Review Article

Incorporation of Brentuximab Vedotin in the Treatment of Lymphoma: Current Evidence and Potential Use in Indonesia

Ibnu Purwanto

Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta

Abstract

Although scientific advances have resulted in significantly improved survival among lymphoma patients, certain subsets of lymphoma patients still have poor prognosis, which includes relapsed and treatment refractory patients. Brentuximab vedotin, an anti-CD30 targeted therapy has shown remarkable results given in both Hodgkin and non-Hodgkin lymphoma, even in cases without CD30 expression. Unfortunately, evidence of its effectiveness in Indonesian patient is still limited as there is only 1 case report of such subject published.
Conclusion: Brentuximab vedotin, an anti-CD30 targeted therapy presents as an effective therapeutic option for relapsed and treatment refractory lymphoma patients.

Keyword: *Lymphoma, brentuximab, CD30, Indonesia*

Abstrak

Perkembangan ilmu pengetahuan telah berdampak pada peningkatan kesintasan secara signifikan pada pasien limfoma. Akan tetapi, masih terdapat sebagian pasien yang memiliki kesintasan buruk, termasuk pasien yang kambuh dan pasien yang refrakter terhadap terapi. Brentuximab vedotin, obat terapi target anti-CD30, menunjukkan hasil yang luar biasa bila diberikan baik pada pasien limfoma Hodgkin maupun non-Hodgkin, bahkan pada kasus – kasus yang tidak mengekspresikan reseptor CD30. Sayangnya, hingga saat ini bukti klinis efektivitas obat ini pada populasi Indonesia masih terbatas dan hingga saat ini baru terdapat 1 laporan kasus mengenai penggunaan obat tersebut pada pasien di Indonesia.
Kesimpulan: *Brentuximab vedotin, obat terapi target anti-CD30, merupakan pilihan terapi yang efektif pada pasien limfoma yang kambuh serta pasien yang refrakter terhadap terapi*

Kata Kunci: *Lymphoma, brentuximab, CD30, Indonesia*

Introduction

Lymphoma, a heterogenous group of neoplasms originating from lymphoid organs, is responsible for 3.2% of all cancer cases and 225,000 cancer-related mortality annually worldwide. [1] Scientific advances have resulted in significantly improved survival among lymphoma patients with 5-year OS reported to be around 67-98% for Hodgkin lymphoma (HL) and 4-year OS ranging from 55% to 94% for non-Hodgkin lymphoma (NHL).[2,3] Although generally associated with good prognosis, some subsets of lymphoma patients still have poor prognosis, which includes relapsed and treatment refractory patients.[4] More effective treatment modalities are needed in these patient subsets, especially for patients who are not suitable to receive autologous stem cell transplant. Brentuximab vedotin, an anti-CD30 targeted therapy presents as an effective therapeutic option for these patients.

CD30 in Lymphoma

CD30 is expressed in 14-25% of B cell lymphoid malignancies and 90% of T cell lymphoid malignancies. [5,6,7] Overexpression of CD30 contributes towards lymphomagenesis through anti-apoptotic mechanism, resulting in cell survival.[8] Inhibition of CD30 by brentuximab vedotin has been proven to be efficacious in lymphoma patients expressing CD30, both in HL and NHL.

Brentuximab Vedotin in Hodgkin Lymphoma

First significant result came from a phase 2 study by Younes *et al*, which demonstrated 75% ORR in relapsed or refractory HL patients with 34% patients experiencing complete remission.[9] Similarly, positive result was also observed in a phase 3 AETHERA trial assessing the effectiveness of brentuximab vedotin given as early consolidation after autologous stem-cell transplantation. In this trial, brentuximab arm showed significantly improved progression-free survival (PFS), with a stratified hazard rate (HR) of 0.57, equivalent to a 43% reduction in the HR for PFS. The median PFS in the brentuximab arm was 42.9 months vs. 24.1 months in the placebo arm.[10] Both trials showed manageable safety profile with peripheral neuropathy and neutropenia reported to be the most common side effects.[9,11] Given as combination with gemcitabine, 57% of pediatric and young adult patients with relapsed or refractory HL showed complete response within the first four cycles of treatment and 31% patients experienced partial response or stable disease after cycle 4.[12]

Positive results in relapsed or refractory HL patients lead to trials to incorporate brentuximab vedotin as first-line treatment in combination with existing modalities. A phase 2 trial by Abramson *et al*, assessed the effectiveness of brentuximab vedotin in combination with adriamycin, vinblastine and dacarbazine (A-AVD) in 34 patients. At the end of treatment, 30 patients (88%) were in complete remission (CR), although side effects are observed to be worse than generally expected in AVD treatment alone. [13] Similarly, Kumar *et al* observed 93.3% 1-year PFS in early stage unfavorable risk HL patients given A-AVD followed by involved-site radiotherapy.[14] Compared to standard ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen, A-AVD is associated with better 2-year PFS (82.1 vs. 77.2%) as first-line treatment in stage 3-4 HL patients.[15] Brentuximab vedotin is also observed to be similarly effective given in combination with other chemotherapy regimen. Eichenauer *et al* reported CR of 94%

(46/49 patients) in advanced HL patients receiving BrECAPP (brentuximab vedotin, etoposide, doxorubicin, cyclophosphamide, procarbazine, and prednisone) and 88% CR (46/53 patients) in patients receiving BrECADD (brentuximab vedotin, etoposide, doxorubicin, cyclophosphamide, dacarbazine, and dexamethasone) as their final treatment outcome, although 58 serious adverse events were reported, 32 events in 21 of 50 patients who received BrECAPP and 26 events in 18 of 52 patients who received BrECADD.[16] Brentuximab vedotin also presents as a unique option for patients unsuitable for standard chemotherapy. Gibb *et al* observed 84% objective response rate (ORR) in this patient segment given 2-16 cycles (median 4) of brentuximab vedotin monotherapy. [17]

Brentuximab Vedotin in non-Hodgkin Lymphoma

Commonly used in treating HL, brentuximab vedotin has shown modest activity in NHL patients expressing CD30. Jacobsen *et al* observed ORR of 44% for relapsed/refractory diffuse large B-cell lymphoma (DLBCL) patients, including 17% CR (8 patients).[18] Given in combination with RCHOP as first-line treatment in CD30-unselected high-intermediate/high-risk DLBCL patients, Yasenchak *et al* observed ORR of 92% (11/12 patients), with 7 CR (58%), 4 partial remission (PR) (33%), and 1 progressive disease (PD), elucidating the potential of brentuximab vedotin in treating certain NHL patients .[19]

Brentuximab Vedotin in Indonesia

Currently, evidence of BV effectiveness in Indonesian patients is still extremely limited, as there is only 1 case report of such subject published. Purwanto *et al* reported a case of complete remission in a 40-year-old Asian female with heavily treated relapsed Hodgkin's lymphoma showed complete remission (CR) who received 8 cycles of BV in combination with gemcitabine as 4th line treatment, however in this report the patient's CD30 status was unknown.[20] Regardless, BV is observed to show activity even in CD30 negative lymphomas, suggesting its potential mechanism of action beyond CD30 inhibition. [21]

An observational retrospective study recently reported that CD30 is expressed in 30% (14/42) of Indonesian HL patients and 100% (3/3) in systemic anaplastic large cell lymphoma (sALCL) patients, suggesting its potential as a target for therapy in Indonesian population. [22] Despite its promising potential, widespread use of brentuximab vedotin in Indonesia might be challenging for 2 reasons. Firstly, examination of CD30 expression is not yet widely available across Indonesia. Secondly, brentuximab vedotin is currently not covered by Indonesian national insurance. Its high price tag may not be affordable by most of Indonesian population without the support of private health insurance. Clinical trial on Indonesian population is needed to provide evidence to support national coverage of brentuximab vedotin for the treatment of lymphoma patients in Indonesia.

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