Current Oncology Reports (2019) 21: 39
https://doi.org/10.1007/s11912-019-0788-0

LYMPHOMAS (MR SMITH, SECTION EDITOR)

Controversies in the Approach to Initial Therapy of Hodgkin Lymphoma

Pamela B. Allen [1] · Jane N. Winter [2]

Published online: 27 March 2019

Abstract

Purpose of Review Availability of highly effective novel agents has altered the approach to initial therapy in patients with classical Hodgkin lymphoma (cHL). We will review controversies in the following areas: (1) the role of radiation in early unfavorable disease and the optimal treatment strategies for (2) advanced-stage disease and (3) elderly patients.

Recent Findings Strategies incorporating brentuximab vedotin into frontline treatment of cHL yielded favorable results in non-randomized elderly studies and were compared to ABVD in advanced disease among adults. Meanwhile, four cycles of escalated BEACOPP yielded unprecedented favorable results for the treatment of advanced disease in the German Hodgkin Study Group 18 study.

Summary The addition of novel agents to conventional treatment strategies has the potential to improve outcomes in high-risk groups of patients while reducing toxicity. The role of radiation therapy remains in question but may see diminished use with the incorporation of more effective agents in the frontline setting.

Keywords Hodgkin lymphoma · Immunotherapy · Checkpoint inhibitors · Nivolumab · Pembrolizumab · Brentuximab vedotin

Introduction

Hodgkin lymphoma (HL) is an increasingly curable malignancy in most adults. Modern therapy results in cure in greater than 85% of early-stage patients with greater than 95% alive at 5 years [1•, 2–5]. Likewise, patients with advanced disease have favorable outcomes with greater than 75% long-term disease-free survival (DFS) [6, 7••]. The highly favorable prognosis has led to increased emphasis on diminishing the acute and late toxicities associated with therapy. Long-term follow-up of patients treated with combined modality therapy (CMT) reveals increased risk of radiation-related toxicities such as second malignancies, cardiac disease including valvular dysfunction, and thyroid deficiency that persists even 40 years after initial treatment [8–14]. While the translation of findings from retrospective analyses to current-day decision-making is difficult because of major changes in radiation fields, dosing, and techniques, the concern for long-term toxicity remains [15–18]. Trials diminishing the number of cycles of chemotherapy and eliminating radiation therapy demonstrate continued high rates of cure, but at the risk of increased relapse rates [1•, 5, 19]. The RAPID-UK analysis included largely early favorable patients and assessed a PET-directed approach comparing 3 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy for PET-negative patients to CMT [1•]. The results could *not* prove that omitting radiation for the PET-negative group did not compromise progression-free survival. Nevertheless, the outcomes of those treated with chemotherapy alone were considered excellent, and many have used these results to support a radiation-free approach with a limited number of cycles of chemotherapy. In contrast to these results, the EORTC H10 trial appeared to show the superiority of CMT over chemotherapy alone in the favorable cohort [20••]. However, the necessity of radiation in early unfavorable disease was less clear [20••]. These differences may be related to the greater number of chemotherapy cycles administered to the unfavorable cohort.

This article is part of the Topical Collection on *Lymphomas*

✉ Pamela B. Allen
pallen5@emory.edu

[1] Division of Hematology/Oncology, Winship Cancer Institute of Emory University, Atlanta, GA 30322, USA

[2] Division of Hematology/Oncology, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA

Patients with advanced-stage disease are often treated with chemotherapy alone [21, 22]. The chemotherapy options for the initial treatment of younger patients with advanced HL have increased with the recent FDA approval of brentuximab vedotin in this setting. Options currently include escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), ABVD, or AVD and brentuximab vedotin. Treatment decisions are further complicated by numerous trials with PET-directed approaches, including the RATHL trial showing that in those initially treated with ABVD, bleomycin may be omitted after a negative interim PET [7••]. Alternatively, those with interim PET positive disease have improved outcomes with escalation to escBEACOPP [7••, 23•, 24••, 25]. The numerous options for initial treatment and the incipient questions of how to handle interim PET-CTs with novel therapies have not been fully elucidated.

The incorporation of novel agents into the treatment of elderly patients with HL has yielded promising results in this traditionally high-risk population [2, 26••, 27••]. However, there have been no randomized comparisons to standard or PET-directed therapy, and larger trials are unlikely given the rarity of this population, leaving many practitioners with little guidance in these difficult to treat patients.

In this review, we will attempt to address some of the most salient controversies in the frontline treatment of Hodgkin lymphoma focusing specifically on three areas where guidelines have fallen short [1•]: the role of radiation therapy in early unfavorable disease [2], the optimal initial treatment for advanced-stage disease, and [3] the recommended treatment for elderly patients. We will also look forward to ongoing trials.

What Is the Role of Radiation Therapy in Early Unfavorable Disease?

Patients with early-stage disease and at least one risk factor fall into the unfavorable category. These risk factors are defined differently for the German Hodgkin Study Group (GHSG), the European Organisation for Research and treatment of Cancer/Groupe d'Etude des Lymphomes de l'Adulte (EORTC/LYSA), and the National Comprehensive Cancer Network (NCCN), although there is considerable overlap. Slightly more than half (54–57%) of all early-stage patients will have one or more risk factors and fall into the unfavorable category, and differences in outcome between favorable and unfavorable subgroups are similar for the GHSG, EORTC/LYSA and NCCN [28]. Patients with early unfavorable disease are heterogeneous and may have bulky disease and high tumor burdens or low volume with multiple nodal sites, though limited to one side of the diaphragm by Ann Arbor staging criteria. In general, the prognosis remains excellent, though slightly inferior to patients with early favorable disease, with 5-year survival estimated at greater than 80% [29, 30].

Historically, radiotherapy was the mainstay of therapy for patients with early-stage disease. The addition of chemotherapy to radiotherapy improved outcomes and permitted reductions in fields and dose [2, 4, 14, 20, 30]. Clinical trials have focused on identifying the most effective and least toxic chemotherapy for use in combined modality programs. The GHSG HD 11 study compared 4 cycles of ABVD to 4 cycles of baseline BEACOPP followed by involved field radiation at either 20 or 30 Gy in a two by two factorial design. There was no difference in overall (OS) or progression-free survival (PFS), but increased toxicity in the BEACOPP containing arms [2], leading to a recommendation for ABVD × 4 followed by 30 Gy consolidation. Similarly, the GHSG HD 14 trial compared ABVD × 4 to a "2 + 2" combination of escBEACOPP and ABVD, with both arms including 30 Gy of IFRT [30]. Although the 5-year freedom from treatment failure of 95% versus 88% ($p < 0.001$) favored the escBEACOPP-containing arm, both arms enjoyed exceptional 5-year survival rates of 97%, thus highlighting the ability to salvage ABVD-treated patients who relapse. Consistently, trials in this setting demonstrated significant grade 3 toxicity in escBEACOPP-treated patients in terms of leukopenia, thrombocytopenia, and infection [2, 30]. Therefore, ABVD is the preferred chemotherapy regimen for CMT for early-stage unfavorable disease in North America.

Concerns about the long-term risks associated with radiation-containing therapy and the excellent outcomes reported in advanced-stage disease with ABVD chemotherapy led to the North American HD.6 trial. This trial compared treatment with chemotherapy consisting of 4–6 cycles of ABVD alone to either radiotherapy alone or a combined modality approach. It had the unusual primary objective of long-term overall survival at 12 years, presumably long enough to begin to see the impact of late effects. Overall survival at 12 years was superior among patients treated with ABVD alone compared to those receiving radiotherapy owing to a lower rate of death from causes other than Hodgkin Lymphoma underscoring the importance of long-term follow-up. This trial has been criticized for its utilization of radiation techniques that had become outdated by the time of reporting and for treatment of some patients with radiotherapy alone [31]. It is remarkable, however, for its long-term endpoint of 12-year survival, emphasizing the need for longer term follow-up in this highly curable malignancy. In addition, the outcomes of early-stage patients treated with as few as 4 cycles of ABVD were excellent providing evidence that short-course chemotherapy might be sufficient for many early-stage patients.

Evidence that a negative interim PET-CT identifies patients with an excellent prognosis when treated with ABVD set the stage for PET-adapted trials in which patients with an early complete metabolic response to short-course ABVD were randomized to receive consolidative radiotherapy or not. In the RAPID-UK trial, early-stage asymptomatic patients excluding those with large mediastinal masses were treated with 3 cycles of ABVD followed by a PET/CT. Those with a complete metabolic response (Deauville 1 or 2) were randomized to either consolidative radiotherapy or observation (see Table 1 for a summary) [1•, 20••, 31]. Results overall were excellent, although the analysis did not show that observation after a negative PET was NOT inferior to radiotherapy with regard to 3-year PFS (94.6% with RT versus 90.8% with ABVD alone). In addition, there was no significant difference in OS, which was also excellent in both arms (97% versus 99%, respectively). Results of the unfavorable risk patients who made up 35% of those assigned to the "no further treatment" arm are not reported separately, so no definitive conclusions can be drawn on the safety of radiation omission in unfavorable patients on the basis of this study. Nonetheless, this study has led to the widespread adoption of short-course ABVD alone as an option for the treatment of early-stage asymptomatic patients without bulk disease who achieve a complete metabolic response.

Additional clinical trial results supporting the omission of radiation therapy in PET-negative early unfavorable patients come from the long-term follow-up of patients enrolled on the EORTC/LYSA/FIL H10 trial [20••]. In this clinical trial, patients with favorable (F) and unfavorable (U) early-stage disease were randomized to PET-adapted therapy versus standard therapy with ABVD followed by involved nodal RT. Patients on the PET-directed therapy arms who had complete metabolic responses to 2 cycles of ABVD received additional ABVD chemotherapy only. It was a large trial including 1950 patients, approximately one quarter of whom had bulky disease. Unfortunately, at a pre-planned interim analysis, more early progressions were noted in the chemotherapy-alone arm than the CMT arm for both F and U cohorts. Therefore, the study was amended to close the ABVD-only arm for PET-negative patients and to add INRT to either 3 (F) or 4 (UF) cycles of ABVD. After a median follow-up of 5.0 years, PET-negative patients in the favorable cohort who received radiation had a 12% superior 5-year PFS compared to those who did not, supporting a role for CMT in early favorable disease. Interestingly, the unfavorable cohort had somewhat different results. The difference in 5-year PFS between CMT and chemotherapy only for the unfavorable subgroup was only 2.5% (HR 1.45 in favor of CMT), suggesting that a

Table 1 Randomized phase 3 studies in adult early-stage Hodgkin lymphoma assessing radiation-free approaches

Trial*	N, Patients	Treatment	PFS %	OS %
NCIC/ECOG H.6 (n=405)	U + F non-bulky	ABVD 4-6 cycles	87%, 12 years	94%, 12 year
		ABVD 2 cycles + STLI	92%, 12 years p = 0.09	87%, 12 year p=0.04
EORTC/LYSA/FIL H10U (n=1,196)	594, U	PET (−)		
		ABVD alone	89.6%, 5 years	98.3%, 5 years
		ABVD + INRT	92.1% , 5 years HR, 1.45	96.7 %, 5 years
	361, U + F	PET (+)		
		eBEACOPP + INRT	90.6%, 5 years	
		ABVD + INRT	77.4%, 5 years p = 0.002	96.3%, 5-year 89.3%, 5-year p=0.62
UK RAPID (n=602)	426, U + F nonbulky	PET (−) ABVD x 3	91%, 3 years	97.1%, 3 years
		ABVD x 3 + 30 Gy ISRT	95%, 3 years p=0.23	99%, 3 years p=0.27
	176, U + F nonbulky	PET (+) ABVD x 4 + RT	85%, 3 years	87.6%, years
GHSG HD17 (NCT00736320)	NR	2 eBEACOPP + 2 ABVD + 30Gy IFRT 2 eBEACOPP + 2 ABVD 2 eBEACOPP + 2 ABVD	Results pending	Results pending

Abbreviations: *PFS*, progression-free-survival; *OS*, overall survival; *U*, unfavorable; *F*, favorable; *ABVD*, doxorubicin, bleomycin, vinblastine, dacarbazine; *AVD doxorubicin*, vinblastine, dacarbazine; *STLI*, subtotal lymphoid irradiation; *INRT*, involved nodal irradiation; *ECOG*, Eastern Cooperative Oncology Group; *LYSA*, Lymphoma Study Association; *FIL*, Fondazione Italiana Linfomi; *UK NCRI*, United Kingdom National Cancer Research Institute; *GHSG*, German Hodgkin Study Group; *PET*, positron emission test; *eBEACOPP*, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; *NR*, not reported chemotherapy-alone strategy was not necessarily inferior to combined modality therapy when a full 6 cycles of chemotherapy were prescribed. The authors concluded that in the unfavorable group, a chemotherapy-only approach could be "considered" and should be individualized.

The most recent data on the expected outcomes from a PET-adapted radiation-free approach were provided by the CALGB 50604 trial, a single-arm risk-adapted study of non-bulky early-stage Hodgkin lymphoma. One hundred sixty-four patients of which 58% were UF by GHSG criteria were treated with ABVD for 2 cycles followed by an interim PET. Those with negative results (Deauville 1, 2, 3) received 2 additional cycles of ABVD and no irradiation. There was no difference between favorable or unfavorable patients in terms of outcomes. Overall, 3-year PFS for interim PET-negative patients was 91% [25].

Ostensibly, patients with bulky disease were excluded from many of these radiation-free trials (with the exception of EORTC H10). CMT has been considered the standard of care for patients with bulky mediastinal masses, although data from the PET era are emerging suggesting that radiation may be omitted for many, especially those with negative interim and end-of-treatment PETs for whom radiotherapy carries additional risk. Approximately one quarter of patients in the H10 trial had bulky mediastinal masses but a subgroup analysis has not yet been published perhaps owing to small numbers [32]. Patients with IIB disease including many with bulky mediastinal masses are considered by many groups to have advanced-stage disease and thus have been included in advanced-stage trials such as the GITIL/FIL HD 0607 which showed no added value to radiotherapy to bulky nodal masses patients with negative interim and end-of-therapy PETs. In addition, retrospective analyses support omitting radiotherapy in those cases with negative end-of-treatment PETs [22, 33]. The safety of radiation omission is questioned by a recent SEER analysis demonstrating an improved survival in patients with HL receiving radiation regardless of stage [34].

Our approach We attempt to enroll early unfavorable patients on clinical trials investigating radiation-free approaches. Off study, we utilize a PET-adapted approach. Patients who are unfavorable due to erythrocyte sedimentation rate, B-symptoms, or number of nodal sites are treated with 4–6 cycles of ABVD alone if an interim PET is negative with the bleomycin omitted beginning cycle 3. The number of cycles of ABVD is individualized, ranging from 4 to 6. We individualize the addition of consolidative involved site radiotherapy to bulky disease, favoring its omission if the interim and end-of-treatment PETs are negative, especially when the fields will be large owing to multiple nodal sites, patients are female, or there are concerns regarding the risk of cardiovascular disease.

Novel approaches in this arena include incorporation of newly approved brentuximab vedotin (BV) or programmed death (PD)-1 inhibition.

In the initial phase 1 trial combining ABVD and BV, there was unacceptable toxicity when BV was combined with bleomycin, leading to its omission in all subsequent trials [35]. Thereafter, a phase 1 clinical trial combining BV (1.2 mg/kg) and AVD chemotherapy followed by 30 Gy of involved site radiation therapy (ISRT) in early unfavorable patients was performed [36]. The combination was safe and effective. Fifty-three percent of patients experienced grade 3–4 neutropenia, and peripheral neuropathy occurred in 40%. After 4 cycles of the combination, and prior to radiation, 93% of patients ($n = 27$) had negative PET scans and 1-year PFS was 93%. "Radiation-free" approaches are also being investigated. A clinical trial of sequential pembrolizumab and AVD in patients with early unfavorable or advanced-stage disease (NCT03226249) omits both bleomycin and radiotherapy. Preliminary results demonstrate safety and efficacy; however, the trial is ongoing and final results are pending at the time of this manuscript.

What Is the Optimal Treatment for Advanced-Stage Disease?

For the past decade, the major controversy in the treatment of advanced-stage disease has centered on the debate between ABVD and the German-derived regimen, escalated BEACOPP. The efficacy and toxicities of these treatments have been well described [37–39]. Six cycles of ABVD result in 5-year PFS of 68–80% and OS of 85–90% [7••, 37, 40•]. Fertility is generally preserved for younger patients treated with ABVD. Neutropenia, while common, does not interfere with dose density, and treatment-related deaths are exceedingly rare [41–43]. Although escalated BEACOPP results in consistently superior PFS, with long-term disease-free survival exceeding 90% in recent analyses [44], randomized trials have failed to show superiority in terms of overall survival [37]. One meta-analysis demonstrated a small improvement (3%) in survival [6] but the improved efficacy is at the risk of increased disease-related acute and long-term toxicity. The rates of infertility, neutropenia, hospitalizations, and second malignancies are increased [43, 45]. However, recent analyses from the GHSG demonstrate that in the hands of experienced providers, the rate of treatment-related deaths is low and second malignancies are overall relatively rare [43, 44, 46]. Reducing the number of cycles of escBEACOPP to only four in selected patients is anticipated to reduce the risks of secondary neoplasia. Furthermore, with fewer cycles administered, fertility remains intact in most patients with no difference in childbirth rates compared to the general population [43, 44, 46, 47]. See

Table 2 for a summary of phase 3 response-adapted trials in advanced Hodgkin lymphoma.

PET-Directed therapy

ABVD

The routine incorporation of PET-directed therapy has further advanced the long-term survival and diminished toxicity among patients with early treatment response. The Response-Adapted Therapy in Hodgkin Lymphoma (RATHL) study assessed PET-directed escalation to escBEACOPP or de-escalation with omission of bleomycin among patients initially treated with ABVD. De-escalation to AVD in patients with a negative PET2 was non-inferior, with 3-year PFS of approximately 85% in both arms and OS exceeding 97% [7••]. Escalation to BEACOPP in patients with positive interim PET scans resulted in a 68% 3-year PFS and 85% 3-year OS. Several additional trials have validated the utility of this approach with PFS and OS of the group as a whole at 2–3 years generally exceeding 80% and 95% respectively [7••, 23•, 24••, 48]. These benchmarks are important to bear in mind when comparing to non-PET-directed approaches, as was the case with the ECHELON-1 phase 3 clinical trial comparing ABVD to brentuximab vedotin and AVD (A + AVD) chemotherapy.

BEACOPP

PET-directed approaches have also been assessed in multiple BEACOPP trials [44, 49]. The most recent PET-directed trial of escBEACOPP, HD18, has provided the highest rate of PFS or OS seen in any advanced-stage clinical trial to date [44]. Patients with advanced-stage disease were treated with escBEACOPP followed by an interim PET. Those with PET negativity received 4 cycles total, whereas PET positive patients received 6–8 (due to an interim protocol amendment). The 5-year PFS was 92.2% for 4 cycles of therapy compared to 90.8% in those receiving 6–8. For patients with a positive PET, the addition of rituximab provided no additional benefit; however, even those with positive PETs had excellent long-term outcomes, with 5-year PFS near 90%. The authors further noted reduced toxicity and limited compromise of fertility in patients who received 4 cycles versus more cycles of escBEACOPP. While these results are impressive, there are several caveats. Escalated BEACOPP is only used in fit patients under the age of 60. Due to the significant treatment-related toxicity, this regimen should only be used in experienced centers with knowledge of dose adjustments and with access to ample resources for frequent laboratory monitoring, transfusion support, and close proximity to a medical center in case of need for urgent hospitalization.

Brentuximab Vedotin and AVD

The newest addition to the armamentarium in advanced-stage Hodgkin lymphoma is the combination of brentuximab vedotin and AVD chemotherapy (A + AVD). This combination was studied in the multicenter phase 3 clinical trial, ECHELON-1 [50]. Patients with stage 3 or 4 HL were randomized to treatment with A + AVD ($n = 664$) versus standard ABVD ($n = 670$). The primary endpoint was modified PFS (mPFS), which included any treatment change or progression event. The trial demonstrated superiority of A + AVD in this endpoint with mPFS of 82.1% and 77.2%, respectively, resulting in a difference of 4.9 percentage points (HR 0.77; $p = 0.03$). A number of issues cloud the interpretation of these results. PET-directed therapy per the RATHL trial has become the standard of care in advanced disease. In the ECHELON-1 trial, patients in the ABVD arm had interim scans, but they did not result in protocol-driven treatment changes (escalation or de-escalation). Therefore, the ABVD or standard of care arm had inferior outcomes to what would have been expected with PET-adapted therapy. Significantly, outcomes of those who continued ABVD in spite of a positive PET were considerably inferior (42% 2-year PFS) when compared to results of patients who escalated to BEACOPP in PET-directed trials (65–70% 2-year PFS with escalation) [7••, 23]. Likewise, there was no change in therapy on the experimental arm in PET positive patients, leaving providers questioning how to react in real-world scenarios. Compared to ABVD, A + AVD was associated with increased incidence of febrile neutropenia (19% versus 8%), which was diminished in those receiving prophylactic granulocyte colony–stimulating factor use compared to those who did not (11% versus 21%). However, the rate of peripheral neuropathy was very high at 67% overall (though 2/3 of these were reversible) and may be unacceptable to the young demographic typically affected. Lastly, the rate of pulmonary toxicity was low in both arms (7% in ABVD versus 2% in A + AVD) but contributed to excess mortality in the ABVD arm with 11 of 13 deaths contributed to pulmonary events. The continued use of bleomycin beyond PET negativity in the standard arm likely contributed to an unnecessarily high risk of pulmonary-related adverse events.

Our Approach

We treat newly diagnosed patients with ABVD for the first 2 cycles, and omit bleomycin if the PET is negative (Deauville score of 1–3) for the subsequent 4 cycles. Patients with an interim positive PET are escalated to BEACOPP for 2–4 additional cycles. Consistent with the NCCN guidelines, we reserve A + AVD for high-risk patients with an IPS score of 4–5, or those who are otherwise at high risk for toxicity with bleomycin due to pulmonary function or smoking status. We do not use escalated BEACOPP initially due to its associated

Table 2 Recent trials of PET-adapted therapy in advanced-stage Hodgkin lymphoma

Study	PET+ % (Deauville definition)	N	Treatment	PFS %	OS %
SWOG 0816	18% (4-5)	336	2 ABVD→	79% (overall)	98% (overall)
			PET (−) 4 ABVD	82%, 2 years	
			PET(+) 6 eBEACOPP	64%, 2 years p=0.04	p=NS
RATHL	16% (4-5)	1412	2 ABVD→	83% (overall)	96% (overall)
			PET(−) 4 ABVD 4 AVD	85%, 3 years 84%, 3 years p=0.48	97.2%, 3 years 97.6%, 3 years p=NS
			PET (+) eBEACOPP BEACOPP14	67.5%, 3 years	87.8%, 3 years
GITL/FIL HD 0607	19% (4-5)	782	2 ABVD→	82% (overall)	97% (overall)
			PET (-) 4 ABVD (no LNM) 4 ABVD (LNM)	*87%, 3 years 86% 93%	99%, 3 years
			4 ABVD + ISRT (LNM)	97% p=0.29	
			PET (+) eBEACOPP BEACOPP+ R	*60%, 3 years 57%, 3 years 63%, 3 years p= .53 p=0.001	89%, 3 years p<0.001
LYSA AHL2011* interim results	12% (4-5)	823	6 eBEACOPP	87% (overall) 86.2%, 5 years	95.2% (overall) 96.4%, 5 years
			2 eBEACOPP → PET2 (−) 4 ABVD	85.7%, 5 years	90.9%, 5 years
			PET2 (+) 4 eBEACOPP	79.4%, 5 years p=0.68	p=0.91
HD0801	20% (3-5)	519	3 ABVD→	80% (overall)	97% (overall)
			PET2 (−) 4 ABVD	81%, 2 years	
			PET (+) HDCT + SCT	76%, 2-years p= NR	
GHSG HD18	48% (3-5)	2100	2 eBEACOPP→ PET2 (−) 2 eBEACOPP 4-6 eBEACOPP	89.4% (overall) 92.2%, 5 years 90.8%, 5 years	95·6% (overall) 97.7%, 5 years 95.4%, 5 years
		434	PET-2 (+) 6 eBEACOPP + R	88.1%, 5 years	93.9%, 5 years
			6 eBEACOPP	89.7%. 5 years p=0.46	96.4%, 5 years p=NS
ECHELON-1	7% (4-5)	1040	6 A + AVD	82% 2 yr Mod PFS (overall) PET (+) 58% PET (−) 85%	96.6%, 2 years
	8% (4-5)		6 ABVD	77%, 2 years PET (+) 42% PET (−) 82% p=0.04	94.2%, 2 years HR 0.72 p=0.20

*No difference based on receipt of radiation for PET2-negativity or rituximab for PET2-positivity

Abbreviations: *PFS*, progression-free-survival; *OS*, overall survival; *SWOG*, Southwestern Oncology Group; *ECOG*, Eastern Cooperative Oncology Group; *EORTC*, Eastern Organisation for the Research and Treatment of Cancer; *UK*, United Kingdom; *GHSG*, German Hodgkin Study Group; *PET*, positron emission test; *ABVD*, doxorubicin, bleomycin, vinblastine, dacarbazine; *AVD*, doxorubicin, vinblastine, dacarbazine; *R*, rituximab; *STLE*, subtotal lymphoid irradiation; *INRT*, involved nodal irradiation; *ISRT*, involved site radiation therapy; *eBEACOPP*, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; *HDCT*, high-dose chemotherapy; *SCT*, stem cell transplantation; *mod PFS*, modified progression-free survival; *NR*, not reported; *LNM*, large nodal mass ≥ 5 cm acute and long-term toxicities. However, in centers experienced in the use of escalated BEACOPP, it is appropriate for initial therapy in young fit patients with high-risk disease.

Novel approaches incorporating PD-1 inhibition or adding BV to a BEACOPP like backbone are currently under evaluation. The results of the frontline trial of nivolumab with AVD chemotherapy in advanced HL demonstrated tolerability of the combination and results that appear at least consistent if not superior to standard chemotherapy regimens [51]. Updated results of 51 patients were reported at the European Hematology Association. The most common grade 3/4 immune-mediated adverse event was hepatitis ($n = 2$; 4%). Eighty-four percent of patients responded to treatment, including 67% with a CR [52]. Similarly, pembrolizumab is being assessed in a sequential approach and also has early promising results when followed by AVD (NCT03226249). Given the promising results of the nivolumab combination, a head-to-head comparison of the ECHELON-1 combination with nivolumab and AVD is being planned. The GHSG has investigated BEACOPP variants to combine with BV [53]. One combination (BrECADD: brentuximab vedotin, etoposide, doxorubicin, cyclophosphamide, dacarbazine, and dexamethasone) was associated with a favorable toxicity profile and was, therefore, selected to challenge standard escBEACOPP for the treatment of advanced classical Hodgkin lymphoma (cHL) in the phase 3 HD21 study by the GHSG (NCT02661503).

What Is the Optimal Treatment for Elderly Hodgkin Patients?

Elderly Hodgkin lymphoma patients are defined as those older than 60 years, and make up approximately 15–30% of all Hodgkin cases [54]. These are a particularly high-risk group of individuals due to increased risk of treatment toxicity, underlying co-morbidities, and generally higher risk features [55, 56]. There is no standard of care at this time, and trials demonstrate 3-year survival rates of approximately 50–70% overall [57–62]. Elderly patients are particularly sensitive to the toxic effects of bleomycin with up to one-third of patients developing bleomycin lung toxicity compared to less than 3% of young patients [56, 62, 63]. Bleomycin lung toxicity proves deadly in up to 22% of cases [32, 56]. Approaches to balancing toxicity and efficacy have resulted in the elimination of bleomycin from initial therapy or following an interim negative PET [7••, 64, 65]. In the GHSG HD 10 and 13 analyses, treatment with AVD chemotherapy in early favorable patients yielded inferior disease control compared to ABVD; however, survival was excellent at 98% [66]. Alternative approaches in favorable patients included 2 cycles of ABVD or AVD followed by radiation therapy. Elimination of bleomycin reduced the risk of bleomycin toxicity and decreased grade 3/4 events [56, 62, 65]. Recently, the results of novel combinations of therapy in elderly patients have been reported and results compared to historic cohorts are impressive.

Brentuximab monotherapy was initially studied in older patients not amenable to frontline chemotherapy and 92% of patients achieved an objective ORR with 73% CRs [26••]. Unfortunately, the risk of relapse was high, so the trial was subsequently amended to add either bendamustine or dacarbazine [26••]. In spite of high disease activity, there was an unacceptable rate of toxicity with the bendamustine combination and this arm was closed prematurely. Among 22 older HL patients treated with the dacarbazine combination, the ORR was 100% and CR rate was 62%, with a median PFS of 17.9 months. The incidence of grade 3 neurotoxicity was 27%. These results are very promising especially for patients unable to receive an anthracycline. Very impressive results have recently been reported from a multicenter phase 2 trial of BV for 2 doses followed by 6 cycles of AVD chemotherapy and 4 doses of consolidative BV [27••]. The trial included many patients with high-risk IPS scores and high co-morbidity scores as assessed on a comprehensive geriatric assessment. The 2-year progression-free and overall survival rates reached an unprecedented 84% and 93% respectively with geriatric-based measures strongly associated with survival.

Our Approach

There is no standard of care for elderly patients and enrollment on clinical trials when available is recommended. Those with early favorable disease may be treated with as little as 2 cycles of AVD followed by radiation. For advanced-stage disease, AVD or CHOP may be considered when there are no cardiac issues [67]. For patients with high-risk features where there is concern that AVD may be insufficient, it is hard to ignore the new yet impressive results from the brentuximab and AVD trial in the elderly [27••]. When anthracycline is contraindicated, brentuximab vedotin and dacarbazine is an alternative. There is unlikely to be a randomized comparison of approaches given the rarity of this subgroup of patients and treatment must be individualized.

Conclusion

Growing controversy regarding the initial treatment of Hodgkin lymphoma is evidence of the recent expansion of several highly effective treatment options, particularly in patients with high-risk features such as advanced disease or older age. As more effective therapies are used in the frontline setting, we foresee the role of radiation therapy decreasing as part of the initial treatment strategy. Patients with advanced-stage disease still represent a large challenge to clinicians. We have many highly effective treatment options, but lack consistent biomarkers or clinical risk stratification to accurately allocate the appropriate treatments at the time of diagnosis. We continue to rely on the IPS score to differentiate high- and low-risk patients who may require more intensive initial therapy (i.e., escalated BEACOPP or incorporation of brentuximab), yet this system is imperfect. Likewise, interim PET-CT identifies some patients who are at high risk for treatment failure after initial treatment with ABVD, but is less sensitive in patients with initial treatment with either A + AVD or escalated BEACOPP. Nevertheless, incorporation of novel agents like brentuximab and possibly checkpoint inhibitors into the initial treatment strategy for high-risk patients including elderly and advanced-stage patients promises to improve outcomes, and we look forward to the results of ongoing clinical trials.

Compliance with Ethical Standards

Conflict of Interest Pamela B. Allen declares that she has no conflict of interest.

Jane N. Winter has received clinical trial funding (paid to her institution) from Merck and GlaxoSmithKline and has received compensation from Merck, Gilead, Janssen, Adicet Bio, and Bayer for participation on advisory boards.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.• Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, Johnson P, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med. 2015;372(17):1598–607 **Established the role of 3 cycles of AVD without radiation for early-stage Hodgkin lymphoma.**
2. Eich HT, Diehl V, Gorgen H, Pabst T, Markova J, Debus J, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol. 2010;28(27):4199–206.
3. Engert A, Franklin J, Eich HT, Brillant C, Sehlen S, Cartoni C, et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. J Clin Oncol. 2007;25(23):3495–502.
4. Engert A, Schiller P, Josting A, Herrmann R, Koch P, Sieber M, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. J Clin Oncol. 2003;21(19):3601–8.
5. Engert A, Plutschow A, Eich HT, Lohri A, Dorken B, Borchmann P, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med. 2010;363(7):640–52.
6. Skoetz N, Will A, Monsef I, Brillant C, Engert A, von Tresckow B. Comparison of first-line chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for people with early unfavourable or advanced stage Hodgkin lymphoma. Cochrane Database Syst Rev. 2017;5:CD007941.
7.•• Johnson P, Federico M, Kirkwood A, Fossa A, Berkahn L, Carella A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. N Engl J Med. 2016;374(25):2419–29 **The largest trial of PET-de-escalation in advanced Hodgkin lymphoma. Established the safety of bleomycin omission following 2 cycles of ABVD in patients with an interim complete metabolic response.**
8. Schaapveld M, Aleman BM, van Eggermond AM, Janus CP, Krol AD, van der Maazen RW, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med. 2015;373(26):2499–511.
9. Hay AE, Klimm B, Chen BE, Goergen H, Shepherd LE, Fuchs M, et al. Treatment of stage I-II A non-bulky Hodgkin's lymphoma (HL): an individual patient-data comparison of German Hodgkin Study Group (GHSG) HD10 and HD11 combined-modality therapy (CMT) and NCIC Clinical Trials Group (NCIC CTG) HD.6 ABVD Alone. Blood. 2015;120(21):548.
10. Ng AK, LaCasce A, Travis LB. Long-term complications of lymphoma and its treatment. J Clin Oncol. 2011;29(14):1885–92.
11. Kobe C, Dietlein M, Kriz J, Furth C, Fuchs M, Borchmann P, et al. The role of PET in Hodgkin's lymphoma and its impact on radiation oncology. Expert Rev Anticancer Ther. 2010;10(9):1419–28.
12. Goodman KA, Riedel E, Serrano V, Gulati S, Moskowitz CH, Yahalom J. Long-term effects of high-dose chemotherapy and radiation for relapsed and refractory Hodgkin's lymphoma. J Clin Oncol. 2008;26(32):5240–7.
13. Brusamolino E, Baio A, Orlandi E, Arcaini L, Passamonti F, Griva V, et al. Long-term events in adult patients with clinical stage IA-IIA nonbulky Hodgkin's lymphoma treated with four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine and adjuvant radiotherapy: a single-institution 15-year follow-up. Clin Cancer Res. 2006;12(21):6487–93.
14. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. J Clin Oncol. 2004;22(14):2835–41.
15. Specht L, Yahalom J, Illidge T, Berthelsen AK, Constine LS, Eich HT, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys. 2014;89(4):854–62.
16. Dhakal S, Advani R, Ballas LK, Dabaja BS, Flowers CR, Ha CS, et al. ACR Appropriateness Criteria(R) Hodgkin lymphoma-favorable prognosis stage I and II. Am J Clin Oncol. 2016;39(6):535–44.
17. Roberts KB, Younes A, Hodgson DC, Advani R, Dabaja BS, Dhakal S, et al. ACR Appropriateness Criteria(R) Hodgkin lymphoma-unfavorable clinical stage I and II. Am J Clin Oncol. 2016;39(4):384–95.
18. Maraldo MV, Brodin NP, Aznar MC, Vogelius IR, Munck af Rosenschold P, Petersen PM, et al. Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma. Ann Oncol. 2013;24(8):2113–8.

19. Raemaekers JM, Andre MP, Federico M, Girinsky T, Oumedaly R, Brusamolino E, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2014;32(12):1188–94.
20.•• Andre MP, Girinsky T, Federico M, Reman O, Fortpied C, Gotti M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2017: Jco2016686394. **One of the largest trials of PET-adapted therapy in early-stage patients. Demonstrated potential safety of omission of radiation therapy in some patients with early unfavorable disease and a complete metabolic remission.**
21. Savage KJ, Connors JM, Klasa RJ, Hoskins P, Shenkier TN, Gascoyne RD, et al. The use of FDG-PET to guide consolidative radiotherapy in patients with advanced-stage Hodgkin lymphoma with residual abnormalities on CT scan following ABVD chemotherapy. J Clin Oncol. 2011;29(15_suppl):8034.
22. Savage KJ, Connors JM, Villa DR, Hapgood G, Gerrie AS, Shenkier TN, et al. Advanced stage classical Hodgkin lymphoma patients with a negative PET-scan following treatment with ABVD have excellent outcomes without the need for consolidative radiotherapy regardless of disease bulk at presentation. Blood. 2015;126(23):579.
23.• Press OW, Li H, Schoder H, Straus DJ, Moskowitz CH, LeBlanc M, et al. US intergroup trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816. J Clin Oncol. 2016. **One of the first trials of PET-adapted therapy in advanced-stage Hodgkin lymphoma.**
24.•• Gallamini A, Tarella C, Viviani S, Rossi A, Patti C, Mule A, et al. Early chemotherapy intensification with escalated BEACOPP in patients with advanced-stage Hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: long-term results of the GITIL/FIL HD 0607 trial. J Clin Oncol. 2018;36(5):454–62 **One of the largest trials of PET-adapted therapy in early-stage patients. Further established safety of escalated BEACOPP in patients failing to achieve complete metabolic remission after 2 cycles of ABVD.**
25. Straus DJ, Jung SH, Pitcher B, Kostakoglu L, Grecula JC, Hsi ED, et al. CALGB 50604: risk-adapted treatment of nonbulky early-stage Hodgkin lymphoma based on interim PET. Blood. 2018;132(10):1013–21.
26.•• Friedberg JW, Forero-Torres A, Bordoni RE, Cline VJM, Patel Donnelly D, Flynn PJ, et al. Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged >/=60 years with HL. Blood. 2017;130(26):2829–37 **The first clinical trial incorporating novel therapy and omitting anthracycline in newly diagnosed elderly Hodgkin patients. Results showed improved safety and efficacy compared to historic cohorts.**
27.•• Evens AM, Advani RH, Helenowski IB, Fanale M, Smith SM, Jovanovic BD, et al. Multicenter phase II study of sequential brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine chemotherapy for older patients with untreated classical Hodgkin lymphoma. J Clin Oncol. 2018:JCO2018790139. **One of the first trials incorporating novel therapy into newly diagnosed elderly Hodgkin lymphoma. Results showed improved safety and efficacy compared to historic cohorts.**
28. Klimm B, Goergen H, Fuchs M, von Tresckow B, Böll B, Meissner J, et al. Impact of risk factors on outcomes in early-stage Hodgkin's lymphoma: an analysis of international staging definitions. Ann Oncol. 2013;24(12):3070–6.
29. Gunther JR, Fanale MA, Reddy JP, Akhtari M, Smith GL, Pinnix CC, et al. Treatment of early-stage unfavorable Hodgkin lymphoma: efficacy and toxicity of 4 versus 6 cycles of ABVD chemotherapy with radiation. Int J Radiat Oncol Biol Phys. 2016;96(1):110–8.
30. von Tresckow B, Plutschow A, Fuchs M, Klimm B, Markova J, Lohri A, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. J Clin Oncol. 2012;30(9):907–13.
31. Meyer RM, Gospodarowicz MK, Connors JM, Pearcey RG, Wells WA, Winter JN, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med. 2012;366(5): 399–408.
32. Fiaccadori V et al. Relapses in early PET-negative stage I/II Hodgkin lymphoma after combined modality treatment or chemotherapy only in the EORTC/LYSA/FIL H10 trial. Abstract # 0066. International Symposium of Hodgkin Lymphoma; Cologne, Germany 2018.
33. Nguyen VT, Pophali PA, Tsai JP, Jagadeesh D, Dean RM, Pohlman B, et al. Early stage, bulky Hodgkin lymphoma patients have a favorable outcome when treated with or without consolidative radiotherapy: potential role of PET scan in treatment planning. Br J Haematol. 2017;179(4):674–6.
34. Master S, Koshy N, Wilkinson B, Rosen L, Mills G, Mansour R, et al. Effect of radiation therapy on survival in Hodgkin's lymphoma: a SEER data analysis. Anticancer Res. 2017;37(6): 3035–43.
35. Younes A, Connors JM, Park SI, Fanale M, O'Meara MM, Hunder NN, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. Lancet Oncol. 2013;14(13): 1348–56.
36. Kumar A, Casulo C, Yahalom J, Schoder H, Barr PM, Caron P, et al. Brentuximab vedotin and AVD followed by involved-site radiotherapy in early stage, unfavorable risk Hodgkin lymphoma. Blood. 2016;128(11):1458–64.
37. Carde P, Karrasch M, Fortpied C, Brice P, Khaled H, Casasnovas O, et al. Eight cycles of ABVD versus four cycles of BEACOPPescalated plus four cycles of BEACOPPbaseline in stage III to IV, international prognostic score >/= 3, high-risk Hodgkin lymphoma: first results of the phase III EORTC 20012 intergroup trial. J Clin Oncol. 2016;34:2028–36.
38. Gordon LI, Hong F, Fisher RI, Bartlett NL, Connors JM, Gascoyne RD, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol. 2013;31(6):684–91.
39. Federico M, Luminari S, Iannitto E, Polimeno G, Marcheselli L, Montanini A, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. J Clin Oncol. 2009;27(5):805–11.
40.• Zinzani PL, Broccoli A, Gioia DM, Castagnoli A, Ciccone G, Evangelista A, et al. Interim positron emission tomography response–adapted therapy in advanced-stage Hodgkin lymphoma: final results of the phase II part of the HD0801 study. J Clin Oncol. 2016. **Additional trial of PET-adapted therapy in advanced Hodgkin lymphoma.**
41. Minuk LA, Monkman K, Chin-Yee IH, Lazo-Langner A, Bhagirath V, Chin-Yee BH, et al. Treatment of Hodgkin lymphoma with adriamycin, bleomycin, vinblastine and dacarbazine without routine granulocyte-colony stimulating factor support does not increase the risk of febrile neutropenia: a prospective cohort study. Leuk Lymphoma. 2012;53(1):57–63.
42. Anderson RA, Remedios R, Kirkwood AA, Patrick P, Stevens L, Clifton-Hadley L, et al. Determinants of ovarian function after

response-adapted therapy in patients with advanced Hodgkin's lymphoma (RATHL): a secondary analysis of a randomised phase 3 trial. Lancet Oncol. 2018;19(10):1328–37.
43. Behringer K, Mueller H, Goergen H, Thielen I, Eibl AD, Stumpf V, et al. Gonadal function and fertility in survivors after Hodgkin lymphoma treatment within the German Hodgkin Study Group HD13 to HD15 trials. J Clin Oncol. 2013;31(2):231–9.
44. Borchmann P, Goergen H, Kobe C, Lohri A, Greil R, Eichenauer DA, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. Lancet. 2018;390(10114):2790–802.
45. Merli F, Luminari S, Gobbi PG, Cascavilla N, Mammi C, Ilariucci F, et al. Long-term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPP-EBV-CAD in untreated patients with advanced Hodgkin lymphoma: a study by Fondazione Italiana Linfomi. J Clin Oncol. 2016;34(11):1175–81.
46. Eichenauer DA, Thielen I, Haverkamp H, Franklin J, Behringer K, Halbsguth T, et al. Therapy-related acute myeloid leukemia and myelodysplastic syndromes in patients with Hodgkin lymphoma: a report from the German Hodgkin Study Group. Blood. 2014;123(11):1658–64.
47. Weibull CE, Johansson ALV, Eloranta S, Smedby KE, Bjorkholm M, Lambert PC, et al. Contemporarily treated patients with Hodgkin lymphoma have childbearing potential in line with matched comparators. J Clin Oncol. 2018;36(26):2718–25.
48. Zinzani PL, Broccoli A, Gioia DM, Castagnoli A, Ciccone G, Evangelista A, et al. Interim positron emission tomography response-adapted therapy in advanced-stage Hodgkin lymphoma: final results of the phase II part of the HD0801 study. J Clin Oncol. 2016;34(12):1376–85.
49. Borchmann P, Haverkamp H, Diehl V, Cerny T, Markova J, Ho AD, et al. Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage Hodgkin's lymphoma: final analysis of the HD12 trial of the German Hodgkin Study Group. J Clin Oncol. 2011;29(32):4234–42.
50. Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med. 2018;378(4):331–44.
51. Ramchandren R, Fanale MA, Rueda A, Armand P, Trněný M, Feldman TA, et al. Nivolumab for newly diagnosed advanced-stage classical Hodgkin lymphoma (cHL): results from the phase 2 Checkmate 205 study. Blood. 2017;130(Suppl 1):651.
52. Ramchandren R DE, Rueda A, et al. CheckMate 205 cohort D: a phase 2 trial of nivolumab for newly diagnosed advanced-stage classical Hodgkin lymphoma. Abstract #S114. 23rd Congress of the European Hematology Association; June 15, 2018; Stockholm, Sweden2018.
53. Eichenauer DA, Plutschow A, Kreissl S, Sokler M, Hellmuth JC, Meissner J, et al. Incorporation of brentuximab vedotin into first-line treatment of advanced classical Hodgkin's lymphoma: final analysis of a phase 2 randomised trial by the German Hodgkin Study Group. Lancet Oncol. 2017;18(12):1680–7.
54. Stark GL, Wood KM, Jack F, Angus B, Proctor SJ, Taylor PR, et al. Hodgkin's disease in the elderly: a population-based study. Br J Haematol. 2002;119(2):432–40.
55. Evens AM, Sweetenham JW, Horning SJ. Hodgkin lymphoma in older patients: an uncommon disease in need of study. Oncology (Williston Park). 2008;22(12):1369–79.
56. Evens AM, Helenowski I, Ramsdale E, Nabhan C, Karmali R, Hanson B, et al. A retrospective multicenter analysis of elderly Hodgkin lymphoma: outcomes and prognostic factors in the modern era. Blood. 2012;119(3):692–5.
57. Zallio F, Tamiazzo S, Monagheddu C, Merli F, Ilariucci F, Stelitano C, et al. Reduced intensity VEPEMB regimen compared with standard ABVD in elderly Hodgkin lymphoma patients: results from a randomized trial on behalf of the Fondazione Italiana Linfomi (FIL). Br J Haematol. 2016;172:879–88.
58. Sonneveld P, Hop W, Mulder AH, Michiels JJ, Blijham G, van de Lelie J, et al. Full-dose chemotherapy for non-Hodgkin's lymphoma in the elderly. Dutch Hematology-Oncology in Adults Study Group. Semin Hematol. 1994;31(2 Suppl 3):9–12.
59. Nabhan C, Smith SM, Helenowski I, Ramsdale E, Parsons B, Karmali R, et al. Analysis of very elderly (>/=80 years) non-Hodgkin lymphoma: impact of functional status and co-morbidities on outcome. Br J Haematol. 2012;156(2):196–204.
60. Evens AM, Hong F, Gordon LI, Fisher RI, Bartlett N, Connors JM, et al. Efficacy and tolerability of ABVD and Stanford V for elderly advanced-stage Hodgkin lymphoma (HL): analysis from the phase III randomized U.S. intergroup trial E2496. J Clin Oncol. 2011;29(15_suppl):8035.
61. Boll B, Bredenfeld H, Gorgen H, Halbsguth T, Eich HT, Soekler M, et al. Phase 2 study of PVAG (prednisone, vinblastine, doxorubicin, gemcitabine) in elderly patients with early unfavorable or advanced stage Hodgkin lymphoma. Blood. 2011;118(24):6292–8.
62. Ballova V, Ruffer JU, Haverkamp H, Pfistner B, Muller-Hermelink HK, Duhmke E, et al. A prospectively randomized trial carried out by the German Hodgkin Study Group (GHSG) for elderly patients with advanced Hodgkin's disease comparing BEACOPP baseline and COPP-ABVD (study HD9elderly). Ann Oncol. 2005;16(1):124–31.
63. Evens AM, Hong F, Gordon LI, Fisher RI, Bartlett NL, Connors JM, et al. The efficacy and tolerability of adriamycin, bleomycin, vinblastine, dacarbazine and Stanford V in older Hodgkin lymphoma patients: a comprehensive analysis from the North American intergroup trial E2496. Br J Haematol. 2013;161(1):76–86.
64. Behringer K, Goergen H, Hitz F, Zijlstra JM, Greil R, Markova J, et al. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. Lancet. 2015;385(9976):1418–27.
65. Stamatoullas A, Brice P, Bouabdallah R, Mareschal S, Camus V, Rahal I, et al. Outcome of patients older than 60 years with classical Hodgkin lymphoma treated with front line ABVD chemotherapy: frequent pulmonary events suggest limiting the use of bleomycin in the elderly. Br J Haematol. 2015;170(2):179–84.
66. Boll B, Goergen H, Behringer K, Brockelmann PJ, Hitz F, Kerkhoff A, et al. Bleomycin in older early-stage favorable Hodgkin lymphoma patients: analysis of the German Hodgkin Study Group (GHSG) HD10 and HD13 trials. Blood. 2016;127:2189–92.
67. Kolstad A, Nome O, Delabie J, Lauritzsen GF, Fossa A, Holte H. Standard CHOP-21 as first line therapy for elderly patients with Hodgkin's lymphoma. Leuk Lymphoma. 2007;48(3):570–6.