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Supplement Article

XII. Hodgkin lymphoma in older patients: challenges and opportunities to improve outcomes

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Advanced age is a known poor prognostic factor in Hodgkin lymphoma (HL) [1]. Further, outcomes for HL patients aged ≥60 years are significantly and disproportionately inferior compared with younger patient populations (Figure 1) [2–4] and a standard treatment paradigm for older HL patients is lacking. The inferior outcome for older patients has been attributed to a variety of factors including presence of co-morbidities, poor performance status, histologic and biologic differences (e.g. mixed cellularity, EBV-related, and advanced-stage disease), inability to tolerate chemotherapy at full dose and schedule, and increased treatment-related toxicity and mortality. Compounding these challenges has been the under-representation of older patients in HL clinical trials, which is a barrier in the evaluation of disease biology and discovery of effective treatment strategies. Nonetheless, outcomes have improved for older HL patients over the past several decades, and there are recently published data and research endeavours in this patient population that are underway. In this review, we discuss the epidemiology, biology, disease characteristics, prognostication, and treatment strategies for older HL patients.

Epidemiology

Within population-based studies, the proportion of HL patients aged ≥60 years in the population ranges between 15% and 35% [5–8]. However, the proportion of patients ≥60 years enrolled onto clinical trials has been considerably lower, typically <5–10% of participants [2,6,9]. Among recent data from the Surveillance, Epidemiology, and End Results (SEER) program, evidence of an age-related bi-modal incidence pattern in HL persists. Furthermore, in an analysis of SEER-13, there were distinct age-related incidence patterns based on race [10]. Figure 2 shows that incidence rates for older HL patients (i.e. aged >64 years) were highest among Hispanics (6.5/100 000), followed by Whites (4.5/100 000) and Blacks (3.4/100 000).

Biology and clinical characteristics

Several sources of evidence have suggested that older HL has a different disease biology compared with younger HL (Table 1) [11]. Mixed cellularity histology occurs with higher frequency in older HL patients ranging from 31% to 50% [2,4,12,13]. EBV-related disease is also more prominent in older patients. Stark *et al.* reported that 34% of older HL cases were EBV-positive and that EBV status correlated with stage at presentation (i.e. early-stage EBV + 9% vs advanced-stage 50%, $p = 0.0006$) [7]. Moreover, EBV + HL was associated with inferior overall survival (OS) compared with EBV-negative cases (median OS 20 months vs not reached, respectively; $p = 0.007$). Older age has also been shown to be associated with *decreased* forkhead box P3 (FOXP3) Tregs and *increased* granzyme-B positive cells in HL tumour samples, which correlated with poor outcomes [14]. Other clinical characteristics more frequently observed in older HL patients include presence of B symptoms, decreased performance status, infra-diaphragmatic disease, and advanced stage disease, while bulky mediastinal presentation is uncommon [4].

Prognostication

One of the most commonly utilized prognostic tools in advanced-stage HL is the International Prognostic Score (IPS) [1]; however, it is important to note that only 9% of patients in the original Hasenclever and Diehl analysis were >55 years, and there were no patients >65 years included. Further, the IPS does not appear to predict outcomes in older HL patient populations [12,15]. Advancing age within the older HL population has been shown to predict survival; age >70 years has been associated with significantly inferior survival versus 60–69 years [5,12,15]. In addition, several analyses have documented the prognostic

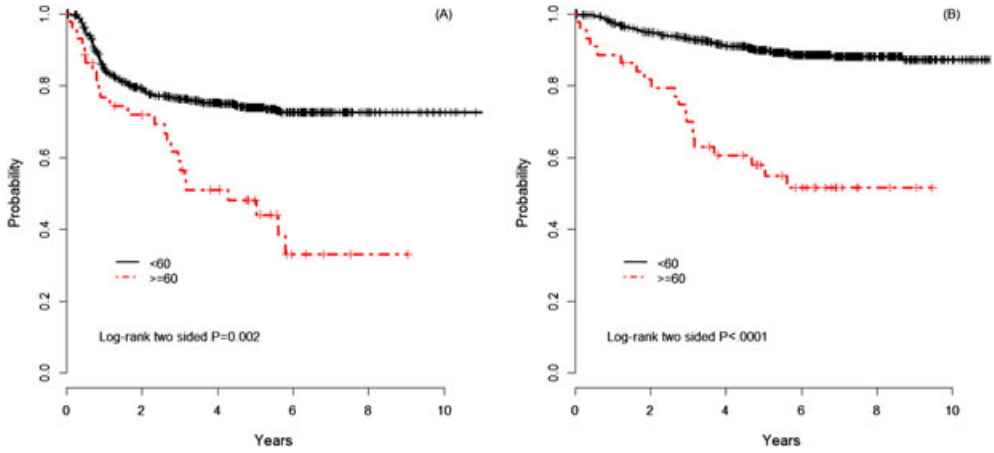

Figure 1. Outcomes comparing older HL with younger patients. (A) The 3- and 5-year FFS for patients aged ≥60 years were 56% and 48%, respectively, which compared with 76% and 74%, respectively, for patients aged <60 years ($p = 0.002$), while (B) the 3- and 5-year OS for patients aged ≥60 years were 70% and 58%, respectively, which compared with 93% and 90%, respectively, for patients aged <60 years ($p < 0.0001$). Modified from original figure; reprinted with permission [3]

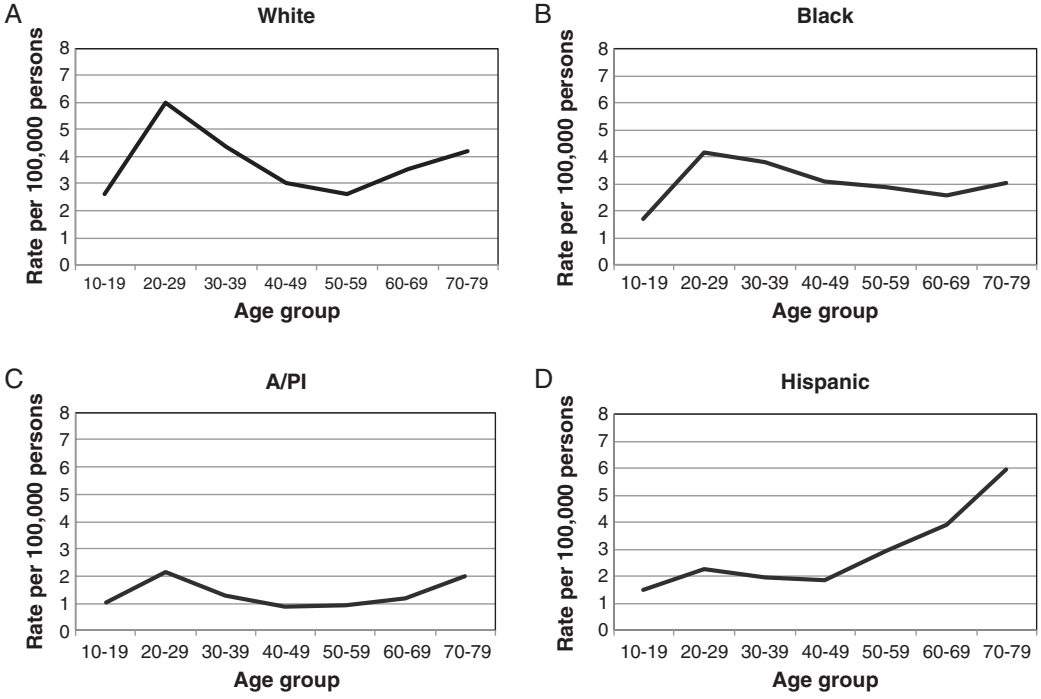

Figure 2. Age-specific incidence of Hodgkin lymphoma by race. Data shown are age-specific incidence rates for 10-year age groups ranging from ages 10 to 79 years for each race (non-Hispanics Whites (referred to as Whites), Hispanic Whites (referred to as Hispanics), Blacks, and A/PIs). Rates are presented in terms of cases per 100 000 population. (A) Whites showed a continued bimodal age-incidence pattern, whereas (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 years followed by an exponential-like rise in incidence. A/PI, Asian/Pacific Islander. Reprinted with permission [10]

importance of co-morbidities in older HL patients [13,16–18]. Levis *et al.* treated 105 older HL patients with vinblastine–cyclophosphamide–procarbazine–etoposide–mitoxantrone–bleomycin (VEPEMB) [16]. On multivariate analysis, in addition to stage and B symptoms, presence of co-morbidity was independently associated with inferior survival [disease specific survival 59% vs 74%, respectively, $p < 0.01$; failure-free survival (FFS) 40% vs 64%, respectively, $p < 0.02$; and OS 54% and 69%, respectively, $p < 0.01$]. The strongest prognostic factor in our Chicago series was loss of activities of daily living (ADLs) at initial diagnosis [12]. On multivariate regression, age ≥70 years and loss of ADLs were the most important pre-treatment factors that predicted survival (Figure 3).

Older HL patients are not able to tolerate chemotherapy at equal dose intensity compared with younger patients

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Table 1. Retrospective population-based analyses (post-2000)

Author, year publish	N	Time period	Median age in years (range)	Histology and stage	Primary therapy	Survival
Stark *et al.* 2002 [7]	102	1991-1998	72 (60-91)	MC: 32%, AS: 60%	Heterogeneous	Median OS: 26 months
Weekes *et al.* 2002 [22]	56	1982-1998	NR	MC: 34%. AS: 73%	ChlVPP and ChlVPP/ABV	5-year OS: ChlVPP/ABV: 67%; ChlVPP 30%
Enblad *et al.* 2002 [15]	77	1985-1988	71 (61-91)	MC: 42%, AS: 53%	MOPP/ABVD-based (71%) and ChlVPP (22%)	5-year OS 45%
Enblad *et al.* 2002 [15]	62	1989-1992	71 (60-88)	MC: 34%, AS: 42%	LVPP/OEPA	5-year OS 48%
Kim *et al.* 2003 [24]	86	1969-1995	68 (60-93)	MC: 38%, AS: 40%	Heterogeneous (RT alone 50%)	5-year OS 48%
Landgren *et al.* 2003 [5]	88	1973-1994	72 (60-92)	MC: 42%, AS: 69%	MOPP- and ABVD-based	5-year OS 39%
Engert *et al.* 2005 [2]	372	1988-1998	65 (60-75)	MC: 35%, AS: 48%	COPP/ABVD, COPP/ABV/IMEP, BEACOPP	5-year OS 65%
van Spronsen *et al.* 2005 [18]	57	1995-2001	NR	MC: NR, AS: 37%	Heterogeneous	5-year crude survival 46%
Evens *et al.* 2012 [3]	95	1999-2009	67 (60-89)	MC: 31%, AS: 64%	Heterogeneous	5-year OS 58% (AS: 46%)

Abbreviations: N, number; MC, mixed cellularity; AS, advanced stage; NR, not reported; COPP, cyclophosphamide, vincristine, procarbazine and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; IMEP, ifosfamide, methotrexate, etoposide and prednisone; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; ChlVPP, chlorambucil, vinblastine, procarbazine, prednisone; LVPP/OEPA, chlorambucil, vinblastine, procarbazine, prednisone/vincristine, etoposide, prednisone, doxorubicin; OS, overall survival; RT, radiotherapy.

Figure 3. Survival model for older Hodgkin lymphoma patients. (A) Progression-free survival and (B) overall survival for older HL patients based on number of the adverse prognostic factors present (age ≥70 years and loss of ADLs). The numbers of patients with 0, 1, or 2 factors at diagnosis were 48, 38, and 9, respectively; increasing number of risk factors portended an increasingly poor survival. A Classification and Regression Trees (CART) survival model based on number of adverse factors present (0, 1, or 2) was formed: 2-year PFS of 68%, 68%, and 13%, respectively ($p < 0.001$); 2-year OS of 83%, 70%, and 13%, respectively ($p < 0.001$); 5-year PFS of 55%, 39%, and 0%, respectively ($p < 0.0001$); and 5-year OS of 73%, 51%, and 0%, respectively ($p < 0.0001$). This research was originally published in *Blood* [12]

[2,19], although the prognostic importance of this has not been well studied. Landgren *et al*. reported that older patients who received adriamycin–bleomycin–vinblastine–dacarbazine (ABVD)-based chemotherapy with a relative dose intensity (RDI) of >65% had significantly improved OS versus RDI of ≤65% ($p = 0.001$) [5]. Unfortunately, a minority of patients tolerated (received) an RDI of >65%. Finally, the achievement of initial complete remission (CR) has been shown to be strongly predictive of survival. In a recent large prospective phase II study of VEPEMB for newly diagnosed older HL patients, Proctor *et al*. documented that achievement of CR was the only factor that predicted OS in multivariate analyses [13]. Similarly, achievement of CR was an important factor in our Chicago series (data not included in original publication [12]: lack of initial CR, OS hazard ratio 6.15, $p < 0.0001$). This likely relates in part to the poor tolerability of more aggressive salvage therapy (e.g. stem cell transplant) for older HL patients.

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Treatment

A standard treatment paradigm is lacking for older HL patients. Decreased tolerance, increased toxicity, and factors such as fragility and co-morbidities pose a significant challenge in implementing aggressive treatment regimens for older HL patients. There has been a number of retrospective series (Table 1) and a handful of prospective clinical trials published over the past several years (Table 2) that have examined the treatment of older HL patients.

Prior studies

Internationally, the most common chemotherapeutic regimen for younger HL patients is ABVD. However, when ABVD is given with curative intent to patients aged >60–65 years, chemotherapy-related toxicities may be prohibitive (especially bleomycin-related) [2,3,8,9,12]. Five-year OS for older patients on the ABVD-based randomized CALGB 8251 trial was 31% versus 79% for patients aged <40 years ($p < 0.0001$) [9]. Levis *et al.* analyzed the outcome of 65 patients aged ≥65 years who received a registry-recommended protocol of ABVD/mechlorethamine–vincristine–procarbazine–prednisone (MOPP) or ABVD/MOPP therapy [8]. Eight-year event-free survival (EFS) and OS rates were 41% and 46%, respectively, both significantly inferior compared with patients aged <65 years. Further, a critical factor associated with sub-optimal survival was the treatment-related mortality (TRM) rate of 23% associated with ABVD/MOPP-based therapy.

Intensive regimens, such as bleomycin–etoposide–adriamycin–cyclophosphamide–oncovin–procarbazine–prednisone (BEACOPP), are too toxic for older HL patients. The German Hodgkin Study Group (GHSG) treated 75 newly diagnosed advanced stage HL patients aged 66–75 years in the randomized study ($HD9_{elderly}$) comparing *baseline*-BEACOPP regimen with cyclophosphamide–vincristine–procarbazine–prednisolone (COPP)/ABVD [20]. There were no remission or survival differences between the regimens with pooled 5-year freedom from treatment failure and OS rates of 46% and 50%, respectively. Furthermore, the TRM associated with baseline-BEACOPP was 21% (8% with COPP/ABVD).

Efforts to improve outcomes for older HL patients have included decreased chemotherapy intensity as well as regimens with individualized dosing in an attempt to mitigate toxicity. Levis *et al.* studied a less intensive regimen, chlorambucil–vinblastine–procarbazine–prednisone/cyclophosphamide–etoposide–bleomycin (CVP/CEB), that resulted in less frequent treatment interruptions and lower TRM [21]. Indeed, the CR rate was 73%; however, relapse rates were high with a 5-year relapse-free survival rate of

Table 2. Prospective studies for older HL patients (post-2000)

Author, year published	No. pts	Median age in years	AS (%)	Treatment	TRM	Survival
Macpherson, 2002	38	72	100%	ODBEP	0	5-year OS 42%
Levis *et al.* 2004 [16]	105	71 (mean)	54%	VEPEMB	3%	5-year OS 64%
Ballova *et al.* 2005 [20]	68	70	100%	COPP/ABVD vs BEACOPP- baseline	BEACOPP 21%, COPP/ABVD 9%	5-year OS: COPP/ABVD 50%, BEACOPP 50%
Kolstad *et al.* 2007 [23]	29	71	62%	CHOP +/- RT	7%	3-year OS: ES: 91%; AS 67%
Klimm *et al.* 2007 [11]	89	66	37%	COPP/ABVD + EFRT or IFRT	NR	5-year OS: EFRT 59%, IFRT 81%
Proctor et al 2012 [13]	103	73	70%	VEPEMB	7%	3-year OS: ES: 81%; AS 66%
Evens *et al.* 2013 [3]	44	65	100%	ABVD vs Stanford V	9%	5-year OS: 58%
Boll *et al.* 2013 [19]	117	65	0 (all ES)	ABVD + IFRT	5%	5-year OS 81%

Abbreviations: No, number; AS, advanced-stage; ES, early-stage; TRM, treatment-related mortality; OS, overall survival; RT, radiation therapy; IFRT, involved field radiation therapy; EFRT, extended field radiation therapy; ODBEP, vincristine, doxorubicin, bleomycin, etoposide, prednisolone; VEPEMB, vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone, and bleomycin; COPP, cyclophosphamide, vincristine, procarbazine and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; NR, not reported.

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43%. Levis *et al.* also reported results from a prospective study with VEPEMB [16]. For advanced-stage patients, the CR rate was 58%, while the FFS and OS rates were 34% and 32%, respectively.

Anthracycline is likely an important component of therapy for older HL patients [22]. In a retrospective analysis, the Nebraska Lymphoma Study Group studied chlorambucil–vinblastine–procarbazine–prednisone (ChlVPP) with or without doxorubicin–bleomycin–vincristine (ABV) in older HL patients. The overall response rate was superior for patients treated with ChlVPP/ABV versus ChlVPP as was 5-year EFS (52% vs 24%, respectively) and 5-year OS (67% vs 30%, respectively).

Current data

The GHSG studied the regimens bleomycin–doxorubicin–cyclophosphamide–vincristine–procarbazine–prednisione (BACOPP) and prednisone–vinblastine–doxorubicin–gemcitabine (PVAG) through two recent phase II studies for untreated older HL patients. With BACOPP, the CR rate was 85%, and the 3-year progression-free survival (PFS) and OS were 60% and 71%, respectively. However, the regimen was associated with substantial toxicity with 30% experiencing early termination (87% with grade 3–4 adverse events), and the TRM was 12%. PVAG was developed in part to eliminate the need for bleomycin or dacarbazine therapy by substituting prednisone and gemcitabine. The CR rate was 78%, and the 3-year PFS and OS rates were 58% and 66%, respectively. Therapy was better tolerated with a TRM rate of 2%.

Kolstad *et al.* reported encouraging results using cyclophosphamide–adriamycin–oncovin–prednisone (CHOP) for older HL patients [23]. They treated 29 patients with CHOP-21 (early-stage: 2–4 cycles with involved field radiotherapy (IFRT); advanced-stage: 6–8 cycles ±IFRT). The CR rate was 93%, and with 41-month median follow-up, the 3-year PFS and OS rates for advanced-stage patients were 67% and 72%, respectively. In addition, Proctor *et al.* reported findings from the largest prospective study conducted to date for older HL patients—known as the Study of HL in the Elderly/Lymphoma Database (SHIELD) project [13]. They treated 103 older HL patients with VEPEMB, of which 72 patients had advanced-stage disease. The 3-year PFS and OS for advanced-stage patients were 58% and 66%, respectively.

We recently reported findings on a subgroup analysis of patients treated on the North American Intergroup trial E2496 [3]. E2496 was a phase III study that randomized advanced stage HL patients to ABVD versus Stanford V. Of the 794 eligible patients, 45 were aged ≥60 years. There were no survival differences between ABVD and Stanford V for older HL patients. Further, toxicities were mostly similar between chemotherapy regimens for older patients, although the incidence of bleomycin lung toxicity (BLT) was 24% with an associated BLT death rate of 18%. Notably, 91% of BLT cases occurred with ABVD. The treatment arms were pooled and stratified for exploratory analyses to compare outcomes on the basis of age. The TRM was significantly higher for older versus younger HL patients (i.e. 9% versus 0.3%, $p < 0.001$). Moreover, survival was markedly lower for older patients with 5-year FFS rates of 48% versus 74%, respectively ($p = 0.002$), and 5-year OS rates of 58% and 90%, respectively ($p < 0.0001$) as shown in Figure 1.

Interestingly, however, time-to-progression (TTP) was not significantly different between age groups (i.e. 5-year TTP: 68% vs 78%, respectively). The latter finding was partly due to the higher cumulative incidence of death without progression in older HL patients (i.e. 22% vs 9%, respectively, $p < 0.0001$, at 5 years). Towards this end, we performed a 'competing risk' survival analysis; this is particularly salient because a straightforward Kaplan–Meier method results in biased estimates of the risk of progression. The Kaplan–Meier method assumes all events are independent such that all events other than the event of interest (e.g. FFS) are censored (e.g. TRM). In E2496, the incidence of progression including competing risks for older HL patients at 2 and 5 years were 19% and 30%, respectively, versus 19% and 23%, respectively, for younger patients ($p = 0.30$) (Figure 4), whereas the incidence of death without progression for older patients at 2 and 5 years were 13% and 22%, respectively, versus 2% and 9%, respectively, for younger patients ($p \leq 0.0001$). These and prior data [17]

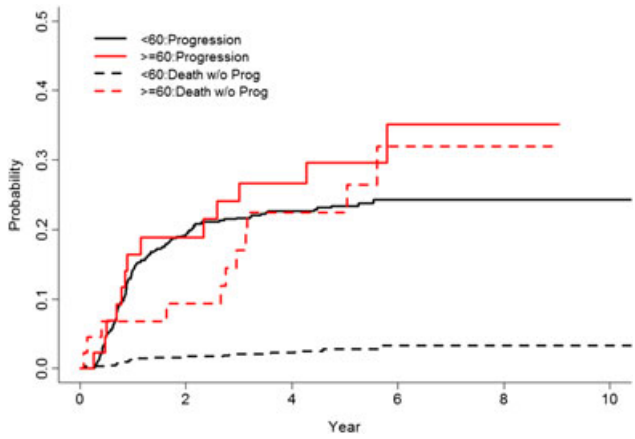

Figure 4. Competing risk survival analysis for older versus younger Hodgkin lymphoma patients. The rates of progression were determined with competing risk analysis because death without progression is a competing risk for disease progression. The incidence rates of progression including competing risks for patients aged ≥60 years at 2 and 5 years were 19% and 30%, respectively, compared with 19% and 23%, respectively, for patients aged <60 years ($p = 0.30$); however, the incidence rates of death without progression for patients aged ≥60 years at 2 and 5 years were 13% and 22%, respectively, compared with 2% and 9%, respectively, for patients aged <60 years ($p = <0.0001$). Modified from original figure; reprinted with permission [3]

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suggest that a significant component of the age-dependent survival difference in HL is due to non-HL events.

Early-stage data

Böll *et al*. recently reported data on 117 older early-stage HL patients treated on two phase III GHSG trials, HD10 and HD11 [19]. They compared data for older versus younger patients treated on these two randomized early-stage HL studies. They documented a TRM rate of 5% for older patients versus 0.3% for patients aged <60 years ($P < 0.001$). Furthermore, the 5-year PFS and OS rates were 75% and 81%, respectively, for older patients versus 90% and 97%, respectively, for younger HL patients. These survival rates are higher compared with a series of early-stage older HL patients treated primarily with radiotherapy (5-year OS 55%) [24], and they appeared comparable with a prior GHSG study that used COPP/ABVD followed by IFRT [25]. In the latter trial, outcomes were improved for older patients who received IFRT versus extended-field radiotherapy. There is also VEPEMB data in early-stage HL patients. Levis had reported a 5-year FFS and OS of 79% and 94%, respectively [16], while Proctor *et al*. recently documented 3-year PFS and OS rates of 74% and 81%, respectively, for 31 early-stage older HL patients treated with 3 cycles of VEPMB followed by radiation [13].

Future strategies

The first step to continue to improve outcomes for older HL patients will be the design of clinical trials specifically for this patient population, as recently has been done [13,26]. Furthermore, there needs to be a continued effort to identify therapeutic regimens that maintain efficacy but are more tolerable. This may potentially be achieved through the integration of novel therapeutic agents such as brentuximab vedotin (e.g. NCT01476410 and NCT01716806) or lenalidomide (e.g. NCT01056679) in lieu of or in combination (or sequence) with standard chemotherapy (Figure 5).

In addition, there should be a concerted effort to include the assessment of co-morbidities and functional status for older HL patients, especially with prospective clinical trials. This should include consideration for the design of HL clinical trials that utilize objective criteria (e.g. Cumulative Illness Rating Scale for Geriatrics for co-morbidity assessment) to allow flexible and patient/functional-specific treatment regimens as has recently been carried out in older patients with diffuse large B-cell lymphoma and chronic lymphocytic leukaemia.

Off of a clinical trial, we advocate treatment with either AVD (i.e. standard ABVD dosing without bleomycin), VEPMB, or PVAG with the choice of regimen being dependent on physician and patient preference. The number of cycles and use of adjunctive radiation should be given according to paradigms similar to younger HL patients. Furthermore, full supportive care measures should be implemented including granulocyte-colony stimulating factor (G-CSF) according to guidelines. However, it is important to highlight that caution should be applied in administering G-CSF if a bleomycin-based regimen is being given. Pre-clinical data and retrospective analyses have strongly suggested that the occurrence of BLT is increased when G-CSF is used concurrently with bleomycin [4,12].

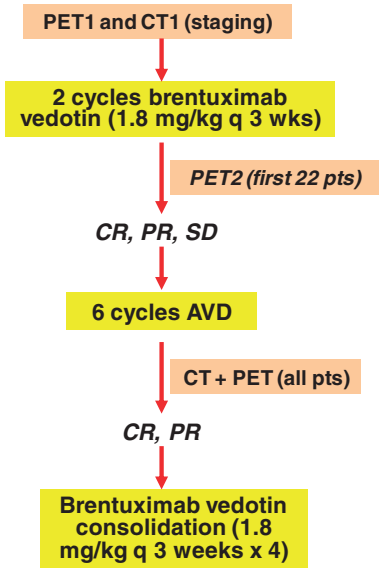

Figure 5. Phase II clinical trial schema for newly diagnosed older Hodgkin lymphoma patients. This is a recently initiated phase II investigator-initiated study for newly diagnosed older Hodgkin lymphoma patients with stage II–IV disease (NCT01476410). There is a lead-in component with single-agent brentuximab vedotin, which is sequentially followed by doxorubicin, vinblastine, and dacarbazine (AVD) chemotherapy for non-progressing patients. This is followed by consolidation with single-agent brentuximab vedotin. Participating sites include Northwestern University, Memorial Sloan-Ketterring, MD Anderson Cancer Center, Stanford University, University of Nebraska, the Ohio State University, and the University of Massachusetts Medical School

Conclusion

Although outcomes have improved over time, older HL is a disease entity in which survival rates remain disproportionately inferior compared with younger patients. Further, it represents a population that is under-represented in HL prospective clinical studies and no standard treatment recommendations exist. Generally, treatment of older HL patients for all disease stages should be given with curative intent; however, caution should be given to potential serious treatment-related toxicity, including TRM. Bleomycin-containing therapy such as ABVD is associated with

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pulmonary toxicity, and intensive regimens such as BEACOPP are too toxic, whereas less intensive regimens such as CVP/CEB and ChlVPP are less effective. Recent prospective studies examining the VEPEMB and PVAG regimens reported encouraging results, however further progress is needed. Finally, the impact of patient co-morbidities and assessment of functional status needs to be examined in prospective studies, while the integration of novel therapeutic agents into older HL treatment paradigms is ongoing.

Conflict of interest

The authors have no competing interest

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