The Management of Older Patients with Hodgkin Lymphoma

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16.1 Introduction

Survival rates for Hodgkin lymphoma (HL) have substantially improved over the past few decades. Using stage-adapted chemotherapy and innovative radiation techniques, 5-year progression-free survival (PFS) has reached almost 90% in younger patients [1–3]. Since the median age at diagnosis is approximately 32 years, these excellent results account for the majority of patients. However, this progress has not translated into similar benefits for older patients, especially for advanced-stage disease [4–8]. Survival rates for HL patients ages ≥60 years have been disproportionately inferior compared with younger patients.

"Older age" is often defined as age over 60 years, in part due to the poor tolerability of aggressive chemotherapy with advancing age. Accordingly, these patients are often excluded

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from randomized controlled trials (RCTs). Thus, the percentage of older patients is often underestimated using data from RCTs [9]. On the other hand, population-based studies estimate that patients over 60 years account for a substantial proportion of patients in clinical practice, i.e., about 20–25% of the total HL population [10]. In part because older patients had historically not been included in clinical trials, a "standard of care" for this patient cohort has been difficult to define [9, 11]. The lack of improvement in outcome for these patients will become magnified as the most rapidly growing segment in the population are patients age > 65 years, especially the age group ≥80 years; the latter has increased >250% between 1960 and 2000 and it is expected that the population age > 75 will triple by the year 2030 [12].

More recent approaches integrating novel therapeutic agents into frontline therapy which appear to be associated with improved outcomes compared with historical controls [13]. In this chapter, we summarize the currently available data on the management of older patients with HL and address the question of including elderly patients into prospective studies in order to improve the outcome of this particular group of patients [14].

16.2 Epidemiology

Many prospective studies and RCTs have excluded older patients on the basis of age or performance status. Historically, only 5–10% of patients included in RCTs have been older than 60 years [5, 15, 16]. The most accurate assessments have come from population-based studies. Two Swedish studies covering from 1979 to 1988 and 1973 to 1994 showed a proportion of 31% and 26% of HL patients older than 60 years, respectively, in the population [4, 17, 18]. The Scotland and Newcastle Lymphoma Group (SNLG) data demonstrated that from 1979 to 2003, 624 (20%) of 3373 patients registered on the population registry were over 60 years [19]. For the registry period 1994–2003, 399 of 1701 patients were > 60 years (23%). This is a percentage confirmed in the Northern UK regional survey of elderly HL, where the age-specific incidence was 1.97/100,000 for patients aged 60–69 and 2.18/100,000 for patients aged 70 or older [10, 11]. The incidence is somewhat higher than that reported by trial study groups since the SNLG data is population-based and, therefore, likely to have fewer exclusions. An analysis of the British National Lymphoma Investigation Group (BNLI) found about 15% of all HL patients older than 65 years, but only 5% had been included in BNLI studies [16], while another population-based study confirmed the proportion of about 20% of older HL patients [10].

Additionally, there are apparent race differences in HL based in part on age. In an analysis of US Surveillance, Epidemiology, and End Results (SEER) data, there were distinct age-related incidence patterns based on race [20]. Incidence rates for older HL patients (i.e., ages >64 years) were highest among Hispanics, followed by Whites and Blacks (see Fig. 16.1).

16.3 Pathology

With regard to histology, there are notable differences between older and younger HL patient populations. The German Hodgkin Study Group (GHSG) published a prior comprehensive retrospective review of elderly patients [5]. Mixed cellularity was more common in older patients (35%) as compared with younger patients (19%) ($p < 0.001$). By contrast, nodular sclerosis was less frequent among older patients with 41 vs. 66% in younger patients ($p < 0.001$). However, this subtype still remains the most common in both groups. The remaining rare subtypes, lymphocyte predominant and lymphocyte depleted, were represented with the same frequency in elderly and younger patients.

Comparable results have been obtained in other studies. A higher frequency of the mixed cellularity subtype was reported by the Nebraska Study Group, CALGB (the Cancer and Leukemia Group B), ECOG (Eastern Cooperative Oncology Group), and a Chicago series [6, 7, 15, 21].

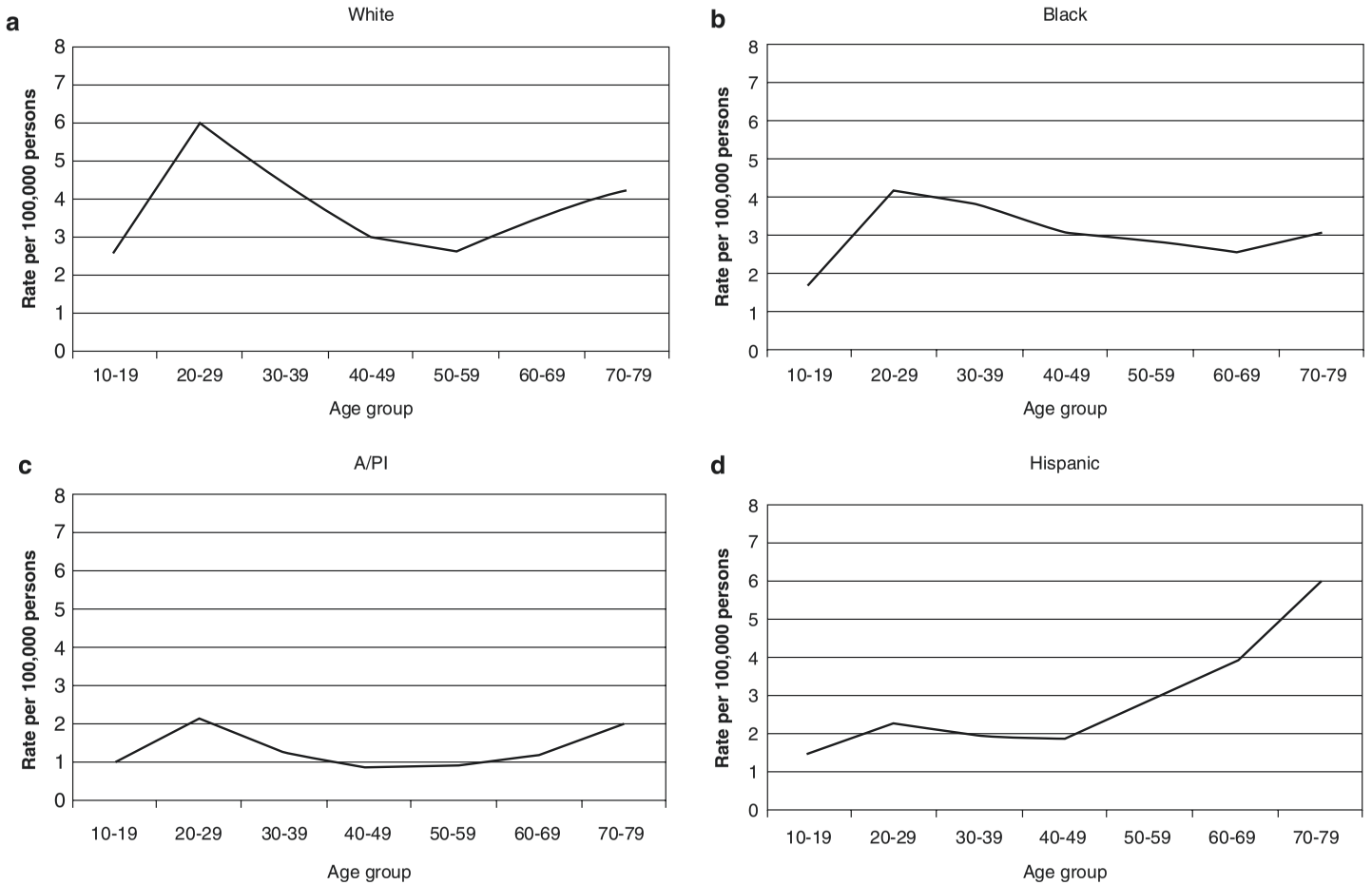

Fig. 16.1 Age-specific incidence of Hodgkin lymphoma by race. Data shown are age-specific incidence rates for 10-year age groups ranging from ages 10 to 79 years for each race (non-Hispanics Whites [referred to as Whites], Hispanic Whites [referred to as Hispanics], Blacks, and A/PIs). Rates are presented in terms of cases per 100,000 population. (**a**) Whites showed a continued bimodal age–incidence pattern, while (**b**) Blacks had a much less clear bimodal distribution. (**c**) A/PIs exhibited a bimodal pattern and have the lowest incidence rates of any race/ethnic group. (**d**) Age-specific incidence in Hispanics was distinctly not bimodal with a small increase at ages 20–29 followed by an exponential-like rise in incidence. Abbreviation: *A/PI* Asian/Pacific Islander. Reprinted with permission [20]

Jarrett et al. have drawn attention to the issue of Epstein–Barr virus (EBV) positivity in the Hodgkin and Reed–Sternberg (H-RS) cells at diagnosis [22]. EBV-associated disease was more often present in patients aged 50 years and older as compared to patients aged 15–34 years and 35–49 years. Importantly, EBV positivity was recognized as a poor prognostic factor for clinical outcome in patients over 50 years, but not in the other groups [22]. Stark et al. also recognized EBV-associated disease as a negative prognostic factor [10]. The EBV-positive status was also associated with advanced-stage disease. It is speculated that such patients have failure of immune response to EBV and present with an enhanced state of immunodeficiency and hence more advanced-stage disease.

16.4 Clinical Presentation

There have been several population-based publications on the clinical presentation of older HL patients [4, 6, 23]. In a study by Erdkamp et al., there were significantly more patients in stage II among younger patients ($p < 0.001$) [6]. Enblad et al. reported in their study more patients with advanced stages among elderly patients ($p = 0.02$) [4]. The comprehensive analysis of elderly HL patients treated within clinical trials of the GHSG among 372 patients aged ≥60 years also found a significant difference in clinical stage with more pronounced incidence of advanced stage in the elderly population [5]. Interestingly, in a recent Swedish registry analysis, the proportion of patients with advanced-stage disease increased in recent decades although these changes could partly be due to the increasing use of PET/CT.

With regard to clinical symptoms, Erdkamp et al. report a trend for a higher number of patients over 50 years presenting with B-symptoms [6]. The GHSG analysis showed statistically significant more female patients and more patients presenting with B-symptoms, elevated erythrocyte sedimentation rate, and worse ECOG performance status. Furthermore, there were less patients with large mediastinal mass and bulky disease as compared with 3879 patients aged <60 years. Additionally, the Nebraska Study Group and a subgroup analysis from the E2496 phase III study that randomized advanced-stage HL patients to ABVD vs. Stanford V showed statistically significant more older patients with poor performance status, B-symptoms at diagnosis, and less with bulky mediastinal disease [7, 21].

To summarize, compared with younger patients, older HL patients present more often with B-symptoms, in a poorer performance status, but with less bulky disease. Furthermore, the stage distribution is also different with older patients presenting more commonly with advanced-stage disease.

16.5 Age Issues Affecting Treatment and Outcome

16.5.1 Comorbidity

Several analyses have documented the prognostic impact of comorbidities in older HL patients. Van Spronsen et al. analyzed 194 HL patients and 904 NHL patients registered between 1993 and 1996 with regard to their age-specific comorbidities and the potential impact on the outcome [24]. The most frequent comorbidity in the HL patient cohort was cardiovascular disease (18%), followed by chronic obstructive lung disease (13%), diabetes mellitus (10%), and hypertension (3%). Taken together, 56% of HL patients aged over 60 years had severe comorbidity. Patients with severe comorbidity received systemic chemotherapy less frequently and had a poorer overall survival (OS) especially within the first 4 months after first diagnosis of the HL. This indicates that comorbidities likely have an impact on survival. Levis et al. reported similar findings noting comorbidities in 35% of 105 older HL patients treated with VEPEMB [25]. A multivariate analysis of this cohort identified comorbidity as an independent prognostic factor for poorer survival. A retrospective analysis of older HL patients across several US medical centers was completed [26]. Among 95 older patients with untreated HL, 61% of patients had at least one

severe comorbidity, 26% were classified as "unfit," 17% had presence of a geriatric syndrome, and 13% had loss of activities of daily living (ADLs) at diagnosis. The presence of loss so far at diagnosis was a strong prognostic factor for survival in this data set.

Guinee et al. compared the outcome of patients aged 60–70 years and 40–59 years, respectively [27]. They investigated the time period between 1977 and 1983. As compared with younger patients, older HL patients had a twofold increased risk of dying due to HL, but even a fourfold increased risk of dying due to other reasons. Surprisingly, the response rates (RR) were not different between the two cohorts with an overall RR of 84% for the older patients and 88% for the younger patients. The strongest prognostic factor in the aforementioned US series was loss of ADLs at initial diagnosis [26]. On multivariate regression, ages ≥70 years and loss of ADLs were the strongest prognostic factors for predicted survival; moreover, patients with both factors present at diagnosis had 3-year OS of 0%.

A recent multicenter phase 2 study reported treatment of 48 elderly HL patients with two initial brentuximab vedotin doses, followed by standard AVD × six cycles with subsequent consolidative brentuximab vedotin for four doses [13]. In this prospective study, geriatric-based measures (e.g., comorbidity score and loss of instrumental ADLs) were strongly associated with patient outcome (see Fig. 16.2). Two-year PFS rates for HL patients treated on this study with high a Cumulative Illness Rating Scale-Geriatric (CIRS-G) comorbidity score (i.e., ≥10 vs. <10) were 45% vs. 100%, respectively ($P < 0.0001$). Furthermore, patients with loss of any instrumental ADL at baseline vs. not had 2-year PFS rates of 25% vs. 94% ($P < 0.0001$), which persisted on multivariable analyses.

To summarize, presence of comorbidities and compromised functional status are relatively common and they represent significant prognostic factors regarding outcome of older patients with HL. There remains a clear need for validation of an age-specific prognostic tool for older HL patients that incorporates comorbidity, frailty, and functional and biological parameters.

16.5.2 Therapy-Associated Toxicity

Therapy-associated toxicities have a major impact on the treatment and outcomes of older HL patients. The reduced tolerability of conventional chemotherapy results in more toxicities overall and more severe toxicities (including fatal outcomes), the inability to maintain the scheduled dose density, and a shorter survival for relapsing or progressing patients [4, 6, 7, 18, 28–30]. This was shown in the GHSG analysis, in which the reduced dose density and the increased mortality during therapy were identified as the major determinants for an inferior outcome of older patients [5]. Landgren et al. reported that older HL patients who received ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine)-based chemotherapy with a relative dose intensity (RDI) >65% had significantly improved OS vs. RDI ≤65% ($p = 0.001$) [18]. However, a significant fraction of older patients are unable to consistently tolerate ABVD with RDI of >65%.

As in younger patients, the GHSG and other studies identified the most prominent toxicities as leukopenia, infections, and cardiopulmonary events [5, 8, 31, 32]. Early termination of the scheduled therapy in older patients had a negative impact on survival [5, 18]. The incidence of severe therapy-associated toxicities varies in the literature for commonly used polychemotherapy regimens ranging between 8% and 20% [4, 6–8, 27, 31]. Using COPP/ABVD, 19% acute toxic deaths were reported [32]; this number was 18% for MOPP/ABVD. In the randomized study comparing baseline-BEACOPP regimen with COPP-ABVD ($HD9_{elderly}$), the treatment-related mortality rates (TRM) among 75 newly diagnosed advanced-stage HL patients aged 66–75 years were 21% and 8%, respectively [31]. Other modified chemotherapeutic regimens designed specifically for older HL patients had a low toxicity, but also a low efficacy [28, 33, 34].

There had been a lack of data examining the tolerability with ABVD for older HL patients in

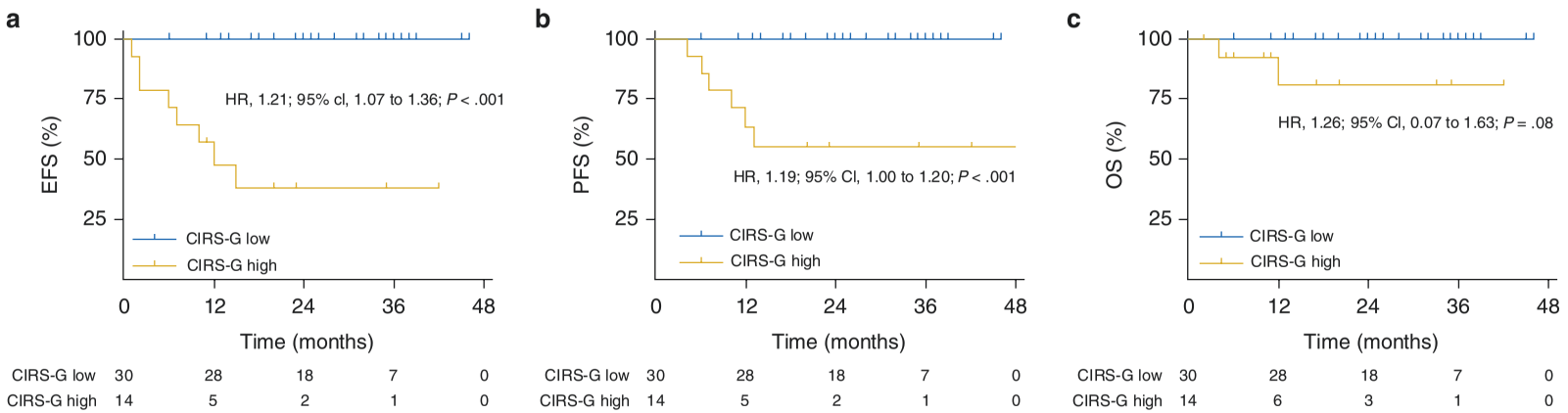

Fig. 16.2 Survival model for older Hodgkin lymphoma patientsKaplan–Meier curves for (**a**) event-free survival (EFS), (**b**) progression-free survival (PFS), and (**c**) overall survival (OS) for newly diagnosed older HL patients treated on phase II clinical trial of sequential brentuximab vedotin and AVD chemotherapy. Patients with a Cumulative Illness Rating Scale-Geriatrics (CIRS-G) score ≥ 10 vs. <10 had 2-year EFS rates of 38% (95% CI, 13% to 63%) vs. 100% (95% CI, 100% to 100%), respectively ($P < 0.001$); 2-year PFS rates of 45% (95% CI, 15% to 71%) vs. 100% (95% CI, 100% to 100%), respectively ($P < 0.001$); and 2-year OS rates of 81% (95% CI, 41% to 95%) vs. 100% (95% CI, 100% to 100%), respectively ($P < 0.02$). Reprinted with permission [13]

the contemporary era; however, two analyses addressed this question. Severe hematologic toxicities were significantly more frequent in older vs. younger HL patients treated on the randomized E2496 study [21]. Additionally, the incidence of bleomycin lung toxicity (BLT) among older HL patients was 24% with an associated BLT death rate of 18%. The vast majority of BLT cases occurred with ABVD. The incidence of BLT in the Chicago series was 32%, which was associated with a mortality rate of 25% [26]. Moreover, the incidence of BLT was 38% vs. 0% among patients who received colony-stimulating factor (G-CSF) vs. not, respectively ($P < 0.0001$). Retrospective analyses and preclinical data have suggested that the risk of BLT is increased when G-CSF is given concurrently [35]. Overall, the TRM rates for older vs. younger HL patients treated on E2496 were 9% vs. 0.3% ($P < 0.001$).

In more recent studies incorporating brentuximab vedotin into frontline therapy for untreated older patients, neurotoxicity has been examined. A multicenter prospective study examined extended dosing of single-agent brentuximab vedotin followed by expanded cohorts combing either bendamustine or dacarbazine (DTIC) for older HL patients deemed ineligible in the investigator's judgment for frontline conventional combination [36, 37]. In these two studies, the incidence rates of grade 3 neuropathy for single-agent BV and BV/DTIC frontline elderly HL studies were 30% and 27%, respectively. In a more recent clinical study utilizing brentuximab vedotin in more limited dosing and sequentially (before and after) AVD chemotherapy, the risk of grade 3 neuropathy was lower at 4% and grade 2 neuropathy was reversible in the majority of patients [13]. Collectively, all grades of neuropathy are important and there should be ardent efforts to closely track and mitigate the occurrence of this toxicity.

16.6 Therapy

16.6.1 Early Stages

In Europe, early stage is of comprised "early favorable" and "early unfavorable" subsets. In young patients, standard of care is a combined modality treatment using two to six cycles of ABVD plus involved field radiotherapy. Recent studies in younger early-stage HL have evaluated the use of PET-guided response-adapted radiotherapy reporting conflicting results. Moreover, these trials included only few, if any, older patients (Table 16.1). In the GHSG HD 8 trial, patients in the early unfavorable stage were randomized to four courses of chemotherapy (COPP/ABVD – cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine, dacarbazine) and either involved field or extended field radiotherapy [38]. The analysis of the older subgroup of patients in this study demonstrated lower 5-year freedom from treatment failure (FFTF) and OS in older patients (FFTF 64 vs. 87%; $p < 0.001$ and OS 70 vs. 94%; $p < 0.001$). Importantly, older patients had a poorer outcome when treated with extended field radiation compared with involved field radiotherapy, 5-year FFTF (58 vs. 70%; $p = 0.034$), and OS (59 vs. 81%; $p = 0.008$), suggesting that EF radiotherapy should be avoided in older patients [39].

A recent analysis focusing on older patients treated within the GHSG HD10 [42] and HD11 [43] trials included 117 older early-stage HL patients treated with 2–4 cycles ABVD followed by IFRT [41]. Mean delay of treatment was twice as high in the older patients (2.2 vs. 1.2 weeks) and WHO grade 3 and 4 toxicities were also more frequent in this group (68 vs. 50%) as compared to younger patients. This resulted in higher treatment-related mortality in older patients. Despite lower dose intensity and higher toxicity, complete response was achieved in 89% of older patients; however, 3% had progressive disease, 11% relapsed, and 28% died within the median observation time of 92 months resulting in a low 5-year progression-free survival of 75% (see Fig. 16.3). Regarding older early favorable HL patients who received 2 cycles ABVD only followed by involved field radiotherapy, feasibility was higher and toxicity during chemotherapy was considerably lower with only 38% of patients experiencing WHO grade 2 to 4 toxicities. Overall, 96% of the patients receiving two cycles of ABVD achieved CR as final treatment

Table 16.1 Selected studies for older HL patients in early stages[a]

Author, year	*N*	Therapy	Outcome	Study comments
Kim, 2003 [29]	52	RT alone ($n = 37$), chemotherapy alone ($n = 9$), combined modality ($n = 6$)	10-year FFTF 71%, 5-year OS 55%, 10-year OS 31%	No significant difference among different treatment modalities; 8.6% second malignancy rate
Levis, 2004 [25]	48	3 cycles VEPEMB followed by IFRT	CR 98%, 5-year RFS 95%, DSS 97%, FFS 79%, and OS 94%	Dose intensity 85%; 5% infection rate, transfusion needed in 2%, hospitalization rate 8%
Landgren, 2006 [40]	68	RT alone—Median dose 40 Gy (IF $n = 28$; MF $n = 20$; TNI $n = 10$; other $n = 10$)	CR 82%; RR 42%	Lower CR rate vs. younger pts. 82% vs. 90% ($p = 0.05$); 16% developed second malignancy
Klimm, 2007 [39]	89	4 cycles COPP/ABVD followed by EFRT or IFRT (both 40 Gy)	5-year FFTF: EFRT 58% vs. IFRT 70%; 5-year OS: EFRT 59% vs. IFRT 81%	Toxicity increased with EF vs. IF (WHO grade 3–4: 27% vs. 9%);
Boll, 2013 [41]	117	4 cycles ABVD followed by 20–30 IFRT	5-year OS and PFS for older patients 81% and 75%, respectively	Mean treatment delay 2.2 weeks in older vs. 1.2 weeks in younger patients; WHO grade 3 and 4) in 68% older patients; TRM 6%

[a]Minimum study size of 45 patients
Abbreviations: *RT* radiation, *FFTF* freedom from treatment failure, *OS* overall survival, *CR* complete remission, *IFRT* involved field radiation therapy, *RFS* relapse-free survival, *DSS* disease-specific survival, *FFS* freedom from treatment failure, *RR* relapse rate, *TNI* total nodal irradiation, *MF* mantle field, *RT* radiation therapy, *IFRT* involved field radiation therapy, *EFRT* involved field radiation therapy, *TRM* treatment-related mortality

outcome. However, rates of progression or relapse (10%) and death (23%) were comparable in both treatment groups, and the 5-year estimates for overall survival (84%) and progression-free survival (79%) did not differ.

Levis et al. reported results of the VEPEMB schedule specifically designed for elderly patients treating 48 patients in stages IA–IIA matching the early favorable risk group [25]. The therapeutic approach was to administer three courses of VEPEMB chemotherapy plus involved field radiotherapy. The CR rate was 98% and 5-year FFS and OS were 79% and 94%, respectively. However, this FFS would be unacceptably low for early favorable HL in younger patients. A retrospective study by a Norwegian group investigated CHOP-21 (cyclophosphamide, vincristine, prednisone, and Adriamycin) in elderly HL patients [44]. Among 29 patients, 11 were stage I–IIA and 18 stage IIB–IV. Patients in early stages received two or four cycles of CHOP-21 (depending on the presence of risk factors) followed by involved field radiotherapy. The CR rate for early stages was 91%; 3-year OS and PFS were 91% and 82%, respectively. The number of patients is too small to allow a fair judgement of this regimen in the treatment of HL.

Three randomized prospective trials recently tested the omission of radiotherapy in patients with negative FDG-PET after ABVD in early-stage HL patients [45–47]. All three trials included only a minority of elderly patients. However, all three trials failed to show non-inferiority of the PET-adapted approach compared with the standard combined modality treatment. Similarly, in a recent multivariate large National Cancer Database analysis including 3795 older early-stage HL patients, the combination of chemotherapy and radiotherapy resulted in improved OS compared with chemotherapy only [48]. Therefore, the omission of radiotherapy in the early stage cannot be recommended in all patients and the expected risks of irradiation should be weighed on an individual basis with the possible gains in efficacy.

Based on currently available data, the GHSG recommends two cycles of A(B)VD followed by 20 Gy involved field radiotherapy for both young and elderly HL patients. Accordingly, four cycles of A(B)VD plus 30 Gy IF radiotherapy are

Table 16.2 Selected published studies for older HL patients in advanced stages[a]

Author, year	*N*	Therapy	Outcome	Therapy-associated death rate
Levis, 1994 [32]	26	ABVD, MOPP/ABVD	CR rate = 61% 8-year OS = 48% 8-year RFS = 75% 8-year EFS = 36%	23%
Levis, 1996 [28]	25	CVP/CEB	CR rate = 73% 5-year OS = 65% 5-year RFS = 47%	4%
Weeks, 2002 [7]	31	ChlVPP	5-year OS = 30% 5-year EFS = 24%	13%
	25	ChlVPP/ABV	5-year OS = 67% 5-year EFS = 52%	16%
Levis, 2004 [25]	57	VEPEMB	CR rate = 58% 5-year OS = 32% 5-year RFS = 66%	3%
Ballova, 2005 [31]	26	COPP/ABVD	CR rate = 77% 5-year OS = 50% 5-year HD-FFTF = 55%	8%
	42	BEACOPP baseline	CR rate = 76% 5-year OS = 50% 5-year HD-FFTF = 74%	21%
Kolstad, 2007 [44]	18	CHOP-21	CR rate = 72% 3-year OS = 67% 3-year PFS = 72%	7%
Halbsguth, 2010 [53]	60	BACOPP	CR rate = 85% 2-year OS = 76% 2-year PFS = 71%	12%
Boll, 2011 [54]	59	PVAG	CR rate = 78% 3-year OS = 66% 3-year PFS = 58%	2%
Proctor, 2012 [55]	72	VEPEMB	CR rate 61% 3-year OS = 62% 3-year PFS = 52%	4%
Evens, 2013 [21]	45	ABVD and Stanford V	CR rate = 64% 5-year OS = 58% 5-year PFS = 48%	9%
Forero-Torres, 2015 [36]	27	Brentuximab vedotin	CR rate = 73% 2-year OS NR 2-year PFS = ~30%	NR
Friedberg, 2017 [37]	42	Brentuximab vedotin and bendamustine or DTIC	CR rate = 62% 2-year OS NR 2-year PFS = ~50%	NR
Evens, 2018 [13]	48	Brentuximab vedotin *sequentially* before and after AVD	CR rate = 95% 2-year OS = 91% 2-year PFS = 84%	2%
Boll, 2018 [56]	25	Lenalidomide and AVD	CR rate = 95% 2-year OS = 91% 2-year PFS = 84%	NR

[a]Prospective clinical studies denoted in italics

Abbreviations: *OS* overall survival, *RFS* relapse-free survival, *EFS* event-free survival, *DFS* disease-free survival, *FFTF* freedom from treatment failure, *PFS* progression-free survival, *ODBEP* vincristine, doxorubicin, bleomycin, etoposide, and prednisolone, *VEPEMB* vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone, and bleomycin, *ChlVPP* chlorambucil, vinblastine, procarbazine, and prednisone, *COPP* cyclophosphamide, vincristine, procarbazine, and prednisone, *ABVD* doxorubicin, bleomycin, vinblastine, and dacarbazine, *BEACOPP* bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone, *BACOPP* bleomycin, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone, *PVAG* prednisone, vinblastine, doxorubicin, and gemcitabine, *DTIC* dacarbazine, *NR* not reported

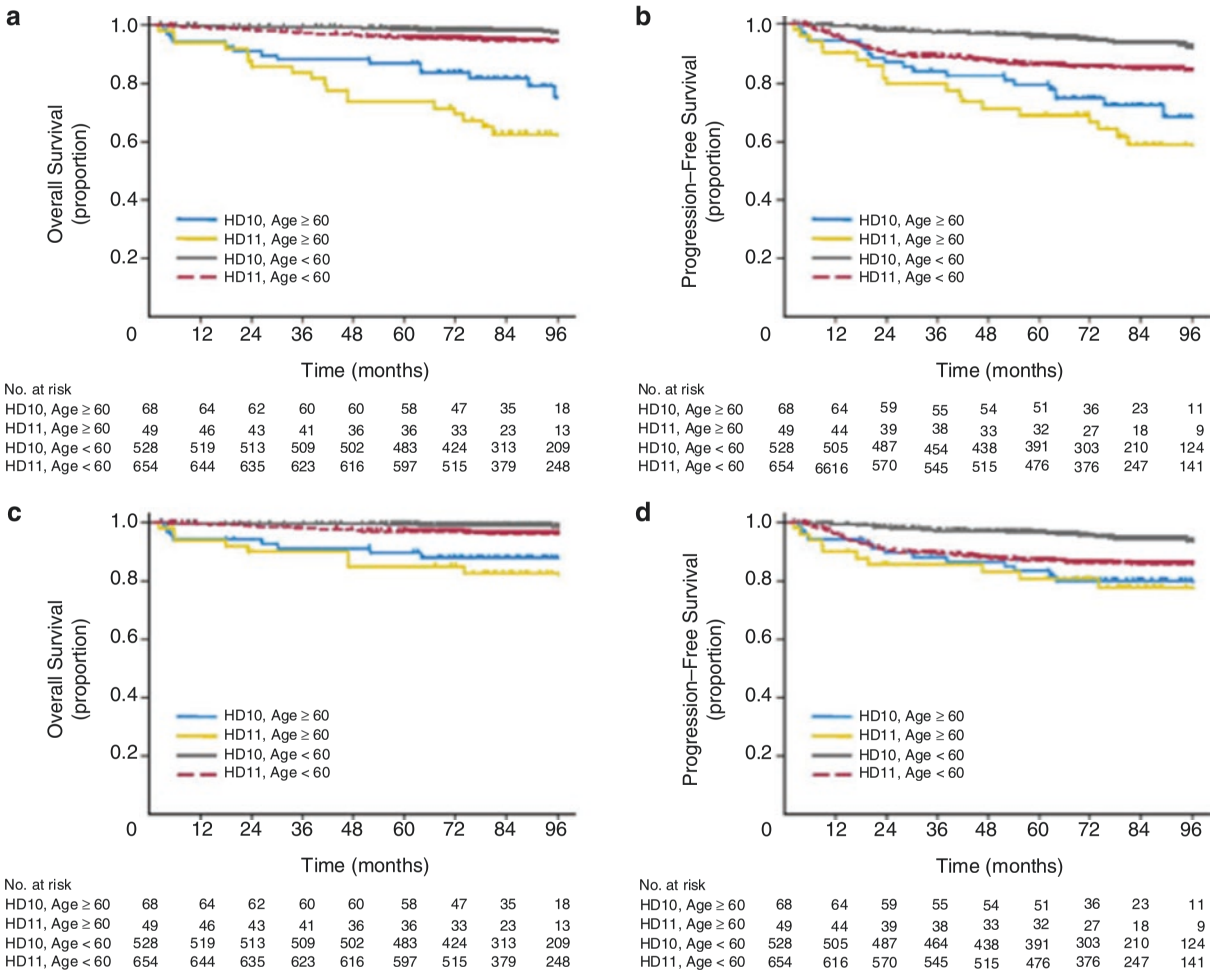

Fig. 16.3 Overall survival/progression-free survival patients in favorable early stage (HD10, GHSG) and patients in unfavorable early stage (HD11, GHSG) [41]. Kaplan–Meier plots of (**a**) overall survival, (**b**) progression-free survival, (**c**) time to HL-related death, and (**d**) time to HL-related failure according to stage and age group. HD10, favorable early-stage patients from German Hodgkin Study Group HD10 trial; HD11, unfavorable early-stage patients from German Hodgkin Study Group HD11 trial

recommended for early unfavorable stage HL in elderly patients. VEPEMB or CHOP may be considered as secondary therapeutic options. Due to potential severe toxicity, the use of bleomycin should be considered cautiously in older patients and bleomycin should not be applied beyond the second cycle to avoid cumulative toxicity [49]. In the case of preexisting pulmonary comorbidity, omitting bleomycin in this group of patients a priori is justifiable (i.e., AVD). If bleomycin is used, patients should be followed closely clinically with low threshold to discontinue it with the development of any clinical symptoms or sequelae suggestive of bleomycin lung toxicity.

16.6.2 Advanced Stages

16.6.2.1 Earlier Data

Although a superior outcome of younger HL patients can be reached by intensification of chemotherapy, ABVD can be regarded as possible for advanced-stage HL [50–52]. However, when ABVD is given with curative intent to patients over 60–65 years, chemotherapy-related toxicities are often prohibitive [5, 15, 18, 32]. This is mainly true for bleomycin. The 5-year OS for older patients treated on the ABVD-based randomized CALGB 8251 trial was 31% compared to 79% for patients aged less than 40 years ($p < 0.0001$) in the late 1980s. Levis et al. analyzed the outcome of 65 patients ages ≥65 years receiving a registry-recommended protocol of ABVD, MOPP (mechlorethamine, vincristine, procarbazine, prednisone), or ABVD/MOPP [32]. Eight-year event-free survival (EFS) and OS in these patients were 41% and 46%, respectively, both significantly inferior compared with patients ages <65 years [32]. Toxicity was prohibitive in this study with a TRM rate of 23%.

Anthracycline is likely an important component of therapy for older HL patients. The Nebraska Group compared ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisone) with the hybrid ChlVPP/ABV (added Adriamycin, bleomycin, and vincristine) in a nonrandomized study including 262 previously untreated HL patients (see Table 18.2) [7]. Among patients age ≥ 60 years, the 5-year EFS was 31% and 5-year OS at 5 years was 39%, compared with 75% EFS and 87% OS for younger patients. In addition, older patients treated with ChlVPP had a poorer outcome as those treated with ChlVPP/ABV. The 5-year EFS were 24% vs. 52%, respectively ($p = 0.011$), and 5-year OS 30% vs. 67%, respectively ($p = 0.0086$).

The Italian group followed another strategy by developing less-intensive polychemotherapy regimens specifically for older patients (see Table 18.1). They started in the early 1990s with the CVP/CEB regimen (chlorambucil, vinblastine, procarbazine, prednisone, cyclophosphamide, etoposide, bleomycin) and subsequently used VEPEMB [28, 32]. CVP/CEB, a low-toxicity regimen, was administered to 25 patients and well tolerated. The CR rate at the end of treatment was 73%. However, the 5-year EFS and OS were disappointing with 32 and 55%, respectively.

The subsequent study investigated the VEPEMB regimen (see Table 16.1). Among 105 patients, 57 were in advanced stages of disease receiving six cycles of this regimen with additional radiotherapy to bulky disease or residual mass. VEPEMB was well tolerated and could be administrated to most patients, and only one patient died during treatment. After the end of treatment, 58% of patients were in CR; the 5-year FFS was 34% and OS 32% [25]. In an analysis of a prospectively randomized phase III study comparing this regimen with ABVD in 56 older HL patients (17 early-stage and 37 advanced-stage disease), the 5-year PFS rates were 48% vs. 70% ($P = 0.07$) and 5-year OS rates were 63% vs. 77% ($P = 0.25$) [57]. Though this was a small randomized study, the data do not support the use of VEPEMB outside clinical studies, since superiority to ABVD cannot be seen so far and only a minority of patients with advanced-stage disease might be cured using this schedule.

The GHSG more recently reported results of two phase II studies for untreated, older HL patients, using BACOPP (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and PVAG (prednisone,

vinblastine, doxorubicin, gemcitabine) [53, 54]. The CR rate with BACOPP was 85% with associated 3-year PFS and OS rates of 60% and 71%, respectively [53]. However, the regimen was associated with significant toxicity with 87% of patients experiencing grade 3–4 adverse events, 30% early termination, and TRM of 12%. PVAG was developed in part to eliminate the need for bleomycin or dacarbazine by substituting prednisone and gemcitabine [54]. The CR rate of this new regimen in elderly HL patients was 78% and the 3-year PFS and OS rates were 58% and 66%, respectively. Therapy was rather well tolerated and the TRM rate was 2%.

Kolstad et al. used CHOP (cyclophosphamide, Adriamycin, Oncovin, prednisone) for older HL patients [44]. They treated 29 patients with CHOP-21 using 2–4 cycles and involved field radiotherapy (IFRT) for early-stage and 6–8 cycles ± IFRT for advanced-stage disease. The CR rate was 93% and the 3-year PFS and OS rates for advanced-stage patients were 67% and 72%, respectively. Proctor et al. reported results from the Study of Hodgkin lymphoma In the Elderly/Lymphoma Database (SHIELD) project (www.shieldstudy.co.uk) [55]. They treated 103 older HL patients with VEPEMB, of which 72 patients had advanced-stage disease. Comorbidities and frailty were objectively assessed; only non-frail patients were eligible for the prospective study. For advanced-stage patients, the CR rate was 61% and 3-year PFS and OS rates were 58% and 66%, respectively. Therapy was generally well tolerated with a TRM rate of 3%. In prognostic factor analyses, achievement of CR strongly predicted survival. Factors associated with CR were comorbidity score (by modified ACE 27) and ADLs. In the same report, there was an additional observational group of older HL patients (frail and non-frail) treated according to physician discretion. Among 13 frail HL patients in this substudy, all died (12 from HL) with median OS of 7 months.

Findings on elderly patients from a subgroup analysis of the North American Intergroup trial E2496 were reported [21]. E2496 was a phase III study that randomized advanced-stage HL to ABVD or Stanford V; 45 patients were ≥60 years. There were no survival differences between ABVD and Stanford V for older HL patients. Toxicities were similar to other chemotherapy regimens used for older patients; however, the incidence of BLT was 24% with 91% of cases occurring with ABVD. Furthermore, the associated BLT death rate was 18%. Altogether, TRM was significantly higher for older vs. younger HL patients (i.e., 9% vs. 0.3%, $p < 0.001$). Moreover, outcomes were markedly inferior for older patients with 5-year FFS rates of 48% vs. 74%, respectively ($p = 0.002$), and 5-year OS rates of 58% and 90%, respectively, when compared to younger patients treated in this trial ($p < 0.0001$) (see Fig. 16.4).

16.6.2.2 Contemporary Data

Brentuximab vedotin has been integrated into the treatment of untreated older HL patients. An initial study examined single-agent BV for older HL patients deemed ineligible in the investigator's judgment for frontline conventional combination treatment [36]. The ORR was 92% with a complete remission (CR) rate of 72%. However, the relapse rate was high with 2-year PFS rates <40%.

This single-agent BV study was amended to combine concurrent bendamustine or DTIC [37]. The bendamustine arm was closed prematurely due to toxicity; response rates were good in the concurrent BV/DTIC arm; however, this approach did not appear curative in most patients (i.e., 2-year PFS rates of approximately 50%) and may be best considered where combination chemotherapy is not feasible.

In the aforementioned clinical study of brentuximab vedotin given before and after standard AVD therapy for untreated older HL patients [13], the choice of sequential therapy (vs. concurrent) was predicated on assumptions that (1) initial brentuximab vedotin therapy could establish earlier disease control and increase the likelihood of successful potentially curative therapy, (2) initial brentuximab vedotin therapy could minimize overlapping neurotoxicity with concurrent brentuximab vedotin/AVD, and (3) consolidation would decrease the risk of relapse. This approach also allowed assessment of the

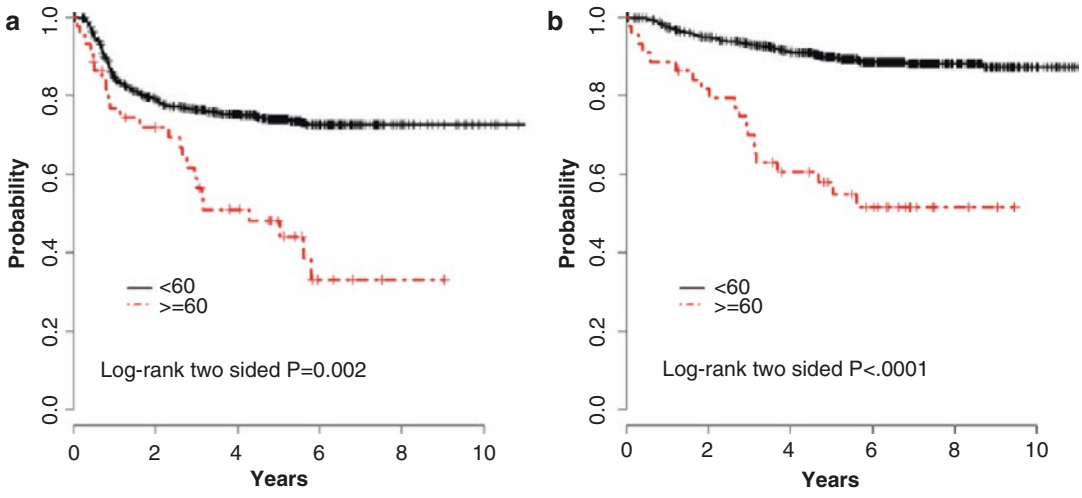

Fig. 16.4 Outcomes comparing older HL with younger patients. The (**a**) 3- and 5-year FFS for patients ages ≥60 years were 56% and 48%, respectively, compared with 76% and 74%, respectively, for patients ages <60 years ($p = 0.002$); while (**b**) the 3- and 5-year OS for patients ages ≥60 years were 70% and 58%, respectively, compared with 93% and 90%, respectively, for patients ages <60 years ($p < 0.0001$). Modified from original figure; reprinted with permission [21]

individual contribution of BV in untreated patients. The median age of patients was 69 years (range, 60–88), 81% stage III/IV and 19% stage II with bulky disease and/or B-symptoms, IPS 3–7 in 60%, median CIRS-G comorbidity score of 7 (52% with grade 3/4), and 12% having loss of instrumental ADL at baseline. Overall, 77% of patients completed the brentuximab vedotin prephase and 6 AVD cycles and 73% received at least 1 dose of brentuximab vedotin consolidation. The ORR and CR rates after the initial 2 lead-in doses of brentuximab vedotin were 82% and 36%, respectively, and 95% and 90%, respectively, after 6 AVD. Survival rates are depicted in Fig. 16.5. The most common grade 3/4 adverse events were neutropenia (44%), febrile neutropenia and pneumonia (8%), and diarrhea (6%). By intention-to-treat analysis, the 2-year PFS and overall OS were 84% and 93%, respectively. TRM for all patients was 2% (i.e., 1 case of pancreatitis, which occurred following the second lead-in dose of single-agent brentuximab vedotin) [58].

A recently published phase 1 study examined lenalidomide given concurrently (daily from days 1 to 21) with AVD chemotherapy for older HL patients [56]. Twenty-five HL patients with a median age of 67 years (range 61–76) were treated with escalating doses of lenalidomide, with DLT evaluation of 20 patients elucidating a recommended dose for phase II of 25 mg. Dose-limiting toxicities were mainly hematologic, but also included 3 thromboembolic events despite documented aspirin prophylaxis. The ORR were 79% for evaluable patients and 86% in patients treated with at least 20 mg lenalidomide. After 12 months' median observation time, the 1-year PFS and OS rates were 69% and 91%, respectively.

The GHSG and the Nordic Lymphoma Group presented recent data using brentuximab vedotin concurrently with cyclophosphamide, doxorubicin, and prednisone (B-CAP) for older HL patients with CIRS-G $\leq$ 6 [59]. Among 48 eligible advanced-stage patients, median age was 67 years (range, 60–84 years) and 50% had IPS 4–7. The ORR was 98% with a CR rate of 65%; with median follow-up of 15 months, the 1-year PFS and OS rates were 74% and 93%. Notably, there was no grade 3 neuropathy observed and the TRM was 2% (infection).

Finally, outcomes were recently analyzed across ages and treatment regimens for the pivotal phase 3 ECHELON-1 study that examined

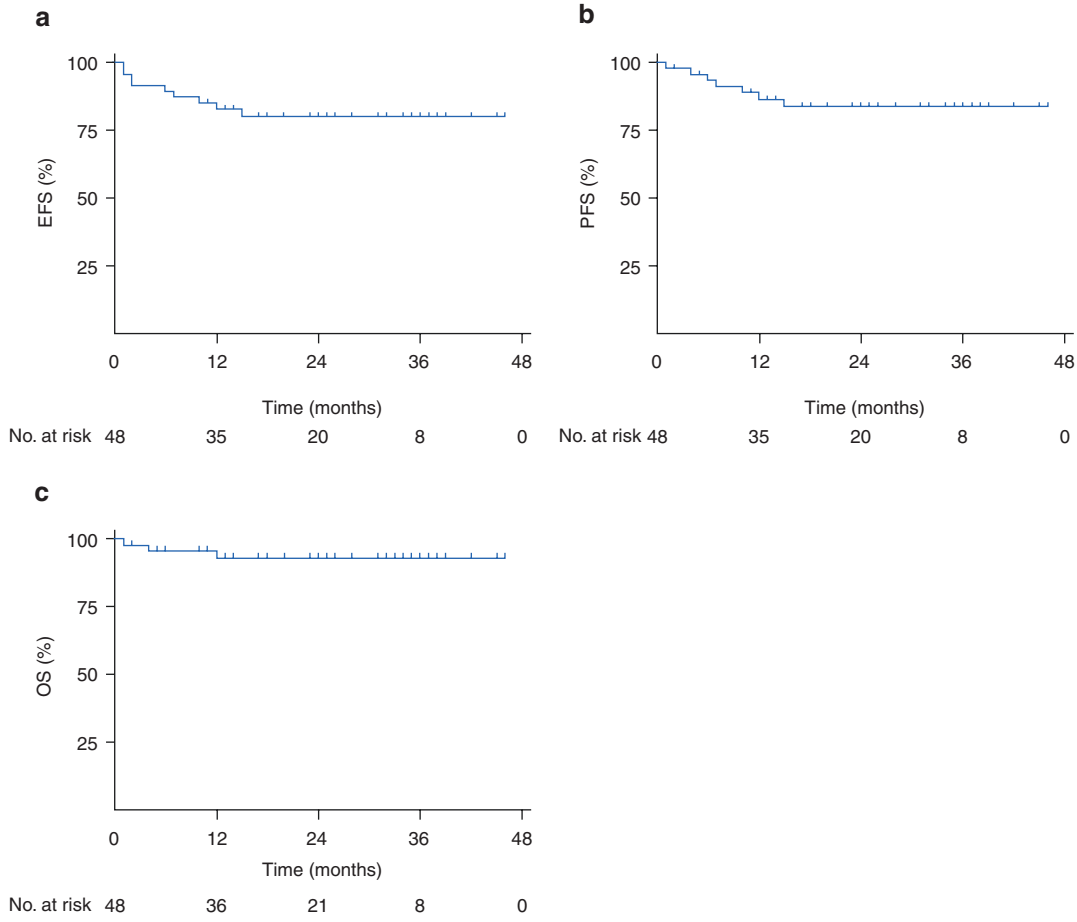

Fig. 16.5 Survival rates of patients treated on sequential brentuximab vedotin and chemotherapy study. Kaplan–Meier curves for (**a**) event-free survival (EFS, 80%; 95% CI, 65% to 89%), (**b**) progression-free survival (PFS, 84%; 95% CI, 69% to 92%), and (**c**) overall survival (OS, 93%; 95% CI, 80% to 98%) for 48 newly diagnosed older HL patients treated on phase II clinical trial of sequential brentuximab vedotin and AVD chemotherapy. Reprinted with permission [13]

the efficacy of brentuximab vedotin + doxorubicin, vinblastine, and dacarbazine (A + AVD) vs. ABVD in patients with previously untreated advanced-stage classical HL [60]. Overall, 186 of 1334 patients in the intent-to-treat population were ≥60 years (A + AVD, n = 84; ABVD, n = 102) and included in a subset analysis. With median follow-up of ~25 months, modified PFS (mPFS) per independent review facility (IRF) was similar between the 2 treatment arms for older patients (70.3% vs. 71.4%). For older patients with stage IV disease (n = 118), there was a numerical increase in median PFS per investigator with A + AVD vs. ABVD (74.0 months [95% CI, 59.5–84.0] vs. 59.9 months [95% CI, 45.6–71.5]; HR, 0.66 [95% CI, 0.34–1.26]; p = 0.20). In addition, the 2-year mPFS and PFS rates were higher in younger vs. older patients in both treatment arms. Furthermore, the TRM for older patients was 4% in the A + AVD arm and 5% with ABVD (all pulmonary related).

In conclusion, the use of anthracycline-based chemotherapy in the treatment of fit older patients with advanced HL appears to be important. In the treatment of older HL patients, at least partial or even complete omission of bleomycin from ABVD should be considered (i.e., AVD) as an

option for frontline therapy [55]. If bleomycin is utilized in older patients, there should be extreme caution overall and especially with the concurrent use of G-CSF. Dose intensification approaches, including BEACOPP variants, have not been successful in elderly patients, mainly due to an unacceptable increase in toxicity including high rates of TRM. Data incorporating brentuximab vedotin sequentially before and after AVD chemotherapy represent among the best-reported outcomes to date for untreated older HL patients. Furthermore, data from this study provided important prognostic guidelines based on geriatric assessments. Standard therapy for unfit/frail patients or ones with high comorbidities is less clear. Lower-intensity chemotherapy programs, including regimens that incorporate brentuximab vedotin, may be considered.

Objectives of future investigations should attempt to maintain these robust outcomes with less treatment (especially chemotherapy). Additionally, integration of other novel agents such as checkpoint inhibitors (e.g., NCT02758717, NCT03226249, NCT03033914, NCT03233347) and associated response-adapted trials should be evaluated, and concerted efforts should be given to prospectively integrate and potentially tailor therapy based upon geriatric assessments, especially for more frail and unfit older patients.

16.6.3 Relapsed Patients

Prospective randomized studies have not specifically evaluated the treatment of relapsed older HL patients. Therefore, treatment recommendations in this setting are largely based on personal experience and retrospective single-center analyses. Treatment options for relapsed or refractory HL in older patients include intensified treatment, poly-chemotherapy, radiotherapy in selected patients, single-agent (palliative) chemotherapy, and best supportive care.

With the development of novel drugs such as brentuximab vedotin having impressive single-agent activity, potentially less toxic alternative treatments are available for older patients in whom conventional treatment is not an option due to comorbidity [61–63].

The use of different treatment strategies is guided by patient preference, comorbidity/functional status, and the duration of response to first-line therapy. In patients with long-lasting remission after first-line treatment, polychemotherapy regimens such as PVAG, ABVD, CHOP, or the oral PECC (prednisolone, etoposide, chlorambucil, and CCNU) [64] are valid options. Furthermore, drugs with known single-agent activity in HL include alkylating agents (e.g., ifosfamide, trofosfamide, and procarbazine), gemcitabine, vinca alkaloids, and platinum derivates.

Smaller retrospective single-center studies have suggested that high-dose chemotherapy followed by autologous stem-cell support might be an effective treatment for selected patients with relapsed HL [65]. A recent, GHSG analysis examined 105 patients with a median age of 66 years [66]. Different second-line treatment strategies were used including intensified salvage regimens in 22%, conventional polychemotherapy and/or salvage-radiotherapy with curative intent in 42%, and palliative approaches such as single-agent chemotherapy and best-supportive care in 31% of the older HL patients. As patient characteristics were varied within the different treatment groups, a prognostic score applied using the risk factors (RFs) early relapse, clinical stage III/IV, and anemia identified patients with favorable and unfavorable prognosis. Median OS for the entire cohort of relapsing older HL patients was 12 months. Survival was significantly different within different risk groups (i.e., $\leq$ one RF, 3-year OS, 59%; 95% CI, 44% to 74%; $\geq$ two RFs, 3-year OS, 9%; 95% CI, 1% to 18%) (see Fig. 16.6). In low-risk patients, the impact of therapy on survival was significant in favor of the conventional polychemotherapy/salvage radiotherapy approach. In high-risk patients, OS was low overall and did not differ significantly between treatment strategies [66]. These results might be useful in guiding treatment decisions, while there remains a significant need to evaluate

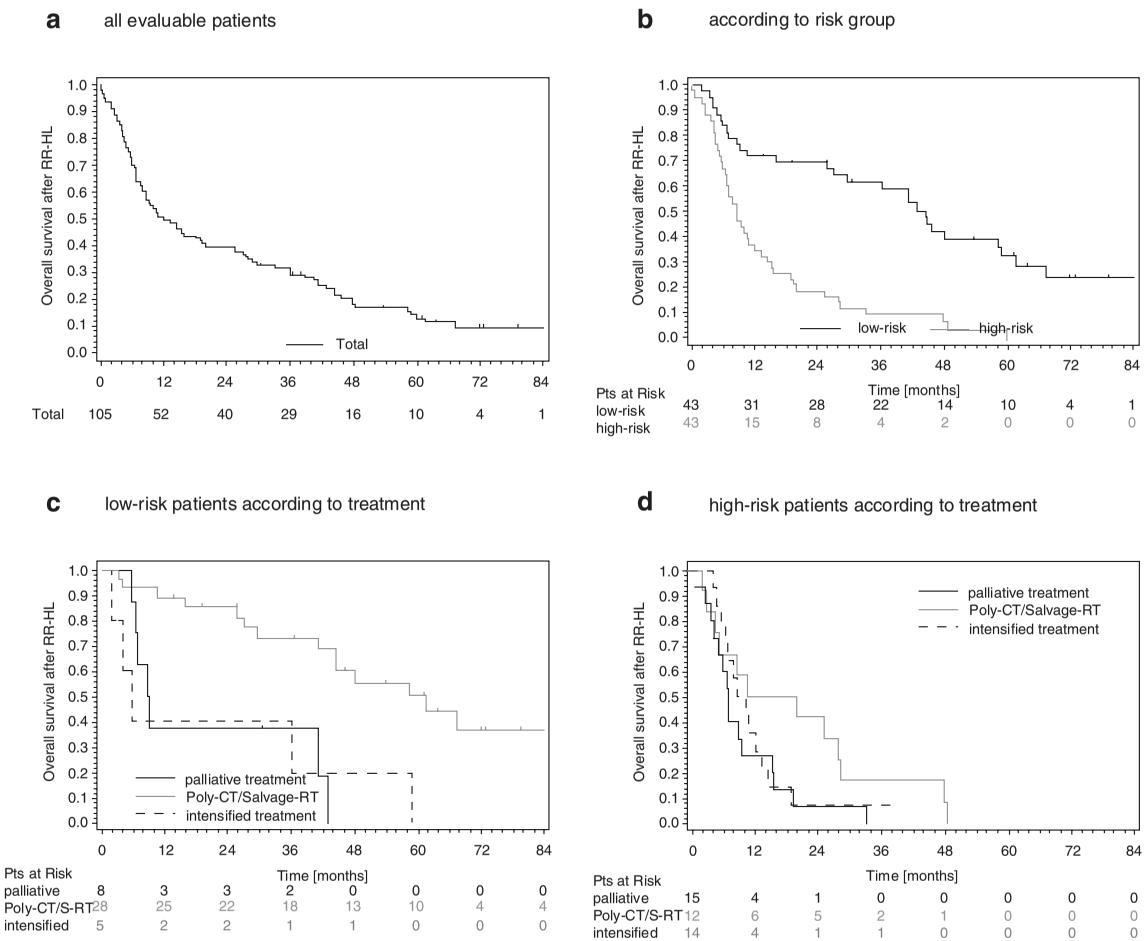

Fig. 16.6 Overall survival of older HL patients after relapse/progression. Kaplan–Meier plots of overall survival (OS) in (**a**) all evaluable patients (median OS, 12 months; 95% CI, 8 to 19 months; 3-year OS, 31%; 95% CI, 22% to 40%), (**b**) all evaluable patients according to risk group (high-risk patients, 3-year OS, 11%; 95% CI, 1% to 22%; low-risk patients, 3-year OS, 57%; 95% CI, 40% to 73%), (**c**) low-risk patients according to treatment (intensified treatment, 3-year OS, 20%; 95% CI, 0% to 55%; polychemotherapy [poly-CT]/salvage radiotherapy [RT], 3-year OS, 71%; 95% CI, 53% to 89%; could not be estimated for patients receiving palliative treatment), and (**d**) high-risk patients according to treatment. RR-HL, relapsed/refractory Hodgkin lymphoma. Modified from original figure; reprinted with permission [65]

novel compounds in older patients with relapsed/refractory HL.

Antibodies against PD-1 have shown remarkable efficacy in Hodgkin lymphoma and were well tolerated. Phase II trials for relapsed and refractory Hodgkin lymphoma patients have been conducted evaluating the anti-PD-1 antibodies nivolumab and pembrolizumab with similar results. Although only few elderly patients were treated within these trials, anti-PD-1 antibodies might provide a valid treatment option for relapsed or refractory elderly Hodgkin lymphoma patients [67, 68]. This new class of drugs are generally well tolerated and not associated with toxicity observed with chemotherapy.

16.7 Conclusions and Perspectives

Although outcomes have improved over time, survival rates for older HL patients remain disproportionately inferior compared to younger patients. Furthermore, HL in older patients remains a disease where standard treatment recommendations are difficult. Generally, treatment of older HL patients for all disease stages should be given with curative intent with treatment paradigms similar to younger patients. This includes abbreviated chemotherapy (2–4 cycles) and involved field radiation for early-stage disease and chemotherapy for 6 cycles for advanced stages. Intensive regimens such as BEACOPP are too toxic for older patients, while less intensive regimens such as CVP/CEB and ChlVPP are not effective enough.

Outside of a clinical trial, ABVD likely remains a standard regimen for older HL patients; however, caution should be given to potential severe treatment-related toxicities, especially bleomycin-related lung toxicity. Balancing the risk/benefit ratio, a priori omission of bleomycin may be considered in older patients (i.e., AVD), especially for patients over ages 65–70 years. Additionally, the impact of patient comorbidities and assessment of functional status should continue to be examined in prospective studies with this consideration of choice of therapy based on this. Finally, the integration of novel therapeutic agents into frontline treatment paradigms should continue to be evaluated.

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