

## Original article

# Brentuximab vedotin in relapse/refractory HL and ALCL among pediatric patients

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## Abstract:

**Background:** While adult patients with relapse or refractory (R/R) CD30+ lymphoma can be successfully treated with brentuximab vedotin (BV), an anti-CD30 monoclonal antibody, clinical results in pediatric patients are scarce. Here, we report the outcomes of children with R/R CD30+ lymphoma treated with BV. **Methods:** Patients with R/R treated with a BV-based regimen were retrospectively included. This was a BV intravenous drip for 1 hr on day 1, 1.4 mg/kg at first dose, titrated up to 1.8 mg/kg in subsequent doses every 21 days, combined with chemotherapy. Those with complete response (CR) underwent autologous hematopoietic stem cell (autoHSCT) transplant, followed by 16 courses of BV monotherapy as a maintenance therapy. **Results:** Of all 6 patients, 4 had Hodgkin lymphoma (HL), and 2 had anaplastic large cell lymphoma (ALCL). Median age at diagnosis was 12.3 (6.6-13.4) years. Four patients (3 HL, 1 ALCL) achieved CR and subsequently underwent autoHSCT with the median dose to CR of 3 (2-4); the other 2 patients attained partial response. All received maintenance monotherapy BV, without evidence of relapse: total median BV doses being 12 (6-16). Pancreatitis grade 3 was observed in 1 patient in the third BV course. Nontuberculous mycobacterial infection was diagnosed in the 1 patient in the fifth BV course. **Conclusion:** As a salvage treatment for CD30+ lymphoma in children, BV appears to show promise, but a larger cohort is warranted to better elucidate the clinical outcomes.

**Keywords :** ● Brentuximab vedotin ● Relapse ● Refractory ● Hodgkin lymphoma  
● Anaplastic large cell lymphoma ● Pediatric

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## นิพนธ์ต้นฉบับ

# Brentuximab Vedotin in Relapse/Refractory HL and ALCL among Pediatric Patients

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## บทคัดย่อ

**บทนำ** การรักษามะเร็งต่อมน้ำเหลือง CD30+ ไม่ตอบสนองต่อการรักษาหรือกลับเป็นซ้ำในผู้ใหญ่มีผลการรักษาที่ดีเมื่อใช้ brentuximab vedotin (BV) แต่ในผู้ป่วยเด็กไม่มีความชัดเจน การศึกษาที่รายงานผลของการรักษาในผู้ป่วยเด็ก **วิธีการวิจัย** เก็บข้อมูลย้อนหลังในผู้ป่วยมะเร็งต่อมน้ำเหลือง CD30+ ไม่ตอบสนองต่อการรักษาหรือกลับเป็นซ้ำที่ได้รับสูตรยาเคมีบำบัดที่มี BV ทางหลอดเลือดดำขนาด 1.4 มก./กก. ในวันแรก และปรับขึ้นเป็น 1.8 มก./กก. ทุก 21 วัน ร่วมกับยาเคมีบำบัด ผู้ป่วยทั้งหมดตอบสนองต่อการรักษาอย่างสมบูรณ์ และทำปฏิกิริยาเซลล์ต้นกำเนิดเม็ดเลือดของตนเอง ตามด้วยการรักษาด้วย BV 16 คอร์ส **ผลการวิจัย** ผู้ป่วย 6 ราย เป็น Hodgkin lymphoma (HL) 4 ราย และ anaplastic large cell lymphoma (ALCL) 2 ราย อายุมัธยฐานตอนวินิจฉัย 12.3 ปี ในผู้ป่วย 4 ราย (HL 3 และ ALCL 1 ราย) ตอบสนองต่อการรักษาอย่างสมบูรณ์ และได้ปฏิกิริยาเซลล์ต้นกำเนิดเม็ดเลือดของตนเอง 2 รายตอบสนองบางส่วน ผู้ป่วยทั้งหมดได้ BV โดยไม่พบโรคกลับเป็นซ้ำ พบตับอ่อนอักเสบ และติดเชื้อ non-tuberculous mycobacterial อย่างละ 1 ราย **สรุป** การรักษามะเร็งต่อมน้ำเหลือง CD30+ ในผู้ป่วยเด็กที่ใช้ BV ร่วมด้วยในการวิจัยนี้น่าจะมีผลการรักษาที่ดี แต่จำนวนผู้ป่วยที่มากขึ้นจะแสดงให้เห็นถึงผลการรักษาได้ชัดเจนยิ่งขึ้น

**คำสำคัญ :** ● Brentuximab vedotin ● Relapse ● Refractory ● Hodgkin lymphoma  
● Anaplastic large cell lymphoma ● Pediatric

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### Introduction

Outcomes of pediatric Hodgkin lymphoma (HL) are favorable with a 5-year event free survival (EFS) > 80%.<sup>1</sup> However, relapsed or refractory (R/R) pediatric HL generally has an EFS of 40 to 60%, and this outcome is worse among diseases unresponsive to chemotherapy.<sup>2,3</sup> Several salvage therapies for pediatric HL, such as the combination of vinorelbine and gemcitabine based regimens, have been used as bridging treatments before autologous hematopoietic stem cell transplant (autoHSCT) with a complete response (CR) rate of 19 to 50%.<sup>4,5</sup>

Anaplastic large cell lymphoma (ALCL) is an uncommon nonHodgkin lymphoma among children. Treatment using a methotrexate-based regimen offers an EFS of 70 to 74%.<sup>6,7</sup> Without a standard regimen, patients with R/R may be treated with a cytarabine-based regimen followed by autoHSCT or allogeneic hematopoietic stem cell transplant (alloHSCT)<sup>8</sup>, or vinblastine monotherapy<sup>9</sup>.

Brentuximab vedotin (BV), an anti-CD30 monoclonal antibody conjugated with monomethyl auristatin-E (MMAE), has demonstrated efficacy on lymphomatous cells expressing CD30 (CD30+), such as HL and ALCL.<sup>10</sup> In clinical studies, BV has been shown to be an effective salvage therapy in both HL and ALCL, having an overall response rate of 80 to 88%<sup>11,12</sup> and 62 to 85%<sup>13,14</sup>, respectively.

Pediatric studies of BV are relatively scarce as compared with adult ones, especially in countries with resource constraints. Herein, we report the clinical use of BV in pediatric R/R HL and ALCL.

### Patients and methods

This retrospective study was conducted at the Department of Pediatrics, Faculty of Medicine, Siriraj Hospital; all applicable pediatric lymphoma patients treated with BV-based regimens were included. This study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand [SIRB 551/2563(IRB1)].

Patients with HL and ALCL were diagnosed from histopathology and immunohistochemistry. The clinical staging of HL was based on complete physical examination, bone marrow aspiration and imaging studies. Imaging studies included positron emission tomography-computed tomography (PET-CT) scans, whereas those patients who could not afford PET-CT would undergo CT and gallium scans.

Treatment protocols were adapted from the P9426<sup>15</sup> for low risk patients and the AHOD 0831 for high risk ones<sup>16</sup>, except for those with slower early responses. These were treated with high dose methotrexate, ifosfamide, etoposide and dexamethasone, which were all previously used as salvage therapies for relapsed HL.<sup>17</sup> Clinical staging and treatment regimens for ALCL were inspired from the ALCL 99 protocol.<sup>18</sup> The diagnosis of R/R diseases were established based on PET-CT scans and then confirmed by biopsy. After diagnosis of R/R, autologous peripheral blood stem cells were collected using salvage therapy and G-CSF as a mobilizing regimen in the first or second course of salvage treatment.

Patients with R/R HL or ALCL were treated with BV intravenous drip for 1 hr on day 1, with the first dose being 1.4 mg/kg which was titrated up to 1.8 mg/kg in subsequent doses every 21 days. For HL, BV was given on day 1 and combined with gemcitabine 1,000 mg/m<sup>2</sup> intravenously for two hours on days 1 and 8 or combined with bendamustine 90 mg/m<sup>2</sup> intravenously for 1 hour on days 1 and 2. For ALCL, BV was given on day 1 and combined with DHAP protocol, consisting of cisplatin 70 mg/m<sup>2</sup> intravenously for six hours on day 1, cytarabine 2,000 mg/m<sup>2</sup> intravenously for 2 hours every 12 hours on day 2 and dexamethasone 20 mg/m<sup>2</sup> on days 2 to 5. The expense of BV was partially supported by the Takeda's Adcetris Patient Assistance Program.

Those treated with DHAP received G-CSF as a primary prophylaxis. Co-trimoxazole was prescribed as a pneumocystis pneumonia (PCP) prophylaxis, and responses were evaluated using PET-CT based on the Deauville five-points scale (5PS).<sup>19</sup> The response after BV

was evaluated after the second courses of BV; however, those unable to be evaluated may have subsequently undergone PET/CT scan later. Patients achieving CR were treated with autoHSCT followed by monthly BV monotherapy to reach a total of 16 doses, whereas those attaining partial response (PR) or stable disease received monthly BV monotherapy for 16 doses. The conditioning regimen for both HL and ALCL combined BCNU, etoposide, cytarabine and melphalan (BEAM) as previously described.<sup>20</sup> Demographic and clinical data were collected and recorded, and toxicities were classified using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.

### Results

Of six patients in this cohort: five males and one female, four patients had HL and two had ALCL. The median age at diagnosis was 12.3 years, ranging from 6.6 to 13.4 years. Median follow-up took place within 12 months (range 5 to 16 months). Patient characteristics, previous treatments and responses to treatments are shown in Table 1. The diagnosis of R/R disease was confirmed by biopsy in patients 1, 2, 3 and 5, whereas diagnoses of patients 4 and 6 were established from PET-CT scans and radiographic findings. All patients responded to BV, four having CR and two with PR. All patients with CR subsequently underwent autoHSCT followed by maintenance single BV. Of all four patients undergoing autoHSCT, the median number of CD34 was  $6.98 \times 10^6$  (range  $5.93$  to  $19.1 \times 10^6$ ) cells/kg, and the median time of neutrophil engraftment was ten (range, 9 to 12) days.

Regarding postBV toxicities, patient 1 had abnormal bilateral pulmonary nodules visible on chest PET/CT scan (Figure 1) after the first BV monotherapy dose after autoHSCT, i.e., the fifth BV course. Broncho-alveolar lavage was positive for acid-fast bacilli (AFB), whereas mycobacteria culture was negative. He received a diagnosis of nontuberculous mycobacterial (NTM) infection and was treated with oral ciprofloxacin, azithromycin

and rifampicin while maintenance BV monotherapy was temporally placed on hold. His two-month PET/CT follow-up revealed marked improvement of pulmonary lesions; thus, BV was restarted without complications.

Patient 2 developed disseminated penicilliosis complicated by fungal infective endocarditis after the second BV and DHAP combination course. He was treated with lipid amphotericin until the disease subsided. He received BV monotherapy, omitting DHAP as a second salvage therapy due to concerns about penicilliosis reactivation. Unfortunately, he developed grade 3 pancreatitis by his third BV course. After discussion with his parents, a decreased BV dose was prescribed at 0.8 mg/kg and gradually increased to 1.2 mg/kg. He responded well to BV; the PET/CT revealed disappearance of intra-abdominal lymphadenopathy (Figure 2). He subsequently underwent autoHSCT after the fourth BV course, without severe toxicity and then received maintenance BV alone, with a titration dose to 1.8 mg/kg at the next, and further doses without complications. All other patients did not present grade 3 to 4 toxicity after BV treatment.

### Discussion

Salvage therapies for relapsed HL among children are usually based on adult studies. Although survival rates appear to be favorable, the EFS of those with relapsed disease were from 40 to 50% and even worse among those with primary refractory disease.<sup>3,21,22</sup> Most relapsed patients then require high dose chemotherapy followed by some kind of HSCT. This is with the exception of those in the early stages of HL who achieved good response to salvage therapies; and thus, may not require HSCT.<sup>23</sup> Unfortunately, all of the patients with HL in our cohort were advanced stage: 3/4 underwent autoHSCT after attaining CR.

The overall response rate (ORR) of the BV-based regimen in R/R HL among adults has ranged from 60 to 78% with 25 to 33% CR<sup>24, 25</sup> the ORR in a pediatric study was 98%<sup>12</sup>. In our cohort, four patients (66.7%) attained

**Table 1** Patient characteristics of relapsed and refractory Hodgkin and nonHodgkin lymphoma pretreated with brentuximab

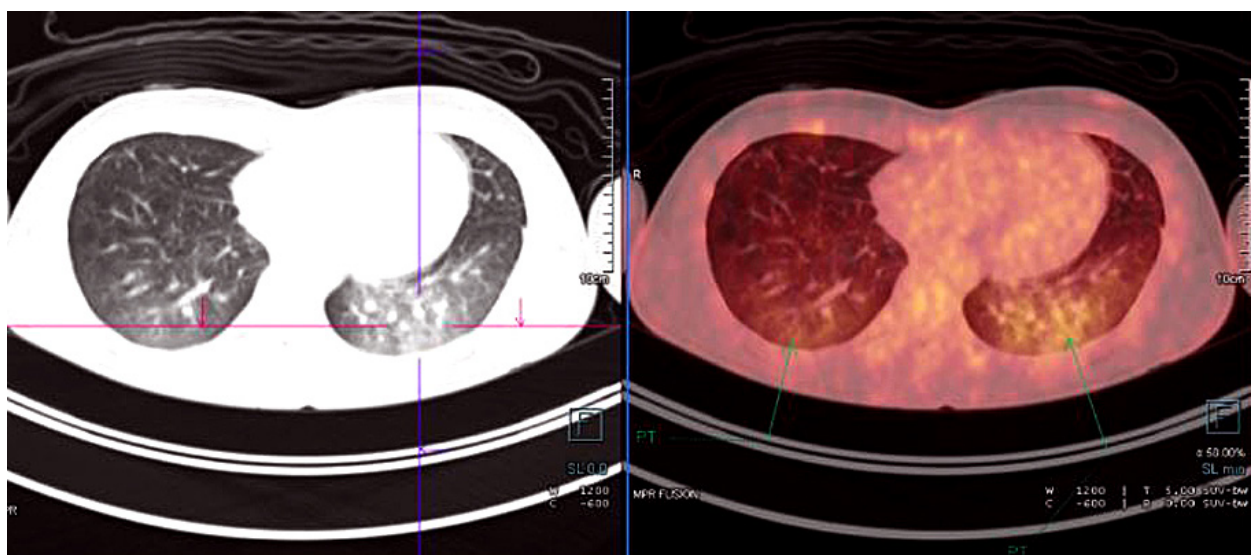
| Patient No.<br>(sex) | Disease                        | Age at diagnosis<br>(year) | Treatment<br>regimen | Response     | Site of relapse/ refractory   |
|----------------------|--------------------------------|----------------------------|----------------------|--------------|-------------------------------|
| 1(M)                 | NSHL stage 3B                  | 12.2                       | AHOD0831             | CR > relapse | Porta hepatis, para-aortic LN |
| 2(M)                 | ALCL HR ALK+                   | 8.5                        | AIEOP ALCL99         | PD           | Para-aortic LN                |
| 3(F)                 | MCHL stage 4A                  | 12.3                       | AHOD0831             | CR > relapse | Cervical and mediastinal LN   |
| 4(M)                 | MCHL stage 2A<br>bulky disease | 5.6                        | AHOD0831             | PD           | Cervical and mediastinal LN   |
| 5 (M)                | NSHL stage 4A                  | 13.4                       | AHOD0831             | PD           | Cervical LN                   |
| 6(M)                 | ALCL HR ALK-                   | 6.8                        | AIEOP ALCL99         | PD           | Bone                          |

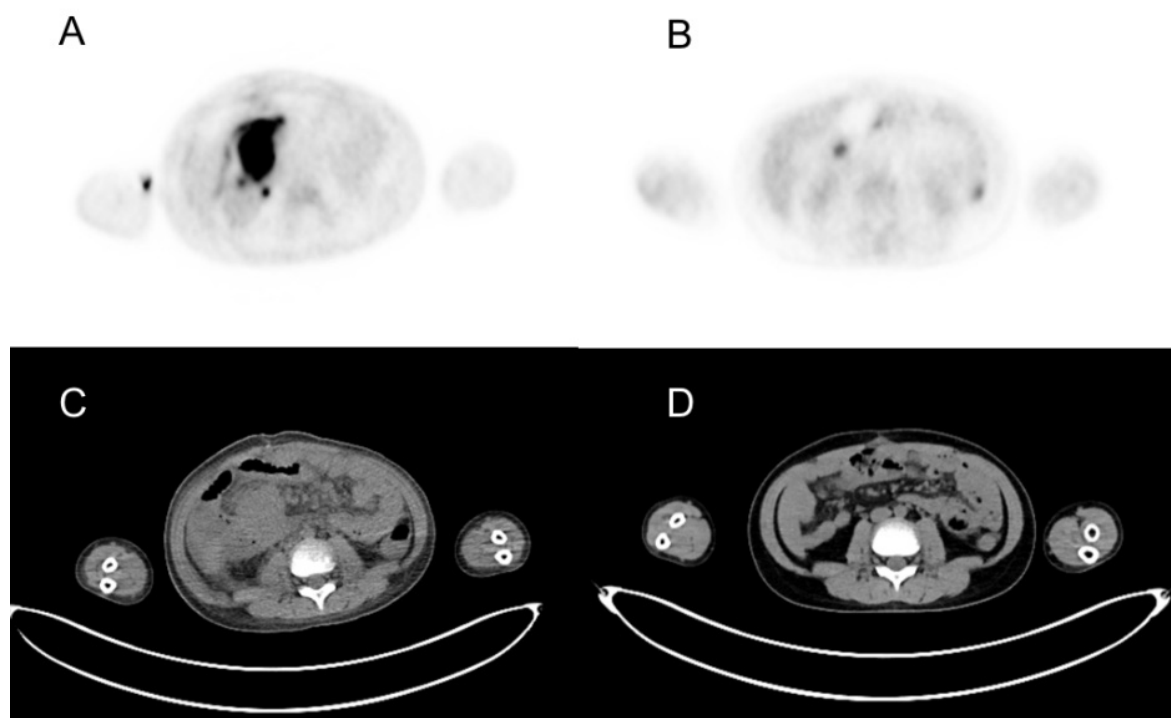
Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; CR, complete response; HR, high risk; LN, lymph node; M, month; MCHL, mixed cellularity Hodgkin lymphoma; NSHL, nodular sclerosis Hodgkin lymphoma; PD, progressive disease

**Table 2** Treatment outcomes of relapsed and refractory Hodgkin and nonHodgkin lymphoma treated with brentuximab

| Patient No. | Regimen        | Cycles to response | ASCT | Complications post Brentuximab                      | Response | F/U time (months)/<br>total courses of BV |
|-------------|----------------|--------------------|------|-----------------------------------------------------|----------|-------------------------------------------|
| 1           | BV+gemcitabine | 4                  | yes  | NTM, aspergillosis                                  | CR       | 15/12                                     |
| 2           | BV+DHAP        | 4                  | yes  | Disseminated penicilliosis,<br>Pancreatitis grade 3 | CR       | 9/10                                      |
| 3           | BV+gemcitabine | 2                  | yes  | none                                                | CR       | 14/16                                     |
| 4           | BV+gemcitabine | 4                  | no   | none                                                | PR       | 12/12                                     |
| 5           | BV+Benda       | 2                  | yes  | none                                                | CR       | 14/16                                     |
| 6           | BV+DHAP        | 2                  | no   | none                                                | PR       | 5/6                                       |

Abbreviations: ASCT, autologous hematopoietic stem cell transplantation; Benda, Bendamustine; BV, brentuximab vedotin; CR, complete response; DHAP, dexamethasone with high dose cytarabine and cisplatin; M NTM, nontuberculous mycobacteria; PR, partial response

**Figure 1** Chest PET/CT scan revealed visible abnormal bilateral pulmonary nodules.



**Figure 2** PET/CT revealed disappearance of intra-abdominal lymphadenopathy

CR after receiving BV as a second line therapy. It is possible that this high CR rate was achievable because most of our patients were not heavily pretreated with other regimens.

Pediatric R/R ALCL has an ORR of 83 to 92%.<sup>8,26</sup> However, almost all patients require either allogeneic or autologous HSCT, as a standard therapy. BV monotherapy as salvage regimen has demonstrated a clinical efficacy of 53 to 100%.<sup>27,28</sup> In our study, the patients received a cytarabine-based regimen combined with BV since high dose cytarabine had been previously used as a salvage therapy for pediatric ALCL.<sup>8</sup>

Albeit uncommon, BV-related pancreatitis is fatal and usually occurs within the first three courses of BV.<sup>29,30</sup> In our case, pancreatitis developed after the third BV course, and obviously without history of alcohol consumption, nor recent infections. Certainly, there may have been other causes of pancreatitis. Nonetheless, physicians should be aware of the possibility of pancreatitis among pediatric patients receiving BV and subsequently developing acute abdominal pain. Re-challenging with close monitoring may be plausible in nonsevere cases.

Neutropenia is a common complication in those treated with BV, but incidence of febrile neutropenia seems to be uncommon among both adults and pediatric studies<sup>27,28,31</sup>. The use of BV is associated with an increased risk of PCP<sup>24</sup> and herpes simplex virus infection (HSV)<sup>32</sup>. PCP prophylaxis should be added in all cases, and HSV prophylaxis should be considered in cases with history of previous HSV infections. In addition, the eradication of CD30+ cells may theoretically increase mycobacterial infection risk and thereby the dysregulation of CD8+ effector cells.<sup>33</sup> One pediatric case was reported of BV-associated pulmonary mycobacterium avium complex infection.<sup>34</sup> Combined with our case of NTM infection, mycobacterial infection should be suspected among children presenting pulmonary symptoms and abnormal chest radiograph after receiving BV treatment.

Some limitations encountered in this cohort need to be addressed. First, because BV is a novel therapy for pediatric studies, longer follow-up times are required to evaluate whether patients can attain long term remission or not. Secondly, most patients in this cohort received BV early on and were not heavily pretreated;

the outcomes of patients having multiple relapses may have poorer responses to BV and worse outcomes than those receiving it as a second line of treatment.

In conclusion, BV combined with chemotherapy as a salvage treatment for CD30+ lymphoma among pediatric patients appears to have promising outcomes with favorable safety profiles. However, complications such as pancreatitis and mycobacterial infections should be closely monitoring after BV treatment. A larger cohort is warranted to better elucidate clinical outcomes.

#### Conflict of interest declaration

We declare no conflict of interest.

#### Finding disclosure

This was an unfunded study.

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