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"

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 real-world study by Basile *et al.*[1] in this issue of *Haematologica* 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 would like to comment on the findings by Basile *et al.*[1] in evaluating the combination of Bv-B in R/R cHL following upfront anthracycline-based treatment. Sixty percent of patients were 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 centers over a 10-year period, patients received a median of four courses (range, 1-7) of Bv-B regimen (consisting of intravenous [i.v.] B 90 mg/m^2 day 1 and day 2 plus Bv 1.8 mg/kg at day 1 for a 21-day cycle).

The authors reported an overall response (OR) rate of 82% (complete response [CR], 69.8%), 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 favorable 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 who ultimately underwent transplantation (N=102). 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 front-line therapy, i.e., interim 2-deoxy-2[F-18] fluoro-D-glucose positron emission tomography (iFDG-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 International Prognostic Score of 5-7 (32%); 52% of patients were male.

This strategy targets patients with early primary refractory disease, aiming to overcome Hodgkin and Reed-Sternberg cell chemoresistance through timely treatment intensification. Bv+Bs21 showed high activity, with an OR rate of 100%, including a 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 favorably 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 collection after two cycles of Bv+Bs21 was successful in all patients without major mobilization difficulties. The median $CD34^+$ cell yield was $4.1x10^6$/kg (range, 1.9-$5.1x10^6$/kg), indicating preserved hematopoietic reserve despite ABVD exposure and treatment intensification with Bs.

Regarding treatment toxicity, the most common hematologic adverse event reported was febrile neutropenia involving 5 patients (11%); cytomegalovirus reactivation with viremia was recorded in 5 patients and was 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 1-3, 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 3 patients (6%) during the first cycle. Overall, 5 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 (an old, 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 Hodgkin and Reed-Sternberg cells of patients aged ≤60 years has highly synergistic activity in an outpatient salvage regimen in combination with Bv in a broad range of disease status, i.e., early refractory (iFDG-PET positive scans after only two cycles of upfront therapy), refractory (EoT-FDG-PET positive scans), and early (<12 months) and late (>12 months) relapse.[1,7]

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Contributions

CG conceived the commentary and drafted the manuscript. MP conceived the commentary and drafted the manuscript, contributed to manuscript revision and provided critical intellectual content. Both authors approved the final version of the manuscript for publication.

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