Title: Optimizing therapy in advanced stage Hodgkin Lymphoma

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Abstract:

The treatment of Hodgkin Lymphoma has evolved continuously since the introduction of extended-field radiotherapy in the 1960s to involved-field then involved-node radiotherapy, multi-agent chemotherapy, combined chemo-radiotherapy, risk-adapted and response-adapted modulation, and most recently, introduction of antibody-drug conjugates and immune checkpoint-blocking antibodies. These changes have translated into progressively increasing cure rates, so that 10-year survival figures now exceed 80%, compared to less than 50% 40 years ago. The challenge now is how to improve upon success while maintaining, or if possible improving, the quality of life for survivors. Steering between under-treatment, with the risk of avoidable recurrences, and over-treatment, with the risk of unnecessary toxicity, remains complex since control of the lymphoma and the probability of survival are no longer closely linked. This requires trials with long follow-up and continuous re-appraisal of the interaction between the illness; the method used to define risk, and the type of treatment involved. One important factor in this is age: outcomes in older patients have not improved at the same rate as those in the population under 60, reflecting the need for different approaches. Recently, treatment has moved from being primarily risk-based, using baseline characteristics such as anatomical stage and severity of the illness, to a more dynamic approach which takes account of the response to therapy, using functional imaging to make an early appraisal, with the option to modulate subsequent treatment. The results of several trials indicate that this has advantages, but that a combination of risk- and response-adaptation is probably ideal.

Introduction: (4097 words, needs to be 4000)

Hodgkin lymphoma (HL) is a malignancy of the germinal center B cell, as evidenced by the presence of clonal immunoglobulin gene rearrangements and somatic hypermutation.[1,2] In contrast to other B-cell tumors, the Reed-Sternberg cell tends to lack classical B-cell antigens (e.g. CD20, B-cell receptor) but consistently expresses CD30. A further distinguishing feature of HL is that the microenvironment usually comprises a diverse infiltrate of immune effector cells, with relatively few tumor cells. Worldwide, an estimated 70,000 new cases of HL are diagnosed annually.[3] The age at presentation of these patients is bimodal, peaking between 20 to 24 years, and 75 to 79 years.[3] This presents two distinct treatment challenges: In the young, more intensive regimens employed to secure high cure rates need to be balanced against the risks of long term toxicity. In seeking to optimize therapy in younger patients, the strategies that have been adopted include risk adaptation by presenting features; intensification of chemotherapy; the use of consolidation radiotherapy; response-adapted treatment, and most recently antibody-drug conjugates. In the older group, more effective but tolerable regimens are required, with late toxicity less of a concern than disease control. It is notable that in recent trials of treatment for patients under the age of 50, causes of death other than lymphoma predominate,[4-6] but in those over 60 the majority of patients still die from the disease.[7] In this review, we will discuss the current data on front-line treatment of patients with advanced stage HL, defined here as stage IIB to IV.

Options for initial therapy in younger patients

Risk-adapted therapy:

Conventional predictors such as the International Prognostic Score (IPS) have been used to stratify patients according to clinical features reflecting the extent and severity of the lymphoma, and the general condition of the patient.[8] However, with the increasing efficacy of modern treatment this score loses some discriminative power, and an updated analysis of patients of all ages treated with the ABVD regimen (Table 1), or similar, in Canada between 1980 and 2010 demonstrated that the worst 7% of patients still showed a 62% freedom from progression at 5 years.[9] Similarly, use of the more intensive BEACOPP regimens (Table 1) showed the IPS to lose prognostic significance.[10]

Other approaches have been taken to explore heterogeneity and differential risk according to the presenting features of the illness. These have included biological parameters such as immunohistochemical features,[11-13] cytokine and chemokine levels[14-18] or gene expression profiles.[19] For example, Scott et al generated a 23-gene expression model from formalin-fixed paraffin-embedded tissue, which appeared to show better discrimination for groups of differing overall survival (OS) (but not progression-free survival (PFS)) than the IPS in patients treated with ABVD and Stanford V regimens.[20] However, the predictive value was not confirmed when applied to other studies[21,22] and this has been a feature of most such tissue analyses: none has proven sufficiently robust and discriminative to enter routine use. Another study assessed the combined predictive value of interim FDG-PET with tissue biomarkers.[13] In this retrospective study, they observed that interim FDG-PET was the single, most effective predictor of outcome in the multivariate analysis. Further, inclusion of CD68 expression and PD-1 staining pattern on tumor-infiltrating cells, and STAT expression on Reed-Sternberg cells together, uncovered a subset of patients with interim FDG-PET negative scans who had poorer

outcomes (3 year PFS 95% vs 63% for low risk vs high risk, respectively). These highly relevant observations will require validation in a prospective study.

The recent widespread use of ^{17}fluoro-deoxyglucose uptake as measured by computed tomography/positron emission tomography (FDG-PET) scans for staging lymphoma has allowed more sophisticated analysis of the extent and metabolic characteristics of HL at presentation. The calculation of parameters such as total lesion glycolysis (TLG) and metabolic tumor volume (MTV) has generated apparently useful prognostic information, and in future this may form the basis for new risk models. Baseline TLG, using a standardized uptake value of 2.5 to determine the volume of disease, was observed to be a strong, independent predictor of outcome in a large international trial,[23] retaining significance in multivariable analysis of progression, along with age and B symptoms. Patients with a high baseline TLG were twice as likely to suffer treatment failure or recurrence as those with low values, a finding which also pertained for those who subsequently showed complete metabolic response on interim FDG-PET scans. Other groups have similarly found baseline MTV values to be an independent prognostic factor for outcomes after salvage therapy.[24] At present these are preliminary observations, and there is a clear need for comparative studies of methodology and validation of the various cut-off points currently being reported.

Intensification of conventional chemotherapy

Since the original observation of cures using 4-drug regimens based on alkylating agents,[25] and the subsequent development of the ABVD regimen,[26] a variety of approaches have been taken to try and improve the results. Initial multi-drug regimens testing alternating,[27] hybrid [28,29] and dose-dense schedules[30,31] did not demonstrate superior outcomes over ABVD. It is important

to note that in the administration of ABVD, dose intensity is critical and needs to be maintained irrespective of neutropenia.[32,33] In the early 2000s, the German Hodgkin Study Group (GHSG) presented data on the escBEACOPP regimen (Tables 1 and 2), which does offer better disease control.[34,35] This however is at the expense of greater short- and long-term toxicity, and a number of studies have been performed to try and optimize its use. In the GHSG HD12 trial, 8 cycles of escBEACOPP were compared against 4 cycles of escBEACOPP followed by 4 cycles of standard BEACOPP, with similar PFS and OS.[36] The GHSG HD15 trial compared 8 cycles of escBEACOPP to 6 cycles of escBEACOPP or 8 cycles of BEACOPP-14. Here, 6 cycles of escBEACOPP provided the best disease control and paradoxically improved OS over 8 cycles.[37]

A number of trials have compared ABVD with BEACOPP regimens directly (Table 2).[38-42] The Fondazione Italiana Linfomi compared 6 cycles of ABVD against 4 cycles of escBEACOPP and 2 standard BEACOPP in 197 patients in the HD2000 study.[43] After 5 years' follow up, the BEACOPP arm demonstrated better PFS, but not OS against ABVD (PFS 68% vs 81% and OS 84% vs 92%), with similar findings after 10 years, when the OS was 84 vs 85%.[42] The lack of survival advantage was due in part to the development of secondary malignancies in BEACOPP survivors. The cumulative risk of developing second malignancies at 10 years was estimated at 0.9% vs 6.6% for ABVD and BEACOPP, respectively. This 6-7% 10-year risk of second malignancy for BEACOPP is comparable to that reported in the BEACOPP arms of the GHSG HD9 trial.[35] Another important factor which prevents improved disease control translating into better survival is that recurrences after ABVD are more readily salvaged by further chemotherapy and high dose therapy/autologous stem cell transplantation. This was demonstrated in a further study from the Italian group, which compared ABVD (6-8 cycles) against BEACOPP (4 x escBEACOPP followed by 4 x standard BEACOPP).[40] Patients

with incomplete response assessed by CT scan or subsequent disease progression proceeded to re-induction chemotherapy followed by high dose therapy and autologous stem cell rescue. In this study, 65/331 patients underwent salvage treatment (45 after ABVD, 20 after BEACOPP). A higher proportion of patients previously treated with BEACOPP had poor responses to salvage therapy (26/45 vs 14/20 patients), indicative of inherent chemo-resistance in these cases. At 7 years' follow up, freedom from first progression was higher in the BEACOPP arm (73% vs 85%) but freedom from second progression was equivalent (82 vs 88%), and again a similar OS was observed (84% vs 89%). The results from a more recent EORTC study in 549 patients with the highest-risk stage III/IV disease were similar, comparing 8 cycles of ABVD to 4 escBEACOPP + 4 baseline BEACOPP.[38] At 4 years, the event-free survival was 63.7% for ABVD vs 69.3% for BEACOPP ($p = 0.312$); and OS was 86.7% versus 90.3% ($p = 0.208$). A meta-analysis of the results of treatment comparing ABVD to escBEACOPP suggested a small survival advantage for the more intensive treatment of about 7% at 5 years,[44] but this included several older studies of ABVD with less favorable outcomes, and at best the results indicate the need to treat at least 13 patients who would have survived after ABVD with a more intensive and toxic regimen, in order to prevent one death. This highlights the need for a better means of selecting those most in need of more intensive treatment, for which response-adapted approaches may be preferred.

Radiotherapy to consolidate the response to chemotherapy

Historically, radiotherapy was administered using relatively high doses and extended fields, resulting in the development of substantial late morbidity. However, progress in radiation therapy technology has improved targeting and decreased exposure to adjacent normal tissues without impairment of disease control.[45] Nonetheless, the high cure rates observed in younger patients still call into question the necessity of radiotherapy in this setting. In the UK

Lymphoma Group LY09 study, comparing ABVD with different multi-drug regimens in 702 patients with advanced HL, the use of radiotherapy was advised but not mandated along these lines.[46] Although more patients received radiotherapy following a partial response or having presented with bulky disease, radiotherapy conferred an improvement in 5-year event-free survival of 15% and OS of 5% overall, with no substantial difference in hazard ratios according to the stage at presentation or other prognostic features. In contrast, a randomized trial by the EORTC showed that in patients with a complete response on CT scans at the completion of hybrid chemotherapy there was no advantage to the use of consolidation radiotherapy.[47] More recently the GHSG has performed a similar trial, HD15, but using FDG-PET imaging to determine whether or not to use radiotherapy on small (<2.5cm) residual masses, with those in complete metabolic remission showing a similar PFS (92% at 4 years) to those with complete anatomical responses on CT despite the omission of radiotherapy, a strategy which reduced the proportion of patients receiving consolidation treatment from 71% in HD9 to 11% in HD15.[4] Further data on the use of FDG-PET in guiding radiotherapy come from the international Response Adapted Therapy for HL (RATHL) trial, where consolidation radiotherapy was not recommended if the interim FDG-PET was negative.[48] Consequently, only a small proportion (6.5%) of patients received consolidation radiotherapy, and there was no indication that the omission of radiotherapy compromised the 5-year PFS, even in patients who had bulky disease or residual non-FDG avid masses[49].

Collectively, these studies indicate a similar conclusion to that drawn from the evidence on chemotherapy intensification: the approach of treating all patients with advanced disease in the same way, even when stratified by baseline prognostic features, risks overtreatment for a substantial majority. The more dynamic assessment of response as a guide to subsequent

therapy holds the promise of more individualized strategies, with more therapy for those who need it, but reduced exposure to toxicity for those in whom it can safely be avoided.

A response-adapted approach using interim FDG-PET

The evidence supporting interim FDG-PET as a means of predicting outcome for HL initially came from retrospective series of patients receiving ABVD, among whom those with a metabolic remission appeared to have a substantially better prognosis than those with persistently FDG-avid disease after two cycles of treatment.[50] This appeared superior to conventional anatomic assessment by CT, and to supersede the impact of baseline prognostic features, such that even those with the highest-risk disease had a PFS of around 95% if the interim FDG-PET was negative.[51] The introduction of a standardized 5-point reporting score for interim FDG-PET has greatly improved reproducibility and reliability, with scores 1-3 usually regarded as negative and 4-5 (uptake greater than normal liver) as positive.[52] This has allowed the conduct of a number of trials testing the strategy of treatment escalation for patients with a positive interim FDG-PET and de-escalation for those with early metabolic remission.

Although ABVD is better tolerated than escBEACOPP, there is still a significant risk of pulmonary toxicity from its bleomycin component.[53] This prompted the design of the RATHL trial.[6] Here, patients with advanced HL received 2 cycles of ABVD and then underwent an interim FDG-PET. Patients with negative interim scans (score 1-3) were randomized to continue with 4 cycles of ABVD or AVD (omitting bleomycin). In interim FDG-PET positive cases (score 4-5), treatment was escalated to 6 cycles of BEACOPP-14 or 4 cycles of escBEACOPP. Using this approach, 937/1119 (84%) of patients had a negative interim FDG-PET. Omission of bleomycin for these patients did not compromise outcomes, as indicated by similar 3-year PFS and OS rates of 86% and 97%, and 84% and 98% in the ABVD and AVD

arms, respectively. The withdrawal of bleomycin reduced the relative risk of pulmonary adverse events by 0.67. In patients treated with BEACOPP following a positive interim FDG-PET, the 3-year PFS rate was 67.5%, results very similar to those seen in the US Intergroup Trial, SO816, which used a similar approach for patients with stage III/IV disease, giving a 2-year PFS of 64% for FDG-PET positive patients who received 6 cycles of escBEACOPP.[54] Although not confirmed in a randomization, these findings compare favorably to earlier reports with 2-3 year PFS figures of 13-28% for patients continuing ABVD after a positive interim FDG-PET.[51,55] The Italian HD0801 trial took a more intensive approach still, in which patients with an interim FDG-PET score of 3 or more proceeded to ifosfamide-based salvage therapy followed by autologous or allogeneic transplantation.[56] This resulted in a 2-year PFS of 75%, very similar to the 81% seen in the interim FDG-PET negative group, although the inclusion of patients with a score of 3 in the group for escalation may have influenced this.

Whilst these trial results are encouraging, it is also clear that a negative interim FDG-PET scan after 2 cycles of ABVD remains an imperfect predictor of progression-free status, with around 15% of patients experiencing recurrence despite their early metabolic remission, in contrast to the reported 95% PFS figures in the previous retrospective series. This appears to be in part determined by the baseline features, such that those with stage IV disease had only 80% 3 year PFS after a negative interim FDG-PET, compared to 90% for those presenting at stage II in the RATHL study.[48]

The predictive utility of interim FDG-PET assessment is also affected by the antecedent therapy. After initial treatment with 2 cycles of escBEACOPP, the GHSG HD18 study found a slightly higher rate of PET-positive patients (23% using cut-off score 4) than the RATHL study, but the outcomes did not differ between PET-positive and PET-negative groups. For

patients with interim FDG-PET score 4-5, 3-year PFS was 90·7%, compared to 93·8% for those with score 1-3 (p=0·30).[10] Interestingly, these results are better than those seen in the previous HD15 study, where the overall PFS was below 90%, suggesting improved patient selection for this more intensive approach.

These data argue for a combination approach to treatment optimization, incorporating both the baseline risk, whether determined by stage, IPS or baseline PET parameters, and the interim FDG-PET result. For those patients at low risk, initial treatment with ABVD allows low toxicity and good predictive power from a negative interim FDG-PET, while for those at higher risk, initial therapy with escBEACOPP appears to improve the disease control and the negative predictive power of the interim FDG-PET. In support of this, the French AHL2011 study[57] used 2 cycles of initial escBEACOPP, with FDG-PET negative cases de-escalated to 4 cycles of ABVD, while FDG-PET positive cases continued 4 more cycles of escBEACOPP. The interim 2 year PFS rates for non-PET-driven, and PET-driven both arms were equivalent (91.6% compared to 88.3%, respectively, p>0.05), suggesting that this may be an effective approach for high risk patients who are less well served by initial ABVD.

For the future, response adapted approaches may be improved by other techniques such as the detection and monitoring of circulating tumor DNA (ctDNA) through peripheral blood sampling. As a proof of principle that this might be applicable in HL, Bruscaggin et al demonstrated in a small cohort of 14 HL patients that the reduction of ctDNA correlated well to the risk of progression.[58]

Addition of targeted agents to initial therapy

A number of antibody-based therapies have now demonstrated good clinical activity on their own and/or in combination with chemotherapy. Whilst some of these directly target the tumor cell (e.g. anti-CD30, brentuximab vedotin), others target the tumor microenvironment (e.g. anti-PD-1, nivolumab or pembrolizumab).

Brentuximab vedotin (BV), an anti-CD30 monoclonal antibody conjugated to a microtubule-disrupting agent via a cleavable linker, was combined with ABVD or AVD in newly diagnosed HL patients in a phase I, dose-escalation study.[59] Dangerous pulmonary toxicity was observed in the BV-ABVD group, but if bleomycin was omitted the maximum tolerated dose was not reached with a 1.2 mg/kg, fortnightly dosing in the BV-AVD group. The 5-year failure free survival and OS rates were reported as 92% and 100%, for BV-AVD,[60] and this combination has now been tested in a randomized comparison in the phase III ECHELON 1 study. The trial compared standard ABVD treatment to the BV-AVD combination for patients with stage III-IV disease[61]. Six cycles of treatment were planned, and an interim FDG-PET scan was performed after cycle 2, but with the option to switch therapy reserved for patients with an interim PET score of 5. A modified progression-free survival endpoint was used, to include as an event the administration of additional anticancer therapy for patients with a PET score of 3 or more at the end of therapy. With median follow-up of two years, among 1334 randomized patients the modified 2 year PFS for those receiving BV-AVD was 82.1% versus 77.2% for ABVD (p=0.04). There was an excess of progressions in the ABVD arm (102/670 versus 90/664) but a substantial contribution to the difference in modified PFS came from the events recorded for subsequent treatment in patients with incomplete response (22/670 versus 9/664), an endpoint potentially prone to bias as the study was unblinded. Overall survival was not significantly different between the two arms (2 year OS for BV-AVD was 96.6% versus 94.2% for ABVD) and among patients receiving BV-AVD there was an excess of peripheral

neuropathy (67% versus 43%, with 11% versus 2% of grade III/IV) and febrile neutropenia, which could be mitigated by prophylaxis with G-CSF. Conversely the ABVD arm showed a small excess of pulmonary toxicity (3% versus 1% grade III/IV)[61]. These results suggest that the addition of brentuximab vedotin may be another useful means to increase the efficacy of initial therapy, particularly among those patients with the highest risk disease, although longer follow-up will be important to define its full potential.

Molecular genetic studies have demonstrated that the majority of HL cases carry an alteration of the PD-L1 and PD-L2 loci.[62,63] Specifically, 9p24.1 amplification was observed in advanced HL and this correlated to increased PD-L1 and PD-L2 expression on the tumor cells. PD-L1 and PD-L2 are ligands for the inhibitory T-cell receptor PD-1. Physiologically, PD-L2 is expressed on many cell types but PD-L1 is only expressed on activated T cells and antigen presenting cells, its primary function being to raise the threshold for T-cell activation. Disruption of the PD-L1/2-PD-1 axis is postulated to reinvigorate exhausted tumor-specific T cells in solid tumors,[64,65] although in HL it may alternatively disrupt growth signalling between the PD-L1-positive malignant B-cells and the T-cell infiltrate. A number of monoclonal antibodies are being use to target this pathway, with nivolumab and pembrolizumab most advanced in clinical development. Both are human IgG4 monoclonal antibodies directed at PD-1 and block ligand binding.[66,67] Nivolumab given to patients with relapsed or refractory HL demonstrated an ORR of in 20/23 patients.[68] In a further single-arm phase 2 trial of nivolumab in patients with HL who have specifically relapsed post-autograft and brentuximab, 53/80 (66.3%) cases responded with a median duration of response of 7.8 months.[69] Similar results were observed in a phase II study of pembrolizumab, where an overall response rate of 69% was achieved.[70] The mechanism of action for these agents remains to be determined, as does the potential for combining them with either conventional chemotherapy or brentuximab

vedotin, both of which are under investigation. The responses seen in relapsed and refractory disease have not proven durable in the majority of patients, but they offer an alternative approach for patients earlier in the course of their treatment, and in particular for those with positive interim FDG-PET scans in whom new approaches are evidently required.

Initial treatment for older patients

A third of all patients with advanced HL present at age 60 or older.[3] There is no standard front-line regimen in this group and a relative paucity of trial data, although overall the outcomes are worse, with more treatment failure and more toxicity. The most commonly employed regimens are ABVD, VEPEMB, PVAG and ChlVPP/EVA and ChlVPP (Table 3). The main difficulties with ABVD in this population are cardiotoxicity with doxorubicin and pulmonary toxicity with bleomycin.[71,72] The GHSG analyzed patients aged 60-75 years within the HD10 and HD11 trials, where 4 cycles of ABVD were administered to early stage HL cases. [71] Compared to the younger cohort, there was over double the amount of grade 4 toxicity, a higher proportion of patients had reduced dosing and longer delays in treatment. Treatment-related mortality of 5% was observed, compared to <1% in younger patients. The 5-year PFS was 75% vs 90%, and 5-year OS 81% compared to 97% in the younger cohort.

VEPEMB has half the total dose of bleomycin of ABVD, and the regimens were compared in a small phase III study, and the 5-year PFS and OS rates were 15-20% lower than seen with ABVD.[73] However, the regimen did have less toxicity compared to ABVD, where cases of grade 4 cardiac and lung toxicity were documented. In older patients where cardiac toxicity is less of a concern, PVAG is an alternative.[74] A small phase II study demonstrated CR, 3-year PFS and OS rates (78%, 58% and 66%, respectively) comparable to VEPEMB. The grade 3/4

infection rate was however double that reported for 4 cycles of ABVD,[71] suggesting that it might be more appropriate for "fitter" older patients.

Another option is a hybrid regimen, ChlVPP/EVA.[75,76] Whilst it is more toxic in terms of infection, neuropathy and mucositis, it does not contain bleomycin and thus is potentially another option for the older but fitter patients where lung toxicity is a particular concern. For the less fit older patients, ChlVPP has been shown in several studies to have moderate activity, [77-79] with 5-year and 10-year OS of around 60% and 40%, with the caveat that the numbers of patients who were 60 and older in these studies are small.

Potentially, the most promising initial treatment for older patients might include BV. BV as a single agent had a good overall response rate, but responses were transient with a median PFS of 10 months and increased toxicity, notably peripheral neuropathy, fatigue and in older patients.[80,81] However, when administered in a sequential manner with AVD, where 2 doses of BV were followed by 6 cycles of AVD and a further 4 cycles of BV, durable and high initial response rates were observed (ORR 81%, CR 77% and 22-month PFS 85%).[82]

Finally, BV combined with bendamustine is also an alternative approach. Bendamustine monotherapy produced an overall response rate of 53% in a small cohort of patients with relapsed and refractory HL, albeit with median duration of response only 5 months.[83] A subsequent phase I/II study examined a combination of escalating doses of BV (1.2 mg/kg to 1.8 mg/kg and bendamustine (70 mg/m^2, 80 mg/m^2 and 90 mg/m^2).[84] In an interim analysis, 36 heavily pre-treated patients were evaluated. The combination was well-tolerated and MTD was not reached. An overall response rate of 67% was observed with 19% of cases in CR.

Clearly these are preliminary data and the final results are awaited, but this may be a potentially useful combination for older patients.

Conclusions:

The strategies for optimizing treatment in advanced HL continue to evolve, as new types of treatment and new means of stratification come into practice. For the present, in fit under 60-year olds with low-risk, advanced stage HL, we give initial treatment with 2 cycles of ABVD, followed by an interim FDG-PET scan, and if this is negative, bleomycin can be safely omitted. For patients with high-risk disease (stage IV disease or IPS $\geq$4) there is a 20% chance of recurrence within 3 years with this approach, despite a negative interim FDG-PET, whereas initial treatment with escBEACOPP, or perhaps BV-AVD, may be preferable, with the option of de-escalation to AVD if the interim FDG-PET is negative. Using this approach, the PFS of all patients might be anticipated to improve, whilst simultaneously reducing the need for intensive chemotherapy (Figure 1). A negative interim FDG-PET indicates that consolidation radiotherapy may be unnecessary, even for those with initially bulky disease. In patients who have a positive interim FDG-PET after ABVD, outcomes appear better if treatment is escalated using BEACOPP, but new approaches are needed in this group. These options might include the replacement of procarbazine with dacarbazine, which demonstrated less toxicity but equivalent efficacy in a pediatric setting,[85] or the incorporation of brentuximab vedotin or anti-PD-1 antibodies into initial therapy, but these await definition.

In patients over 60 years old, at the time of writing, there is clearly no established front-line standard of care and the choice of therapy remains dependent on individual co-morbid risk factors as well as institutional experience.

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Figures and Tables

Table 1. Schedules and doses used in regimens for younger patients

Table 2. Selected front-lien trials in younger patients

Table 3. Schedules and doses used in regimens for older patients

Figure 1. Merging of different risk-adapted approaches.

The flow chart shows the hypothetical numbers of patients who would receive escBEACOPP if the RATHL and AHL2011 approaches are merged. The estimated figures are derived from the results of both trials, with extrapolation from the results of RATHL assuming that, after a negative interim PET, AVD is equivalent to ABVD.

Table 1:

Trial	Regimen	n	Mean/Median age (range)	% Stage III/IV	% IPS ≥4	CR/Cru (%)	PFS (%)	OS (%)	TRM (%)	Secondary malignancies
HD2000	ABVD x6	99	32 (NA)	67	30*	84	69 (10 yr)	85 (10 yr)	0	1
	escBEACOPP x4, then BEACOPP x2	98	29 (NA)	69	43*	91	75 (10 yr)	84 (10 yr)	2	6
	COPPEBVCAD x6	98	33 (NA)	71	44*	83	76 (10 yr)	86 (10 yr)	0	6
GHSG HD12	escBEACOPP x8 +RT	392	36 (16-65)	83	15	93	89 (5 yr)	92 (5 yr)	2	3.6
	escBEACOPP x8 -RT	395	35 (16-65)	84	18	93	87 (5 yr)	91 (5 yr)	2.8	2.3
	escBEACOPP x4, then BEACOPP x4 +RT	393	36 (16-65)	83	19	92	87 (5 yr)	91 (5 yr)	4.3	2.5
	escBEACOPP x4, then BEACOPP x4 -RT	394	35 (16-65)	85	15	90	84 (5 yr)	90 (5 yr)	2.5	0.8
Viviani et al, 2011	ABVD x6-8, then re-induction & HDT/ASCT if less than CR or PD	168	NR	NR	53*	76	73 (7 yr)	84 (7 yr)	1	1
	escBEACOPP x4, then BEACOPP x4 then re-induction & HDT/ASCT if <CR or PD	163	NR	NR	53*	81	85 (7 yr)	89 (7 yr)	2	1
GHSG HD15	escBEACOPP x8	705	33 (18-60)	83	15	90	86 (5 yr)	92 (5 yr)	2.1	4.7
	escBEACOPP x6	711	34 (18-60)	85	15	94	90 (5 yr)	95 (5 yr)	0.8	2.4
	BEACOPP-14 x8	710	33 (18-60)	85	17	92	86 (5 yr)	95 (5 yr)	0.8	3.1
GHSG HD18	esBEACOPP x2, if PET-2 positive, randomization escBEACOPP x4-6	219	30 (18-60)	78	13	97	91 (3 yr)	97 (3 yr)	<1	3
	escBEACOPPx2, if PET-2 positive, randomization escBEACOPP+R x4-6	220	29 (18-60)	75	22	93	93 (3 yr)	94 (3 yr)	1	1
EORTC 20012	ABVD x8	275	35 (16-67)	100	100*	83	73 (4 yr)	87 (4 yr)	3.3	3
Intergroup trial	escBEACOPP x4, then BEACOPP x4	274	35 (16-61)	100	100*		83 (4 yr)	90 (4 yr)	2.2	4
RATHL	ABVD x2, if PET-2 negative, randomization to AVD x4	470	32 (18-79)	59	16	100	86 (3 yr)	97 (3 yr)	0.9	2.8
	ABVD x2, if PET-2 negative, randomization to ABVD x4	465	33 (18-76)	58	14	100	84 (3 yr)	98 (3 yr)	0	2.4
	ABVD x2, if PET-2 positive, for escBEACOPP x4 or BEACOPP-14 x6	172	32 (18-70)	58	30	74.4	66 (3 yr)	88 (3 yr)	2.3	1.7
US Intergroup	ABVD x2, IF PET-2 negative, for ABVD x4	370	32 (18-60)	100	51	96	82 (2 yr)	NA	<1	1
SWOG trial SO816	ABVD x2, if PET-2 positive, for escBEACOPP x6	55				55	64 (2 yr)	NA	4	6.1
AHL2011	escBEACOPP x2, if PET negative, for ABVD x4	319	30 (16-60)	88	58*	NA	88 (2 yr)	NA	<1	NA
Lysa study	escBEACOPP x2, if PET positive, for escBEACOPP x4	49				NA		NA	8	NA
	escBEACOPP x6 (no PET-adaptation)	401				NA	92 (2 yr)	NA		NA

***IPS ≥3**

NA = not available

Table 2:

Regimen	Drug	Dose, mg/m²	Route of administration	Days of administration	Length of cycle, days
ABVD	Doxorubicin	25	IV	D1 & D15	28
	Bleomycin	10	IV	D1 & D15	
	Vinblastine*	6	IV	D1 & D15	
	Dacarbazine	375	IV	D1 & D15	
stdBEACOPP/	Bleomycin	10	IV	D8	14-21
BEACOPP-14	Etoposide	100	IV	D1-3	
	Doxorubicin	25	IV	D1	
	Cyclophosphamide	650	IV	D1	
	Vincristine**	1.4	IV	D8	
	Procarbazine	100	PO	D1-7	
	Prednisone†	40-80	PO	D1-14 or D1-7	
	GCSF			D9-13	
EscBEACOPP	Bleomycin	10	IV	D8	21
	Etoposide	200	IV	D1-3	
	Doxorubicin	35	IV	D1	
	Cyclophosphamide	1200	IV	D1	
	Vincristine**	1.4	IV	D8	
	Procarbazine	100	PO	D1-7	
	Prednisone	40	PO	D1-14	
	GCSF			D9 until recovery	

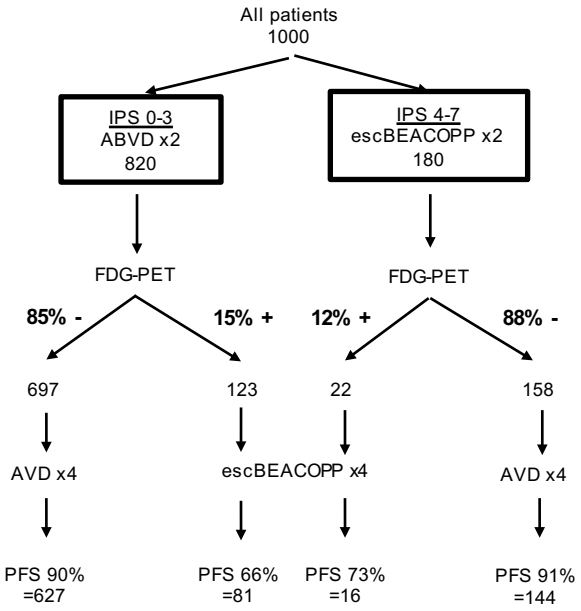
*Vinblastine is capped at 10 mg per administration, **Vincristine is capped at 2 mg per administration, †Prednisone is given as 40 mg from D1-14 in stdBEACOPP and 80 mg from D1-7 in BEACOPP-14.

Table 2:

Regimen	Drug	Dose, mg/m^2	Route of administration	Days of administration	Length of cycle, days
ChlVPP/EVA	Chlorambucil†	6	PO	D1-7	28
	Vinblastine*	6	IV	D8	
	Procarbazine	90	PO	D1-7	
	Prednisone	50	PO	D1-7	
	Etoposide	75	PO	D1-5	
	Vincristine**	1.4	IV	D1	
	Doxorubicin	50	PO	D8	
ChlVPP	Chlorambucil†	6	PO	D1-14	28
	Vinblastine	6	IV	D1& D8	
	Procarbazine	100	PO	D1-14	
	Prednisone	40	PO	D1-14	
VEPEMB	Vinblastine*	6	IV	D1	28
	Cyclophosphamide	500	IV	D1	
	Procarbazine	100	PO	D1-5	
	Prednisone	30	PO	D1-5	
	Etoposide	60	PO	D15-19	
	Mitoxantrone	6	IV	D15	
	Bleomycin	10	IV	D15	
PVAG	Prednisone	40	PO	D1-5	22
	Vinblastine*	6	IV	D1	
	Doxorubicin	50	IV	D1	
	Gemcitabine	1000	IV	D1	

*Vinblastine is capped at 10 mg per administration, **Vincristine is capped at 2 mg per administration, †Chlorambucil is capped at 10 mg per administration.

Figure 1.



Overall PFS = 868/1000 = 87%

escBEACOPP exposure:

0 cycles	697 patients
2 cycles	158 patients
4 cycles	123 patients
6 cycles	22 patients