bjh review

The treatment of older Hodgkin lymphoma patients

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Summary

The outcome of patients with Hodgkin lymphoma (HL) has dramatically improved over the past decades and continues to improve with the development of novel targeted therapies, such as the immunoconjugate brentuximab vedotin and the checkpoint inhibitors nivolumab and pembrolizumab. Moreover, with the use of response-adapted strategies using positron-emission-tomography (PET), the overall intensity of treatment for most patients can be reduced, resulting in less acute and late toxicity. However, these advances are mainly restricted to younger patients, as advances in patients above the age of 60 years ('older' patients) have been much less pronounced. Furthermore, about one third of all HL patients are among the older population, but only 5–10% of the patients treated in current HL clinical trials are ≥60 years old. HL in older patients is characterized by aggressive disease and unfavourable prognostic features as B symptoms and predominance of advanced stages. In addition, tolerance to curative chemotherapy is drastically reduced in older patients resulting in excessive toxicity and insufficient treatment due to therapy delays and dose reductions. Therefore, there is a significant unmet medical need in older HL patients for less toxic and effective therapies, and an important gap of knowledge concerning this growing population of patients. Recent advances on epidemiology, characteristics and treatment of older HL patients will be summarized in this article.

Keywords: Hodgkin lymphoma, older patients, elderly, brentuximab vedotin, checkpoint inhibitors.

To date, most young patients with first diagnosis of classical Hodgkin lymphoma (HL) are cured with chemo- and radiotherapy owing to consequent treatment within clinical trials and the constant refinement of stage-adapted treatment strategies (Eichenauer *et al*, 2018). Current strategies focus on the reduction of late toxicities, such as secondary malignancies and cardiovascular toxicity, by reducing treatment, incorporating novel substances substituting chemotherapy, refining radiotherapy techniques and by the use of positron emission tomography (PET) as a means to allow response-adapted treatment (Engert *et al*, 2010; Borchmann *et al*, 2017; Eichenauer *et al*, 2018). However, most of these advances have been restricted to younger patients, as older patients are mostly treated outside clinical trials and recruitment in trials specifically designed for older HL patients has been challenging over the past decades (Stark *et al*, 2002; Böll *et al*, 2011; Proctor *et al*, 2012). Although HL is often considered a disease of young adults, epidemiological data from registry studies indicates that about one third of all patients with first diagnosis of HL is above the age of 60 years (Björkholm *et al*, 2018). This population of patients is commonly considered 'older', due to the fact that these patients clearly represent a specific population with distinct features in comparison to younger patients (Engert *et al*, 2005; Evens *et al*, 2013; Björkholm *et al*, 2018). Given the demographic change in the western hemisphere, the proportion and absolute number of older HL patients is expected to increase over the next years (Weir *et al*, 2015).

Several differences in presentation between younger and older HL patients have been described, including a different predominant histology in older patients, with more patients diagnosed as mixed cellularity HL and less patients diagnosed as nodular sclerosis HL (Mir *et al*, 1993; Weekes *et al*, 2002; Engert *et al*, 2005; Evens *et al*, 2012). In addition, more older patients are diagnosed with advanced-stage HL, B Symptoms and Epstein–Barr virus (EBV)-positive HL (Jarrett *et al*, 2005). In contrast, mediastinal involvement and bulky lymphoma are less common in older compared to younger patients (Engert *et al*, 2005; Klimm *et al*, 2007). One important characteristic in older HL patients is their low tolerance to treatment due to pre-existing comorbidities, resulting in dose reductions, therapy delays and, ultimately, excessive treatment-related toxicity and mortality (Proctor *et al*, 2012; Böll *et al*, 2013a, 2016; Zallio *et al*, 2016; Björkholm *et al*, 2018). Remarkably this increased vulnerability towards therapy-associated toxicity is not restricted to patients above the age of 60 years but treatment-related toxicity and mortality is increased even at the age of 40 or 50 years compared to younger patients (Wongso *et al*, 2013; Björkholm *et al*, 2018). In a recent retrospective study of 3402 patients treated

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with eBEACOPP (escalated-dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone), patients aged >40 years who had poor performance status (Eastern Cooperative Oncology Group [ECOG] performance status of 2 or Karnofsky performance status <80%) and patients age >50 years were at highest risk for treatment-related mortality, particularly due to neutropenic infection (Wongso *et al*, 2013). Similarly, data from a recent Swedish registry study extending over 40 years suggest a lack of continued improvements in survival among HL patients aged 45–69 years since 2000 (Björkholm *et al*, 2018) (Fig 1).

In summary, there is an unmet medical need in older HL patients for therapies targeted specifically at the aggressive HL biology and considering the vulnerability towards therapy-associated complications.

Epidemiology and characteristics

Only about 5–10% of patients included in clinical trials are aged ≥60 years. For example, of 4959 HL patients included in six clinical trials by the German Hodgkin Study Group (GHSG) between 1988 and 1998, only 372 (9%) were ≥60 years old (Engert *et al*, 2005). Similarly, in the North American intergroup trial E2496 comparing first line regimens in advanced stage HL, only 45 of 794 included patients (6%), were aged ≥60 years (Evens *et al*, 2013). Therefore, HL is often perceived as a disease of young patients and most clinical trials in adult patients report a median age in the mid-thirties (Radford *et al*, 2015; Borchmann *et al*, 2017; Connors *et al*, 2018). However, this reflects the neglect of older patients in clinical trials rather than the true age distribution, as registry data consistently report a much higher proportion of older patients (Proctor *et al*, 2009; Björkholm *et al*, 2018).

A registry study conducted by the British Scotland and Newcastle Lymphoma Group (SNLG) showed a proportion of 20% (624) older patients out of 3373 patients in the registry with an increasing proportion for the later decades of life (Proctor *et al*, 2009). Similarly, the age-specific incidence was 1·97/100 000 for patients aged 60–69 years and 2·18/100 000 for patients aged 70 or older in the Northern UK regional survey of older HL patients (Proctor *et al*, 2009). In a more recent Swedish population-based study including 7997 HL patients diagnosed between 1973 and 2013, about

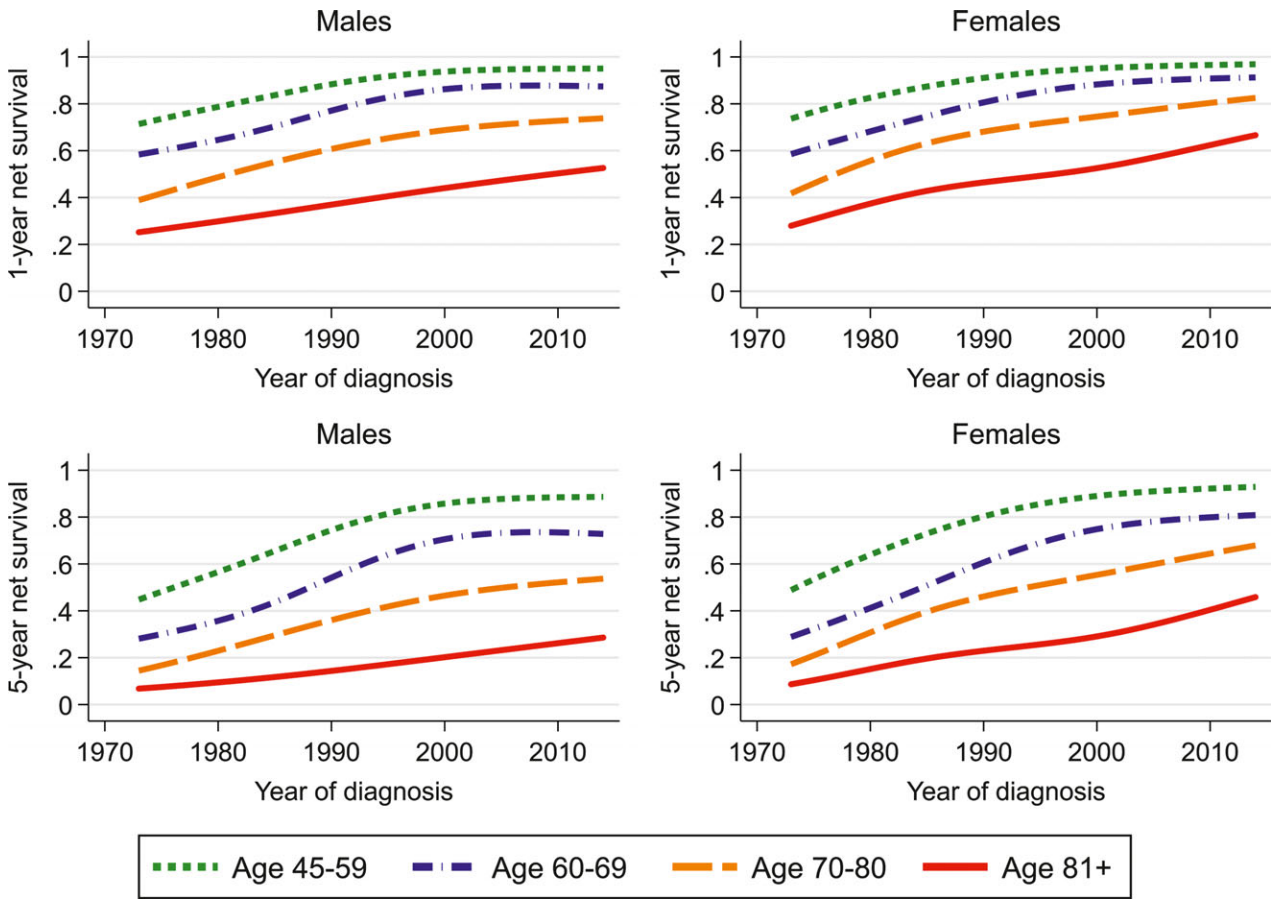

Fig 1. Temporal trends in 1- and 5-year net survival for Hodgkin lymphoma patients in Sweden. Estimates are from a flexible parametric model fitted to the first 6 years of follow-up for patients aged 45 years and older at diagnosis. Reproduced with permission from Björkholm *et al.* (2018). ©2018 John Wiley and Sons.

one third of the patients (34%) were ≥60 years of age and incidence rates remained stable for the older patients in the last decades (Björkholm *et al*, 2018) (Fig 1). Interestingly, the authors observed an increase of older patients with advanced-stage disease. This is consistent with several studies showing a higher proportion of patients with advanced-stage disease and B symptoms in older patients (Engert *et al*, 2005; Proctor *et al*, 2009). In addition, a distinct distribution of histological subtypes with more older patients diagnosed with EBV-positive HL and with mixed cellularity subtype compared to younger patients was reported (Stark *et al*, 2002; Engert *et al*, 2005; Jarrett *et al*, 2005). In addition to intolerance to therapy and comorbidities, these disease characteristics might explain the inferior outcome of older patients.

Staging and initial assessment

As in younger patients, choice of treatment modality and intensity in older patients are based on initial staging, usually with the use of fluorodeoxyglucose (FDG)-PET-computed tomography (CT) and classification into risk groups (Eichenauer *et al*, 2018). However, in older patients, comprehensive geriatric assessment should be included into the work-up routine, as comorbidities and pre-existing organ dysfunctions might preclude curative polychemotherapy. In addition, comorbidities do not only guide treatment decisions, but also have a prognostic impact (Proctor *et al*, 2012).

Previous studies focusing on older HL patients showed severe comorbidities in the majority of older patients and patients with comorbidities were less likely to receive polychemotherapy and had a lower survival rate (van Spronsen *et al*, 1999; Zallio *et al*, 2016). Evens *et al* (2012) investigated a cohort of 95 HL patients with a median age of 67 years (range, 60–89 years) in a multicentre retrospective study over a period of 10 years (1999–2009). In their analysis, 61% of the patients had significant comorbidity, defined as a Cumulative Illness Rating Scale (CIRS) score of 3–4, and 17% had a geriatric syndrome, defined as presence of dementia, delirium, depression, osteoporosis, incontinence, falls, failure to thrive and/or neglect/abuse (Evens *et al*, 2012). Moreover, 13% had loss of activities of daily living (ADLs) and the loss of ADLs at initial diagnosis was a particularly strong unfavourable prognostic factor as 3-year survival in patients ≥70 years of age with loss of ADLs was 0% (Evens *et al*, 2012).

The prospective multicentre SHIELD study (Study of Hodgkin lymphoma in the Elderly/Lymphoma Database) in HL patients ≥60 years of age evaluated clinical features and outcome in a cohort of 175 patients, including the objective assessment of comorbidity using a modified Adult Comorbidity Evaluation 27 (ACE-27) comorbidity scale, ADLs and instrumental ADLs (Proctor *et al*, 2012). Interestingly, among many other findings in this study, of 116 patients considered for polychemotherapy by the treating physicians, 13 (11%) were assessed as frail using the objective comorbidity scale. Moreover, frailty and ECOG performance status, but not age, were factors significantly associated with complete remission (CR) after chemotherapy. None of the 13 patients considered frail using the comorbidity rating scale achieved CR on any form of therapy and all of these patients died during the study period (Proctor *et al*, 2012).

Therefore, part of the initial assessment in elderly patients, in addition to recent and past medical history, thorough clinical examination and staging procedures, should include formal co-morbidity assessment, screening for frailty and assessment of ADLs. Most current trials focusing on older HL patients implement comprehensive geriatric assessment to guide treatment decisions and identify patients who are unlikely to benefit from, or not tolerate, chemotherapy (Björkholm *et al*, 2011).

Treatment

Early stages

Although staging definitions slightly differ between various study groups worldwide, early-stage disease can be further classified as favourable or unfavourable risk depending on further risk factors, such as large mediastinal masses and number of involved nodal areas (Klimm *et al*, 2013; Eichenauer *et al*, 2018).

In young early-favourable-stage patients, commonly defined as stages I–II without risk factors, two cycles of ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) followed by 20 Gy involved-field radiotherapy (IF-RT) is internationally accepted as standard of care based on results of the GHSG HD10 trial (Engert *et al*, 2010; Sasse *et al*, 2017). Recently, some groups have advocated the use of FDG-PET after chemotherapy as a means to omit radiotherapy in early-favourable stage HL with PET-negative restaging after ABVD (André *et al*, 2017).

Although results are excellent in younger patients, older early-stage HL patients treated with ABVD followed by RT had higher rates of protocol deviation, lower dose intensity and higher severe toxicity, resulting in higher treatment-related mortality compared to younger patients in a recent large subgroup analysis of patients treated within prospective GHSG trials (Böll *et al*, 2013a). Importantly, although 88% of the older patients had a complete response in this analysis, 3% of the older patients had progressive disease, 11% relapsed, and 28% died within the observation period. This resulted in a 5-year PFS of only 79% (95% confidence interval [CI]: 67–87%) in older patients compared to 96% (95% CI: 93–97) in younger patients (Böll *et al*, 2013a).

In early-unfavourable-stage patients, commonly defined as stages I–II with risk factors, treatment intensification using regimens, such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone), has been proposed in younger patients (Von Tresckow *et al*, 2012) in order to increase efficacy and avoid

relapse. However, intensified treatment is not feasible in older patients, because the GHSG HD9 elderly study showed excessive treatment-related mortality in older advanced stage patients treated with BEACOPP, even at standard dose level (Ballova *et al*, 2005). Similarly, the use of extended-field radiotherapy (EF-RT) compared to IF-RT after four cycles chemotherapy in early-unfavourable-stage patients resulted in poorer outcome and more toxicity in patients, with overall survival (OS) of 59% compared to 81% ($P = 0{\cdot}008$) after 5 years for older patients treated with EF-RT and IF-RT, respectively (Klimm *et al*, 2007).

Therefore, four cycles of chemotherapy followed by localized radiotherapy are widely regarded as standard of care in older early-unfavourable-stage HL patients and ABVD is frequently chosen as chemotherapy. Although ABVD is commonly well tolerated in younger patients, this regimen is associated with considerable toxicity in older patients, particularly bleomycin-induced lung toxicity (BLT). For example, among the 45 older HL patients enrolled in the prospective randomized E2496 study, 11 (24%) developed BLT, of whom 2/11 (18%) died due to acute pulmonary fibrosis/respiratory failure (Evens *et al*, 2013). Regarding the risk of BLT, a recent study compared the feasibility, toxicity and efficacy of AVD (adriamycin, vinblastine and dacarbazine) or ABVD in 287 older early-stage HL patients treated within the GHSG HD10 and HD13 trials (Engert *et al*, 2010; Behringer *et al*, 2015; Böll *et al*, 2016). Rates of early treatment termination and grade 3–4 toxicity were similar in patients receiving two cycles of AVD and two cycles of ABVD (grade 3–4 toxicity in 40% and 39%, respectively). However, 18% of the patients receiving four cycles of ABVD terminated therapy early and toxicity was considerably higher in patients receiving four cycles of ABVD (≥ grade three toxicity: 65%). Moreover, while BLT was rare in patients receiving two cycles of ABVD or AVD, 10% (7/69) of the patients randomized to four cycles of ABVD experienced severe BLT, including fatal three cases (Böll *et al*, 2016). These results implicate a high risk of severe toxicity and limited benefit in older HL patients receiving more than two cycles of bleomycin. Moreover, the risk of severe toxicity might outweigh the possible benefits of bleomycin in terms of efficacy in older patients, particularly if bleomycin is administered for more than two cycles.

Several trials tested regimens other than ABVD in older early stage HL patients, including the VEPEMB schedule (vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone and bleomycin) specifically designed for older patients (Levis *et al*, 2004; Zallio *et al*, 2016) and the well-established NHL-derived CHOP regimen (Kolstad *et al*, 2007; Björkholm *et al*, 2018). However, although the evidence is limited due to small patient numbers, in these trials, no regimen thus far was better tolerated with equal or better efficacy than ABVD.

In an attempt to reduce treatment toxicity, younger early-stage HL patients with negative FDG-PET after ABVD were randomized to either continue standard treatment with irradiation or to proceed without radiotherapy in two very similar prospective randomized trials (Radford *et al*, 2015; André *et al*, 2017). Both trials included only a few elderly patients and do not allow specific conclusions about the older population. However, both trials failed to show noninferiority of the PET-adapted approach compared with the standard combined modality treatment (Radford *et al*, 2015; André *et al*, 2017). Moreover, the omission of radiotherapy based on PET-CT mainly aims at reducing the rate of secondary malignancies, which might not be a priority in older HL patients, as secondary malignancies generally develop up to decades after therapy (Schaapveld *et al*, 2015). Importantly, in a recent large National Cancer Database analysis of 3795 older early-stage HL patients, multivariate analysis, showed that the combination of chemotherapy and radiotherapy resulted in improved OS compared with monotherapy (Goyal *et al*, 2017). The OS rate after a median follow-up of 40·4 months in patients treated with combined modality treatment was 78% compared with 58% and 54% for patients receiving chemotherapy and radiotherapy alone, respectively ($P < 0{\cdot}0001$) (Goyal *et al*, 2017). Therefore, the benefit of radiotherapy as consolidation in elderly patients needs to be balanced against possible toxicity in an individual.

Advanced stages

Ann Arbor stages III–IV and stages II with B symptoms and other risk factors, such as bulky mediastinal involvement or extranodal disease, are commonly defined as advanced stages (Eichenauer *et al*, 2018).

In younger advanced-stage HL patients, intensive treatment using 4–6 cycles of eBEACOPP and PET-guided radiotherapy results in an excellent 5-year PFS of 89% (95% CI: 88–91) and 5-year OS of 96% (95% CI: 95–97) as recently reported in the GHSG HD18 trial (Borchmann *et al*, 2017). In older patients, however, treatment with six to eight cycles of BEACOPP, even at a baseline dosage, resulted in toxic death in up to 21% of the patients in the HD9elderly trial (Ballova *et al*, 2005). BACOPP (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone), a modified BEACOPP regimen without etoposide, was highly effective in older advanced-stage HL patients, with CR achieved in 85% of 60 patients treated in a phase II trial, but toxic deaths occurred 12% of the patients (Halbsguth *et al*, 2010).

Recently, the combination of brentuximab vedotin with AVD (A-AVD) was compared to ABVD in a large randomized trial in an attempt to gain the highest possible efficacy in the international randomized phase-III ECHOLON-1 study (Connors *et al*, 2018). The primary end-point, modified PFS (mPFS; time to progression, death or incomplete response and use of subsequent anticancer therapy) after 2 years, was significantly higher in the A-AVD compared to the ABVD group with mPFS of 82% (95% CI: 79–85) and

77% (95% CI: 74–80), for A-AVD and ABVD, respectively. However, the mPFS showed that the subgroup of older patients did not benefit from A-AVD [hazard ratio (A-AVD vs. ABVD): 1·0 (0·6–1·7)] (Connors *et al*, 2018). In addition, A-AVD caused increased severe toxicity in older patients, including febrile neutropenia in more than one third of the patients (37%) (Borchmann *et al*, 2018; Connors *et al*, 2018).

All these results indicate that intensification beyond conventional ABVD-based chemotherapy is associated with excessive toxicity.

Several earlier trials evaluated regimens in older advanced-stage HL patients that aimed to reduce chemotherapy-associated toxicity (Proctor *et al*, 2009; Björkholm *et al*, 2011). Although some of these regimens induced less toxicity, these earlier attempts failed with regard to their efficacy. Some crucial findings, however, emerged from these earlier trials: the role of anthracyclines and the importance of high relative dose intensity (RDI). The Nebraska Lymphoma Study Group evaluated two regimens in a non-randomized retrospective study: the ChlVPP regimen, containing chlorambucil, vinblastine, procarbazine and prednisolone, and the hybrid regimen ChlVPP/doxorubicin, bleomycin, and vincristine (ABV) (Weekes *et al*, 2002). In 56 patients ≥60 years of age, 5-year OS was 30% and 67% for patients receiving ChlVPP and ChlVPP/ABV, respectively ($P = 0{\cdot}0086$), indicating improved efficacy for the anthracycline-containing regimen (Weekes *et al*, 2002). Along the same line, Landgren *et al* (2003) analysed the long-term outcome of 59 consecutive older (>60 years) HL patients diagnosed between 1973 and 1994 in the area of Stockholm, Sweden. They found, that older patients who received ABVD-based regimens with a RDI >65% had a significantly better OS ($P = 0{\cdot}0011$) than those who were treated with ABVD-based chemotherapy with a RDI ≤65%, or an anthracycline-free regimen, irrespective of RDI (Landgren *et al*, 2003).

The GHSG developed the gemcitabine-based regimen PVAG, substituting bleomycin and dacarbazine from the ABVD regimen with prednisone and gemcitabine (Böll *et al*, 2011). In this small phase II study including 55 older advanced-stage HL patients, one patient (2%) died of treatment-related toxicity and the overall tolerability of 6–8 cycles of chemotherapy was moderate with grade 3–4 toxicity in 75% of the patients. Efficacy was promising in this small study as responses included 78% CRs and 3-year PFS and OS were 58% and 66%, respectively (Böll *et al*, 2011).

As described above, the reduced-intensity regimen VEPEMB was developed specifically targeted at older HL patients and evaluated by the Italian Lymphoma Group with promising results a phase II study (Levis *et al*, 2004) and a British multicentre trial incorporating comprehensive geriatric assessment (Proctor *et al*, 2012). However, a follow-up randomized phase-III study comparing VEPEMB with ABVD in HL patients >65 years, who were considered fit according to an initial comprehensive geriatric evaluation, did not confirm these earlier results (Zallio *et al*, 2016). In the trial including 37 older advanced-stage HL patients, treatment-related mortality occurred in 4% of the patients in both arms of the study and five-year PFS rates were 48% and 70% for VEPEMB and ABVD, respectively (Zallio *et al*, 2016).

In summary, several smaller studies have not yet achieved a balance between sufficient efficacy to treat advanced-stage HL in elderly patients without associated toxicity and treatment-related mortality, putting patients at risk of harm (Proctor *et al*, 2009; Björkholm *et al*, 2011, 2018). Therefore, 6–8 cycles of ABVD are often regarded as standard of care in advanced-stage elderly HL patients, although efficacy, tolerability and survival rates are much lower in older compared to younger patients (Ballova *et al*, 2005; Evens *et al*, 2013). In the randomized North American Intergroup Trial E2496, 5-year OS for elderly patients was 58% compared to 90% in younger patients, using either ABVD or the alternative regimen Stanford V (doxorubicin, vinblastine, chloromethine, vincristine, bleomycin, etoposide and prednisone) (Evens *et al*, 2013). Importantly, in line with previous findings of fatal BLT in 5–20% of older patients treated with ABVD, Evens *et al* (2013) reported a BLT rate of 24% in older patients and a BLT-related mortality rate of 18%. As a recent GHSG analysis of older early-stage HL suggests, the risk of BLT increases with the number of ABVD cycles applied. In 287 patients analysed, BLT was rare in patients receiving two cycles of either ABVD or AVD, but occurred in 7/69 (10%) of patients randomized to receive four cycles ABVD, including three fatalities (Böll *et al*, 2016). This ABVD-associated risk of BLT probably reflects the clinical scenario outside clinical trials, as a retrospective analysis including older patients with mostly advanced-stage HL found that pulmonary toxicity was the most frequent toxicity, with a total incidence of BLT of 27%, and that five of the seven patients who died of pulmonary toxicity had received more than two cycles of ABVD (Stamatoullas *et al*, 2015). Taken together, these finding suggest a high risk of severe toxicity and limited benefit in older advanced-stage HL patients receiving bleomycin-containing regimens, such as ABVD, particularly in excess of two cycles. Therefore, the omission of bleomycin after two cycles ABVD at the latest, seems reasonable to avoid toxicity in older patients – even more so, as the omission of bleomycin with PET-negative restaging after two cycles of ABVD resulted in reduced toxicity without loss of efficacy in a recent study in younger advanced-stage HL patients (Johnson *et al*, 2016). In addition to the choice of chemotherapy, close monitoring and screening for signs of toxicity, pre-phase therapy to reduce tumour load and supportive measures, such as granulocyte-colony stimulating factor, might be helpful in older patients to avoid and manage hazardous toxicity.

Novel substances

As conventional chemotherapy is often accompanied by severe toxicity in elderly HL patients, the use of novel non-

chemotherapeutic compounds with known activity in HL is one obvious strategy to overcome the limitations of ABVD and other current treatments for older HL patients. These compounds include the immunoconjugate brentuximab vedotin (Younes *et al*, 2012a); immunomodulatory substances, such as lenalidomide (Böll *et al*, 2010; Fehniger *et al*, 2012); the mammalian/mechanistic target of rapamycin (mTOR)-inhibitor, everolimus (Johnston *et al*, 2018); histone deacetylase inhibitors, such as panobinstat (Younes *et al*, 2012b); the inhibitor of PI3Kδ, idelalisib (Gopal *et al*, 2017) and several others compounds. As a limitation for the application in older patients, the clinical trials evaluating these novel compounds in relapsed/refractory HL (RR-HL) patients have mainly focused on younger patients, precluding any solid conclusions on the tolerability of these substances in older patients.

The immounoconjugate brentuximab vedotin targets the CD 30 antigen, which is highly expressed on Hodgkin-Reed-Sternberg cells, the malignant cell population in HL. Brentuximab vedotin as single agent was well tolerated in studies including RR-HL patients after high dose chemotherapy and autologous stem-cell transplantation (ASCT), inducing responses in 75% of the patients, with a CR in 34%.

Moreover, in a follow-up analysis of 34 patients who obtained CR after treatment with brentuximab vedotin, 16 (47%) remained progression-free after a median of 53·3 months (range: 29·0–56·2 months) of observation and 12 of the 16 patients remained progression-free without a consolidative allogeneic stem cell transplant. As mentioned below, available data on older patients suggests that combination therapy with conventional chemotherapy or other non-chemotherapeutic compounds is necessary to achieve long-lasting remissions with brentuximab vedotin (Forero-torres *et al*, 2016; Friedberg *et al*, 2017). In this regard, a Nordic Lymphoma Group-GHSG intergroup trial recently completed recruitment in the B-CAP trial, combining brentuximab vedotin with cyclophosphamide, doxorubicin and prednisone, for elderly advanced-stage HL patients (Cliicaltrials.gov NCT02191930).

Recent findings on the molecular pathogenesis of HL have shown a frequent elevated expression of ligands and receptors driving T cell inhibition in HL namely the PD-1/PD-L1 ligand (also termed PDCD1/CD274) signalling system (Green *et al*, 2010). This overexpression is mainly driven by alterations of chromosome 9p24.1 resulting in PD-L1 overexpression (Roemer *et al*, 2016). Consequently, antibodies against PD-1 have shown remarkable efficacy in relapsed/refractory HL and compounds, such as nivolumab and pembrolizumab, are therefore likely candidates for older patients (Ansell *et al*, 2015; Younes *et al*, 2016; Chen *et al*, 2017). Although, again, trials testing nivolumab and pembrolizumab included only a few older patients, the antibodies had little toxicity compared to chemotherapy, and trials testing combinations brentuximab vedotin and nivolumab are currently recruiting (Herrera *et al*, 2018).

Frail patients

A significant proportion of older HL patients is considered frail by their treating physician at first presentation, and might not tolerate chemotherapy and radiotherapy. Notably, the vast majority of the clinical trials evaluating treatment strategies in older HL patients exclude patients with severe comorbidity and organ dysfunction and therefore data specific to the treatment of frail older HL patients are sparse (Proctor *et al*, 2009). However, several studies in older HL patients indicate that severe comorbidities are present in the majority of older HL patients and therefore most trials conducted in older HL patients might not be representative of the general population of older HL patients (van Spronsen *et al*, 1999; Evens *et al*, 2012; Proctor *et al*, 2012).

Although different methods have been proposed, assessment of frailty has consistently demonstrated added value in the prediction of outcome in patients with haematological malignancies (Abel & Klepin, 2018). Irrespective of the methods used, such assessment should ideally consider several domains of frailty, including comorbidity, psychological health, current quality of life, medication burden, physical health, cognitive function and social support. Some recent studies evaluating treatment in older HL patients have used comprehensive geriatric assessment to either exclude patients with frailty or geriatric syndromes who were unlikely to tolerate intensive treatment (Proctor *et al*, 2012; Zallio *et al*, 2016), or to stratify patients to different treatment modalities (Proctor *et al*, 2012).

In the aforementioned VEPEMB study, Zallio *et al* (2016) used co-morbidity according to the CIRS, the ADL index, index of Instrumental Activity of Daily Living and Geriatric Depression Scale (GDS). Patients were defined as frail and excluded from the study, if they met one or several of the following conditions: age ≥80 years, ≥3 grade 3 comorbidities or ≥1 grade 4 comorbidity according to the CIRS scale, ADL score <6 and/or geriatric syndrome. Proctor *et al* (2012) applied a modified ACE-27 comorbidity scale, ADLs and instrumental ADLs in the prospective multicentre SHIELD study. Patients designated as 'non-frail' on the comorbidity assessment were assigned to the phase 2 VEPEMB protocol and patients designated as 'frail' were included in the registration arm of the study and treated at their physician's discretion (Proctor *et al*, 2012).

Although both studies added valuable data on patients considered non-frail and treated with VEPEMB, the results allow only limited conclusions on the optimal treatment of frail patients, because frail patients were either excluded (Zallio *et al*, 2016) or treated according to the treating physician's discretion (Proctor *et al*, 2012).

Remarkably, although many, if not the majority, of the older HL patients in the general population meet the criteria for frailty, only very recently have clinical trials been initiated particularly targeting frail patients. Forero-torres *et al* (2016)

investigated brentuximab vedotin as an upfront treatment in a prospective multicentre phase-II trial including older HL patients, who were either ineligible for frontline conventional combination treatment of HL using standard approaches, such as chemotherapy with ABVD, according to the investigator's judgment or had declined the available chemotherapy options after being informed of the potential benefits and risks. About two thirds (63%) of the 27 patients included in the trial had stage III or IV disease, 14 patients (52%) had been deemed ineligible for treatment with conventional multi-agent chemotherapy by the investigator. Regarding geriatric assessment, 81% (22 patients) were impaired in at least one aspect, 67% (18 patients) reported being 'limited a lot' for one or more physical activities and 52% (14 patients) reported having significant comorbidities. Patients received a median of eight cycles of brentuximab vedotin 1·8 mg/kg every 3 weeks over a period of 3–23 months, with dose delays in 52% and permanent dose reductions to 1·2 mg/kg in 41% of the patients. Concerning haematological toxicity, no cases of thrombocytopenia or febrile neutropenia were reported and grade 2–3 anaemia and neutropenia were reported for two patients each. Grade 3 toxicity was reported in 48% of the patients, and of note, neuropathy was common, with grade 3 peripheral sensory neuropathy in seven patients (26%) and peripheral motor neuropathy in two patients (7%). Treatment was highly effective with an overall response rate of 92% (95% CI: 74·9–99·1), a CR rate of 73% (95% CI: 52·2–88·4%) and tumour size reductions in all patients treated. However, median duration of response was only 9·1 months and only 3/17 patients experienced a PFS longer than 12 months (Forero-Torres *et al*, 2016). In continuation of the study, brentuximab vedotin was combined with either dacarbazine or bendamustine in 42 older HL patients. Brentuximab vedotin combined with bendamustine was effective in 20 treated patients (CR rate 88% and overall response rate 100%), but caused severe toxicity in the majority of the patients (Friedberg *et al*, 2017). A total of 65% of the patients experienced adverse events and two of the patients (10%) died due to treatment-induced toxicity, resulting in discontinuation of the brentuximab vedotin plus bendamustin arm of the study. The combination of brentuximab vedotin with dacarbazine was better tolerated, however the CR rate was only 62% and the median PFS was 17·9 months (Friedberg *et al*, 2017).

In summary, a significant proportion of older HL patients at first presentation is unlikely to benefit from conventional chemotherapy due to comorbidity and frailty increasing the risk of therapy-related toxicity. These patients are candidates for novel non-chemotherapeutic substances and clinical studies evaluating combination therapies.

Relapsed and refractory HL

Given the higher rate of therapy-associated complications that often result in insufficient treatment at first diagnosis of HL, progression or relapse of HL is common among older patients. This is particularly relevant in advanced-stage patients, given that dose reductions and cumulative toxicity increases with the intensity of the necessary treatment (Landgren *et al*, 2003; Evens *et al*, 2012; Böll *et al*, 2013a). The vast majority of younger patients achieves long term remission of HL (Eichenauer *et al*, 2018). In the long term, the risk of dying from treatment-related secondary malignancy or cardiovascular disease in young patients surviving HL exceeds the risk of HL recurrence (Schaapveld *et al*, 2015; Van Nimwegen *et al*, 2015). In contrast, several studies suggest that RR-HL remains the most common cause of death in older HL patients (Weekes *et al*, 2002; Landgren *et al*, 2003; Engert *et al*, 2005). Although several studies have been conducted in younger patients with RR-HL, no prospective trial or randomized comparison of different treatment strategies of RR-HL in older patients is available, thus far.

In younger patients, salvage chemotherapy followed by high dose chemotherapy (HDCT) and ASCT has become standard of care based on studies resulting in 50–60% failure-free survival or PFS at 3 years (Linch *et al*, 1993; Schmitz *et al*, 2002). Both studies showed superiority of the intensified treatment over conventional salvage in terms of PFS, which was confirmed in a recent Cochrane review (Rancea *et al*, 2014). However, both studies showing superiority of HDCT excluded older patients; the British National Lymphoma Investigation trial only included patients up to the age of 40 years (Linch *et al*, 1993) and the German HDR1 trial did not include patients older than 60 years (Schmitz *et al*, 2002). Therefore, treatment decisions in older patients are based on mostly smaller retrospective, single centre studies. Regarding the question of feasibility and efficacy of HDCT in older patients, a Canadian single centre retrospective study from the Princess Margaret Hospital in Toronto analysed 15 consecutive older HL patients (≥60 years), who underwent HDCT with etoposide 60 mg/kg and melphalan 160 mg/m^2 (Puig *et al*, 2011). Results of HDCT and ASCT in the older patients were compared with a cohort of younger patients treated in a similar manner at the same institution, showing no transplant-related deaths and no differences in terms of toxicity and outcome between both patient groups: PFS at 3 years after ASCT was 73% (95% CI 37–90) for the older group and 56% (95% CI 46–64) for the younger group ($P = 0·8$). Importantly, only patients who had completed HDCT and ASCT were included in this retrospective study; patients who were considered frail or had insufficient response to salvage therapy were excluded from the analysis (Puig *et al*, 2011). Registry data, such as the comprehensive Swedish study, suggest that only a very small minority of older patients with RR-HL proceed to HDCT and ASCT, as only 6% of the 407 reported ASCTs in the registry were performed in patients ≥60 years of age (Björkholm *et al*, 2018). The largest analysis including older RR-HL patients (≥60 years of age) with included older patients treated within GHSG first-line studies between 1993 and 2007 (Böll *et al*, 2013b). RR-HL was documented 115 older patients, of whom

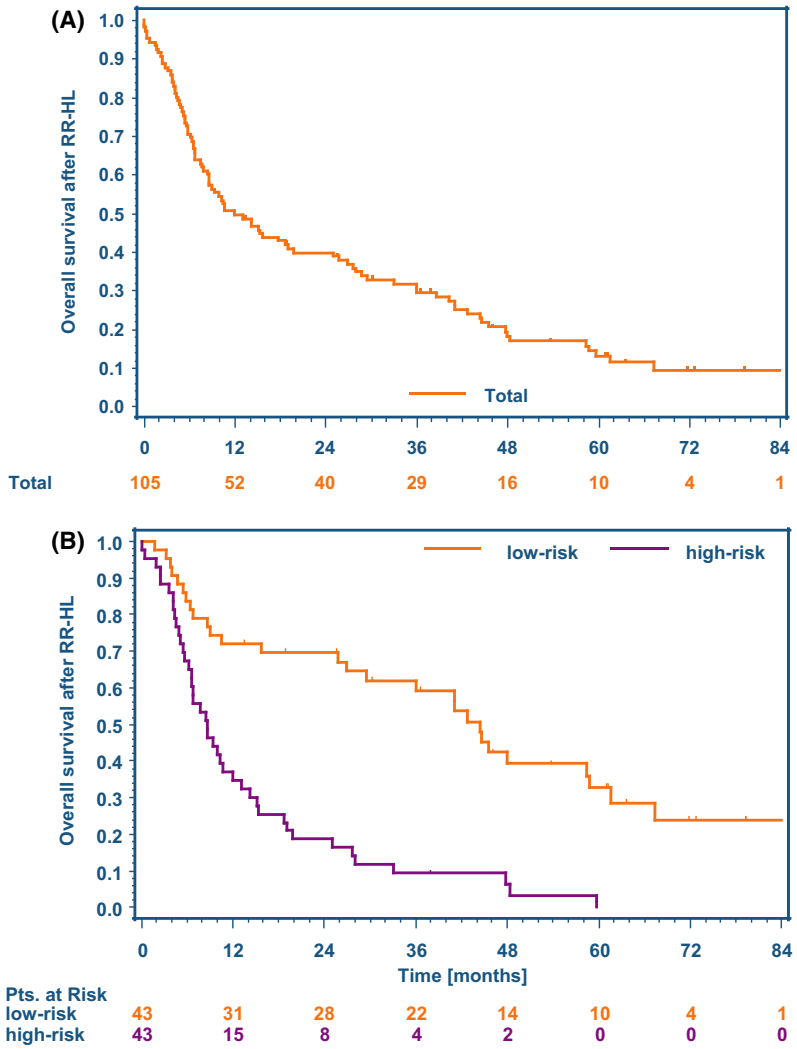

Fig 2. Survival in 115 older Hodgkin lymphoma patients after disease relapse or progression (Böll *et al*, 2013b). (A) Kaplan–Meier plot of overall survival (OS) in all evaluable patients (median OS, 12 months; 95% confidence interval [CI], 8–19 months; 3-year OS, 31%; 95% CI, 22–40%). (B) Kaplan–Meier plot of OS according to risk group (high-risk patients: 3-year OS, 11%; 95% CI: 1–22%; low-risk patients: 3-year OS, 57%; 95% CI: 40–73%). From Böll *et al*. (2013b). Reprinted with permission. © 2013 American Society of Clinical Oncology. All rights reserved.

38% had not completed first-line treatment as planned. First-line therapy was mostly incomplete because of toxicity or progressive lymphoma, again stressing the importance of dose-intense first-line treatment. More than half of the patients had progression or early relapse (28% and 31%, respectively), and the majority had clinically advanced-stage disease at progression/relapse. Notably, median OS for older patients with RR-HL was only 12 months and the 3-year OS was 31% (95% CI: 22–40%) (Böll *et al*, 2013b) (Fig 2A). Using the previously published risk factors of early relapse, clinical stage III/IV and anaemia in a score (Josting *et al*, 2002), patients could be classified into groups with a favourable (≤1 risk factor) and unfavourable (≥2 risk factors) prognosis. OS at three years was 59% (95% CI: 44–74%) and 9% (95% CI: 1–18%) in patients with ≤1 risk factor and ≥2 risk factors, respectively (Böll *et al*, 2013b) (Fig 2B). Considering the treatment strategy at relapse/progression of HL in a multivariate analysis, patients in the low-risk category had most benefit from the conventional poly-chemotherapy/salvage radiotherapy approach. Median OS for low-risk patients treated with conventional chemotherapy/radiotherapy was 61 months, compared to 6 and 9 months for patients within the same risk groups who received intensified or palliative treatment, respectively. In the high-risk subgroup, median OS was short, and no difference between the treatment groups could be detected, suggesting a limited benefit of intensified salvage treatment in patients with ≥2 risk factors (Böll *et al*, 2013b).

In conclusion, the treatment of older RR-HL patients is particularly challenging, as studies specifically addressing this group of patients are scarce and limitations, such as comorbidity and low tolerance towards treatment, can even be aggravated in the relapsed setting. Thus, there remains a

significant unmet medical need in these patients and concerted efforts with collaborations of different study groups are required to establish new strategies for older RR-HL patients.

Authorship

BB reviewed the literature and wrote the manuscript. HG reviewed the literature and revised the manuscript.

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