line R/R patients because a complete response obtained before transplantation is one of the stronger predictors of long-term survival.10 BV could represent an optimal therapeutic option as a bridge to either autologous or allogeneic SCT in patients achieving a suboptimal response after salvage treatment.11,12 Recent updates on the pivotal study have shown that BV can induce long-lasting complete responses in pretreated cases of systemic ALCL even without additional consolidation therapies, suggesting that BV may be curative for some patients.11,14 The pooled overall response rate and complete response rate reported for patients with R/R systemic ALCL (globally 46) in the Named Patient Program cohorts were both 69.5%11,15-17

After accelerated approval by the US Food and Drug Administration, eligible patients in Italy were granted early access to BV through a Named Patient Program. After closure of this program in 2012, BV was available in Italy for patients with R/R systemic ALCL, based on a local disposition of the Italian Drug Agency (AIFA) issued in accordance with a national law (Law 648/96: “medicinal products that are provided free of charge on the national health service”): a boundary zone in the passage from clinical trials to marketing and free use phases in which patients can be treated in any case.

On the basis of our previous exploratory study,18 a large observational retrospective study was conducted on the use of BV in R/R systemic ALCL patients in everyday clinical practice in Italy to check whether clinical trial results are confirmed in a real-life context.

Methods

An observational retrospective study was conducted among patients with systemic ALCL treated from November 2012 to July 2014 with BV in 38 Italian centers outside of clinical trials, in accordance with national law n. 648/96.19 The study was approved by the institutional board of the Policlinico S.Orsola-Malpighi Hospital in Bologna, the coordinating center of the study, and by all the ethical committees involved and registered in the Italian Registry of Observational Studies. All participants gave written informed consent in accordance with the Declaration of Helsinki. A shared database was used after the approval of all the co-investigators and variables were strictly defined to avoid bias in reporting data.19 We obtained special permission (for scientific purposes) from our ethical committee to collect data regarding patients who could not consent because they had died or been lost to follow up.

BV was administered as a 30-min infusion at the dose of 1.8 mg/kg of body weight every 3 weeks for a maximum of 16 cycles. A dose reduction to 1.2 mg/kg was recommended in the case of grade 3 toxicity and the treatment had to be interrupted in the case of grade 4 toxicity.

The primary endpoint of the study was the best response
achieved during BV therapy; secondary endpoints were the overall response rate at the end of the treatment, duration of response, overall survival, progression-free survival, disease-free survival, and the drug’s safety and tolerability. Duration of therapy was defined as the number of cycles of treatment administered. Effectiveness was also evaluated through the occurrence of long-term responders, defined as patients who had a response (complete or partial) lasting ≥12 months. Response was assessed by positron emission tomography or computed tomography scanning after cycles 4, 8, 12 and at drug discontinuation by each investigator using the International Working Group revised response criteria for malignant lymphoma. Safety and tolerability were evaluated by recording the incidence, severity, and type of any adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Overall survival was defined as the time from initiation of therapy to death from any cause and was censored at the date of the last available follow up. Progression-free survival was measured from initiation of therapy to progression, relapse, or death from any cause and was censored at the date of the last available follow up. Disease-free survival was calculated for patients who achieved a complete response from the first documentation of response to the date of relapse or death due to lymphoma or acute toxicity of treatment. Duration of response was calculated from the first objective tumor response (complete or partial) to first documentation of progression or death. Patients who were lost to follow up (n=2) were censored at the date of their last available information.

Demographics and patients’ characteristics as well as adverse events were summarized by descriptive statistics. Survival functions were estimated using the Kaplan-Meier method and compared using the log-rank test. Statistical analyses were performed with Stata 11 (StataCorp LP, TX, USA) and P values <0.05 were considered statistically significant.

Results

Of the estimated 40 patients who received BV under Law 648/96, all participated in this observational study. All had histologically confirmed CD30+ disease. Their median age at the time of being treated with BV was 47 years (range, 17-80 years) with 14 (35.0%) being considered elderly (age >60 years). There were 28 males and 12 females. Eleven (27.5%) had systemic symptoms at baseline (Table 1).

The median number of prior lymphoma-related systemic regimens was two (range, 2-10) and included high-dose chemotherapy and autologous SCT (in 13, 32.5% of the patients). Eight patients (20%) had received prior radiation therapy. Eighteen were negative for anaplastic lymphoma kinase (ALK-negative), while 22 were positive (ALK-positive). Each patient’s status after both frontline therapy and most recent therapy was recorded: 24 (60%) patients had disease that was refractory to frontline therapy and 25 patients (62.5%) had disease that was refractory to the last therapy before BV.

Response to treatment

Best response was observed after a median of four cycles of treatment in 31 (77.5%) patients: 19 (47.5%) obtained a complete response and 12 (30%) achieved a partial response. The overall response rate at the end of the treatment was 62.5% (25 patients), represented by 18 (45%) complete responses and seven (17.5%) partial responses; of the remaining patients, one had stable disease, and 14 patients showed disease progression.

The best response rate was higher in the elderly subset (>60 years): nine (64.3%) complete responses and three (21.4%) partial responses for an overall response rate of 85.7%. Four patients who were in complete remission at first restaging relapsed during further BV courses; two patients who had a partial response at first restaging converted to complete response status after the four subsequent infusions.

None of the patients who had stable or progressive disease at first restaging had an improvement in their status at the end of therapy. The median number of treatment cycles administered was eight (range, 1-16).

With a median follow up of 18 months, the global overall survival rate was 56.9% at 24 months (Figure 1) and the median had not been reached. The progression-free survival rate at 24 months was 39.1%, with the median achieved at 12.5 months (Figure 2). The disease-free survival rate at 24 months was 54% (Figure 3). Of the 19 patients who had a complete response, 4 (21%) relapsed and 15 were in continuous complete response at the last follow up with a median duration of response of 12 months (range, 9-24 months). After controlling for confounding variables, no differences were observed between ALK-negative and ALK-positive patients for any times to endpoints.

Among the patients who achieved complete responses, three were given consolidation with transplantation (1 autologous and 2 allogeneic SCT). Currently, 15 patients are

Figure 1. Overall survival.

Figure 2. Progression-free survival.
still in complete response, including the three who underwent a consolidation procedure. Of the nine elderly patients, six (66.7%) are still in continuous complete response without any consolidation procedure after a median of 14 months.

There were five long-term responders, all of whom were still in continuous complete response at the last available follow up. Of note, they were all aged <35 years at the time of starting BV therapy and only one of them had a subsequent consolidative transplant.

At the latest follow-up, 27 (67.5%) patients were alive and 13 had died. Of the 13 deaths, 11 were due to lymphoma and two were caused by complications after allogeneic SCT (1 case of respiratory failure related to graft-versus-host disease and 1 case of pneumonia).

**Safety**

All patients who received at least one BV infusion were included in the safety analysis. In general, the treatment was well tolerated and the toxicity profile was very similar to that previously published. Twelve patients had at least one toxicity. All hematologic toxicities were grade 1-2, except one case of grade 3 neutropenia. The extra-hematologic side effects were mostly represented by peripheral sensory neurological toxicity (15/20), including three cases of grade 3. The other adverse events were nausea grade 1-2 (2 patients), erythema grade 2 (2 patients), and hyposthenia grade 2 (1 patient). Neurological toxicity always reversed completely after the end of treatment. No long-term toxicity related to BV was observed during the follow-up period, even in patients later subjected to consolidation with transplantation.

**Discussion**

This retrospective, large, multicenter Italian study on 40 patients with R/R systemic ALCL treated with BV outside a clinical trial represents the largest ever reported in a real-world context. Our results are in accordance with the pivotal phase II study and its updates and the other national experience studies with an overall response rate of 77.5% and a complete response rate of 47.5% in terms of best response.

In addition, we gained some interesting insights into the role of BV in everyday clinical practice. First, both the best response rate and overall response rate were higher among elderly patients: 85.7% versus 77.5% and 64.3% versus 62.5%, respectively.

It was confirmed that having a complete response after four cycles of treatment is very important for classifying a patient as a real good responder; however, the best number of cycles to give with a view to evaluating potential consolidation with transplantation (in most cases with allogeneic transplantation) or continuation with BV until cycle 16 remains an open issue, mainly because in the case of a complete response the choice between the two options is at the physician’s discretion. According to the recent update from Pro et al. on the pivotal phase II study, the 5-year progression-free survival rate was 68% in patients who achieved a complete response and underwent allogeneic SCT versus 47% in patients who continued BV treatment even though they had obtained a complete response after the first four cycles of treatment. In this update the authors reported that 27.6% of the whole study population achieved long-term remission, lasting for more than 5 years, in response to single agent BV without any additional anticancer therapy, other than transplantation. In our study the estimated disease-free survival rate at 2 years was 54% and 15 patients (37.5%) were in continuous complete response with a median duration of response of 12 months (range, 9-24 months). As only three of those 15 patients had had transplant consolidation, a comparison between these patients and those who did not undergo a SCT procedure was not possible. Thus, the duration of response and disease-free survival in the real-life experience, confirming the findings of the pivotal study, indicate that a substantial subset of patients with R/R systemic ALCL who have a complete response with single agent BV obtain long-term disease control and may potentially be cured. One important question remains unanswered: which of the patients in complete response may benefit from transplant consolidation? In our series there were five long-term responders, all of whom were still in continuous complete response at the latest follow-up, but of whom only one had undergone a consolidative allogeneic SCT procedure. Updates from the pivot-
otal study and our data could indicate that long-term disease control can be obtained even without transplant consolidation, with a real chance of curing a subset of patients with R/R systemic ALCL with BV alone.¹⁴ Physicians are still divided on whether or not to offer a consolidative transplant to patients in complete response because solid clinical trial data are lacking on this issue. A large, well-designed randomized control study is needed, but ALCL is so rare that we are unlikely ever to have a definitive answer.

Differences in survival outcomes between ALK-positive and ALK-negative patients have often been reported: no statistically significant difference was observed between and ALK-negative patients have often been reported: no statistically significant difference was observed between the two subgroups in our sample.²¹

Our study indicated that for patients who had stable or progressive disease after four cycles of BV the potential conversion rate to partial or complete response with further cycles is close to zero. The final message is that when patients have stable or progressive disease at first restaging, they should be changed rapidly to another treatment. On the other hand, for patients who achieve a partial response by the first restaging, it could be important to continue to treat: in our series 2/12 (16.7%) patients showed a complete response after four cycles from a partial to a complete response.

In conclusion, the results of this large retrospective study on 40 cases of R/R systemic ALCL in daily practice support the efficacy of single-agent BV, which appears to be a treatment with manageable toxicity without evidence of cumulative toxic effects with previous regimens. We acknowledge that this kind of report has a potential bias given the lack of a predictable and calculated sample size and the risk of underreporting toxicity. However, ALCL is a very rare disease, accounting for approximately 2% to 3% of all lymphoid neoplasms. The phase II study that led to Food and Drug Administration-accelerated approval of BV enrolled 58 patients globally, thus 40 ALCL patients from a single nation is a substantial sample related to this pathology. Nevertheless, we could not analyze prognostic features due to the small sample and we have reported the raw observed data. Compared with randomized controlled trials, observational studies may better identify clinically important adverse events for several reasons. These include longer follow-up times, the inclusion of patients with concomitant illnesses who may be more likely to experience drug interactions or other side effects and the probability of detecting infrequent or rare complications. With regards to the retrospective nature of this specific study, AIFA demands strict monitoring of drugs prescribed under law 648/96 and physicians must report any adverse event occurring during treatment: thus, all the safety data were already in the patients’ chart at the time our retrospective study started.²²

Our report confirms the activity of BV in elderly patients, the relation of the clinical response independently of transplant consolidation, and the relevance to the final response of achieving a complete response after four cycles of treatment. BV is the first drug which has led to a drastic change in the management of ALCL, with an overall response rate of 80%. The next research efforts could be aimed at developing combination regimens with BV to reach a 100% rate of responses in patients with R/R ALCL.

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