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Front-line Treatment of Older Patients with Hodgkin Lymphoma

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Introduction

The evolution of treatment for classical Hodgkin lymphoma (cHL) represents a great success in oncology, with disease outcomes evolving from universally fatal to vastly curable. However, not all patients benefit equally from modern therapies, which include response-adapted regimens and the addition of novel, targeted agents to the front-line setting. Although patients older than 60 years account for the later peak in cHL's characteristic bimodal age distribution and represent approximately 20–25% of all patients with cHL, their outcomes remain inferior compared to younger patients.[1] A retrospective study including 401 patients >60 years treated in British Columbia between 2000 and 2019 revealed modest progression-free survival (PFS) and disease-specific survival rates of 50% and 63%, respectively, with a median follow-up of nine years. While these outcomes have improved relative to cohorts treated prior to 2000, they nevertheless fall short of those experienced by younger patients. Furthermore, the gap in outcomes between young and older patients progressively worsens with each increasing age decile, with patients >70 years having a particularly poor prognosis.[2] This shortfall has been attributed in part to patient-specific factors such as comorbidities and frailty, which may limit treatment tolerance, but also to differing disease biology, with negative prognostic features including advanced stage disease, Epstein-Barr virus positivity, and mixed cellularity histology often present in those with older age.[3] Adding to the challenges in treating older patients is the fact that this group is frequently underrepresented in clinical trials, or excluded altogether, making their optimal treatment ill-defined.

Treatment of Anthracycline-eligible Patients

For several decades, the multiagent ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) regimen has represented a North American standard for the front-line treatment of fit patients with cHL. However, ABVD is more toxic for older patients, with rates of bleomycin-induced lung toxicity (BLT) as high as 35% in this subpopulation. The risk of BLT rises with increased age, resulting in mortality rates that approach 30%.[4] The randomized RATHL trial aimed to minimize pulmonary toxicity through a positron emission tomography (PET)-directed approach wherein bleomycin was omitted from ABVD after two cycles for patients with advanced-stage disease achieving an early metabolic complete response. While this study reported decreased pulmonary events (3.2% vs. 0.6% in cycles 3–6 for ABVD and AVD, respectively) with similar 3-year PFS for patients who were PET-negative after two cycles (PET2-negative), only 9% of enrolled patients were >60 years of age, challenging the extrapolation of these results to routine clinical practice.[5]

The impact of omitting bleomycin from the ABVD backbone has likewise been evaluated in the limited-stage setting. The German Hodgkin Study Group (GHSG) HD13 trial randomized favourable risk patients with early-stage disease to one of four arms: two cycles of ABVD with or without bleomycin, dacarbazine, or both, prior to consolidative radiotherapy. Freedom from treatment failure was not found to be non-inferior for patients receiving AVD (93.1% vs. 89.2%), leading investigators to conclude that ABVD remained the preferred regimen in this setting.[6] Older patients, for whom the slight loss in treatment efficacy may be offset by decreased toxicity and improved treatment-related mortality, comprised only a small proportion of the enrolled population (13%). A subsequent analysis of patients >60 years enrolled in GHSG trials was undertaken, all of whom were meant to receive 2–4 cycles of ABVD (HD10 and HD13 trials) or two cycles of AVD (HD13). This pooled analysis of 287 patients demonstrated no significant increase in BLT for patients receiving ABVD compared to AVD when chemotherapy was limited to two cycles (1.5% vs. 0.0%, respectively), but showed a striking increase (10%, including three fatal cases among the seven reported) when ABVD was extended to four cycles. Response and efficacy outcomes were similar across groups and not different from the main HD13 analysis, including both young and older patients.[7] These data suggest that bleomycin may be safe and tolerable for fit older patients, but should be limited to two cycles, beyond which the risk of BLT becomes unacceptably high. Ultimately, the decision to include bleomycin in the treatment of older patients should be individualized, with careful consideration of additional patient-specific risk factors for the development of BLT.

More recently, the anti-CD30-directed antibody-drug conjugate, brentuximab vedotin (BV), has presented an additional treatment option for cHL. In addition to its use in the relapsed setting, BV is licensed for use in combination with AVD as front-line treatment for patients with advanced-stage disease in the US and for patients with stage IV disease in Canada. The BV-AVD regimen was evaluated against standard ABVD in the randomized ECHELON-1 trial, which enrolled newly diagnosed patients irrespective of age. The overall analysis revealed a modified PFS advantage and, with longer follow-up, a small but statistically significant OS advantage favouring BV-AVD. However, these benefits appeared to be limited to younger patients. In a subgroup analysis of patients >60 years, BV-AVD conferred a trend toward improved 5-year modified PFS; however, this was not statistically significant (67.1% vs. 61.6% for ABVD; p=0.443)[8] and no OS benefit was observed (hazard ratio [HR] for death 0.83, 95% CI 0.47–1.47).[9] Rates of treatment-emergent adverse events were similar among patients treated with ABVD vs. BV-AVD; however, pulmonary toxicity was predictably less frequent in the absence of bleomycin. In contrast, treatment with BV-AVD was associated with increased rates of neuropathy and febrile neutropenia, particularly in older patients, mandating the use of granulocyte colony-stimulating factor (G-CSF) prophylaxis. Collectively, these data suggest that BV-AVD may be an effective regimen for selected fit older patients with advanced stage cHL, but its use requires careful supportive care and toxicity monitoring.

An alternative strategy aimed at improving the tolerability of BV has been to use it sequentially rather than in combination with AVD. In a phase 2 study of patients >60 years with stage II-IV cHL, a lead-in phase of two cycles of single-agent BV was followed by six cycles of AVD and an additional four cycles

of consolidative BV for patients responding to treatment. Encouragingly, rates of neuropathy and neutropenia appeared more favourable than those reported in the ECHELON-1 study, suggesting better tolerability with this sequential treatment approach. The 2-year PFS and OS were compelling, at 84% and 93%, respectively.[10]

The escBEACOPP (escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen, established by the GHSG for front-line treatment of advanced-stage cHL, has long been recognized as prohibitively toxic for older individuals, limiting its use to those <60 years of age. Recent efforts to decrease acute and late toxicity with this regimen have resulted in the development of the novel BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone) regimen, which incorporates BV into a modified, less toxic version of the escBEACOPP backbone. When used in a PET-adapted manner for the treatment of patients with advanced-stage disease, including those having stage 2 disease with risk factors, BrECADD was shown to be better tolerated and non-inferior with respect to PFS to escBEACOPP, leading investigators to declare it a new treatment standard.[11] While HD21 did not enrol patients >60 years, the improved toxicity profile associated with BrECADD has led to its evaluation in an older cohort of patients, the results of which are expected soon.

Another promising approach to the management of older patients with cHL has emerged from the US intergroup study S1826, which evaluated the role of programmed cell death protein 1 (PD-1) inhibition in combination with chemotherapy as a first line of treatment.[12] This randomized, phase 3 trial compared six cycles of BV-AVD to six cycles of nivolumab-AVD (N-AVD). Patients >60 years accounted for only 10% of the 994 patients enrolled, all of whom had advanced-stage disease. A pre-planned analysis of outcomes among older patients revealed a dramatic improvement in PFS favouring N-AVD. With a median follow-up of 12.1 months, the 1-year PFS was 93% for N-AVD, compared with 64% for BV-AVD (HR: 0.35, 95% CI: 0.12–1.02; p=0.022). Remarkably, the PFS observed in this study mirrored the one observed in the overall cohort, where the median age was 27 years. Among older patients, fewer deaths were observed in the N-AVD group, leading to improved 1-year OS, though this did not reach statistical significance (95% vs. 83%, HR: 0.35, 95% CI: 0.07-1.75, p=0.091). Predictably, rates of neuropathy were significantly lower with the absence of BV. Immune-related toxicities were similar between arms, except for hypothyroidism (15% vs. 0.0%) and rash (16.0% vs. 2.0%), which were predominantly low-grade.[13] Although longer follow-up is eagerly awaited and PD-1 inhibitors are not yet approved in the front-line setting, the very promising results from S1826 and other trials incorporating these drugs into front-line therapy[14], have led to the early adoption of N-AVD as a treatment of choice in the US, for older, fit patients with advanced stage cHL.

Treatment of Anthracycline-ineligible Older Patients

Older individuals unfit for anthracycline-based chemotherapy represent a challenging group of patients. Given the important contribution of anthracyclines in achieving cure through conventional front-line chemotherapy regimens, it is paramount to determine which patients are fit enough to receive anthracycline-based therapy. Geriatric assessment (GA) has been increasingly recognized as valuable in the pre-treatment evaluation of older patients with cHL. While few trials have prospectively incorporated GA, a growing body of retrospective data underscores the utility of standardized tools in predicting treatment response and outcomes, including the cumulative illness rating scale – geriatric (CIRS-G), the adult comorbidity evaluation 27 (ACE-27), the Charleston Comorbidity Index, screens for impaired activities of daily living, and the presence of geriatric syndromes. The use of GA may ultimately guide treatment decisions, sparing patients unlikely to benefit from more intensive and more toxic therapies, while offering them alternatives with more favourable risk-to-benefit profiles.[15,16]

Treatment outcomes for unfit older patients are largely informed by non-randomized trials that enrolled small numbers of patients, leaving this demographic without a clearly defined treatment standard. Given the poor outcomes for low-intensity multi-agent chemotherapy regimens such as ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisone), for which 5-year event-free survival (EFS) and OS rates are reported to be only 24% and 30%, respectively, there has been great interest in developing more rational novel approaches.[17] To this end, targeted agents, including BV and PD-1

inhibitors, have been assessed in the front-line setting as monotherapies and doublets. While both BV and nivolumab (or pembrolizumab) have shown disappointing results when administered alone, combinations of BV or PD-1 inhibitors with chemotherapy or with each other have shown more promise. The SGN-015 phase 2 trial evaluated BV in cohorts of older patients with cHL, either alone or in combination with other agents (dacarbazine, bendamustine, or nivolumab). Recently reported results from the combination cohorts receiving BV plus dacarbazine or BV plus nivolumab revealed that with a median follow-up of over four years, the median PFS was a remarkable 47.2 months and not reached, respectively.[18] This compares favourably to a cohort receiving BV monotherapy, in which only a modest median PFS of 10.5 months was observed, despite a high overall response rate of 92%.[19] Responses to doublet therapy were more durable, and the median OS was not reached in either group. Furthermore, for patients who received no further therapy beyond the end of the study treatment (a median of 12.5 cycles in the dacarbazine cohort, and 10 cycles in the nivolumab cohort), the 5-year OS was 90% in the dacarbazine and 78% in the nivolumab cohort, invoking the possibility of cure for a subset of patients treated with these regimens. Neuropathy rates were high, however, underscoring the need to carefully select and monitor patients for this common side effect of BV. These data support the use of novel agent-containing doublet therapies for the treatment of patients with cHL who are unfit to receive more intensive therapy, which merits further investigation.

Conclusion

The treatment of cHL in elderly patients presents a unique set of challenges necessitating a tailored approach that considers the individual's overall health, comorbidities, and treatment preferences. While traditional chemotherapy regimens remain the backbone of therapy, incorporating novel agents into the front-line setting is poised to raise the bar, improving both outcomes and tolerability. GAs will likely become increasingly important in defining which patients are fit for standard treatment versus those requiring novel approaches. For those patients unfit to receive conventional treatments, novel doublet therapies may offer hope for long-term disease control. Together, these approaches promise to improve outcomes for this vulnerable patient population.

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