Editorial

Role of bentuximab vedotin in relapsed/refractory classical Hodgkin lymphoma

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In general, we stratify adult patients with classical Hodgkin lymphoma (cHL) into 2 risk groups consisting of early-stage (Ann Arbor stage I or II) and advanced-stage (stage III or stage IV) disease. In contrast, pediatric patients with cHL are stratified into 3 risk groups consisting of low-risk (nonbulky Ann Arbor stage IA or IIA), intermediate-risk (stage IB or IIB without bulk, bulky stage IA or IIA, stage IIAE regardless of bulk, or stage IIIA regardless of bulk), and high-risk (stage IIB with bulk, stage IIIB, or stage IV) disease. For decades, the prognosis of newly diagnosed early-stage cHL in adults and low-risk cHL in children/adolescences receiving combination chemotherapy and radiotherapy is excellent, with estimated 5-year overall survival (OS) ranging from 93-100%. However, unmet clinical needs remain in adults with advanced-stage cHL with 5-year progression-free survival (PFS) of 81% and 5-year OS of 92% and in children/adolescences with high-risk cHL with 5-year event-free survival (EFS) of 83% and 5-year OS of 94% after an initial standard treatment.

Since treatment-related morbidity (TRM) is in great concern; without compromising the PFS after the first CR, one strategy to reduce such TRM is to omit radiation or reduce radiation dose and/or replace bleomycin in the standard combination regimen of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) with an approved novel therapy in high-risk patients, such as brentuximab vedotin (BV)-a chimeric CD30 monoclonal antibody (mAb) brentuximab and an antimitotic agent monomethyl auristatin E (MMAE), or a check-point anti-program death-1 (PD-1) monoclonal antibody.[1]

Relapsed/refractory (R/R) cHL is also challenging in terms of bridging therapy prior to ASCT. A patient with primary refractory cHL is defined as newly diagnosed one who fails to achieve a CR with an initial treatment or who relapses within 3 months from the end of an initial treatment while a patient with relapsed cHL is defined as reoccurrence of his/her cHL more than 3 months after the attainment of a CR.

Approximately 10-15% and 15-30% of adult patients with early- and advanced-stage cHL are failure to respond or relapse after the first-line treatment, respectively. In pediatric cHL, 0-11%, 12-16%, and 6-17% of those with low-risk, intermediate-risk, and high-risk disease are failure to respond or relapse after the first-line treatment, respectively.

Although novel agents are approved for relapsed/refractory (R/R) patients with cHL, salvage combination chemotherapy followed by autologous stem cell transplantation (ASCT) remains the standard of care for these patients. Achieving salvage therapy induced CR before ASCT is the most predictive factor for outcome. With standard salvage treatment followed by ASCT, R/R cHL adult and pediatric patients who attained CR had 10-year PFS of 49% and 10-year OS of 45% and 5-year PFS of 60% and 5-year OS of 76%, respectively.[2-3]

Two phase II studies demonstrated that single agent BV was an active first-line salvage therapy for R/R cHL patients with CR rates of 27-35% while another 30-49% of whom could achieve CR with additional salvage radiotherapy or combination chemotherapy. Consequently, the majority of these patients could proceed to undergo ASCT.[4-5] In the first study, CR and PR rate of 37 evaluable patients receiving BV (1.8 mg/kg every 3 weeks for a total of 4 cycles) were 35% and 32%, respectively.[4] Eighteen patients received additional radiotherapy prior

to undergo ASCT. After a median follow-up of 17.8 months, the 18-month post-transplant PFS was 73%.[4] Few patients experienced grade 3/4 adverse events, including lymphopenia (3%), neutropenia (8%), rash (5%), and hyperuricemia (3%).[4] In the second study, 45 patients were treated with single agent BV (1.2 mg/kg on days 1, 8, and 15 of every 4-week cycle for 2 cycles). Forty-four patients (98%) eventually proceeded to ASCT while one patient (2%) lost to follow up. After completion of the BV treatment, twelve patients (27%) achieved positron emission tomography (PET)-negative CR without additional radiotherapy or combination chemotherapy while thirty-two patients with PET-positive disease received 2 cycles of augmented Ifosfamide, Carboplatin, and Etoposide (ICE). After the second cycle of augmented ICE, 22 of the 32 patients (69%) with PET-positive disease after single BV achieved PET-negative CR. One patient (2%) received 1 additional cycle of ICE. Six patients (13%) received involved-field radiotherapy while 3 patients (7%) did not receive any treatment. After a median follow-up of 20.1 months, the 2-year EFS and 2-year OS was 80% and 95%, respectively.[5] Single agent BV was well tolerated and associated with few grade 3-4 adverse events including hyperglycemia (4%), nausea (2%), hypoglycemia (4%), and hypocalcemia (4%).

Phase II trials demonstrated that BV in combination with conventional salvage chemotherapy is a good candidate to make more R/R cHL patients eligible for ASCT with acceptable toxicities. In the GELTAMO phase 2 trial, R/R cHL patients were treated with BV (1.8 mg/kg every 3 weeks) and Etoposide, Solu-Medrol, High-dose Cytarabine, and Cisplatin (ESHAP) for 3 cycles. Sixty-six patients were enrolled. The overall response rate (ORR) before and after ASCT was 91% (CR 70%, PR 21%) and 92% (CR 82%, PR 10%), respectively. After a mean follow-up of 27 months, the 30-month time to treatment failure, PFS, and OS was 74%, 71%, and 91%, respectively.[6] Thirty-nine adverse events were reported in 22 patients including febrile neutropenia, non-neutropenic fever, grade 3/4 hematological toxicities, and hypomagnesemia.[6] In a phase 1/2 study, BV (1.8 mg/kg every 3 weeks) and bendamustine (90 mg/m^2 on days 1 and 2 every 3 weeks) for up to 6 cycles was tested in patients with R/R cHL. A total of 53 patients were recruited. The ORR, CR, and PR were 93% (49/53), 74% (39/53), and 19% (10/53), respectively.[7] Thirty-seven patients underwent ASCT and the estimated 12-month PFS was 80% for either all and transplanted ones.[7] Thirty-one patients (56.4%) experienced manageable infusion-related reactions.[7]

Recently, a phase I/II trial of 2 cycles of BV in combination with ICE followed by PET evaluation in 39 R/R cHL patients has been published. Only those achieving complete metabolic response (CMR) received the third cycle of treatment followed by 1 cycle of single agent BV before ASCT. There were 27 patients (69%) achieved CMR and 20 patients (51%) underwent ASCT. The median PFS was not reached. The 1-year PFS and OS were 69% and 100%, respectively.[8] Grade 3-4 adverse events were reported in 35 patients (83%) including hematologic toxicities (71%), infections (21%), and gastro-intestinal disorders (10%).[8]

More recently, Vathana N and colleagues have conducted a small retrospective study to evaluate the efficacy and safety of salvage combination of BV with either gemcitabine or bendamustine as bridging treatment prior to ASCT followed by BV consolidation in pediatric R/R cHL. The investigators demonstrated that 3/4 patients (75%) had achieved CR and then proceeded to ASCT followed by single agent BV consolidation for 16 cycles. One patient suffered from non-tuberculous mycobacterial infection. So far, only a few studies to test clinical efficacy and safety of BV in pediatric patients with RR cHL have been conducted. In a phase 2 trial, pediatric and young adult patients with R/R cHL treated with BV (1.8 mg/kg every 3 weeks) and gemcitabine (1,000 mg/m^2 on days 1 and 8 every 3 weeks) for up to 4 cycles had ORR and CR rate of 73% (29/40) and 58% (23/40), respectively.[9] The common adverse events were maculopapular rash (36%), neutropenia (33%), and

elevated serum transaminases (21%).[9] The rationale of BV consolidation therapy post-ASCT for patients with R/R cHL was confirmed by a multicenter, randomized, double-blinded controlled trial.[10] As compared with 164 adult patients with R/R cHL receiving placebo, a total of 165 ones receiving consolidation BV (1.8 mg/kg every 3 weeks) for 16 cycles post-ASCT had significantly longer median PFS (42.9 vs. 24.1 months, hazard ratio [HR] 0·57, 95%CI: 0·40-0·81; $p = 0·0013$).[10] As compared with 160 patients in the placebo group, two most common adverse events of 167 patients in the BV group were peripheral sensory neuropathy [94 (56%) vs. 25 (16%)] and neutropenia [58 (35%) vs.19 (12%)].[10]

In agreement with these 2 trials, a majority of Vathana N's patients treated with the same salvage therapy could achieve CR prior to ASCT and successfully received at least 9 cycles of post-transplant BV consolidation.

In conclusion, BV in combination with either gemcitabine or bendamustine is highly efficacious and has a good safety profile as a pre-transplant salvage therapy and the role of post-transplant BV consolidation is promising in pediatric patients with R/R cHL. However, these clinical results are preliminary and should be further evaluated in some prospective trials of Thai patients.

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