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Classic Hodgkin Lymphoma: The LYSA pragmatic guidelines

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ABSTRACT

Classic Hodgkin lymphoma (HL) is a distinct entity among hematological malignancies of B-cell origin. It is characterized by its unique histopathological features and generally favorable prognosis. Over the years, advancements in understanding its pathogenesis, coupled with refined diagnostic and evaluation modalities, as well as therapeutic strategies, have significantly transformed the landscape of HL management. In this article, we present a comprehensive set of recommendations for the management of HL, encompassing various aspects of diagnosis, risk stratification, evaluation, and treatment. These recommendations are based on the latest evidence-based guidelines, expert consensus opinions, and clinical trial data, aiming to provide clinicians with a practical framework for delivering optimal care to patients with HL.

1. Introduction

Classic Hodgkin lymphoma (HL) is considered a highly curable disease. Frontline treatment typically consists of chemotherapy with or without radiotherapy (RT). Although these treatments are curative for most patients, a subset of patients experience refractory disease or relapse, requiring salvage therapy. Consequently, there remain several key unsolved questions in HL: what is the best approach to cure patients with minimal late toxicities, and what is the optimal strategy and regimen for refractory patients?

There is a wealth of evidence-based medicine available, but also various practices that have been adopted by centers of expertise in HL. The LYmphoma Study Association (LYSA) group proposes consensus guidelines that reflect the best available evidence-based medicine while considering reasonable proposals that have been widely adopted and are applied in clinical practice by LYSA experts in the field.

Levels of evidence and grades of recommendations have been applied according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) nomenclature[1].

Of note, other important aspects of HL patient care which are the specific follow-up, especially for second cancer screening, supportive care, and fertility, are not mentioned here.

2. Role of positron emission tomography (PET) in the overall management of Hodgkin lymphoma

PET/CT is currently used in standard clinical practice to guide the following aspects of clinical management of HL: staging [2–4], prognostics [5,6], treatment guidance (including consolidation radiotherapy) [2] and response assessment [2, 4, 6].

During lymphoma staging, PET/CT leads to the upstaging of up to 15 % of patients staged with conventionally based on contrast-enhanced computed tomography (Ce-CT) and bone-marrow trephine biopsy (BMB) [5,7]. PET/CT proved more sensitive that Bone Marrow Biopsy, being able to detect Bone Marrow Invasion (BMI) in several patients with a negative BMB: However, only a focal FDG uptake pattern has been considered an harbinger of HL in bone/bone marrow [8].

Thanks to the introduction of semiquantitative metrics for PET/CT reading, is now possible to measure the total tumor burden (total metabolic tumor volume (TMTV)), using a standardized uptake value (SUV) segmentation threshold to delineate tumor uptake of each individual tumor lesion. Regardless of the method used to measure its value, TMTV is a proven means of predicting the treatment outcome with high accuracy both in early and advanced-stage disease [6, 9, 10]. In the standard arm of the H10 trial, a high TMTV identified high-risk early--stage HL patients. The presence of a small TMTV reclassified more than 70 % of EORTC/GELA unfavorable early-stage HL patients into a low-risk group.

In the LYSA study BREACH, conducted in early-stage unfavorable HL, a high TMTV was associated with significantly shorter progression-free survival (PFS) regardless of the study arm with or without brentuximab vedotin (BV) (hazard ratio (HR) 17.9; 95 % CI, 2.2 to 145.5; $P < .001$). High TMTV was associated with a 2-year PFS rate of 90.9 % (95 % CI, 74.4 to 97.0) and 70.7 % (95 % CI, 39.4 % to 87.9 %) in the BV-AVD and ABVD arms, respectively [11].

In advanced-stage disease, TMTV along with the International Prognostic Score (IPS), patients with a negative interim PET after 2 cycles of frontline ABVD and candidate to continue ABVD, those with low IPS score (0−1) and low TMTV had a PFS of 100 %, while patients with high TMTV and high IPS had a very poor outcome with a 3-year PFS of only 57 %. Patients with both a high TMTV and a low IPS score, or a low TMTV and an IPS score ≥ 2 had an intermediate outcome, with 3-year PFS of 85 % [12]. In advanced disease in patients treated with upfront escalated BEACOPP, TMTV was also shown to impact PFS. In the AHL2011 study [13–15], the high TMTV group had 5-year PFS of 84 % compared to 90 % in the low TMTV group (HR 1.68; 95 % CI: 1.09–2.6; $p < 0.02$). Other baseline PET metrics are currently being explored, including the maximal distance (Dmax) which measures the Euclidian distance between the furthest lesions. Dmax was also found to identify patients with different outcomes. In the AHL2011 study, the combination of baseline TMTV and Dmax identified a high-risk group of patients (high Dmax and high TMTV patients had lower PFS compared to other groups: 5-year PFS 83 % vs 92 %; HR 2.4 95 % CI: 1.45–3.96). These metrics overcome the prognostic value of IPS and provide additional prognostic information to interim PET [15].

Interim PET/CT, when performed after 2 cycles of chemotherapy (PET2), can be used to assess tumor chemosensitivity and appears to be the most accurate predictor of treatment outcome both in early and advanced stage HL [12]. In early-stage disease, the sensitivity, specificity, and accuracy of PET2 were 65.5 %, 92 %, and 89 %, respectively. The positive and negative predictive values (PPV and NPV) of PET2 were 30–54 % and 88–95 %, respectively. In advanced-stage disease, the sensitivity, specificity, and overall accuracy of PET2 for predicting 2-year PFS were 77–81 %, 83–97 %, and 92 %, respectively. The PPV and NPV were 57–93 % and 90–92 %, respectively. It is important to note that, in the AHL2011 study, the threshold used for a Deauville score of 3 was $\leq$ 140 % of liver SUVmax, which should be used systematically for patients with advanced-stage HL[16]. In summary, the performance

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of PET2 was not as good in early compared to advanced-stage disease due to lower sensitivity and positive predictive value in limited stage disease and to a patient "rescue" of Radiotherapy when performed after ABVD chemotherapy. Moreover, preliminary data from the RAFTING trial seem to suggest that end-of-therapy PET has a higher predictive role in early favorable HL compared to PET2 [10]. The inferior performance of PET2 in early-stage disease was confirmed in three large, randomized clinical trials in early-stage favorable disease comparing chemotherapy alone versus combined-modality treatment (CMT) with ABVD x 2–4 cycles versus the same treatment plus involved nodal radiotherapy (INRT). In the RAPID [17], H10 EORTC [18] and GHSG HD16 trials [19], totaling 1519 patients, the 5-year PFS of patients with a negative PET2 treated with chemotherapy alone (2–4 ABVD cycles) were 90.8 %, 87 % and 86 % versus 94.6 %, 99 % and 93.2 % for patients treated with CMT. In these studies, most treatment failures were recorded in the first year of follow-up.

The standard Deauville score should be used with caution to assess treatment response in HL patients during and after immune checkpoint inhibitors (ICI) treatment, confirming that inflammation secondary to a restored cellular immune response underpins the mechanism of action of this category of drugs. Therefore, the concept of "indeterminate response (IR)", defined as a higher uptake of one or several lesions without new lesions or size change, was proposed to assess the response to ICI therapy in the so-called LYRIC (Lymphoma Response to Immune Checkpoint inhibitors) by introducing the paradox of assessing the response with the so-called "Indefinite Response" (IR) criteria [20]. Unfortunately, these criteria, which sound contradictory, are also scarcely reproducible in clinical practice, and pseudo progressions occur more seldom in HL than in solid cancers. No prospective reports to validate IR criteria have been published so far.

Expert point of view:

- PET is required at baseline and for response assessment [I, A].
- Bone marrow biopsy is unnecessary for disease staging at baseline if PET was performed [IV, A].
- PET2 should be performed regardless of stage and treatment regimen, because of its excellent prognostic value and ability to guide treatment intensity [I, A].
- $\leq$ 140 % of liver SUVmax should be used to define a Deauville-3 score in advanced HL (stages III-IV and IIB with risk factors) [I, B].

3. Management of early-stage Hodgkin lymphoma

HL is commonly classified as early-stage (Ann Arbor stage I-II) or advanced-stage (stage III-IV) disease. Patients with early-stage disease are then further stratified into favorable or unfavorable (i.e. "intermediate") based on clinical features that are summarized in Table 1. In stage IIB HL, bulky mediastinal or extranodal disease is an adverse prognostic factor, and these patients should be treated like those with advanced disease. Nevertheless, patients with early-stage disease have a very favorable prognosis and, in general, a very good response after salvage therapy. Therefore, in this patient subset, it is particularly important to consider the acute (infections, cytopenias) and late effects of chemotherapy and radiotherapy (e.g. secondary malignancies, cardiac and pulmonary toxicities, thyroid disease, carotid fibrosis) when deciding on the optimal first-line therapeutic approach.

Table 1
Risk factors for early-stage Hodgkin lymphoma.

LYSA/EORTC	*GHSG*	*NCCN*
Large mediastinal mass: Med/Tho > 0.33 – 0.35 *		
B symptoms and ESR $\geq$ 30mmESR $\geq$ 50 mm		B symptoms or ESR $\geq$ 50 mm
Age $\geq$ 50 years	Extranodal disease	Bulky > 10 cm
$\geq$ 4 out of 5 areas (sus-diaphragmatic)	$\geq$ 3 out of 11 areas (sus and subdiaphragmatic)	$\geq$ 4 regions

* med/tho: mediastinum-to-thorax ratio measured at the T5-T6 vertebral disk level. *EORTC/LYSA, 0.*35; GHSG/NCCN, 0.33.
EORTC, European Organisation for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; LYSA, Lymphoma Study Association, NCCN, National Comprehensive Cancer Network

3.1. Early favorable Hodgkin lymphoma (early-F HL)

The GHSG HD10 study proved that two courses of ABVD followed by 20 Gy involved-field RT (IFRT) is an appropriate treatment approach in patients presenting early-F HL. Long-term follow-up showed that 87 % of patients were progression-free at 10 years [21]. Based on GHSG criteria, this strategy should be applied only to patients with two involved nodal areas (Table 1); patients with three areas should be treated with the standard described in the EORTC/LYSA group. The LYSA/EORTC/FIL H10 study reported excellent results in the standard arm (3 ABVD + 30 Gy INRT) in early-F HL patients (according to LYSA/EORTC risk factors, Table 1**,** Fig. 1), with a 10-year PFS rate of 99 % in the PET2 negative group [22,23] (Fig. 2).

Three trials have studied the RT-free approach compared to CMT in early-F HL. The H10 (EORTC/LYSA/FIL), RAPID (UK group) and HD16 (GHSG) trials compared respectively 4, 3 and 2 ABVD courses with or without RT in patients with negative interim PET (after 2 ABVD in H10 and HD16, 3 ABVD in RAPID) [17, 19, 22]. None of these trials demonstrated non-inferiority of radiotherapy-free regimen. However, the 5-year PFS of patients with negative interim PET (after 2 or 3 ABVD) treated with chemotherapy alone was approximately 90 %; the omission of RT may therefore be discussed if the risks appear to outweigh the expected benefit of 5–10 % of PFS, without an expected benefit in overall survival (OS) due to the efficacy of the salvage regimen. Indeed, a recent update of the H10 trial with 10-year follow-up in PET2 negative patients confirmed that the outcome with chemotherapy alone was similar to that of patients treated with CMT: 10-year OS of 100 % versus 98 % [23].

In patients with a positive PET2 (defined as a Deauville score > 2 according to IHP criteria), the LYSA/EORTC/FIL H10 study reported excellent results for treatment escalation with 2 courses of eBEACOPP (escalated BEACOPP) followed by RT in comparison with 2 ABVD + RT (PFS 90.6 % vs. 77.4 % at 5 years). It should be noted that after 10 years of follow-up of the H10 trial, the outcome of PET2 + patients (involving a smaller number of patients than in the initial publication) switching from ABVD to eBEACOPP was no longer showed a statistically significant benefit in favor of BEACOPP escalation, maybe related to the follow-up loss of some patients in this analysis. Nevertheless, this extended follow-up found that BEACOPP escalation is not associated with greater toxicity.

The IFRT used in GHSG trials and the less extensive involved-node radiotherapy (INRT) used in the EORTC/LYSA groups have not been compared prospectively, but both have shown excellent results with long-term toxicities that are expected to be lower than those associated with INRT. Since INRT (meaning PET-CT in radiotherapy treatment position) is difficult to use in everyday practice, the International Lymphoma Radiation Oncology Group (ILROG) now recommends **involved-site radiotherapy** (ISRT) if INRT cannot be use due to the lack of proper baseline imaging [24]. These guidelines are regularly updated by the ILROG [25].

Otherwise, in order to avoid long-term toxicities, extremely safe new radiation techniques can be used, such as intensity modulated radiation therapy (IMRT) or protons in selected cases [26].

Expert point of view:

- The treatment of early-F HL relies on 2 or 3 courses of ABVD (according to the number of areas) and radiotherapy (20 or 30 Gy, 2Gy/

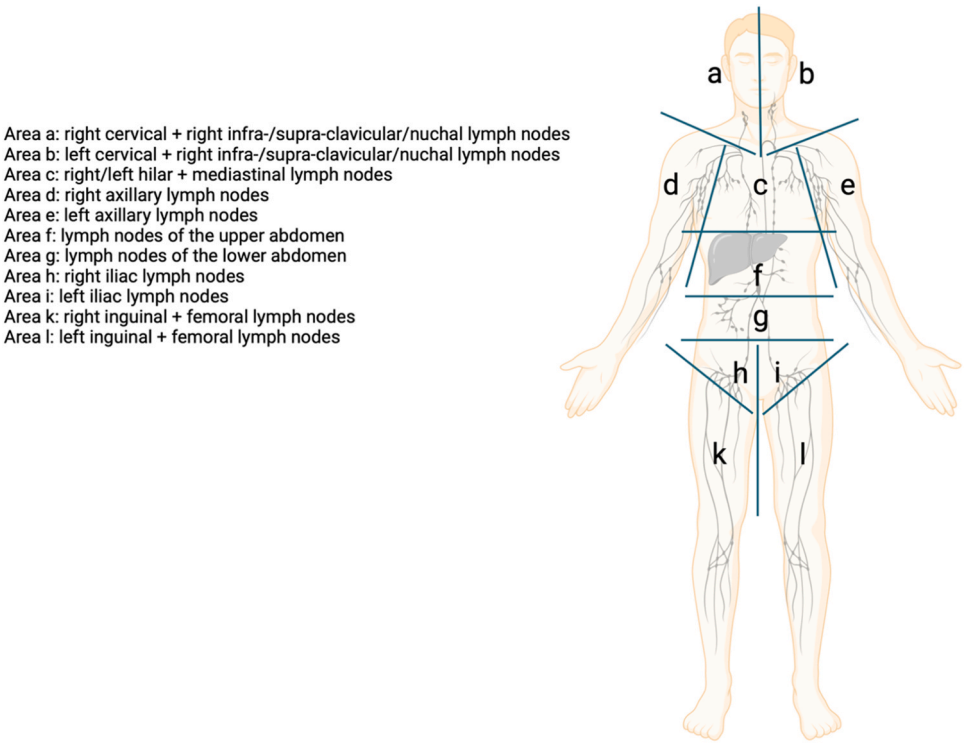

Fig. 1. Lymph nodes areas counted in the prognostic classification for early-stage Hodgkin lymphoma *(created with BioRender.com)*.

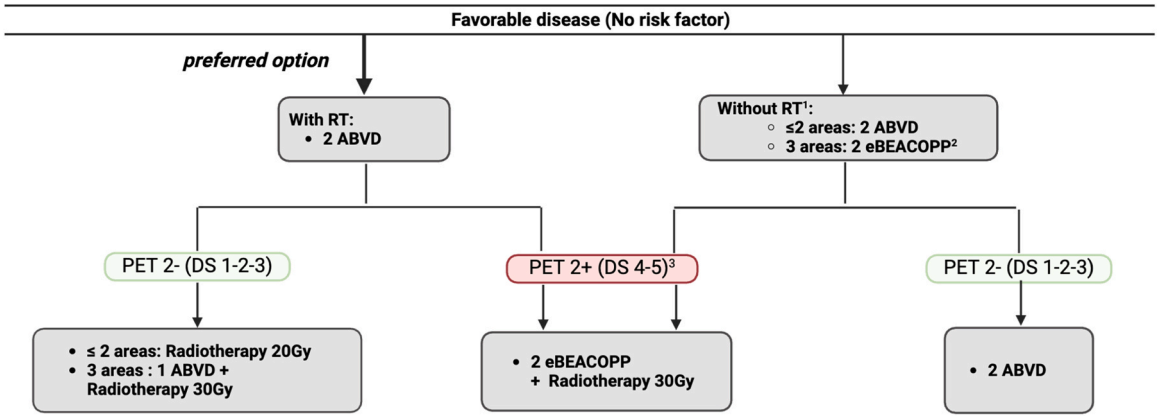

Fig. 2. Management of favorable early-stage classic Hodgkin lymphoma/ [1]Avoid RT in young patients (notably women) < 30 y-o, subcarinal adenopathy, large RT field. [2]According to HD17 study. [3]PET pos = DS ≥ 4, Consider salvage therapy if progression on TEP2.

fraction), as no study has proven the non-inferiority of chemotherapy alone [I, A].

- ISRT is currently the standard of treatment, using modern and safe RT techniques [III, A].
- In patients considered at risk of long-term effect (eg. Subcarinal lymph nodes, <30 years old, large RT field) following RT, a regimen including 4 courses of ABVD is an acceptable option [IV, C], or according to HD17 if 3 areas are involved [I, B].
- Two courses of eBEACOPP + 30 Gy in 15 fractions are recommended in case of positive PET2 [II, B].

3.2. Early unfavorable Hodgkin lymphoma (early-U HL)

ABVD-based strategies.

The historical standard of treatment for early-U HL is CMT with 4 courses of ABVD followed by 30 Gy IFRT, resulting in 3-year PFS of around 85–90 % [27,28]. The EORTC/GELA-H9 trial demonstrated that this schedule was non-inferior to 6 courses of ABVD + radiotherapy, or 4 courses of standard BEACOPP + radiotherapy [28]. The field of radiotherapy is nevertheless often extensive in early-U (numerous areas or bulk), which may raise late toxicities of RT. In patients with a negative PET2, continuation with 4 additional courses of ABVD (i.e. 6 in total)

without consolidative radiotherapy was associated with a small excess risk of relapse compared with the standard CMT in the EORTC/LYSA/FIL-H10 trial (5-year PFS 89.6 % vs. 92.1 %) [18]. It was recently demonstrated that this excess of risk vanished after 10 years of follow-up (10-year PFS 86.5 % vs 91.4 %, p = 0.8577) [23]. In patients with positive PET2, escalation with 2 courses of eBEACOPP followed by RT improves PFS in comparison with 2 ABVD + IFRT (90.6 % vs. 77.4 % at 5 years in the H10 trial) [18].

Expert point of view:

- ABVD-based treatments of early-U HL consist of 2 courses of ABVD followed by 2 additional courses of ABVD + ISRT 30 Gy in 15 fractions or 4 additional courses of AVD alone in case of negative PET2 [II, A].
- Two courses of eBEACOPP + ISRT 30 Gy in 15 fractions are recommended in case of positive PET2 [II, B].

eBEACOPP-based strategies.

The HD14 trial demonstrated that the "2 + 2" regimen, combining 2 courses of eBEACOPP plus 2 courses of ABVD (followed by RT 30 Gy) was superior to 4 ABVD + RT (5-year PFS 95.4 % vs. 89.1 %), but without a benefit in OS [28]. The HD17 trial subsequently demonstrated that omitting consolidative RT in CMR patients after the "2 + 2" regimen was feasible without increasing the risk of relapse (5-year PFS 96 %) [29]. 10-year follow-up data from the HD14 trial was reassuring regarding the long-term toxicity of the "2 + 2" regimen and showed an identical rate of secondary neoplasia between the "2 + 2" and ABVD x4 arms (around 2 - 3 %, including < 1 % myeloid malignancies) [30]. In women under 30, the impact on fertility also appears to be modest, with similar rates for the recovery of a regular menstrual cycle (around 95 %) [31]. Considering its efficacy and safety profile, the "2 + 2" regimen may be considered as the standard treatment of patients with early-U HL deemed eligible for eBEACOPP.

In the HD17 trial, only an end-of-chemotherapy PET (PET4) was performed, and patients with a Deauville score of 4 on PET4 had a lower 5-year PFS of 81.6 %, even after irradiation, compared to patients with a Deauville score of 3 or less. On the contrary, patients with a Deauville score of 3 were considered as having a per protocol positive PET4, but had outcomes similar to patients with a Deauville score < 3. These patients should therefore not be considered for subsequent radiotherapy.

It should be emphasized that the value of PET2 in patients treated with the "2 + 2" regimen has not been formally demonstrated. Given the known prognostic value of positive PET after 2 courses in ABVD-based strategies [18,32] as well as eBEACOPP-based strategies in advanced HL [13], the expert panel advises that a PET2 assessment should be performed in early-U HL patients treated with a "2 + 2" schedule. In poor responder patients, continuation with 2 additional courses of eBEACOPP may be discussed after the 2 initial courses. In positive PET4 patients, a biopsy should be performed to rule out residual disease, and irradiation should be reserved for non-refractory patients or those for whom a biopsy is not possible (Fig. 3).

Expert point of view:

- The eBEACOPP-based strategy should be the standard treatment for fit patients rather than the H10 strategy. It consists of a "2 + 2" schedule without consolidative radiotherapy [I, A].
- In the case of PET4 positivity, consolidative RT may be proposed only after a biopsy has been performed (if feasible) to rule out refractory disease [V, B].

4. Management of advanced stages of Hodgkin lymphoma

4.1. Strategy with conventional chemotherapy

Traditional treatment of advanced HL is based on multi-agent chemotherapy regimens like ABVD or eBEACOPP. The original eBEACOPP protocol designed with 6 or 8 cycles was shown to cure ~80 % of patients and improve PFS but not OS compared to ABVD [23,33]. It was related to substantial acute toxicities such as neutropenia, or late toxicities such as secondary malignancies and infertility, highlighting the need to better balance therapeutic intensity and curative goals.

In the last decade, the LYSA group designed the AHL2011 non-inferiority study [13,14], proposing the de-escalation strategy for ABVD after 2 cycles of eBEACOPP in patients with a good response and thus mitigating toxicities. This strategy took into account the very good negative predictive value of interim PET. 5-year PFS was similar in the two arms (86.2 % in the standard arm versus 85.7 % in the PET-driven

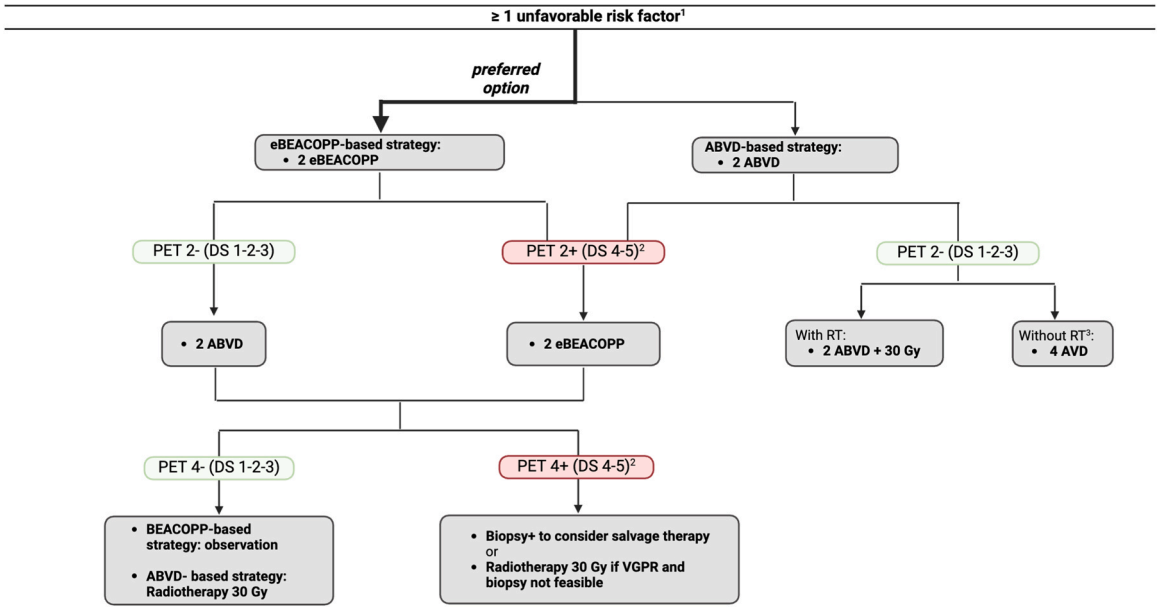

Fig. 3. Management of unfavorable early-stage classic Hodgkin lymphoma. [1] IIB bulky / extra-nodal: consider treating as advanced stages. [2] PET pos = DS ≥ 4, Consider salvage therapy if progression on TEP2. [3] Avoid RT in young patients (notably women) < 30 y-o, subcarinal adenopathy, large RT field.

therapy arm, HR=1.084 p = 0.65) with 84 % of patients from the PET-driven arm receiving a de-escalated treatment. This strategy could be still improved to decrease the risk of lung toxicity by omitting bleomycin. In the RATHL trial, early responders after 2 ABVD cycles were randomly assigned to the ABVD or AVD arm, and the 3-year PFS was similar in both groups, with a significant drop of treatment related to lung toxicity in the AVD group (3 % compared to 10 % in the ABVD group) [32,34]. Another strategy is the maintenance of the intense eBEACOPP regimen while limiting the total number of cycles to 4 in good responders. In the HD18 study [35], 1505 patients with a negative PET2 after two cycles of eBEACOPP were randomized to receive 6 more cycles (4 after protocol amendment) versus two more cycles. The 5-year PFS was similar in both groups, at 91.4 % (95 % CI, 89.0 to 93.2) in the standard group compared to 88.9 % (95 % CI, 86.4 to 91.0) in the experimental group treated with only 2 additional cycles. Hence, patients with negative PET2 could safely receive fewer cycles of eBEACOPP without affecting long-term outcomes.

Despite the caveats of a direct comparison between studies, the strategy starting with eBEACOPP seems to improve tumor control in both PET2 positive and negative patients. The data provided by these trials provide solid arguments that a negative PET2 offers the possibility for de-escalation, thereby reducing toxicity without compromising disease control. Moreover, when comparing the various first-line strategies from a medico-economic and cost-effectiveness point of view, the PET-guided de-escalation strategy is preferable [36], as proposed in the decision algorithm (Fig. 4**)**. According to the strategy selected and the PET response, the number of cycles will be adjusted for eBEACOPP and then ABVD. Even though no prospective randomized trials have been published comparing the de-escalation of AVD versus ABVD after 2 upfront eBEACOPP cycles in PET2 negative patients, we suggest de-escalating with AVD to mitigate toxicities while providing similar outcomes, as demonstrated in the RATHL trial.

Compared to patients with a negative PET2, enrolled in the AHL2011 trial, the 5-year OS of PET2 positive patients was significantly poorer (92.4 vs 96.7 %, HR=3.73, p = 0.0029), and positive PET4 was the main prognostic factor impacting OS [14], leading to salvage therapy proposal for those patients. Inclusion in clinical trials is warranted in this high-risk population. The therapeutic proposals are discussed below.

Regarding patients non eligible for eBEACOPP (ie. age > 60 years old, frail patients and/or with organ dysfunction), we recommend either ABVD or BV-AVD according to the availability of BV. The ECHELON-1 trial demonstrated the superiority of BV-AVD versus ABVD, particularly in patients with stage IV disease and high IPS 4–7 [37,38]. Moreover, it took 11 times more PET2 negative patients compared to PET2 positive to demonstrate a superiority of the experimental arm versus standard ABVD. A 6-year update showed a significant benefit of BV-AVD which resulted in PFS of 82.3 % versus 74.5 % with ABVD (hazard ratio 0.68; 95 % CI, 0.53 to 0.86) and respective OS of 93.9 % (95 % CI, 91.6 to 95.5) in the BV+AVD group versus 89.4 % (95 % CI, 86.6 to 91.7 in the ABVD group. However, this advantage was less clear for patients older than 60 years [39], women, and patients in the low-risk IPS subgroup. Patients in the BV-AVD group experienced more cytopenia and more peripheral neuropathy.

Expert point of view:

- Among the different strategies (HD18, AHL2011, RATHL and ECHELON-1), we recommend de-escalation strategies based on frontline eBEACOPP (HD18 or AHL2011 depending on tolerance of the first two cycles and physician/patient choice) and an approach based on the powerful negative predictive value of PET2 [I, A].
- In patients < 60y ineligible to eBEACOPP, BV-AVD can be used as an alternate [I, A].
- When ABVD is used, we recommend limiting bleomycin to the first two cycles (e.g. 2 eBEACOPP + 4 AVD) [III, B].

4.2. *Incorporation of new drugs*

Strategies involving new drugs have been explored to decrease toxicities while maintaining efficacy. In particular, several trials have tested BV or checkpoint inhibitors combined with chemotherapy as a frontline therapy.

As per the results of the ECHELON-1 study, BV-AVD is now part of the standard frontline therapy options.

The GHSG tested BV-containing eBEACOPP variants in a randomized phase II study for untreated advanced-stage HL. The 3-year PFS was

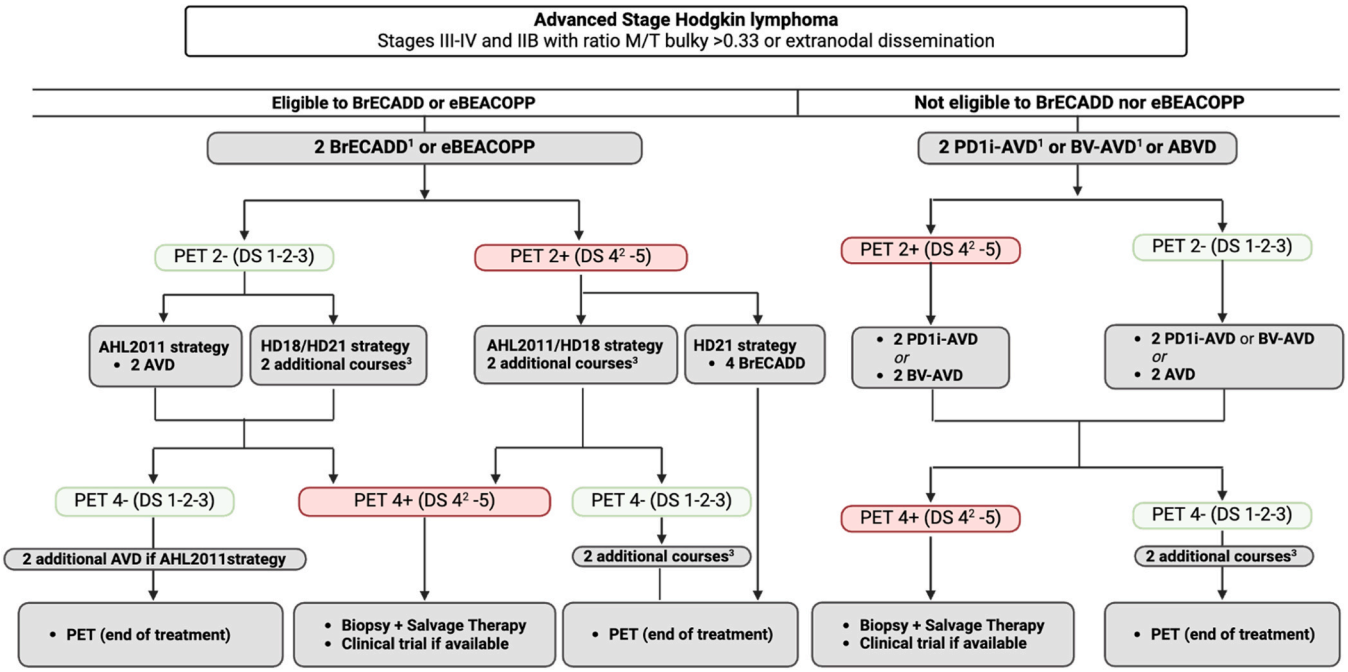

Fig. 4. Management of advanced-stage classic Hodgkin lymphoma. [1]Preferred options, according to access to BV and PD1i. [2]With 140% of liver background as treshold. [3]Pursuing the frontline regimen that led to PET-.

89.7 % with BrECADD (BV plus etoposide, doxorubicin, cyclophosphamide, dacarbazine and dexamethasone) and 90.2 % with BrECAPP (BV plus etoposide, doxorubicin, cyclophosphamide, procarbazine and prednisone). Results were non inferior to standard eBEACOPP and BrECADD protocol was associated with more favorable toxicity profile and thus, was selected to challenge eBEACOPP in the HD21 trial [40]. The results of HD21 after 48 months of follow-up showed that the efficacy of BrECADD was superior to eBEACOPP (94.3 % PFS for BrECADD and 90.9 % PFS for eBEACOPP; HR: 0.66; $p < 0.035$). The BrECADD regimen was also associated with a significant reduction in clinically meaningful hematological adverse events (AEs) [41].

Regarding a frontline regimen containing anti-PD1, the CheckMate 205 study included a cohort of 51 advanced-stage HL patients (IIB high risk-III-IV) receiving frontline therapy [42]. Patients were administered four doses of nivolumab monotherapy followed by six cycles of nivolumab and AVD (Nivo-AVD) combination therapy. After 21 months of follow-up, the ORR was 84 %, including 67 % of complete response (CR), and the rate of PFS was 83 % [43]. The SWOG S1826 study compared Nivo-AVD to BV-AVD. With a median follow-up of 12.1 months, PFS was superior in the Nivo-AVD arm (HR 0.48, 99 % CI 0.27–0.87, $p = 0.0005$), and 1-year PFS was 94 % for Nivo-AVD versus 86 % for BV-AVD [44]. The tolerance seemed similar but with more immune AEs in the Nivo-AVD arm. An extended follow-up is required to assess OS but these results might lead soon to a shift towards PD-1 inhibitors as first-line therapy. Beyond the medical benefit, some questions are raised as the cost-efficiency or the approval by health authorities varies within the different institutions (FDA, EMA and by country; Table 2).

First-line treatment for HL remains debated and depends on standard-of-care based on the efficacy/safety ratio (infertility and secondary cancer), treatment authorizations, and the management of medical care within countries. Nivolumab and pembrolizumab are promising drugs, but their long-term safety when combined with chemotherapy is unknown, and the PD1-chemo regimen has to be compared with the better PET-driven strategies. In addition, their cost remains a major concern.

Expert point of view:

- The BrECADD or Nivo-AVD regimens have better efficacy and safety compared with eBEACOPP and ABVD/Bv-AVD, respectively; these regimens might become the new standard of care [I, A].

4.3. Focus on Stage IIB high risk

Stage IIB high-risk patients are characterized by a mediastinum-to-thorax (M/T) ratio of ≥ 0.33 or ≥ 0.35 (according to the GHSG or the EORTC groups, respectively) or extranodal disease or a bulky tumor ≥ 10 cm (NCCN and NCIC/ECOG groups). These patients are managed differently in different parts of the world, with either an intensive approach like the one used in advanced stage patients or a combined treatment (mostly ABVD and radiation therapy). While no clinical trial so far has focused on stage IIB high-risk patients, two prospective randomized trials, H10 [18] and AHL2011 [14] that enrolled patients with this profile found similar outcomes [9]. Nevertheless, their analyses independently highlighted a significant unfavorable PFS outcome in patients with positive PET2 (HR 6.26), but also for those who had a baseline total metabolic tumor value (TMTV0) superior to 155 cm^3 (HR 3.37). Patients with a TMTV0 > 155 cm^3 treated in the AHL 2011 trial seemed to have better disease control than those in the H10 trial, indicating the possible benefit of eBEACOPP over a combined therapy [14].

Expert point of view:

- Patients with high-risk stage IIB HL (either one or both risk factors of large mediastinal mass and extranodal lesions) should be treated similar to patients in advanced stages [III, A].

4.4. Focus on older patients

Older patients with HL are a challenging and heterogeneous population to treat since there is no consensual standard of care. Patients over 60 years (about 25 % of all HL patients) or with major organ dysfunction are commonly considered ineligible for intensive chemotherapies due to

Table 2
FDA, EMA, and France-approved indications of immunotherapies, namely brentuximab vedotin, nivolumab, and pembrolizumab, for adult patients with classical Hodgkin lymphoma.

		FDA			EMA			France		
		1st line localized	1st line advanced	Relapse	1st line localized	1st line advanced	Relapse	1st line localized	1st line advanced	Relapse
Brentuximab vedotin	Monotherapy			• After failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates • Consolidation post-ASCT for patients at high risk of relapse or progression			• After failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates • Consolidation post-ASCT for patients at high risk of relapse or progression			• After failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates • Consolidation post-ASCT for patients at high risk of relapse or progression
	Combination		Previously untreated stage III or IV, in combination with doxorubicin, vinblastine, and dacarbazine			Previously untreated stage III or IV, in combination with doxorubicin, vinblastine, and dacarbazine				
Nivolumab	Monotherapy			Relapsed or progressed Hodgkin lymphoma after ASCT and post-transplantation brentuximab vedotin			Relapsed or refractory classical Hodgkin lymphoma after ASCT and treatment with brentuximab vedotin			Relapsed or refractory classical Hodgkin lymphoma following ASCT and treatment with brentuximab vedotin.
Pembrolizumab	Monotherapy			Relapsed or refractory classical Hodgkin lymphoma after at least one multiagent regimen			Relapsed or refractory classical Hodgkin lymphoma who have failed ASCT or after 2 or more lines of therapy when ASCT is not a treatment option			Relapsed or refractory classical Hodgkin lymphoma who have failed ASCT or after 2 or more lines of therapy when ASCT is not a treatment option

FDA: Food and Drug Administration, EMA: European Medicines Agency, ASCT: autologous stem cell transplantation

the high risk of serious toxicity. At the same time, these patients have a poorer prognosis [45] attributed to biological disease characteristics (EBV positivity, mixed cellularity subtype more common) and comorbidities.

While ABVD remains a relevant option for fit patients, several studies have reported a significantly elevated risk of pulmonary toxicity in older patients [46]. For these reasons, AVD with bleomycin omission could be proposed for elderly patients with a more favorable safety profile [47]. PVAG (prednisone, vinblastine, doxorubicin, gemcitabine) regimen seems to be a safer alternative with a lower rate of grade III/IV infection and pulmonary toxicity, with a 3-year PFS of 58 % and 3-year OS of 66 % [48]. Likewise, the PVAB (prednisone, vinblastine, doxorubucin, bendamustine) regimen is associated with a better tolerance profile, and 4-year PFS and OS were 50 % and 69 %, respectively [49]. In the PVAB trial, a MNA scale (≥17) was required for patients aged of 70 or older to select "fit" patients and avoid acute toxicity during treatment [50].

The recent development of targeted therapies opens up new perspectives in this population, even if the BV-AVD combination showed no benefit compared to ABVD in the phase 3 ECHELON 1 trial in patients over 60 years old [39]. The results of the phase 2 trial suggested that the sequential use of BV and chemotherapy was an interesting option [51], leading to the proposal of a sequence of 2 BV followed by 6 AVD and then 2 BV. The resulting rate of CR was 93 % at the end of treatment, with 2-year PFS of 84 % and a good safety profile (42 % of grade III toxicity, mainly neutropenia).

Anti-PD1 is a promising first-line option that has yielded encouraging results. It is a low-toxicity therapy that allows patients to be treated as outpatients, which likely improves quality of life, and sequential management (retreatment on progression). The NIVINHO study, which used first-line nivolumab (+/- vinblastine) in patients ineligible for chemotherapy, found a CR rate of 28.6 %, a PFS of 9.8 months, and 2-years OS of 78.6 % [52]. Similarly, the results of a single-arm prospective study including 25 patients ineligible for ABVD (median age 77 years), treated with pembrolizumab, found a CR rate of 20 %, mDOR was 10.6 months, and 2-year OS was 83 % [53]. In the subanalysis dedicated to older patients from the SWOG S1826 study [54], in which median follow-up was 12.1 months, PFS was superior in the N-AVD arm [HR 0.35, p = 0.022] resulting in 1-year PFS of 93 % (95 % CI 79–98 %) for N-AVD and 64 % (95 % CI 45–77 %) for BV-AVD. While grade ≥ 3 hematologic toxicity occurred in 52 % of pts on N-AVD and 38 % on BV-AVD, infections were less frequent in patients who received N-AVD vs BV-AVD. Additionally, a higher proportion of patients stopped BV-AVD (39 %) vs 15 % in N-AVD arm, reflecting a better safety profile for N-AVD for these patients older.

In older adults, special guidelines were developed by ILROG for ISRT seeing as it is an important part of curative treatment for patients with localized disease [55].

To better evaluate this category of patients, and thus offer the treatment with the best tolerance/effectiveness profile, the use of appropriate geriatric evaluation scales seems essential.

Expert point of view:

- In older but fit patients: anthracyclines-based regimens without bleomycin, such as AVD, PVAG, and PVAB, are a reasonable option that balance efficacy and safety. Geriatric evaluation with functional scales is needed to identify patients at risk of acute toxicity [III, B].
- A sequential approach with BV then AVD and a short maintenance of BV showed interesting efficacy with a favorable safety profile [III, B].
- While the results for PD-1 blockers reveal a good safety profile and efficacy, accessing the drug remains challenging.

4.5. Focus on adolescents and young adults (AYA)

With 1260 new cases *per year* in the French AYA population (15 – 25 years old), HL represent 85 % of AYA lymphomas and 20 % of AYA cancers[56]. With a cure rate of more than 95 %, the question of limiting long-term toxicity arises, especially in younger patients. To date, AYAs with HL can be treated in adult or pediatric hospitals. Despite very different therapeutic approaches, both strategies share the objective of maintaining optimal efficacy while reducing long-term toxicity. However, few studies have compared their outcomes according to the treating center. We will discuss here the specificities of AYA with HL and the pediatric strategy in order to provide insights into the best therapeutic choice for each patient.

4.6. Current pediatric standards of care

French pediatric patients with HL were until recently treated according to the EuroNet PHL-C1 trial [85]. In this study, patients received two courses of OEPA, followed by an early-response assessment (ERA) by high quality CT-scans and PET-FDG. Involved-field radiotherapy (IFRT) was restricted to patients with inadequate response (IR) after the first 2 courses. Consolidation treatment consisted in 2 or 4 cycles of randomized chemotherapy (COPDAC or COPP every 28 days), followed by RT according to ERA. Radiotherapy was omitted in 40 % of patients with adequate response (AR), with a 5-year EFS remaining at 90 %. Both consolidation regimens yielded similar outcomes, with COPDAC being less gonadotoxic. The French Pediatric Lymphoma Expert Group recently adjusted frontline treatment recommendations based on preliminary results from the EuroNet PHL-C2 trial (NCT02684708), refining treatment approach and response criteria in order to further reduce radiation exposure. Risk groups were adjusted based on the results of C1 trial (treatment levels:TL1, TL2, and TL3). Every patient still received two courses of OEPA followed by ERA. TL1 patients followed the C1 strategy, with 19.8 Gy IFRT of all initial sites for patients with IR, and one COPDAC course for patients with AR. TL2 and TL3 patients were randomized 1:1 between C1 strategy (COPDAC) and an intensified chemotherapy regimen (2 or 4 DECOPDAC courses every 21 days). Radiotherapy was further reduced: none for patients with AR at the late-response assessment (LRA), and 28.8 Gy on residual active sites in patients with IR at LRA. The OEPA, COPDAC, and DECOPDAC regimens are detailed in supplementary table 1. Intermediate results from this trial were recently presented (SIOPe 2024 congress), and warranted a revision of the current standards: TL1 patients continue with the same strategy, TL2–3 patients in IR should receive DeCOPDAC, TL3 patients in AR should receive DeCOPDAC, and TL2 patients in AR may benefit from DeCOPDAC but the benefit-risk balance should be discussed.

4.7. Should AYAs with HL be treated as children or adults?

Optimal treatment approaches for AYAs with HL is a subject of debate. Few studies have investigated the question of which strategy yields better outcomes, and these were in different populations with discrepant results [57–61]. Thus, therapeutic recommendations for AYAs are mainly based on physician choices and local referral patterns rather than on the results of prospective trials.

A recent single-center retrospective study comparing AYA HL patients treated with a pediatric or adult approach reported similar EFS and OS in the 2 groups, regardless of risk stratification, with a 5-year PFS of 85 % and 86 % in the pediatric and adult group, respectively [59]. These results were consistent with those of Gupta *et al.*, who reported an equivalent 10-year EFS between patients treated in pediatric centers and those treated in adult centers (83.8 % versus 82.8 %, p = 0.7)[58] However, a large North American retrospective study reported inferior outcomes in 114 AYA HL patients treated in the adult ECOG-ACRIN E2496 study compared to 391 AYA HL treated in the pediatric COG AHOD0031 study. The 5-year FFS and OS rates in the adult E2496 trial were 68 % and 89 % respectively, versus 81 % and 97 % respectively in the pediatric COG study (p = 0.001)[57]. It should be noted that treatment regimens and therapeutic strategies used in the USA at that time were not comparable to those used in Europe.

Despite similar efficacy, adult and pediatric regimens remain significantly associated with different short and long-term toxicity profiles. In a recent French monocentric study, the pediatric regimen was associated with a higher risk of short-term steroid-related toxicities and more constraints due to more hospitalizations, and the adult regimen yielded a higher expected risk of late toxicities related to radiation therapy and gonadotoxicity (not evaluated due to insufficient follow-up time) [59].

However, adult and pediatric protocols have gradually evolved over the past decades with the common aim of limiting toxicities. Significant reductions have been obtained through the omission of bleomycin [62], replacement of procarbazine by dacarbazine [63,64], reduction of chemotherapy in early responders [14] and limitation of doses, fields, and indications of radiotherapy [64]. The long-term toxicity of both protocols has therefore considerably changed and warrants re-evaluation. Moreover, the addition of immunotherapy, such as BV or anti-PD1, to initial chemotherapy has improved OS and PFS in adult and pediatric HL [44, 65, 66]. These new treatments have different toxicity profiles, which could be a key step towards the harmonization of pediatric and adult treatments.

Current treatment stratifications are compared and cumulative doses of both adult and pediatric approaches are described, respectively in supplementary tables 2 and 3.

Expert point of view:

- The pediatric EuroNet PHL-C2 strategy refine risk stratification, treatment approach and response criteria to reduce radiation exposure and intensify chemotherapy regimen in high-risk patients, according to initial risk factors and the quality of response [I, A].
- Although the therapeutic strategies and toxicity profiles are different, adult and pediatric regimens provide excellent and comparable results in AYA HL [II, B].
- Recent advances in adult and pediatric protocols justify a reassessment of the new long-term toxicity profiles of each approach.
- Management of AYA HL requires close collaboration between pediatric and adult hematologists, with professionals specializing in AYA and familiar with both pediatric and adult treatment strategies.

5. Management of refractory or relapsing Hodgkin lymphoma

In patients with refractory or relapsing (R/R) HL, overall survival outcomes have improved significantly in the modern era, driven by the increased use of BV (approved in 2012 in France) and PD-1 inhibitors (nivolumab and pembrolizumab, approved in 2017 and 2018 respectively), both as part of salvage therapy before autologous stem cell transplantation (ASCT) and for relapse after ASCT (Fig. 5).

Histological confirmation with biopsy is recommended before initiating salvage treatment.

Options for fertility preservation should be discussed prior to any treatment.

5.1. *Patients eligible for high-dose chemotherapy and ASCT*

Patients eligible for ASCT are patients with primary refractory disease or relapse less than 1 year after completion of a first line of therapy, or disseminated relapse, or extranodal relapse [67]. For localized relapse more than 1 year after completion of first treatment, there is no recommendation for ASCT according to the LYSA and GHSG groups criteria[67,68].

In current practice, salvage therapy is recommended followed by ASCT and Brentuximab vedotin maintenance therapy for young and fit patients. Young patients may be defined as age < 60 and fit patients as performance status ≤ 2 and no comorbidities for ASCT.

Expert point of view:

- Age alone is not the right criteria for defining eligibility for ASCT, and some fit patients aged > 60 could be eligible for high dose chemotherapy [I, A].

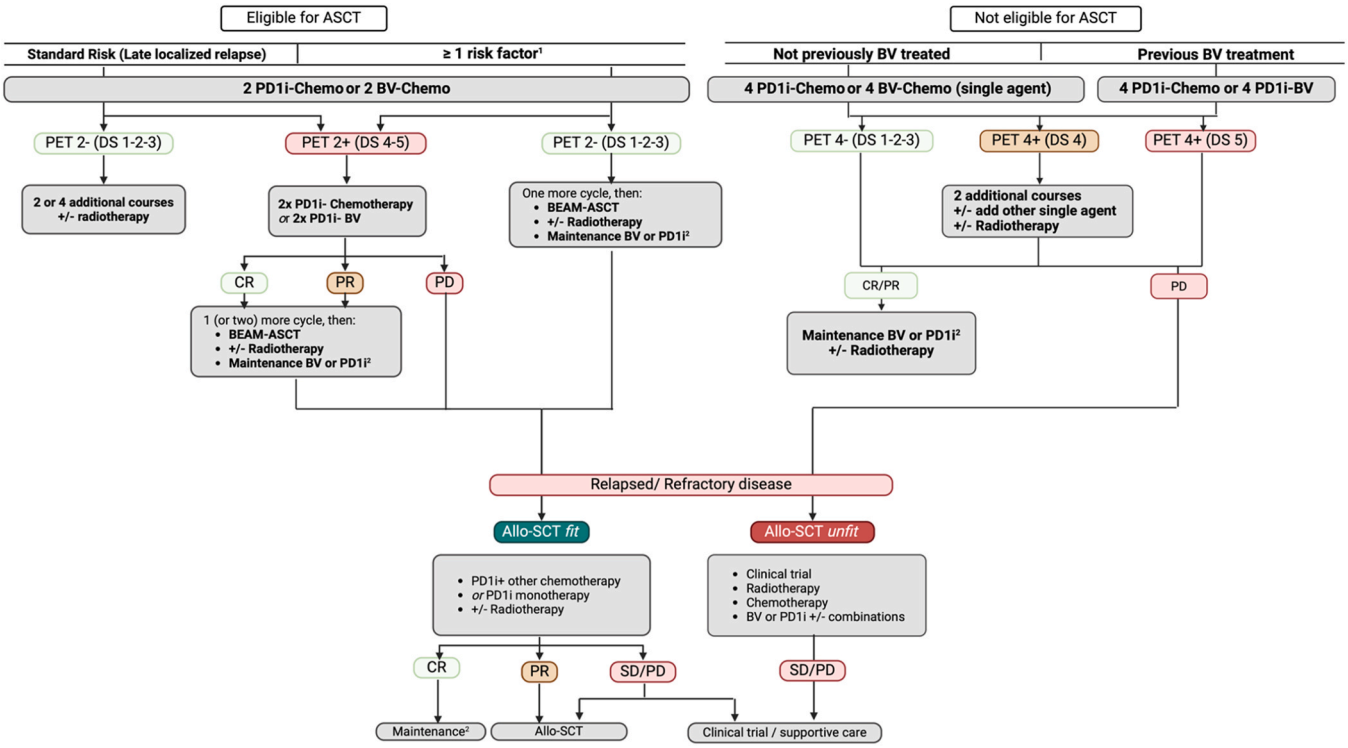

Fig. 5. Management of refractory or relapsing Hodgkin lymphoma. [1]Early relapse (<12 months) or disseminated stage at relapse. [2]Continue PD1i or BV according to access and pre-ASCT treatment.

Salvage regimen in the modern era: The goal of salvage therapy is to achieve a complete remission assessed by PET at 2 cycles (PET2) and before ASCT, defined by Deauville score (DS) of 1-3. Achieving a complete metabolic response before ASCT is a key prognostic factor; PET2-negative patients have been found to have a 5-year PFS of 75 % vs only 31 % in PET2-positive patients [69].

Several phase 2 studies incorporating novel agents into salvage therapy have reported higher complete remission rates than with standard chemotherapy regimens. BV in combination with chemotherapy led to CR ranging from approximately 75 to 90 %. BV-DHAC/DHAOx, BV-ICE or BV-Bendamustine are the most commonly used regimens. Gemcitabine-based combination regimens such as GVD, IGEV, GEMOX, and BEGEV have also been effective. PD1-inhibitor and chemotherapy combinations such as nivolumab plus ICE or pembrolizumab plus GVD have resulted in a high complete remission rates. BV plus nivolumab may be an effective option with a CR rate of 67 %, and less toxic than BV plus polychemotherapies (BV-DHAP [70], BV-Benda [71], BV-ESHAP [72], BV-GVD [73], Nivo-ICE [74], pembro-GVD [75], BV-Nivolumab [76,77].

Expert point of view:

- BV in combination with chemotherapy is approved in France for first-line salvage therapy: we recommend two cycles of BV associated with chemotherapies such as DHAC, DHAOx, Bendamustine, ICE, or, as an outpatient regimen, GVD, excluding ESHAP because of toxicities [III, B].
- Pembrolizumab + GVD or BV + nivolumab should be proposed as a second line of salvage in case of DS > 3 at PET2 [III, B].
- As first-line salvage therapy, pembrolizumab associated with chemotherapy (such as GVD) could be an option for patients refractory to first-line BV + AVD, BrECADD or for patients with pre-existing neuropathy. Future clinical trials randomizing PD1-inhibitors in combination with chemotherapy could provide definitive evidence supporting the use of PD1-inhibitors as first-line salvage therapy [III, B].

For eligible patients, we recommend high-dose chemotherapy (the BEAM regimen) followed by ASCT [78]. In addition, stem cell collection should be done quickly after the first cycle of salvage treatment to prevent stem cell collection failure and interference with PET assessment.

Expert point of view:

- The contribution of high- dose chemotherapy for patients in complete remission after treatment with novel agents, such as PD1-inhibitors, remain to be confirmed: a trial assessing pembrolizumab + GVD followed by pembrolizumab maintenance is ongoing. Cure might be achieved without ASCT for selected patients.
- We strongly recommend radiation therapy for selected sites (uptake in the PET images) that have not been previously irradiated. Time to radiation therapy may vary, but the best time for this type of therapy is after ASCT to limit toxicities [V, B].
- For patients with localized relapse > 1 year, without indication for ASCT, we recommend the administration of 4 cycles of salvage treatment followed by radiation therapy. When consolidative radiation therapy is not feasible, the administration of a total of 6 cycles of salvage therapy or 2 cycles of salvage treatment followed by ASCT is recommended [III, B].

Maintenance therapy is recommended according to the AETHERA criteria: in this phase 3 study in patients at high risk for relapse, BV maintenance led to a 5-year PFS of 59 % vs 41 % with placebo [79,80]. None of the patients received BV in salvage therapy in the AETHERA study. Since the introduction of second-line BV, tandem SCT (auto/auto or auto/allo) has no benefit versus maintenance [80,81]. To know if there is a benefit of maintenance in patients achieving CR before HSCT is still a challenging question.

Expert point of view:

- Most relapsed patients receive BV in salvage therapy. The preASCT CR rate increased to 80-90 % following the use of BV in salvage therapy, as described in the AMAHRELIS study [82]. This study also found 2-year PFS of 75 % (95 % CI: 68.4-84.3) [IV, B].
- We currently recommend 12 to 16 cycles of BV including the number of preASCT BV cycles [III, C].
- We recommend decreasing the dose of BV (1.2mg/Kg/3weeks) at the first signs of peripheral neurotoxicity (grade 1) and stopping BV in case of motor grade 2 or sensory grade 3 neurotoxicity [III, A].
- Maintenance treatment with PD1-inhibitors has been evaluated in a phase 2 trial with excellent results (18-month PFS of 82 % and 95 % with pembrolizumab and BV nivolumab, respectively) [83,84]: we recommend its use for patients refractory to BV (defined by progression on BV) or for patients with BV-associated toxicities. The number of cycles reported previously with pembrolizumab was 8 cycles over 3 weeks [III, B].

5.2. *Patients with post ASCT relapse*

Patients who relapse after ASCT have poor outcomes, particularly those with early relapse within 1 year. The use of novel agents and/or allogenic SCT improved PFS outcomes for this population from 43 % to 71 % [85].

Given the broad use of BV before and after ASCT, therapy based on PD1-inhibitors is recommended. When used as a single agent after failure of ASCT, the median PFS with PD1 inhibitors is 14 months. Response to PD1 inhibitors should be evaluated according to HL response to immunomodulatory therapy criteria (Lyric), with a PET assessment after 4 cycles of immunotherapy.

In some cases, radiation therapy may be combined with PD1-inhibitors: for patients who relapse in non-irradiated sites, radiation could also be used as consolidation [86].

Patients not in complete remission after PD1-inhibitor therapy should be offered a combination treatment with chemotherapy, which can be curative in some cases [87]. BV re-exposure could be effective in combination with PD1-inhibitors.

Clinical trials assessing novel agents or CD30-directed CAR-T cell therapy or CD70-directed NK cell therapy could be an option.

For young and fit patients in progression after treatment with PD1-inhibitors, or PD1-inhibitors plus chemotherapy or BV, allogenic SCT remains an important consideration, even though acute graft versus host disease (GVHD) may occur more frequently (30–40 %). A 6-week washout period between PD1-inhibitor treatment and allogenic SCT is also recommended to mitigate the risk of GVHD, as well as the use of post-transplant cyclophosphamide [88].

Expert point of view:

- For patients responding to PD1 inhibitors, we recommend continuing treatment for up to 2 years, with no need for an allogeneic stem cell transplant. The feasibility of discontinuing PD-1 inhibitors in patients achieving CR after 1 year of therapy is currently being evaluated in the Checkmate 205 and Keynote 087 trials [III, B].
- We fully recommend adapting the strategy to the previous treatment received, thus choosing between PD-1 inhibitors (for PD-1 inhibitor naive patients) or PD-1 inhibitors + chemotherapy (for patients who received previous PD-1 monotherapy) or BV + /- chemotherapy or BV + PD-1 inhibitor for BV naive patients [V, A].

5.3. *Patients not eligible for ASCT*

Salvage treatment is personalized for patients who are not eligible

for ASCT due to advanced age, inadequate performance status, or comorbidities.

For patients who have not previously received BV, BV alone or in combination with chemotherapy (bendamustine/dacarbazine/gemcitabine/vinorelbine/pegylated doxorubicin) could be proposed. In the pivotal phase 2 study on single-agent BV, patients achieving CR (34 %) had a durable response, with 38 % remaining in remission for more than 5 years [89].

For patients with localized relapse, radiotherapy can be highly effective and should be considered [90,91].

In third-line therapy, PD1-inhibitors alone [89] or in combination with BV or chemotherapy are well tolerated. Compared to BV, PD1-inhibitors were associated with longer PFS (13 vs 8 months) in the randomized phase 3 Keynote 204 trial.

Re-evaluation can be offered after 4 cycles of salvage therapy. In our practice, we continue treatment with PD1-inhibitors for responding patients for up to two years.

For patients whose disease continues to progress, clinical trials or retreatment with an effective previously-used drug can be discussed.

Expert point of view:

- In current practice, we consider first-line therapy, time to progression, disease characteristics, and patient-related factors to guide the choice of regimen [II, B].

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CRediT authorship contribution statement

Hannah Moatti: Validation. **Mohamed Touati:** Validation. **Loïc Renaud:** Writing – original draft, Validation. **Salim Kanoun:** Validation. **Franck Morschhauser:** Validation. **Stephanie Guidez:** Validation. **Marion Alcantara:** Writing – original draft, Visualization, Formal analysis. **Bénédicte Deau-Fischer:** Writing – original draft, Validation, Supervision. **Milena Kohn:** Validation. **Luc-Mathieu Fornecker:** Writing – original draft, Visualization, Validation. **Sebastien Bailly:** Validation. **Hervé Ghesquières:** Writing – original draft, Validation, Supervision. **Nadia Diop:** Validation. **Anne-Segolene Cottereau:** Validation. **Youlia Kirova:** Validation. **Lysiane Molina:** Writing – original draft. **Anthony Ceraulo:** Writing – original draft. **Sydney Dubois:** Writing – original draft. **Agathe Waultier:** Validation. **Sophie Bernard:** Validation. **Karine Peignaux-Casasnovas:** Writing – original draft, Validation. **Robin Noël:** Writing – original draft, Validation. **Marilyne Poirée:** Writing – original draft, Formal analysis. **Jean Galtier:** Writing – original draft. **Caroline Delette:** Writing – original draft. **Amandine Segot:** Writing – original draft. **Daphne Krzisch:** Validation. **Remy Dulery:** Validation. **Adrien Grenier:** Validation. **Thomas Gastinne:** Validation. **Marie_Émilie Dourthe:** Validation. **Mathieu Simonin:** Validation. **Thierry Leblanc:** Validation. **Laurent Quero:** Writing – original draft, Validation. **Andréa Gallamini:** Writing – original draft, Validation. **Amira Marouf:** Writing – original draft, Visualization, Data curation, Conceptualization. **Aurélie Cabannes-Lamy:** Writing – original draft. **Olivier Casasnovas:** Writing – original draft, Validation, Supervision. **Emmanuelle Nicolas-Virelizier:** Writing – original draft. **Marc André:** Visualization, Validation. **Marie Maerevoet:** Writing – original draft. **Cedric Rossi:** Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Guillaume Manson:** Writing – original draft, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115073.

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