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Early Intensification with bendamustine supercharge plus brentuximab vedotin following failure to obtain complete metabolic remission after two cycles of ABVD in patients aged ≤60 years with classic Hodgkin lymphoma. Comment on: "Brentuximab-vedotin and bendamustine for relapsed or refractory Hodgkin lymphoma: the LYSA real-world experience"

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Author Contributions

C.G and M.P conceived the commentary and drafted the manuscript. M.P contributed to manuscript revision and critical intellectual content. Both authors approved the final version of the manuscript.

Disclosures / Conflict of Interest

The authors declare no conflicts of interest related to this work.

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Comment to the Editor

Treatment intensification with salvage therapy, high-dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT) is the best course of action for young adults and adults (YA&A) with refractory or relapsed (R/R) classic Hodgkin lymphoma (cHL). The recent real-world study by Basile et al.[1] provides the largest dataset to date on brentuximab vedotin plus bendamustine (Bv-B) as salvage therapy for cHL, including both transplant-eligible and -ineligible patients. In this context, we comment on the findings by Basile et al[1] evaluating the combination of Bv-B in R/R cHL following anthracycline-based upfront treatment, including 60% of patients refractory at the end of treatment (EoT), while the remaining patients relapsed either within 12 months (14.8%) or after 12 months (24.4%)[1]. In a cohort of 222 patients (median age, 44 years; range, 18–86 years) treated across multiple French centres over a 10-year period, patients received a median of four courses (range, 1–7) of Bv-B regimen (consisted of *i.v.* B 90 mg/m^2 D1 and D2 plus Bv 1.8 mg/kg at D1 for a 21-day cycle). The authors reported overall response (OR) rate of 82% (complete response [CR], 69.8%), and 4-year progression-free survival (PFS) of 50% (95% confidence interval [CI], 42.6%-56.9%) and overall survival (OS) of 74% (95% CI, 66.6%-79.1%). The favourable toxicity profile with relatively low rates of severe hematologic toxicity and peripheral neuropathy, together with the feasibility of outpatient administration, further supports the practical applicability of this regimen in routine clinical practice. Transplant-eligible patients (n= 150; median age, 36 years [range, 18–71 years]) achieved substantially improved outcomes, with 4-year PFS of 59.2% (95% CI, 50%-67.2%) and OS of 84.3% (95% CI, 76.5%-89.6%), rising to 72.6% (PFS; 95% CI, 61.1%-81.3%) and 95.1% (OS; 95% CI, 87.2%-98.2%) among those (102 patients) who ultimately underwent transplantation. In contrast, 72 patients, deemed ineligible for ASCT, experienced substantially inferior outcomes, with 4-year PFS of only 30.6% and OS of 51.5%, despite achieving similar initial response rates.

The clinical impact of Bv plus B combination in patients who fail to achieve early complete metabolic remission (CMR) during frontline therapy, *i.e.*, interim 2-deoxy-2[F-18] fluoro-D-glucose positron emission tomography (*i*-FDG-PET) positive scans after only two cycles of anthracycline-based therapy, remains to be confirmed[2,3]. In these patients with primary chemo-refractory illness, the prognosis is dismal with disease progression within 12 months from ASCT. Emerging in vitro data suggest that high-dose B administered shortly after Bv may enhance anti-CD30 auristatin activity against chemo-resistant Hodgkin and Reed–Sternberg cells[4,5]. Accordingly, early bendamustine “supercharge” (Bs) may potentiate Bv activity and improve remission rates compared with conventional salvage regimens[4-6]. In this regard, our multicenter retrospective study[7] explored the use of an intensified regimen combining Bv with Bs (Bv+Bs21) for four cycles (the cycle schedule consisted of 3-day outpatient *i.v.* infusions of 1.8 mg/kg of Bv on day 1 of each 3-week cycle combined in sequence with bendamustine [at least 24 hours after Bv, precisely on days 2 and 3 of the treatment cycle] at a fixed dose of 120 mg/m^2 per day) as early salvage therapy in patients aged ≤60 years who failed to achieve CMR after two cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), as defined by positive interim PET (Deauville score 4–5). In our cohort of 46 patients treated between 2013 and 2023 in three Hemato-Oncology Units in Southern Italy, median age was 37 years (range, 19–60 years), with high-risk clinical features including stage III–IV disease (76%), mediastinal bulky involvement (39%), and IPS scores of 5–7 (32%). Male sex accounted for 52% of patients. This strategy targets patients with early primary refractory disease, aiming to overcome H&RS cells chemoresistance through timely treatment intensification. Bv+Bs21 showed high activity, with OR rate of 100%, including CR rate of 91%. The regimen served as an effective bridge to ASCT, with 91% of patients proceeding to transplantation. After a median follow-up of 60 months, 5-year PFS and OS were 82% (95% CI, 65%–91%) and 90% (95% CI, 76%–96%), respectively. These outcomes

compare favourably with those reported by Basile et al[1], particularly in the transplanted population, where long-term disease control remains a key therapeutic objective. The main point of convergence between the LYSA analysis and our study is the high rate of YA&A patients achieving CMR after four cycles of Bv-based salvage therapy before ASCT. In our experience, peripheral blood stem cell (PBSC) collection after two cycles of Bv+Bs21 was successful in all patients without major mobilization difficulties. The median CD34+ cell yield was 4.1 × 10^6/kg (range, 1.9–5.1 × 10^6/kg), indicating preserved hematopoietic reserve despite ABVD exposure and treatment intensification with Bs. Regarding treatment toxicity, the most common hematological adverse event reported was febrile neutropenia involving five patients (11%); cytomegalovirus reactivation with viraemia was recorded in five patients successfully treated with valganciclovir pre-emptive therapy. Notably, due to the specific premedication (methylprednisolone at 400 mg and diphenhydramine at 50 mg *i.v.* on days 1 to 3, febuxostat at 80 mg orally on days 1-5, plus hyperhydration) against acute toxicity during the administration of Bs, serious infusion-related reactions were reported only in three patients (6%) during the first cycle. Overall, five patients (11%) required temporary treatment interruption due to treatment-related adverse events. Specifically, at least one dose modification of Bv and/or Bs, including treatment delays (n= 3) or dose reductions (n= 2), was required. Our findings support the feasibility of Bv+Bs21 without compromising stem cell mobilization or transplantation. However, as highlighted by Basile et al.[1], patients in both cohorts were naïve to Bv and checkpoint inhibitors, which may limit the generalizability of these findings to current clinical practice.

In conclusion, several attempts have been made in the R/R cHL setting to define the optimal partner agents to combine with Bv[2,3]. Bendamustine (old and low-cost cytotoxic agent) used in different schedules (*i.e.*, standard dose or increased dose, and simultaneously or after the antibody drug conjugate targeting CD30) against H&RS cells of patients aged ≤60 years has highly synergistic activity in outpatient salvage regimen in

combination with Bv in a broad range of disease status, *i.e.*, early refractory (*i*-FDG-PET positive scans after only two cycles of upfront therapy), refractory (EoT-FDG-PET positive scans), early relapse (<12 months) and late relapse (>12 months)[1,7].

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