Abstract
The treatment of classical Hodgkin lymphoma in young patients is one of the success stories of modern medicine. The use of risk- and response-adapted approaches to guide treatment decisions has led to impressive cure rates while reducing the long-term toxicity associated with more intensive therapies. Tissue biomarkers have not yet proven more effective than clinical characteristics for risk stratification of patients at presentation, but functional imaging features such as metabolic tumor volume may be used to predict response, if early observations can be validated. The success of treatment in younger patients has unfortunately not been mirrored in those over 60, where complex decision-making is often required, with a paucity of data from clinical trials. The use of PD1 blocking antibodies and brentuximab vedotin in this cohort, either alone or in combination with chemotherapy, may provide attractive options. The incorporation of frailty assessment, quality-of-life outcomes, and specialist geriatric input is also important to ensure the best outcomes for this diverse group.

KEYWORDS
antibody–drug conjugate, checkpoint blocking antibody, FDG-PET, Hodgkin lymphoma

1 | INTRODUCTION
Classical Hodgkin lymphoma (cHL) is a malignancy of germinal center B cells, characterized by the presence of the Hodgkin Reed-Sternberg (HRS) cell. It is the most common lymphoid malignancy diagnosed in children and young adults in developed countries, with a bimodal distribution peaking in the 2nd and 7th decades. Treatment with radiotherapy, multimodality chemotherapy regimens, newer antibody–drug conjugates, and immunotherapy checkpoint inhibitors (ICI), using 2-[(18)F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (FDG-PET) to direct therapy has translated into 10-year overall survival (OS) rates above 80%.[1] However, the ongoing challenge remains of identifying patients with high-risk disease who will benefit the most from intensified therapy, while de-escalating treatment in those likely to be cured by less toxic regimens, to minimize the long-term morbidity and mortality seen in a minority of survivors, without comprising outcomes. This article will outline the emergence of new biomarkers to aid risk stratification and guide treatment decisions at diagnosis, the use of different response-adapted approaches, and the incorporation of new targeted agents in the treatment of both younger and older patients, in a more personalized approach to therapy.

2 | APPROACHES IN YOUNGER PATIENTS WITH HODGKIN LYMPHOMA
The initial treatment of advanced-stage HL with either bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (escalated BEACOPP) or doxorubicin, vinblastine,
bleomycin, and dacarbazine (ABVD) is guided by risk stratification at diagnosis, comorbidity, and patient preference. Excellent disease control is achieved with more intensive BEACOPP regimens; however, this is at the price of increased acute toxicity and long-term morbidity, including second malignancies, infertility and cardiovascular disease among survivors, when compared to less intensive regimens. The use of six cycles of ABVD compared to four cycles of escBEACOPP plus two cycles of standard BEACOPP in the Italian HD2000 study showed no difference in 10-year OS, despite a significant difference in progression-free survival (PFS) in favor of the BEACOPP group at 5 years. This is perhaps explained by the significantly lower rates of second malignancy in patients treated with ABVD than when compared to escBEACOPP (0.7% vs. 6.6%) and the success of autologous stem cell transplant (ASCT) in the salvage of relapsed disease. In the modern era, morbidity is predicted to be lower as the number of BEACOPP cycles has been reduced using a PET-directed approach; however, identification of patients with higher risk disease at diagnosis seems important for choosing the correct intensity of therapy, to optimize the chance of cure.

Risk stratification of patients’ disease by the International Prognostic Score (IPS) has previously been used to guide clinicians with initial treatment decisions; however, compared to the dynamic assessment of response by PET, it is less able to identify those patients with high-risk disease that have a poorer outlook. The incorporation of biologic features such as gene expression profiles in addition to IPS has so far not yielded any prospectively validated biomarkers, but measurement of metabolic tumor volume (MTV) and total lesional glycolysis (TLG) at the baseline PET may provide a more quantifiable assessment of tumor burden, a known predictor of poor outcome. The European collaborative group retrospectively analyzed baseline total MTV (TMTV) in 258 patients with early-stage HL in the standard combined modality arm of the H10 trial and showed that both TMTV and interim PET (iPET) following two cycles of ABVD were independently prognostic of response to treatment, and when combined, allowed identification of a high-risk patient group with a 5-year PFS of only 25% (TMTV >148 cm³ and iPET positive—Deauville Score [DS] 4–5). In this study, the TMTV was calculated by summing all the extranodal and nodal lesions using the 41% maximum standardized uptake value threshold (SUVmax) method. In advanced-stage disease (stage IIB–IV), 848 patients enrolled in the RATHL trial had baseline total/bulk MTV and TLG measured using SUV ≥ 2.5 when compared to the liver (the 41% SUVmax method was found not to be associated with PFS or 3-year HL events in this patient cohort). Patients with a positive iPET following two cycles of ABVD had a significantly higher total/bulk MTV and TLG when compared to iPET-negative patients (p = 0.0002); however, in a multivariate analysis, only total TLG, B symptoms, and age were significantly associated with PFS. Patients with a negative iPET and high-volume TLG at baseline (defined as >3318 g) had a 5-year treatment failure rate of 31%, compared with 13.1% in low-volume TLG. A study which retrospectively analyzed a total of 392 patients enrolled in both arms of the AHL 2011 LYSA trial identified a small number of patients with a high-baseline PET TMTV (set at a threshold of 350 ml using the 41% SUVmax method) who had a positive iPET (DS 4–5) following two cycles of escBEACOPP, with a 2-year PFS of 61% compared to 88% and 96% in patients with a low MTV/positive iPET and a low MTV/negative iPET, respectively. The rate of progression among patients with stage IV disease and a negative iPET in the RATHL trial was 20% compared with less than 10% of patients enrolled in the GHSG H18 trial and LYSA study, suggesting a more reliable negative predictive value of iPET after more intensive regimens such as escalated BEACOPP in patients with high-risk disease. Thus, baseline total MTV and TLG may prove useful in the context of guiding initial intensity of treatment, by identifying those at risk of treatment failure despite a negative iPET.

Prospective validation of this potential biomarker in a large clinical trial is needed to ascertain its true prognostic value.

Patients with advanced-stage HL and a positive iPET after two cycles of ABVD in the RATHL trial went on to receive escalated treatment with more intensive BEACOPP regimens (four cycles of escBEACOPP or six cycles of BEACOPP-14), with a 5-year PFS of 65.7% and OS of 85.1%. This compares favorably to continuation of ABVD following iPET in previous studies, where the PFS was consistently less than 40%. The South West Oncology Group (SWOG) 0816 trial showed at 5-year follow-up, 59 patients with advanced-stage HL (here defined as stage III–IV) and a positive iPET (DS 4–5) escalated to escBEACOPP after two cycles of ABVD had a similar PFS of 66%, but the rate of second malignancy was 14% with a short median onset of 4.2 years. In this study, six cycles of escBEACOPP were given compared to four cycles in RATHL, which may partly explain the high rate of secondary malignancy. The GHSG H18 trial showed that patients with iPET-positive disease following two cycles of escBEACOPP who were treated with a total of six cycles of escBEACOPP had a secondary malignancy rate of 9% at 5.5 years of follow-up.

In the RATHL study, the treatment failed despite escalation to BEACOPP regimens in 20 out of 37 patients with a DS of 5 on iPET, and this group almost certainly requires a different approach to improve their survival. The use of salvage therapy with high-dose chemotherapy (HDT) followed by ASCT is an option for patients with initial chemorefractory disease, and was investigated by the Italian HD0801 trial. Here a positive iPET was defined as a DS of 3–5, and therefore included a more favorable patient group when compared to outcomes from RATHL and LYSA trials. Following two cycles of ABVD, 81 (19%) patients remained iPET positive and received HDT ASCT, with a 2-year PFS of 75% suggesting that early intensification might improve outcomes for this group. The use of newer agents such as brentuximab vedotin (BV) and anti-PD1 antibodies in the frontline treatment of patients with high-risk iPET-positive disease may provide an alternative to ASCT, given their activity in the relapsed/refractory disease; however, there is as yet little data to support their use in a PET-driven approach for this selected group of patients. The Phase III ECHELON-1 trial
incorporated six cycles of brentuximab with AVD chemotherapy (A + AVD) and showed a 3-year modified PFS (including a DS 3–5 at the end of treatment as an event) of 83.1% compared with 76.2% in patients' receiving six cycles of ABVD (7.1% difference \( p = 0.005 \)), with a beneficial trend observed in iPET-positive patients <60 years receiving A+ AVD (3-year PFS 69.2% vs. 54.7%, respectively). Therefore, A+ AVD may be an attractive option for those patients with high-risk disease who wish to reduce the risk of long-term toxicity associated with BEACOPP regimes or who are unable to tolerate escalation of therapy following a positive iPET.

In early stage unfavorable disease, the addition of BV to four cycles of AVD within in a phase II PET-directed pilot study in the United States allowed the reduction of dose and intensity of radiotherapy without apparently compromising treatment efficacy, with a 2-year PFS of 97% among 29 patients who did not receive any consolidation radiotherapy. \(^1^\) The phase III GHSG H17 trial in a similar patient cohort also showed that the omission of radiotherapy in those with a negative PET following two cycles of ABVD plus two cycles of escBEACOPP was noninferior in terms of 5-year PFS (2.2% difference in favor of the radiotherapy group). \(^2^\) An initial high-intensity approach in the early-stage disease thus appears to maximize cure rates without the need for consolidation radiotherapy in those patients with a negative PET at the end of the treatment, showing an improvement in the negative predictive value of iPET when compared to the use of less intensive regimens.

The RATHL trial showed that the omission of bleomycin in patients with a complete metabolic response at iPET did not compromise survival outcomes, and resulted in a lower incidence of pulmonary toxicity (5-year PFS and OS 84% and 98% vs. 86% and 97%, respectively). \(^3^\) Similarly in the AHL 2011 LYSA trial, 5-year PFS was not significantly different between patients treated with combined escBEACOPP or de-escalated to ABVD (86.2% standard arm vs. 85.7% PET-driven arm) leading to the conclusion that therapy can be reduced in those patients whose disease responds to initial therapy without compromising survival outcomes. \(^4^\) The optimal number of escBEACOPP cycles was investigated by the GHSG H18 trial in this context, and showed that in patients with a negative iPET (DS 1–2) following two cycles of escBEACOPP, the duration could be safely reduced to two further cycles, with a small but statistically significant improvement in 5-year survival outcomes when compared to four cycles (PFS 92.2% vs. 90.8% OS 97.7 vs. 95.4%, respectively). \(^5^\) For patients with an IPS score of 1–2 and favorable baseline characteristics, an initial two cycles of ABVD with de-escalation to AVD if iPET negative and escalation to four cycles of escBEACOPP if iPET positive has a high probability of cure while minimizing the number of patients exposed to the acute and long-term toxicity of BEACOPP regimes. The omission of radiotherapy in those patients with a complete metabolic response did not affect survival outcomes in the GHSG H15 study \(^6^\) and only 6.5% of patients received consolidation radiotherapy without loss of disease control in the RATHL trial. \(^7^\) There may be a role for radiotherapy in single-site iPET-positive disease to reduce the number of patients escalated to more intensive chemotherapy regimens; however, there is currently a lack of prospective data supporting this approach.

### 3 IMMUNE CHECKPOINT INHIBITORS AND EMERGING BIOMARKERS

The use of immune checkpoint inhibitors (ICI) in relapsed Hodgkin lymphoma is well established, and the use of anti-PD1 antibodies combined with multi-agent chemotherapy is being explored in the first-line setting. A study of affected nodes in those treated with anti-PD1 antibodies showed modification of the HL microenvironment in response to anti-PD1 therapy, with rapid depletion of HRS cells and a reduction in PDL1-expressing tumor-associated macrophages and regulatory T cells. \(^8^\) There was no clonal expansion and activation of cytotoxic T cells as is seen in solid tumors, suggesting a mechanism of action that is particular to HL, involving interruption of T cell–B cell signaling pathways. Combination of nivolumab with AVD chemotherapy (N + AVD) for advanced-stage HL (stage IIB–IV) was investigated by Ramchandren et al. who first gave nivolumab monotherapy for 4 doses, followed by combination therapy (N + AVD) for 12 doses every 2 weeks, with response assessment at the end of monotherapy, after two combination cycles and at the end of the therapy. \(^9^\) Interestingly, at the end of monotherapy, the complete response rate was 21%, with all patients in the highest quartile for expression of PDL1 on HRS cells achieving a CR after combination therapy, maintained at 32 weeks of follow-up. Discontinuation rates were low (10%) with a febrile neutropenia rate of 10%. The most common endocrine immune-mediated adverse event (IMAE) was hypothyroidism, and the main nonendocrine IMAE was rash (grade 1–2). Generally, the regimen was well tolerated, but there was one treatment-related death in an older patient, in CR after two cycles of combination therapy who experienced four grade 3–4 adverse events. \(^10^\) The use of pembrolizumab monotherapy prior to 4–6 cycles of AVD in 30 patients with early unfavorable and advanced disease showed an impressive 100% CR rate by the end of two cycles of AVD. Responses were durable, with no progression or death at 22 months of follow-up, with no consolidation radiotherapy given at the end of the treatment. \(^11^\) Phase III trial data comparing N + AVD versus BV + AVD in the first-line setting are awaited.

The pattern of disease response in the context of anti-PD1 therapy has prompted revision of the Lugano Classification lymphoma response criteria, to include immunomodulatory therapy (LYRIC), due to early imaging suggestive of progressive disease (PD) in patients who later gained clinical benefit. \(^12^\) The phenomenon of tumor flare or pseudo-progression is well documented in patients with solid tumors treated with ICI, as a result of immune cell infiltration or the delayed effect of these drugs allowing early tumor growth. The use of early iPET to guide response-adapted treatment in HL may be particularly difficult to interpret in this context, with the risk of tumor flare interpreted as a positive iPET and patients subsequently escalated to more intensive regimes and exposed to unnecessary toxicity whose disease may have responded at a later time point. This resulted in the addition of indeterminate response (IR) to CR PR and PD and allows the flexibility for patients to continue treatment with further imaging at 12 weeks to confirm either PD or response (Table 1). There may be a role for anti-PD1...
therapy in those patients with a DS of 5 on iPET as an alternative to escalation of therapy to more intensive regimes, whose disease is refractory to traditional chemotherapy.

4 | APPROACHES FOR OLDER PATIENTS WITH HODGKIN LYMPHOMA

The use of BV and ICI in the elderly may be an attractive option as monotherapy, or in combination with less toxic chemotherapy regimens, to improve the poorer survival outcomes when compared to the younger population. The problems of comorbidity, poor performance status (PS), increased adverse events, and low tolerance of chemotherapy regimens at full dose in this heterogeneous population have resulted in the reported 3-year PFS and OS rates of 55% and 78%, respectively. Evens et al. investigated BV in sequential combination with AVD in 48 patients over 60 with untreated HL (stage II–IV) in a Phase II trial, which showed encouraging 2-year PFS and OS of 84% and 93%, respectively. Patients were given two cycles of lead-in and consolidation BV, based on previous studies which have shown poor durability of responses in older patients treated with BV monotherapy or BV plus dacarbazine. Only 52% of patients completed the full course.
of therapy owing to side effects, but 75% of patients who completed less than six cycles of AVD remained in CR at 2 years. Longer follow-up is needed to ascertain if these responses are durable and to assess the long-term cardiotoxicity associated with receiving anthracycline chemotherapy in this patient cohort which included eight patients >80 years and 9 patients with a PS of 2.

The combination of N + AVD may prove to be a promising strategy in fit older patients able to tolerate anthracycline chemotherapy plus ICI therapy as initial treatment. The Phase II trial by Ramachandren et al. detailed above included six patients over 60, five of whom obtained a CR, while one died from toxicity related to treatment. Data from a larger Phase II trial combining nivolumab with AVD in older patients with high-risk disease (IPS score ≥3) and a positive iPET (DS 4–5) are awaited (NCT03033914) to assess the activity and safety of this regimen in a larger cohort of patients.

A chemotherapy-free approach in older patients is an attractive one in those with poor performance status. A Phase II study combining nivolumab and BV (N + BV) in elderly patients with a PS of 0–1 by Yasenchak et al. showed a CR rate of 72% following 16 cycles of treatment that was well tolerated. A subsequent interim analysis of a similar phase II trial which included a patient population with poorer PS (0–2) showed a more modest ORR of 61% with CR of 48% following eight cycles of treatment, which unfortunately did not meet the predefined ORR of 68% and was therefore terminated early. The frequency of adverse events was reduced compared to the smaller trial (26% vs. 37% sensory neuropathy [all grades], respectively) which may be explained by the difference in the number of cycles received. The strategies to reduce the number of treatment cycles without compromising survival should be explored in future, to minimize toxicity and allow the majority of patients to complete therapy with minimal dose reductions and treatment interruptions.

The use of comprehensive geriatric assessment (GCA) and quality-of-life (QOL) outcomes in older patients are recommended, but data on their feasibility are lacking in the prospective clinical trial setting. Evens et al. used the Cumulative Illness Geriatric (CIRS-G)
comorbidity score (https://www.mdcalc.com/cumulative‐illness‐rating‐scale‐geriatric‐cirs‐g) to stratify patients into high or low groups at diagnosis (CIRS‐G score cut‐off 10); however, in a multivariable analysis, this was not significant in predicting PFS, while the loss of instrumental activities of daily living (IADLs) was predictive of both OS and PFS, with 2‐year PFS of 94% versus 25% in patients with no IADL loss versus IADL loss and 2‐year OS of 97% versus 67%, respectively. This assessment is quick and convenient for the busy oncologist to use in the clinic, to inform the initial treatment decisions, and help tailor initial therapy to each individual patient’s circumstances (Table 2).

5 | CONCLUSIONS

The use of PET‐directed therapy in younger patients with advanced HL has allowed safe de‐escalation of treatment for those with responsive disease at iPET, sparing the acute and long‐term toxicity of more intensive chemotherapy regimens and consolidation radiotherapy. Figure 1 summarises the approaches currently in use, and some of the areas of emerging evidence for new treatments. Further information regarding high‐risk features at diagnosis in the PET‐directed era is required, however, and measurement of baseline PET characteristics may prove a valuable predictive biomarker. The use of ICI therapy as part of initial therapy, guided by prospective trials incorporating biomarkers related to the tumor microenvironment is awaited, although the use of PET‐directed therapy in this context is likely to be more complex, with the phenomenon of tumor flare and delayed response making interpretation harder. The use of BV and ICIs in older patients appears promising; however, prospective incorporation of geriatric and QOL assessment into clinical trials is currently lacking. The use of IADL assessment may provide oncologists with a tool to quickly assess patients in the clinic and help with decision‐making in this complex patient population.

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