Hodgkin lymphoma treatment for older persons in the modern era

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There has been a renewed effort globally in the study of older Hodgkin lymphoma (HL) patients, generating a multitude of new data. For prognostication, advancing age, comorbidities, altered functional status, Hispanic ethnicity, and lack of dose intensity (especially without anthracycline) portend inferior survival. Geriatric assessments (GA), including activities of daily living (ADL) and comorbidities, should be objectively measured in all patients. In addition, proactive multidisciplinary medical management is recommended (eg, geriatrics, cardiology, primary care), and pre-phase therapy should be considered for most patients. Treatment for fit older HL patients should be given with curative intent, including anthracyclines, and bleomycin should be minimized (or avoided). Brentuximab vedotin given sequentially before and after doxorubicin, vinblastine, dacarbazine (AVD) chemotherapy for untreated patients is tolerable and effective, and frontline checkpoint inhibitor/AVD platforms are rapidly emerging. Therapy for patients who are unfit or frail, whether due to comorbidities and/or ADL loss, is less clear and should be individualized with consideration of attenuated anthracycline-based therapy versus lower-intensity regimens with inclusion of brentuximab vedotin +/− checkpoint inhibitors. For all patients, there should be clinical vigilance with close monitoring for treatment-related toxicities, including neurotoxicity, cardiopulmonary, and infectious complications. Finally, active surveillance for "postacute" complications 1 to 10 years post therapy, especially cardiac disease, is needed for cured patients. Altogether, therapy for older HL patients should include anthracycline-based therapy in most cases, and novel targeted agents should continue to be integrated into treatment paradigms, with more research needed on how best to utilize GAs for treatment decisions.

LEARNING OBJECTIVES

- Describe prognostic factors associated with inferior outcomes for older Hodgkin lymphoma patients in population-based and clinical studies
- Examine contemporary clinical trial results for older Hodgkin lymphoma patients with emphasis on integration of targeted treatment agents
- Discuss treatment-related toxicities, including lethal events, with attention to cardiac disease and postacute survivorship considerations

CLINICAL CASE

A 70-year-old Hispanic man presents with increasing generalized fatigue, low back pain, and unintentional 20-pound weight loss over the preceding 4 months. Physical examination revealed large nontender adenopathy in the left axilla. The patient's hemoglobin was 9.5 g/dL with mean corpuscular volume (MCV) 98 fL, percent transferrin saturation 8%, ferritin 780 ng/mL, normal B12 and folate, and an absolute reticulocyte count of 45 000.

The patient has a history of coronary artery disease status post stent 5 years prior, well-controlled hypertension, type 2 diabetes on oral therapy, prior smoker (30 packs per year), hiatal hernia, and past history of basal cell cancer (Cumulative Illness Rating Scale-Geriatric [CIRS-G] score = 10). He is a retired mechanic and lives alone; he performs all self-care and instrumental activities of daily living (ADLs) without restriction, but ECOG performance status was 2.

Excisional lymph node biopsy of a left axillary node showed effacement by a mixed population of lymphocytes, plasma cells, eosinophils, neutrophils, and histiocytes. Scattered large cells stained positive for CD15, CD30, PAX5, and EBER. The diagnosis was consistent with

classic Hodgkin lymphoma, mixed cellularity type with Epstein-Barr virus positivity by EBER in situ hybridization.

A staging positron emission tomography (PET) scan for the patient showed hypermetabolic disease in the left axilla node (3.5×5.9cm) with standardized uptake volume max of 24, precaval nodal region with standardized uptake volume max of 19, a discrete liver lesion, and diffuse bony uptake (axial and appendicular skeleton). The baseline cardiac left ventricular ejection fraction was 55% with a global longitudinal strain of −27%.

Introduction

Older patients ages ≥60 years represent approximately 20% to 25% of all classic Hodgkin lymphoma (HL) cases diagnosed in Western and European countries.[1-5] Survival rates for older HL patients have historically been inferior compared with younger patient populations[2,6-9] and age- and sex-matched controls.[5,10] The poorer outcomes for older HL patients are likely multifactorial, including comorbidities, poor performance status, histologic differences (eg, mixed cellularity and Epstein-Barr virus–related disease), frequent advanced-stage disease, inability to tolerate chemotherapy at full dose and schedule, and increased incidence of severe treatment-related toxicity. Previous underrepresentation of older patients in HL clinical trials has compounded these factors.[6,11-13] In addition, the unique bimodal age distribution in HL results in an uncommon comparison of outcomes of individuals primarily in their 20s versus those in their 70s, which disproportionately magnifies the survival disparity.

More recently, there has been a renewed effort across the world to study older HL patients, resulting in a multitude of new data, including the prognostic impact of geriatric measures and the importance of anthracyclines for patient survival. Additionally, multiple recent prospective clinical studies have emphasized the integration of novel targeted therapeutic agents into frontline treatment paradigms. Collectively, outcomes appear to have improved for older HL patients in the contemporary era.[14-17] However, unlike other aggressive lymphoma subtypes, a standard treatment paradigm has been mostly absent, and treatment-related toxicity remains a critical issue to navigate, especially bleomycin lung toxicity (BLT), infectious complications, and neurotoxicity. In this review, we examine contemporary real-world and clinical trial treatment data for older HL patients with an emphasis on prognosis, geriatric measures, treatment intensity, anthracycline use, tolerability, integration of targeted therapeutic agents, and postacute survivorship.

Prognostication

The International Prognostic Score (IPS) included ages >45 years as an adverse covariate.[18] Of note, only 9% of patients were >55 years in the IPS, and no patients aged >65 years were included. Several analyses have shown that the IPS was not prognostic in older HL patients,[9,19,20] while 2 recent population studies from British Columbia and Sweden identified a correlation with survival.[15,17] Increasing age beyond 30 years (continuous variable) was an adverse factor for survival on the recently published advanced-stage Hodgkin Lymphoma International Prognostic Index, but only a minority of patients were >60 years.[21]

Race/ethnicity

There are intriguing racial differences seen in older HL patients. In a US Surveillance, Epidemiology, and End Results (SEER) analysis, incidence rates for older HL patients (ie, ages >64 years) were highest among Hispanics, followed by non-Hispanic Whites and Blacks (Supplementary Figure S1).[22] Furthermore, 5-, 10- and 15-year overall survival (OS) rates were inferior for Hispanics and Blacks compared with non-Hispanic Whites and Asian/Pacific Islanders, which persisted on multivariable analyses. In a contemporary SEER analysis of older HL patients treated across 2 time periods (2006-2010 and 2011-2015), Shah et al. documented improvement in OS across the 2 cohorts. However, this was primarily seen in non-Hispanic Whites (Table 1).[16] Furthermore, survival disparity persisted across the study periods between non-Hispanic Whites and Hispanics, while other factors associated with worse OS were increasing age, male sex, stage III-IV, unmarried status, and lack of chemotherapy.

Functional status

The impact of geriatric assessments (GA) in older patients with cancer is well recognized,[23] and a multitude of analyses have documented the frequent occurrence and prognostic importance of GAs in older HL patients (Supplementary Table S1).[20,24-28] Retrospective Chicago-based real-world evidence (RWE) of older HL patients treated from 2000 to 2009 found that 61% of patients had at least 1 severe comorbidity, 26% were "unfit" (using the original simplified GA tool[29]), 17% had a geriatric syndrome, and 13% had a loss of self-care activities of daily living (ADLs) at diagnosis.[20] Loss of any ADL was strongly prognostic in this data set. A recent SEER-based prediction model for 1-year mortality of older HL patients treated with curative intent was developed and validated (Table 1).[30] In addition to the presence of B-symptoms, advanced stage, and older age at diagnosis, increased comorbidities via the Charlson Comorbidity Index correlated with inferior survival.

In a multicenter phase 2 clinical trial, older HL patients were treated with 2 initial doses of single-agent brentuximab vedotin (BV), followed sequentially by adriamycin, vinblastine, dacarbazine (AVD) for 6 cycles, with subsequent consolidative single-agent BV.[19] Two-year progression-free survival (PFS) rates for HL patients with a low CIRS-G comorbidity score (ie, <10 vs ≥10) were 100% vs 45%, respectively ($P < 0.0001$). Furthermore, patients with no loss of instrumental ADLs vs a loss of *any* instrumental ADL at baseline had 2-year PFS rates of 94% vs 25% ($P < 0.0001$). A recent US multicenter RWE analysis of older HL patients treated from 2010 to 2018 confirmed the significance of ADLs on survival (Table 1 and Figure 1A/B).[28] Taken together, these studies support the prognostic importance of baseline GAs in older patients with HL.

However, more research is needed to delineate the optimum classifications of *fit* vs *unfit* vs *frail* for older HL patients based on functional status and advancing age. For example, the elderly prognostic index from the Fondazione Italiana Linfomi (FIL) group for older diffuse large B-cell lymphoma (DLBCL) patients defined a "modified simplified GA" based on model building in multivariable analysis that better accounted for age and varying levels of comorbidities,[31] and a large Norwegian analysis used the Charlson Comorbidity Index, ADLs, ages ≥85 years, and a nutritional index to delineate fitness and frailty

Table 1. Contemporary real-world data for older Hodgkin lymphoma patient outcomes

Citation	Study type	Population (study years)	Study objectives	Findings
Moccia et al. 2020[35]	Retro	Ages ≥60, N = 269 (2000–2017)	5-yr survival analyses and toxicity evaluation	BLT 17%; 5-yr PFS 53%, OS 64%, and CSS 86%; survival poorer ages >70 vs 60–70 yrs
Rodday et al. 2020[38]	SEER	Ages ≥65, N = 2825 (1999–2014)	Factors associated with first-line tx: full (25%), partial (36%), single-agent/RT (13%), no tx (26%)	Less-aggressive tx, frailty, heart disease, advanced stage, and treatment in Southern US associated with not receiving full chemotherapy
Kumar et al. 2021[30]	SEER	Ages ≥65, N = 1315 (2000–2013)	Prediction model of 1-yr mortality on standard chemotherapy	Final OS model: CCI, B-symptoms, advanced-stage disease, and older age
Orellana-Noia et al. 2021[28]	Retro	Age ≥60, N = 244 (2010–2018)	Predictors of survival based on GA and chemotherapy tx	BLT 18%; TRM 3.3%; inferior PFS and OS with ADL loss and with alternative tx vs conventional chemotherapy
Wahlin et al. 2021[17]	Registry	Age >60, N = 691 (2000–2014)	Survival by period, age, stage, sex, and ABVD vs CHOP	OS improved: 2010–2014 vs 2000-2009, with ABVD vs CHOP, and ages ≤70 vs >70 yrs
Rodday et al. 2021[37]	SEER	Ages ≥65, N = 2686 (2000–2013)	Survival by tx and stage with Cox regression, competing risk, and propensity	HL-specific survival for full tx vs partial tx (for advanced stage): HR 3.26 and "other cause" survival HR 1.76
Overgaard et al. 2022[40]	Retro	Ages ≥60, N = 1554 (2000–2021)	Survival by stage and tx with multivariable analyses	5-yr OS: AVD 64% vs ABVD 63% vs CHOP 46% (multivariable: AVD and ABVD > CHOP)
Cheng et al. 2022[15]	Registry	Ages ≥60, N = 744 (1961–2019); N = 401 (2000–2019)	5-yr survival by decade and age with toxicity analyses	BLT 21%; survival improved by decade; post 2000: 5-yr PFS 60%, OS 65%, and DSS 76%; improved survival <70 vs ≥70 yrs
Shah et al. 2022[16]	SEER	Ages ≥60, N = 4957 (2006–2015)	Comparison 2006–2010 vs 2011–2015 and by race and clinical factors	Median OS by period 4 yr vs 4.8 yr, respectively; 5-year OS inferior among Hispanics
Goh et al. 2023[39]	Registry	Ages >60, N = 195 (2011–2020)	Survival analyses, including by treatment (with Cox regression)	TRM 5.2%; 2-yr PFS 64%, OS 71%; 2-yr PFS with anthracycline 70% vs 33% without; Cox OS model: CCI and anthracycline use

ADL, activities of daily living; AVBD, doxorubicin, vinblastine, bleomycin, dacarbazine; AVD, doxorubicin, vinblastine, dacarbazine; BLT, bleomycin lung toxicity; CCI, Charlson Comorbidity Index; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; CSS, cause-specific survival; DSS, disease-specific survival; GA, geriatric assessments; HR, hazard ratio; N, number; OS, overall survival; PFS, progression-free survival; pts, patients; retro, retrospective; RT, radiation therapy; SEER, Surveillance, Epidemiology, and End Results registry; TRM, treatment-related mortality; tx, treatment; US, United States; yrs, years.

for untreated DLBCL (Supplementary Tables S2 and S3).[32] Most reports describing patient fitness for older HL patients have been retrospective analyses and have utilized the Tucci classification published for DLBCL.[29] It is essential that prospective studies for older HL patients include objective measures of GA and other measures of fitness in part for consistency and to aid cross-study interpretation as well as to assist in identifying potential fitness-based therapeutic recommendations. Notably, objective GAs were shown to be more effective than subjective clinical judgment in identifying older B-cell lymphoma patients likely to benefit from aggressive, curative therapy.[33,34]

Advancing age

Advancing age within the older HL population is associated with inferior survival.[3,9,15-17,20,27,30,35] In the Chicago RWE series, ages ≥70 years and loss of any self-care ADLs were the dominant prognostic factors.[20] Moreover, patients with both factors present at diagnosis had a 3-year OS of 0%. In recent British Columbia RWE,[15] survival correlated with increasing age (ie, ≥70 vs 60-69 years), and similar data were reported from Swedish[17] and Swiss[35] RWE (Table 1). However, despite the use of multivariable analyses, it is not clear if advancing age alone is an independent risk factor for inferior survival among older patients vs a proxy for increased comorbidities with decreased functional status and/or use of less-intensive chemotherapy treatment, especially anthracyclines. In the US RWE, patients aged 70 to 79 years who received conventional anthracycline-based regimens had comparable survival with patients aged 60 to 69 years ((Table 1).[28]

Dose intensity and anthracyclines

Dose intensity and use of anthracyclines have been cornerstones of HL treatment for decades.[36] Landgren et al. reported that

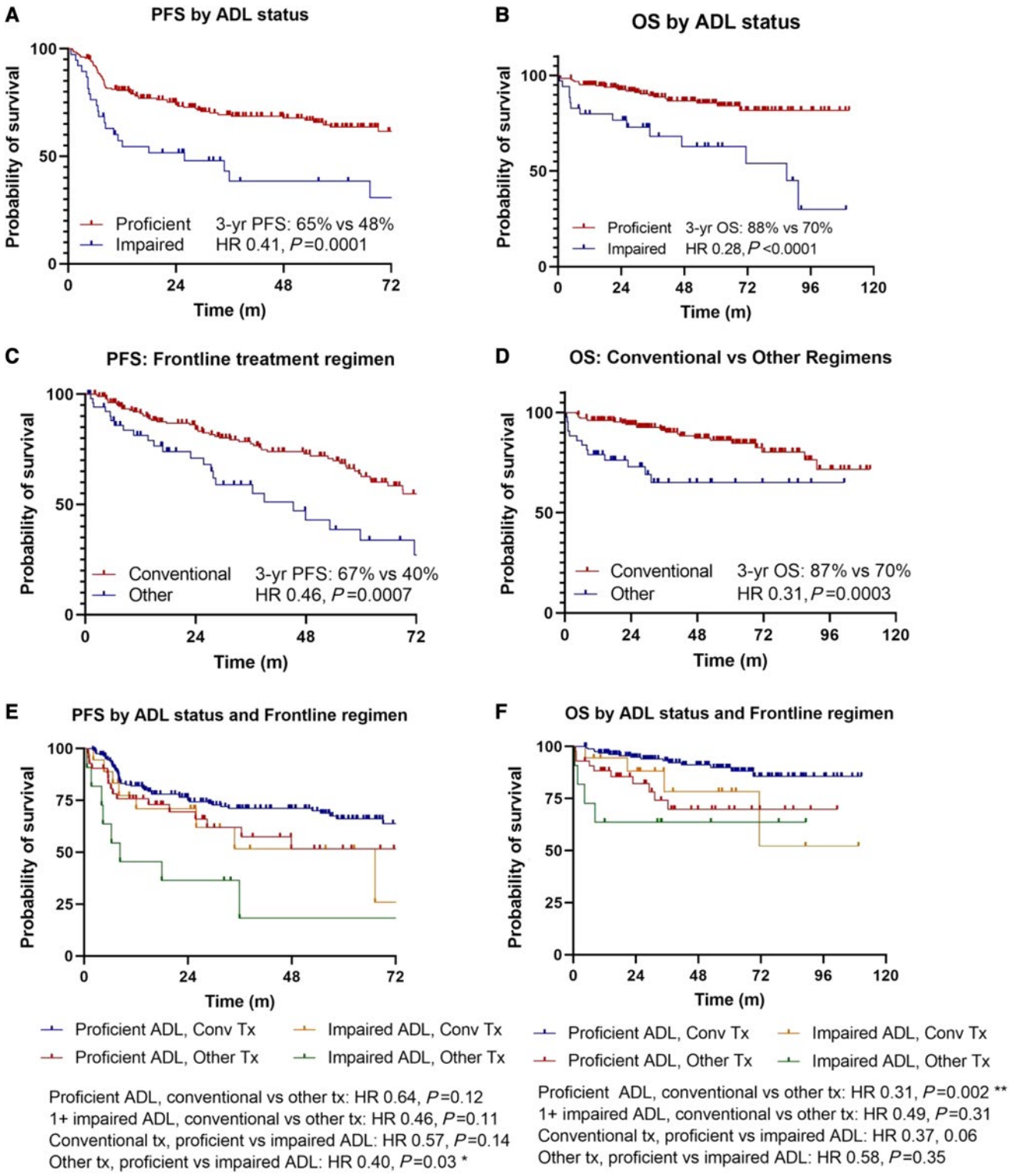


Figure 1. Outcomes of older HL patients based on functional status and conventional therapy. PFS and OS by geriatric fitness measures in stage II to IV disease. Time is listed in months for all figures. (A) PFS by ADL status. (B) OS by ADL status. (C) PFS by frontline treatment regimen. (D) OS by treatment regimen. (E) PFS by ADL status and frontline regimen. (F) OS by ADL status and frontline regimen. Tx, treatment. Reprinted with permission.[28]

older HL patients treated with ABVD-based chemotherapy from 1973 to 1994 had significantly improved OS with relative dose intensity (RDI) of >65%.[3] In a large German Hodgkin Study Group (GHSG) analysis of older HL patients treated on 5 consecutive clinical trials from 1988 to 1998, reduced RDI was a major factor associated with inferior outcomes.[6]

RWE supports the importance of treatment intensity with the use of conventional combination chemotherapy, in particular anthracyclines (Table 1).[16,28,37-39] In a SEER-Medicare study of 2686 older HL patients, only 49% received a full regimen (defined as conventional multiagent chemotherapy for a minimum of 2 cycles).[37] In advanced-stage, treatment with a full regimen was associated with markedly improved OS and HL-specific survival vs partial treatment. In a related SEER analysis, Medicaid dual eligibility, marital status, frailty, cardiac comorbidity, prior cancer, advanced-stage disease, B-symptoms, and residence in the Southern US were independently associated with not receiving full chemotherapy regimens.[38] Recent Australian RWE identified that the use of anthracycline was associated with superior PFS and OS after adjusting for comorbidities, age, and performance status (Table 1).[39] Previous data from the Nebraska Group compared ChlVPP with ChlVPP/ABV in a nonrandomized study of previously untreated HL patients.[8] In older patients treated with ChlVPP, the 5-year EFS and OS rates were 24% and 30% vs 52% and 67%, respectively, for patients treated with ChlVPP/ABV.

Several recent analyses in older HL patients have also shown improved survival with the use of classic HL regimens (ie, ABVD/AVD) over CHOP.[17,28,40] In a Nordic RWE study, older patients who received CHOP had significantly poorer outcomes than those treated with ABVD or AVD (Table 1).[40] Additionally, there were no apparent survival differences identified in patients who received AVD vs ABVD.

Overall, it remains unclear if improved outcomes for older HL patients treated with anthracyclines are due to selection bias for patient fitness and more robust functional status. In the aforementioned Norwegian study, the use of R-CHOP (attenuated or full-dose) was associated with superior survival vs anthracycline-free regimes in unfit and frail DLBCL patients.[32] In the US RWE HL analysis, the use of conventional anthracycline-based therapy was associated with improved PFS and OS, which persisted after adjustment for ADL status (Figure 1).[28]

Therapy for newly diagnosed patients

Pre-phase treatment

In DLBCL, Pfreundschuh et al. showed that the use of steroids as a pre-phase at least 1 week before the start of therapy improved patient performance status as well as reduced therapy-associated deaths.[41] We advocate a similar pre-phase paradigm for most newly diagnosed older HL patients utilizing a short course of pulse steroids (eg, prednisone 60-100mg daily for 5 days), which was done in the aforementioned sequential BV-AVD-BV study.[19] At a minimum, this ameliorates disease-related symptoms and improves functional status while testing and approval processes are being completed. The use of a "pre-phase" therapy before the start of definitive therapy needs to be better studied in HL.

Early stage

Most published early-stage HL studies have uncommonly included older patients. In the GHSG HD8 trial, patients with early unfavorable stage were randomized to 4 courses of chemotherapy cyclophosphamide, vincristin, procarbazine, prednisone (COPP) and doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and involved field radiotherapy (IFRT) or extended field radiotherapy.[42] The 5-year freedom from treatment failure (FFTF) and OS were lower in older patients (FFTF 64% vs 87%; $P<0.001$ and OS 70% vs 94%; $P<0.001$). Moreover, older patients had poorer outcomes when treated with extended field radiotherapy vs IFRT (5-year FFTF 58% vs 70%, respectively, $P=0.034$; and 5-year OS 59% vs 81%, respectively, $P=0.008$).[43]

An analysis of older patients within the GHSG HD10 and HD11 trials included 117 older early-stage HL patients treated with 2 to 4 cycles of ABVD followed by IFRT.[44] Mean delay of treatment was twice as high in the older patients (2.2 vs. 1.2 weeks), and WHO grade 3 and 4 toxicity was also more frequent in this group (68% vs 50%) than in younger patients, which resulted in a higher treatment-related mortality (TRM) in older patients. Boll et al. analyzed the outcomes of older HL patients treated in the GHSG HD10 and HD13 trials.[45] In patients receiving 2 cycles of ABVD, respiratory adverse events were uncommon; however, the incidence of BLT was 10% (including several related deaths) for early-stage patients who received 4 cycles of ABVD. Other studies have analyzed other chemotherapy regimens for older early-stage HL patients (eg, VEPEMB or CHOP followed by IFRT)[24,46] or IFRT alone.[47,48]

Advanced stage

Historical data. Three-to-five-year PFS rates for advanced-stage older HL patients treated with ABVD therapy range from 28% to 55%, with OS rates of 31% to 67% (Supplementary Table S4).[4,9,11,13,49,50] Efforts to improve outcomes for older HL patients have included the development of chemotherapy platforms with decreased intensity and regimens with individualized dosing to mitigate toxicity.[4,8,9,50-54] A non-anthracycline regimen studied in an advanced-stage HL ECOG study, BCVPP (carmustine, cyclophosphamide, vinblastine, procarbazine, and prednisone), was well tolerated and associated with good outcomes.[55]

Proctor et al. reported results from the Study of Hodgkin in the Elderly/Lymphoma Database (SHIELD) project consisting of a prospective trial and RWE component.[4] For prognostication, achievement of CR strongly predicted survival. Factors associated with CR were comorbidity score and ADLs. In the observational group of advanced-stage patients treated according to physician discretion (most often ABVD), the overall response rate (ORR) was modest and the TRM was 18%. Furthermore, all 13 frail HL patients died (12 from HL).

Contemporary data with chemotherapy +/− targeted therapy. Targeted therapeutic agents have been incorporated into frontline treatment for older HL patients (Table 2). In the study of BV given before and after AVD chemotherapy for untreated older HL patients,[19] the choice of sequential therapy was predicated on the following: (1) initial single-agent BV would improve performance status, establish early disease control, and increase the likelihood of tolerability to chemotherapy; (2) to minimize overlapping neurotoxicity with vinblastine; and (3) consolidation would decrease the risk of relapse. The ORR and CR rates after the initial 2 lead-in doses of BV were 82% and 36%, respectively, and 95% and 90%, respectively, after AVD. Survival was robust (Figure 2). The most common grade 3/4 adverse events were

Table 2. Contemporary clinical trials for newly diagnosed older HL patients*

Author, year	N	Therapy	Median age (years)	Baseline GA and patient fitness	Outcomes	Febrile neutropenia	Peripheral neuropathy (≥ grade 3)	Treatment-related mortality rate
Anthracycline-based chemotherapy +/− targeted therapy								
Evens 2018[19]	48	Brentuximab vedotin *sequentially* with AVD	69	Median CIRS-G 7 (31%≥10); 14% pts loss IADL	2-yr PFS 84% 2-yr OS 93%	8%	4%	2%
Boll 2018[61]	49	Brentuximab vedotin + CAP (*concurrent*)	66	Limited GA; all pts CIRS-G ≤6	1-yr PFS 74% 1-yr OS 93%	27%	0%	2%
Boll 2019[60]	25	Lenalidomide + AVD (*concurrent*)	67	Limited GA; all pts CIRS-G ≤7 (mean 2)	3-yr PFS 70% 3-yr OS 84%	4%	NR	NR
Salvi 2019[57]	47	MBVD	75	Limited GA; CIRS-G grade 3/4 in 11%	3-yr PFS 43% 3-yr OS 70%	6.3%	NR	6.4%
Ghesquieres 2021[58]	89	PVAB	68	Limited GA; median CIRS-G 3	4-yr PFS 50% 4-year OS 69%	NR	NR	NR
Evens 2022[59]	84	A+AVD (*concurrent*)	68	ND	2-yr PFS 70% 2-yr OS ~85%	37%	18%	3.6%
	102	ABVD	66	ND	2-yr PFS 71% 2-yr OS ~85%	17%	3%	5.1%
Torka 2023[64]	40	N+AVD (*concurrent*)	66	Median scores: ADL 83, IADL 14, TUG 11.5sec	2-yr PFS 86% 2-yr OS 96%	8%	0%	0%
Wilson 2023[62]	41	ACOPP**	74	Limited GA; median CIRS-G 5	2-yr PFS 73% 2-yr OS 94%	15%	0%	2%
Targeted therapy +/− low-intensity chemotherapy								
Forero-Torres 2015[65]	27	Brentuximab vedotin	78	7% loss IADL; 30%≥1 fall; TUG >13.5sec in 48%	2-yr PFS ~25% 2-yr OS ~70%	0%	26%	NR
Friedberg 2017[66]	21	Brentuximab vedotin + DTIC	69	20% loss IADL; 26%≥1 fall; TUG >13.5sec in 70%	2-yr PFS ~45% 2-yr OS ~90%	5%	27%	0%
Gibb 2020[67]	35	Brentuximab vedotin	77	Limited GA, median CIRS-G 6	2-yr PFS 7% 2-yr OS 42%	0%	~10%	3%
Yasenchak 2020[66]	42	Brentuximab vedotin + nivolumab	72	NR	2-yr PFS ~60% 2-yr OS ~90%	NR	33%	0%
Cheson 2020[68]	46	Brentuximab vedotin + nivolumab	72	ND	2-yr PFS ~40% 2-yr OS NR	0%	11%	2%
Lazarovici 2021[69]	64	Nivolumab +/− vinblastine	78	Median CIRS-G 10; median G8 score 12.5	2-yr PFS ~20% 2-yr OS 77%	0%	0%	3%
Dickinson 2023[70]	25	Pembrolizumab	77	Limited GA; median CIRS-G 7	2-yr PFS ~15% 2-yr OS 83%	0%	0%	0%

* Since 2018; minimum 20 patients; **retrospective.

A+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ACOPP, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone; ADL, activities of daily living; AVD, doxorubicin, vinblastine, dacarbazine; CAP, cyclophosphamide, doxorubicin, prednisone; CIRS-G, cumulative illness rating score-geriatric; DTIC, dacarbazine; ECOG, Eastern Cooperative Oncology Group performance status; G8, geriatric 8 score; GA, geriatric assessment; IADL, instrumental activities of daily living; KPS, Karonfsky performance scale; MBVD, nonpegylated liposomal doxorubicin (myocet), bleomycin, vinblastine, dacarbazine; mPFS, modified progression-free survival; N+AVD, ; ND, not done; NR, not reported; OS, overall survival; PFS, progression-free survival; pts, patients; PVAB, prednisone, vinblastine, doxorubicin, bendamustine; PVAG (prednisone, vinblastine, doxorubicin, and gemcitabine); sec, seconds; TUG, timed up and go.

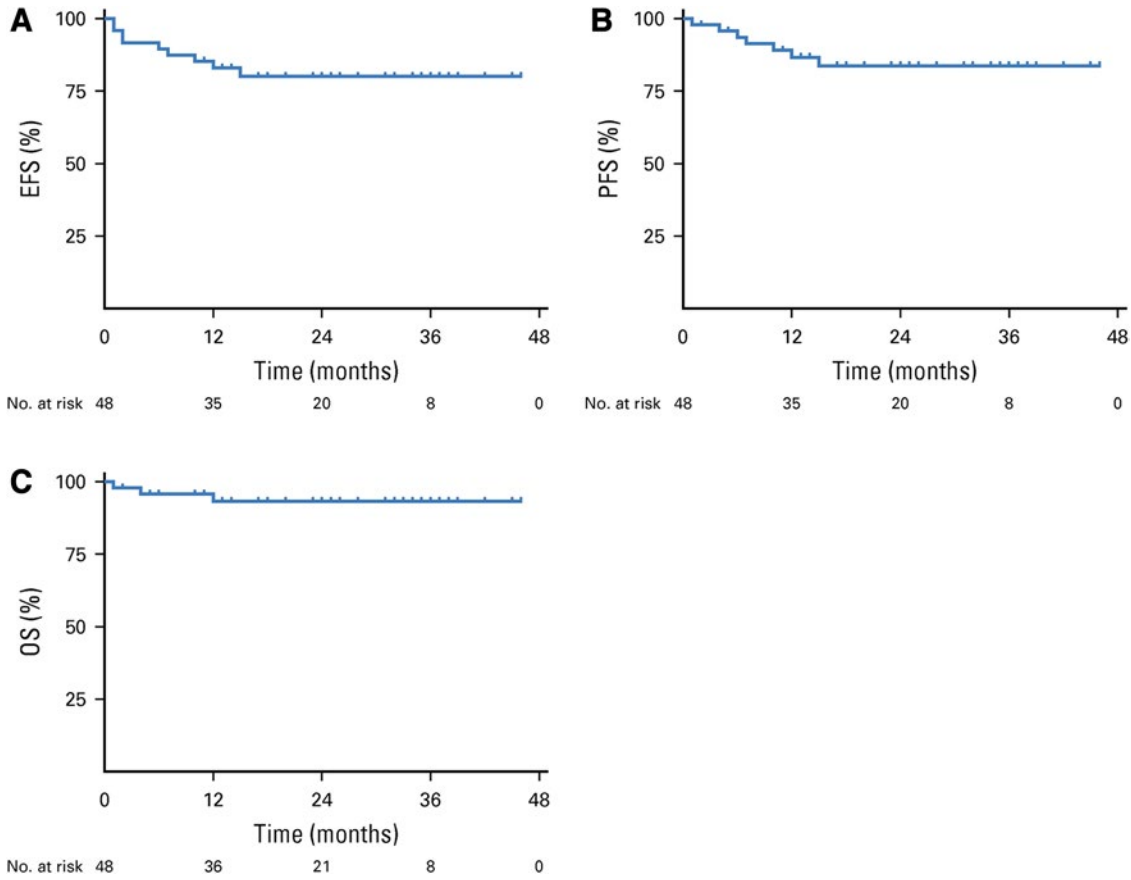


Figure 2. Survival among older patients treated on the frontline HL study with sequential brentuximab vedotin and AVD chemotherapy. Kaplan-Meier curves at 2 years for (A) event-free survival (EFS; 80%; 95% CI, 65% to 89%), (B) progression-free survival (PFS; 84%; 95% CI, 69% to 92%), and (C) overall survival (OS; 93%; 95% CI, 80% to 98%) for all 48 patients. In addition, patients with a Cumulative Illness Rating Scale-Geriatrics (CIRS-G) score <10 had 2-year event-free survival (EFS), PFS, and OS rates of 100% (95% CI, 100% to 100%), and patients who had preserved functional status without loss of instrumental activities of daily living (IADL) at baseline had corresponding 2-year EFS, PFS, and OS rates of 89% (95% CI, 73% to 96%), 94% (95% CI, 79% to 99%), and 97% (95% CI, 82% to 99%), respectively. Reprinted with permission.[19]

neutropenia (44%); febrile neutropenia and pneumonia (8%); and diarrhea (6%). Response to the initial 2 doses of BV (ie, CR/PR vs not) was strongly associated with survival (2-year PFS 100% vs 50%, respectively, $P = 0.007$).

Response-adapted therapy has not been well studied in older HL patients, but if ABVD therapy is utilized, bleomycin should be eliminated for all patients with an interim negative PET-2 scan vis-à-vis the RATHL study design.[56] In fact, there should be great caution in giving any older HL patient more than 2 full cycles of bleomycin. Additionally, therapy should *not* be intensified to bleomycin, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) therapy with positive PET-2 as older patients do not tolerate this regimen, as highlighted below. Changing therapy for early nonresponders to initial ABVD/AVD to a non-cross-resistant regimen (or added targeted agents) needs to be further tested in prospective studies.

For older and nonfit patients with HL, attempts have been made to mitigate toxicity of conventional doxorubicin by substituting it with liposomal doxorubicin. In a phase 2 trial of 47 older HL patients with median age of 75 years, patients were treated with bleomycin, vinblastine, dacarbazine, nonpegylated liposomal doxorubicin (MBVD).[57] Two patients had cardiac events and 49% had grade 3 or higher neutropenia, with 15% of patients having ≥ grade 3 infections. Overall tolerability to MBVD was poor in advanced-stage patients, with 38% of patients prematurely discontinuing treatment. An alternative approach included modification of the prednisone, vinblastine, doxorubicin, and gemcitabine (PVAG) regimen substituting gemcitabine with bendamustine in older HL patients.[58] The majority of patients completed 6 treatment cycles (88%), but TRM was seen in 4 patients and 32% had at least one serious adverse event.

Outcomes were analyzed across ages in phase 3 ECHELON-1 study (BV + doxorubicin, vinblastine, and dacarbazine [A+AVD] vs ABVD in untreated advanced-stage HL patients), which included 186 patients ≥60 years (Table 2).[59] The mean RDI for older patients who received BV+AVD chemotherapy was 92% to 97%. With a median follow-up of 61 months, the 5-year PFS rates per investigator with A+AVD vs ABVD were 67.1% vs 61.6%, respectively. Pulmonary adverse events were higher with ABVD vs A-AVD (13% vs 3%, respectively), and the incidence of any-grade and severe

peripheral neuropathy was higher in the A+AVD arm. However, rates of resolution or improvement in peripheral neuropathy were similar in patients treated with A+AVD and ABVD (80% vs 83%, respectively).

A phase 1 study added lenalidomide concurrently with AVD chemotherapy for older HL patients.[60] Dose-limiting toxicities were mainly hematologic but also included 3 thromboembolic events despite documented aspirin prophylaxis. The ORR was 79% for evaluable patients and 86% in patients treated with at least 20mg of lenalidomide. The GHSG and the Nordic Lymphoma Group presented data using BV concurrently with cyclophosphamide, doxorubicin, and prednisone (B-CAP) for fit older HL patients with CIRS-G ≤6.[61] Among eligible advanced-stage patients, the ORR was 98% (CR rate 65%). Notably, there was no grade 3 neuropathy and TRM was low (Table 2).

A recent multicenter retrospective review from the United Kingdom examined the elimination of bleomycin and etoposide from BEACOPP for older, less-fit HL patients. The analysis included 41 older HL patients who received ACOPP with dose-reduced cyclophosphamide.[62] Best overall response was 95% (CR 83%) and survival was strong. While there was 1 TRM, treatment was generally tolerated without severe side effects, though nearly 60% of the population required hospitalization at one point during the treatment process.

Checkpoint inhibitor therapy combined with multiagent anthracycline-based chemotherapy has been studied in the frontline setting for older HL patients. There were 4 patients ages ≥60 years treated in a study using sequential pembrolizumab before AVD chemotherapy.[63] The PFS and OS were 100% for all patients in the study, and there were no unexpected toxicities seen in

Table 3. Select ongoing or planned clinical trials for newly diagnosed older HL patients

Trial title	Trial phase	Study number	Disease stage	GA-based inclusion/ GA-directed therapy	Study design
Phase II Trial of Individualized Immunotherapy in Early-Stage Unfavorable Classical Hodgkin Lymphoma *(INDIE)*	2	NCT04837859	IA-IIB	Yes (CIRS-G)/no	2 cycles tislelizumab; PET neg: 4 cycles tislelizumab +30 gy ISRT; PET pos: 4 cycles T-AVD +30 gy ISRT
Response Adapted Incorporation of Tislelizumab Into the Front-line Treatment of Older Patients With Hodgkin Lymphoma *(RATiFY)*	2	NCT05627115	I-IV	No/no	3 cycles tislelizumab; PET neg: 2 cycles T +/− RT followed by tislelizumab until PD or toxicity for fav ES or 2–4 cycles T+AVD +/− RT for unfav ES and AS; PET pos: 4–6 cycles T+AVD +/− RT for ES and AS
Fitness-Adapted, Pembrolizumab-Based Therapy for Untreated Classical Hodgkin Lymphoma Patients 60 Years of Age and Above	2	NCT05404945	II-IV	Yes/yes (CIRS-G + ADLs)	Pembro + BV followed by repeat GA/ fitness; fit induction: 3 cycles Pembro q6w + 4 cycles AVD; unfit induction: 3 cycles Pembro q6w + 3 cycles BV; consolidation for all: Pembro +2 doses BV
A Study of Brentuximab Vedotin With Hodgkin Lymphoma (HL) and CD30-Expressing Peripheral T-cell Lymphoma (PTCL)	2	NCT01716806	II-IV	Yes/yes (CIRS-G + ADLs)	Cohorts E and F: single-agent BV for patients unsuitable or unfit for initial conventional combination chemotherapy by GA (ie, CIRS-G ≥10 and/or loss of any instrumental ADL)
BrEPEM-LH-22017 for Older Patients With Untreated Hodgkin Lymphoma (HL)	1/2	NCT03576378	IIB-IV	No/no	6 cycles BV-EPEM
HD21 for Advanced Stages Treatment Optimization Trial in the First-line Treatment of Advanced Stage Hodgkin Lymphoma; Comparison of 6 Cycles of Escalated BEACOPP With 6 Cycles of BrECADD (elderly extension)	2	NCT02661503	IIB with LMM or EN, III/IV	Yes (CIRS-G)/no	2 cycles BrECADD; PET neg: 2 cycles BrECADD; PET pos: BrECADD 4 cycles +/− RT
Immunotherapy (Nivolumab or Brentuximab Vedotin) Plus Combination Chemotherapy in Treating Patients With Newly Diagnosed Stage III-IV Classic Hodgkin Lymphoma *(S1826)**	3	NCT03907488	III/IV	No/no	6 cycles Nivo + AVD vs 6 cycles BV + AVD

* Approximately 10% of patients in the study population were ages 60 years and above.

ADL, activities of daily living; AVD, adriamycin, vinblastine, dacarbazine; AS, advanced stage disease; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BrECADD, brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; BV, brentuximab vedotin; CIRS-G, cumulative illness rating score-geriatric; EN, extranodal disease; EPEM, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone; ES, early-stage disease; fav, favorable; GA, geriatric assessment; gy, gray; ISRT, involved site radiation therapy; LMM, large mediastinal mass; neg, negative; Nivo, nivolumab; PD, progressive disease; Pembro, pembrolizumab; PET, positron emission tomography; pos, positive; q3w, every 3 weeks; q6w, every 6 weeks; RT, radiation therapy; T, tislelizumab; unfav, unfavorable.

older patients (personal communication, Dr. Jane Winter, June 5th, 2023). A single-arm phase 2 multi-institutional study of concurrent nivolumab and AVD (N-AVD) was recently reported.[64] Of 33 evaluable patients, the ORR was 100%, with a 97% CR rate. At 37-month median follow-up, survival rates were robust (Table 2). There was no correlation between baseline GAs and outcome, although most patients were deemed fit. We eagerly await additional data from recently completed studies that incorporated nivolumab concurrently with AVD chemotherapy (Table 3).

Targeted therapy +/− low-intensity chemotherapy. A host of varied phase 2 clinical studies have leveraged targeted therapeutic agents with or without low-intensity chemotherapy (Table 2). The clinical intent in these trials was to target patients who had increased comorbidities and/or compromised functional status. However, delineation of patient fitness was not consistently performed, and ineligibility for standard anthracycline-based therapy was typically determined subjectively by the investigator.

In a prospective phase 2 study of single-agent BV for older untreated HL patients deemed ineligible for frontline conventional combination chemotherapy in the investigator's judgment, the ORR was 92% (CR 72%).[65] However, the relapse rate was high (Table 2). The study was amended to combine concurrent bendamustine or dacarbazine.[66] The bendamustine arm closed prematurely due to unexpected toxicity, including several treatment-related deaths. An additional treatment arm added nivolumab to BV and the initial data is encouraging with median PFS and OS not reached. Rates of grade 3 peripheral neuropathy were 25% to 35% across the 4 treatment arms (Table 2).

A United Kingdom study examined single-agent BV for HL patients ages ≥60 years or ages <60 years and considered unfit or ineligible for combination chemotherapy by cardiac ejection fraction <50%, significant cardiac morbidity, and/or compromised lung function (Table 2).[67] Therapy was tolerable but response and durability were modest, with a CR rate of 26% and median PFS of 7.3 months. Additionally, 29% of patients permanently stopped treatment due to unacceptable toxicity, 8 due to sensory neuropathy.

A single-arm US trial studied frontline BV and nivolumab for 8 cycles in older patients unsuitable for standard chemotherapy due to cardiac ejection fraction <50%, pulmonary diffusion capacity <80%, 0.5 to 1.0 mL/s, or those who refused chemotherapy.[68] The ORR was 64% (CR rate 48%) and the median PFS was 18.3 months. However, the study did not meet its prespecified activity criteria. The Lymphoma Study Association examined untreated older HL patients with CIRS-G score ≥6 using nivolumab +/− vinblastine, all administered for a maximum of 18 cycles.[69] At end of therapy, the ORR was only 47% (CR rate 29%) and it similarly did not meet the prespecified efficacy endpoint. Additionally, adverse events led to treatment discontinuation in 30% of patients, with immune-related adverse events noted in 34%, including 3 pneumonitis, 1 myocarditis, 1 encephalitis, and 1 colitis.

A recent phase 2 Australian study of single-agent pembrolizumab in patients ≥65 years or who were considered unfit to receive frontline ABVD was presented.[70] Ineligibility for ABVD-based therapy was subjectively determined at provider discretion. Of the 27 who enrolled, 25 patients received a median of 11 cycles of pembrolizumab. The ORR was 72% (CR 32%) with a median duration of response of 10.6 months. The PFS was modest with most patients experiencing progression, though 2-year OS was 83%.

Treatment recommendations: newly diagnosed advanced-stage disease

Figure 3 depicts overarching treatment recommendations for untreated advanced-stage older HL patients, highlighting the importance of baseline GAs, comorbidity management, and pre-phase therapy. There are published guidelines on the GA testing and screening options (Supplementary Table S1),[23] but there is not "one right" tool for screening older HL patients who warrant referral for more detailed geriatric consultation/intervention. We assess at least comorbidities via CIRS-G and self-care and instrumental ADLs at baseline diagnosis.[71] Additionally, we offer most patients pre-phase therapy whether single-agent prednisone (eg, 60-100 mg/daily for 5 days) +/− single-agent brentuximab vedotin as published.[19] If brentuximab vedotin is not available, single-agent vinblastine 3-6 mg/m^2 may also be utilized. Furthermore, we recommend reassessment of functional status after pre-phase therapy as the initial physical determinant and debilitation may be due to tumor burden.

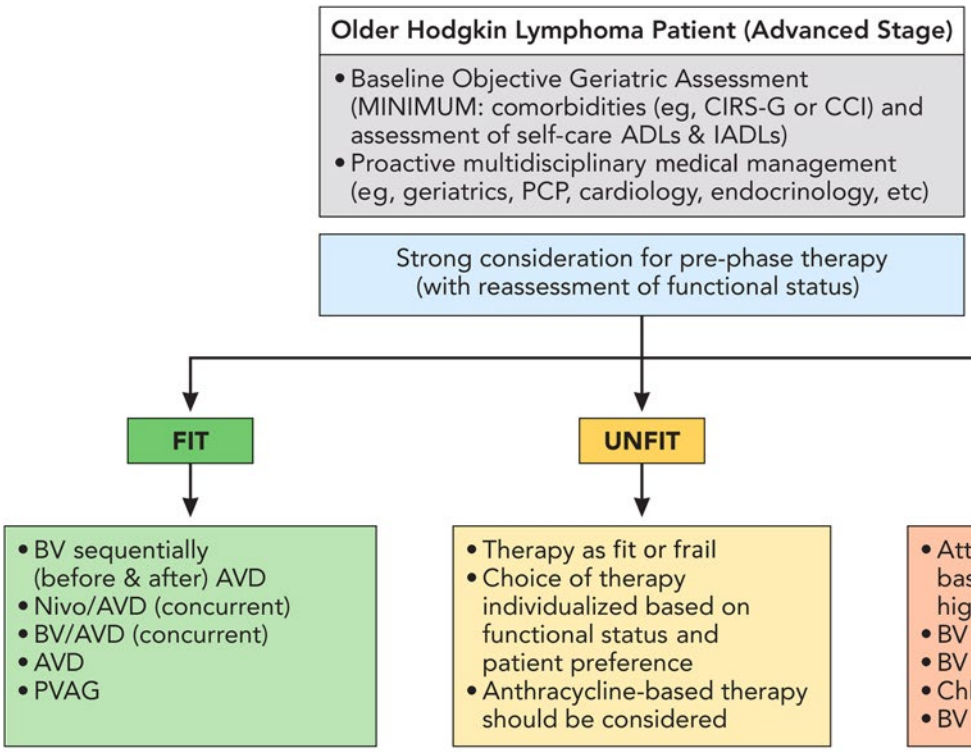
For primary therapy, anthracycline-based chemotherapy platforms are associated with the most robust outcomes for older HL patients, especially fit patients. Optimum therapy for patients objectively classified as unfit or frail are less clear. Unfit HL patients and highly select frail patients may be considered for anthracycline-based therapy, with reduced dosing and/or number of treatment cycles. There remains an unmet need to identify effective and tolerable HL treatment regimens with attenuated anthracycline dosing. In addition, we advocate aggressive supportive care measures for all older HL patients, including weekly office visits for assessments of fluid status and basic blood count and chemistry laboratory studies and concurrent comanagement with other disease specialties (eg, cardiology, endocrinology, primary care, etc). This often proves essential to determining and managing individualized treatment tolerability.

There are several ongoing and planned prospective studies for untreated older HL patients (Table 3). These span all disease stages with studies incorporating BV and/or checkpoint inhibitors into treatment regimens. It is crucial to incorporate *objective* GAs into prospective clinical studies, and similar tools and measures of fitness should be utilized across studies. In addition to establishing consistency of data and more accurate measurement of treatment effect across varying studies, there remains a critical need to identify HL-specific GA models that can aid in therapy decision-making. This includes understanding which older HL populations should receive anthracycline-based combination chemotherapy (full-dose or dose-attenuated), including unfit or highly select frail patients, and who may benefit most from frontline targeted therapeutic approaches (with or without low-intensity chemotherapy).

Therapy for relapsed disease

Prospective studies have not specifically evaluated the treatment of relapsed older HL patients. Therefore, treatment recommendations in this setting are largely based on small subset analyses or retrospective studies. Small single-center studies have suggested that high-dose chemotherapy followed by autologous stem cell support is effective for selected older patients with relapsed HL.[72]

A large GHSG analysis examined 105 older relapsed/refractory HL patients.[73] Different second-line treatment strategies were used, including intensified salvage regimens in 22%, conventional



Criteria	Fit	Unfit	Frail
ADL	6	5	≤4
IADL	8	6-7	≤5
CIRS-G	0 score of 3-4 and <5 of score 2	0 score of 3-4 and 5-8 of score 2	≥1 score of 3-4 and/or >8 of score 2
Age	<80 years	≥80 years FIT	≥80 years UNFIT

Figure 3. Treatment algorithm for newly diagnosed, advanced-stage older Hodgkin lymphoma (HL) patients. All patients should undergo a geriatric assessment to determine fitness before initiation of treatment, which should include at least an evaluation of ADLs, comorbidities, and calculation of noncancer expected survival (https://eprognosis.ucsf.edu/leeschonberg.php). The associated table of geriatric risk categories is adapted from Tucci et al. (with permission).[29] Scoring for ADL and IADL indicate number of *residual functions*. There should also be consideration of pre-phase therapy before initiation of definitive therapy, especially in unfit or frail and/or symptomatic patients with high tumor burden. Furthermore, patient fitness should be reassessed *following pre-phase therapy*. Aggressive supportive care measures should be pursued, including increased office evaluations (eg, weekly fluid assessments) and intentional comanagement with other disease specialists. Treatment options are based on published data and investigator experience (listed by order of preference); a clinical trial should always be considered. Treatment for unfit and frail patients is highly individualized. Anthracyclines may be considered for unfit patients with minor fitness limitations and preserved cardiac function; dose-attenuated anthracyclines may be considered for select fit patients ages ≥80 years or highly select frail patients ages <80 years with close monitoring of cardiac function (eg, comanagement with cardiology with assessment of ejection fraction q 2 cycles, etc). ADL, activities of daily living; AVD, doxorubicin, vinblastine, dacarbazine; BV, brentuximab vedotion; CCI, Charlson Comorbidity Index; ChlVPP, chlorambucil, vinblastine, procarbazine, prednisone; CIRS-G, Cumulative Illness Rating Scale-Geriatric; IADL, instrumental activities of daily living; PCP, primary care provider; PVAG, prednisone, vinblastine, doxorubicin, and gemcitabine. Scoring for ADL and IADL indicates the number of residual functions.

polychemotherapy and/or salvage radiotherapy with curative intent in 42%, and palliative approaches and best supportive care in 31%. A prognostic score applied the risk factors (RFs) of early relapse, clinical stage III/IV, and anemia. The median OS for the entire cohort of relapsing older HL patients was 12 months. Survival varied within different risk groups (ie, ≤1 RF: 3-year OS, 59%; ≥2 RFs: 3-year OS, 9%). In low-risk patients, the impact of therapy on survival was significant in favor of the conventional polychemotherapy approach.[73] There is a continued need to evaluate the safety, efficacy, and optimal timing (ie, sequential or concurrent) of established and experimental therapeutic compounds specifically in older patients with relapsed/refractory HL.

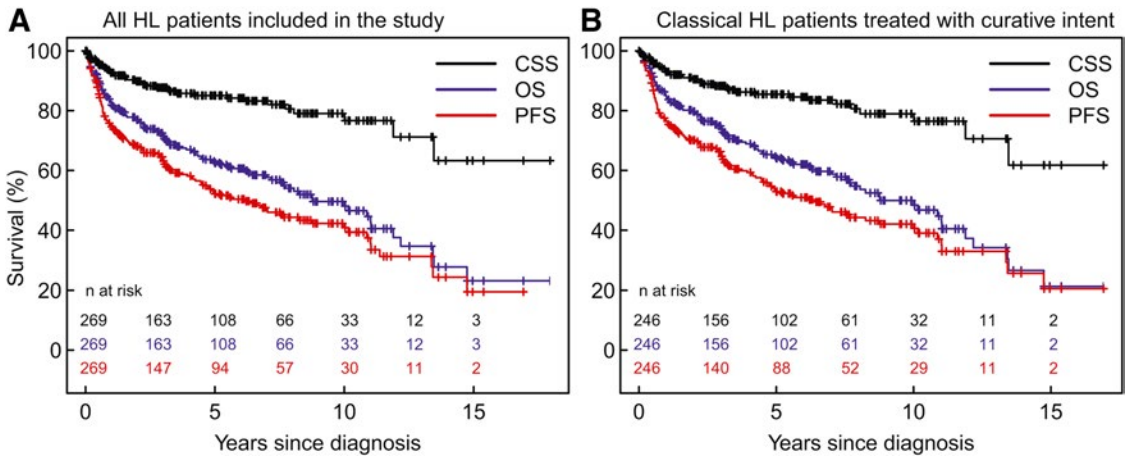


Figure 4. Outcomes analyzing cause-specific survival in a large older Hodgkin lymphoma Swiss cohort. Kaplan-Meier estimate of cause-specific survival (CSS), overall survival (OS), and progression-free survival (PFS) of the entire cohort (A) and of patients treated with curative intent (B). Reprinted with permission.[35]

Therapy-associated toxicity

Conventional chemotherapy in older HL patients may result in reduced tolerability with severe toxicities, including treatment-induced fatalities.[2,3,7,8,35,47,51,74] The most common toxicities for patients treated with ABVD-based therapy are hematologic, neuropathic, infectious, and cardiopulmonary.[6,9,15,20,28,35,39,49,75] Severe hematologic and other toxicities were significantly more frequent in older vs younger HL patients treated on the randomized E2496 study (ABVD vs Stanford V)[13] as well as the recent ECHELON-1 study.[75]

In the Swiss RWE, the 5-year PFS, OS, and cause-specific survival (CSS) rates were 53%, 64%, and 86%, respectively, for older HL patients treated with curative intent (Figure 4).[35] The prominent difference in CSS and PFS highlights the impact that tolerability and toxicity have on outcomes in older patients. Similarly, competing risk analyses within the E2496 study demonstrated that the age-related survival disparity between older and younger patients was due primarily to non-HL-related causes (Supplementary Figure S2).[10]

Providers should remain vigilant with close clinical monitoring and full supportive care measures for all patients, and proactive, multidisciplinary management of coexistent comorbidities (eg, cardiology, endocrinology, primary care, etc) is highly encouraged throughout all phases of therapy.

Treatment-related mortality

Acute toxic deaths in older HL patients are commonly reported in the literature. In the randomized study comparing baseline BEACOPP regimen with COPP-ABVD ($HD9_{elderly}$), the treatment-related mortality (TRM) rates among advanced-stage HL patients aged 66 to 75 years were 21% and 8%, respectively (Table 1).[49] TRM rates across ABVD studies have ranged from 8% to 23%.[4,9,11,13,49,50] Contemporary chemotherapy-based analyses have suggested a lower incidence of TRM (3%-8%) for older HL patients.[15,28,35,39]

Bleomycin lung toxicity

The incidence of BLT in most studies of older HL patients ranges from 5% to 32% with associated mortality rates of 10% to 25%.[13,15,20,28,35,39,44,45,76] The primary risk factor for BLT is age, with an exponential increase in risk with rising age due in part to declining creatinine clearance as bleomycin is primarily metabolized renally.[77] In a Veterans Administration analysis of >800 HL patients, the incidence of BLT by ages ≤49, 50 to 59, 60 to 69, and ≥70 years were 3%, 7%, 13%, and 24%, respectively.[78] Rates of BLT in the Swiss series for HL patients ages 60 to 69 and ≥70 years were 12.6% and 25%, respectively (Table 1).[35]

The incidence of BLT in the Chicago RWE series was 32%, with an associated mortality rate of 25%.[20] The incidence was 38% vs 0% among patients who received colony-stimulating factor (G-CSF) vs not, respectively ($P<.0001$), which has been noted in other series.[78] The incidence of BLT among older HL patients treated on E2496 was 24% with an associated death rate of 18%[13]; the vast majority of cases occurred with ABVD. Data supporting the number of doses of bleomycin as a risk factor comes in part from GHSG HL data in older adults showing that BLT was uncommon in early-stage patients who received 2 cycles of ABVD but occurred in 10% who received 4 ABVD cycles, including several lethal events.[44] However, recently reported data from BC RWE identified an overall BLT incidence of 21% (TRM 14%), and 38% of cases occurred during the first 2 cycles of treatment.[15]

Neuropathy

In contemporary studies, neurotoxicity has been more closely examined, especially studies incorporating BV (Table 2). In the prospective study of extended dosing of single-agent BV followed by cohorts combining either bendamustine or dacarbazine for older HL patients as described before,[65,66] the incidence rates of grade 3 neuropathy were high (Table 2). In the above-mentioned study utilizing sequential and more limited dosing of BV with AVD, the risk of grade 3 neuropathy was 4%.[19] Importantly, clinically significant neurotoxicity is also seen in patients who receive ABVD as was seen in the ECHELON-1 study with grade 2 and 3 peripheral neuropathy rates of 13% and 3%, respectively.[75] Continual surveillance and repeated examination of patients with individualized dose reductions are important to mitigate anti-tubulin-related neurotoxicity.

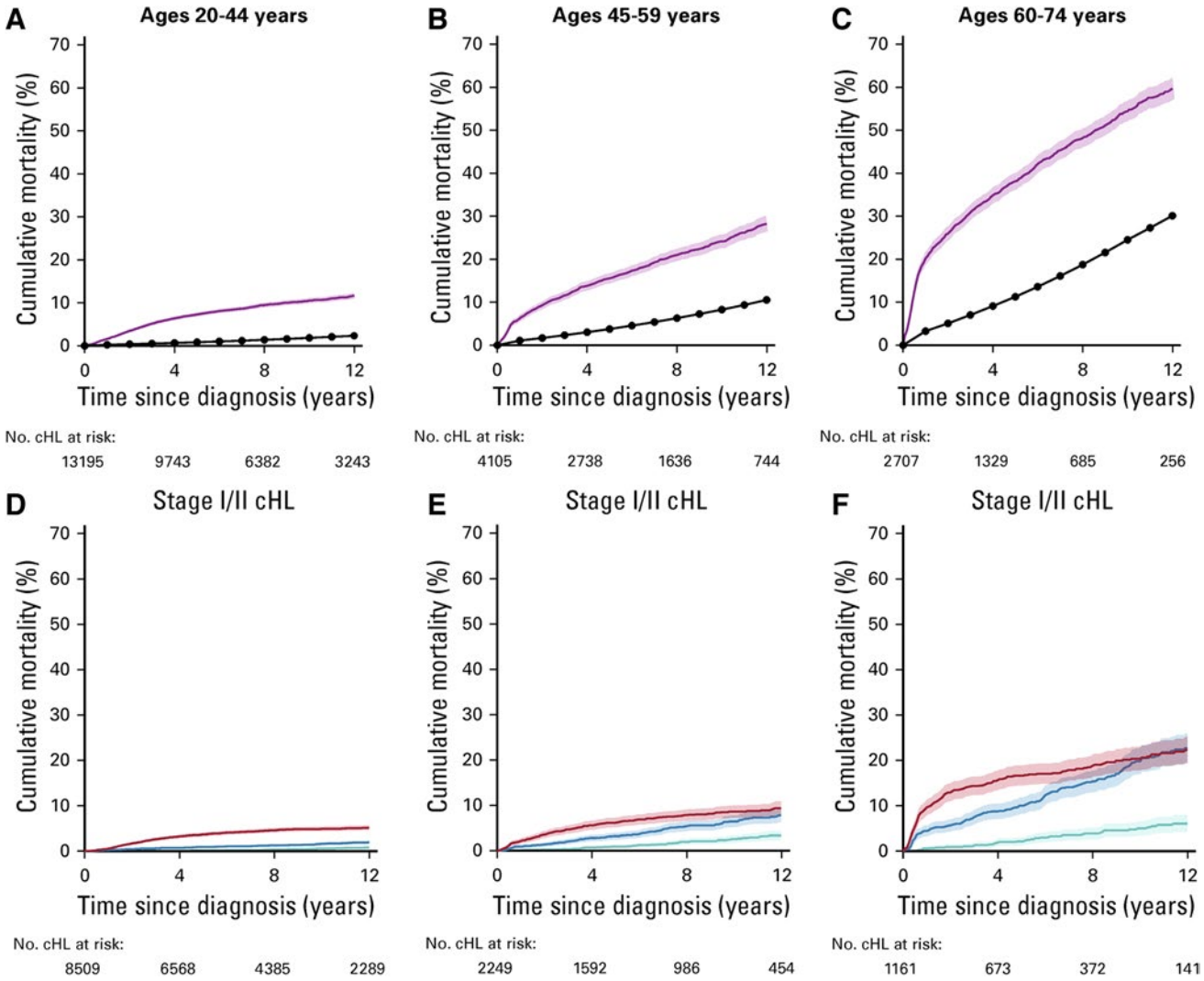


Figure 5. Cumulative mortality among a simulated general US population and 20 007 individuals diagnosed with cHL at ages 20–74 years and treated with initial chemotherapy. 17 SEER cancer registry areas, 2000–2015 (followed through 2016). (A-C) Cumulative mortality from all causes in the general population and classical Hodgkin lymphoma (cHL) population according to age group. (D-F) Cumulative mortality from lymphomas, noncancers, and other neoplasms among patients diagnosed with stage I/II cHL according to age group. (G-I) Cumulative mortality from lymphomas, noncancers, and other neoplasms among patients diagnosed with stage III/IV cHL according to age group. Shaded areas (and error bars) represent the upper and lower bounds of the 95% CI for cumulative mortality. Reprinted with permission.[96]

Cardiac

Older patients with preexisting structural heart disease or multiple cardiac risk factors have an elevated risk of heart failure (HF) with anthracyclines.[79] Among patients with preexisting HF or cardiomyopathy, HL-related mortality was fourfold higher than cardiovascular mortality (37% vs 8%, respectively) in a SEER-Medicare analysis, with 1-year all-cause mortality >60%.[80] This high HL-related mortality was likely in part due to the lower use of anthracyclines amongst those with preexisting HF or cardiomyopathy.

In patients with established HF or cardiomyopathy, optimization of HF guideline-directed medical therapy[81] and consideration of infusional cardioprotective strategies such as dexrazoxane, liposomal doxorubicin, or continuous infusion doxorubicin may be considered to allow patients with well-compensated HF or cardiomyopathy to receive anthracycline-containing regimens. In randomized trials in adults with solid tumors or children with hematologic malignancies, dexrazoxane before doxorubicin administration,[82-85] the substitution of doxorubicin with liposomal doxorubicin,[86,87] or continuous infusion of doxorubicin[88] were associated with a decrease in clinical HF events with preserved oncologic efficacy. However, the safety and efficacy data of these strategies in older adults with HL are limited.[58,89] Close collaboration with cardiology and shared decision-making with the patient, oncology, and cardiology are necessary.

In addition to infusional strategies, cardiovascular medications should be optimized to improve cardiovascular outcomes. There are 4 foundational medications recommended for the treatment of HF with reduced ejection fraction: (1) beta-blockers; (2) the angiotensin receptor–neprilysin inhibitor, sacubitril-valsartan;

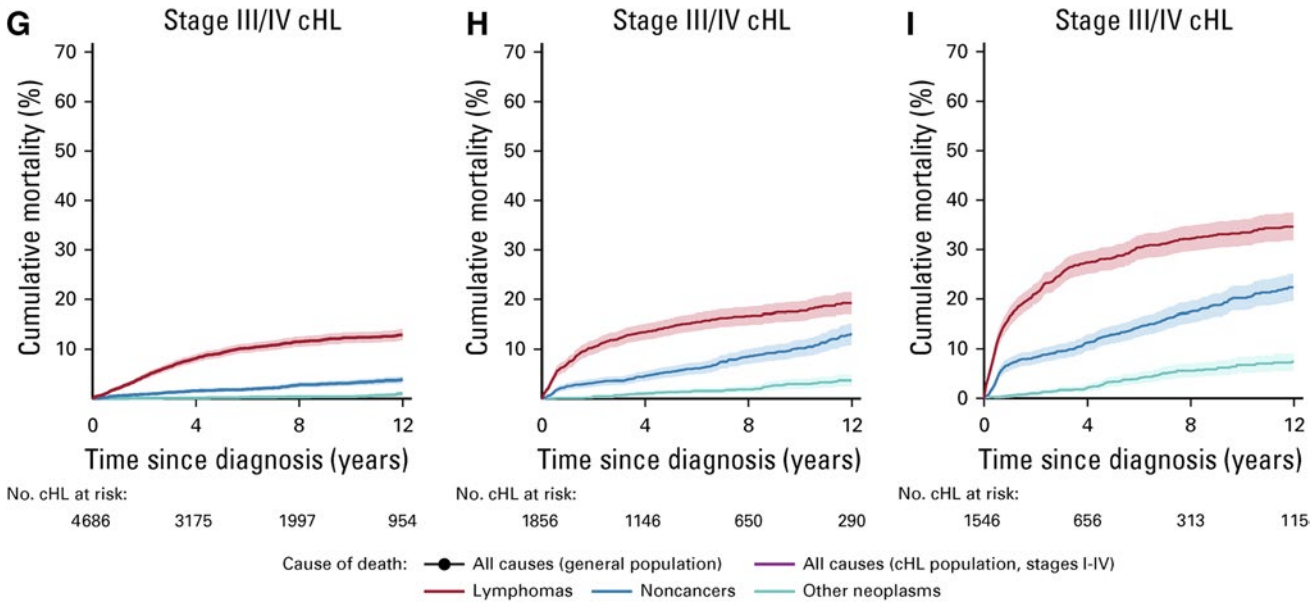


Figure 5. Continued

(3) aldosterone antagonists; and (4) sodium-glucose cotransporter 2 inhibitors. These are associated with improved survival, functional capacity, and left ventricular ejection fraction.[81] Neurohormonal antagonist therapy with beta-blockers and/or angiotensin II receptor blockers /angiotensin-converting enzyme inhibitors may be cardioprotective in patients receiving anthracyclines and should be used in all patients with reduced left ventricular ejection fraction (LVEF). They can also be considered for cardioprotection in patients with a normal baseline echocardiogram but with cardiac risk factors, especially hypertension.[90] Atorvastatin reduced the incidence of LVEF declines in a randomized trial of patients with lymphoma receiving anthracycline-based chemotherapy,[91] although another study in patients with breast cancer and lymphoma did not demonstrate a benefit in LVEF at 2 years.[92]

Guidelines from the European Society of Cardiology (ESC), American Society of Clinical Oncology, and the National Comprehensive Cancer Network endorse the optimization of prevalent cardiovascular disease and cardiac risk factors, use of screening echocardiograms in patients at high risk for HF with anthracycline after therapy, and referral to cardiology or cardio-oncology in patients with cardiovascular symptoms, abnormal cardiac testing, or inadequately managed cardiac risk factors.[81,90,93-95] According to the 2022 ESC risk stratification schema, patients receiving anthracycline-chemotherapy are at "very high risk" in the setting of preexisting HF or cardiomyopathy and "high risk" with any of the following high-risk factors: valvular heart disease, coronary artery disease, angina, LVEF <50%, age >80 years, prior anthracycline or chest radiation exposure, or >5 moderate risk factors (eg, age 65 to 79 years, LVEF 50%-54%, hypertension and diabetes).[90]

Survivorship

Survivorship in the "postacute" period 1 to 10 years post therapy is clinically relevant for older individuals. A large SEER analysis of 20,007 HL survivors diagnosed between ages 20 and 74 years treated with initial chemotherapy in US population-based cancer registries during 2000 to 2015 was reported.[96] With a mean follow-up of 8 years, all-cause mortality exceeded the general population, with noncancer cumulative mortality comprising a substantial number of total deaths, especially those ages 60 to 74 years at diagnosis (Figure 5). There were strikingly elevated risks among HL survivors in the 60-to-74-year group, with excess deaths as a result of heart disease (excess absolute risk [EAR] stage III/IV, 59.6), interstitial lung disease (EAR 36.9), infections (EAR 31.3), adverse events (EAR 33.0), and solid tumors (EAR 24.6). Notably, excess non-HL mortality started within 1 year of completion of therapy compared with the general population. Similar findings of increased noncancer mortality were documented in another SEER analysis that included competing risks.[97] In a separate SEER-Medicare analysis of older patients treated with anthracycline-based chemotherapy who were free from HF at the time of HL diagnosis, the cumulative incidence of HF was 15% at 1 year and 25% at 4 years.[98] Older age, cardiac risk factors such as diabetes and hypertension, intrinsic heart disease, and vascular disease are associated with increased risk of incident HF.[79,98]

For cardiac disease, the American Society of Clinical Oncology and NCCN survivorship guidelines suggest a screening echocardiogram 6 to 12 months after completing anthracycline therapy in those at elevated risk for anthracycline cardiotoxicity.[94,95] The ESC guidelines recommend a screening echocardiogram 1 year after completing anthracycline therapy in all anthracycline-treated patients and more frequent screening in patients at high or very high risk for heart failure (echocardiograms after 2 cycles, 3 months, and 1, 3, and 5 years after therapy completion).[90] Cardiac risk factors such as hypertension, hyperlipidemia, and diabetes should be aggressively managed according to standard guidelines.[90,94,99]

CLINICAL CASE (continued)

The patient received pulse steroids 100 mg po daily for pre-phase therapy and had rapid improvement in his B-symptoms, bone pain, and performance status. He was subsequently treated with

sequential brentuximab vedotin (BV) for 2 cycles. He had grade 2 diarrhea after the second cycle of BV that was treated with supportive care measures. Therapy was otherwise tolerated well; he achieved a partial remission by CT imaging, and he proceeded with full-dose AVD chemotherapy.

After cycle 2 of AVD, the patient had grade 1 sensory neuropathy that evolved to grade 2 after cycle 3 (eg, difficulty using the phone). Vinblastine was decreased by 1 dose level and the neuropathy improved to grade 1. He achieved metabolic complete remission after cycle 3 AVD. The patient had increasing fatigue and asthenia after the fifth AVD cycle, and chemotherapy was stopped. He proceeded with 4 sequential, attenuated dosed BV cycles and remained disease-free for 2+ years.

However, 28 months post diagnosis, he had dyspnea on exertion, orthopnea, and lower extremity edema. An echocardiogram showed a mildly dilated left ventricle with left ventricular ejection fraction of 35%. He was referred to cardiology and started on sacubitril-valsartan, carvedilol, spironolactone, and dapagliflozin, which resolved his heart failure symptoms. A coronary angiogram showed the prior stent was patent with nonobstructive coronary artery disease, and statin and aspirin were continued. He completed cardiac rehabilitation. A repeat echocardiogram 4 months later showed normal left ventricular size and improvement in left ventricular ejection fraction to 55%.

Conclusions

Outcomes have improved in the modern era for older HL patients, in part due to the integration of targeted agents. Additionally, the importance of dose intensity and the inclusion of anthracycline therapy strongly correlates with optimized survival in the contemporary era. Clinical factors that drive prognosis include advancing age and GAs, the latter of which should be objectively measured in all studies at baseline and include assessment of ADLs and comorbidities. However, more research is needed to delineate which GAs are most relevant and prognostic for older HL patients.

Collectively, treatment for fit older HL patients should be given with curative intent that includes anthracycline for most patients, and bleomycin should be minimized (ie, maximum 2 cycles) or avoided altogether, especially in patients ages ≥70 to 75 years. Proactive multidisciplinary management of comorbidities is strongly recommended, and the use of pre-phase treatment should be considered for most patients. Therapy for early-stage disease should follow similar treatment paradigms to younger patients using more limited cycles of ABVD (or AVD) therapy followed by IFRT. In advanced-stage disease, BV given sequentially before and after AVD chemotherapy for untreated older HL patients is highly effective and well tolerated, and we eagerly await emerging data incorporating checkpoint inhibitors into frontline chemotherapy platforms.

Therapy for patients who are unfit or frail, whether due to comorbidities or ADL loss, is less clear and should be individualized with consideration of attenuated anthracycline-based therapy vs lower-intensity treatment with inclusion of BV +/− checkpoint inhibitor therapy. For all patients, there should be continual vigilance with close clinical monitoring of treatment-related toxicities, with attention to dehydration, neurotoxicity, cardiopulmonary, and infections.

In addition, all-cause mortality is significantly elevated in older HL individuals during the postacute period 1 to 10 years after treatment, which includes a prominent fraction of non-HL causes (especially cardiac). Older patients should be evaluated in survivorship clinics and referred to clinically pertinent disease specialists for optimum management of comorbidities, with attention to excess secondary cancers and cardiac, pulmonary, and infectious complications. Finally, more research is needed to delineate HL-specific GA-based clinical prognostic models that can aid in treatment decisions, including fit and unfit patients who should receive anthracycline-based combination chemotherapy vs patient populations who may benefit most from targeted therapeutic approaches, with or without low-intensity chemotherapy.

Conflict-of-interest disclosure

Andrew M. Evens: advisory board or educational forum (with honorarium): Bayer, Seattle Genetics, Affimed, Verastem, Pharmacyclics, Research to Practice, and Physician Education Resource; research support: Takeda, Seattle Genetics, Merck, NIH/NCI, Leukemia and Lymphoma Society, and ORIEN.
Marshall McKenna: no competing financial interests to declare.

Yun Kyoung Ryu Tiger: no competing financial interests to declare.

Jenica N. Upshaw: no competing financial interests to declare.

Off-label drug use

Andrew M. Evens: frontline use of checkpoint inhibitors.
Marshall McKenna: frontline use of checkpoint inhibitors.
Yun Kyoung Ryu Tiger: frontline use of checkpoint inhibitors.
Jenica N. Upshaw: frontline use of checkpoint inhibitors.

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DOI 10.1182/hematology.2023000449