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ORIGINAL ARTICLE

Hodgkin lymphoma: an Australian experience of ABVD chemotherapy in the modern era

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Abstract Approximately 560 new cases of Hodgkin lymphoma (HL) are diagnosed annually in Australia. Standard first-line therapy is ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). It is unknown how survival outcomes in patients receiving ABVD in current clinical practice, with routine positron emission tomography (PET) imaging and modern supportive measures, compare with results from published trials. This is a retrospective multi-centre study of patients with previously untreated HL between November 1999 and December 2014 receiving ABVD induction. Baseline characteristics, treatment details, toxicity and outcome data were collected from hospital records. The primary endpoint was overall survival (OS). Secondary endpoints included overall response rate (ORR), progression-free survival (PFS), response to treatment and toxicity. One hundred and eighty-nine eligible patients were identified. Median age was 32 years (range 17–79). Nodular-sclerosing HL was the most common subtype (78 %), 44 % had B symptoms and 11 % had marrow involvement. Median number of cycles of ABVD administered was 6 (range 3–8). Eighteen patients (11 %) had dose delay, 21 (13 %) had dose reductions and 11 (8 %) had both. The ORR, defined predominantly by PET scan, was 96 % (CR 89 %). Five-year OS and PFS were 93 and 84 %, respectively in early disease (stage I–IIA) and 89 and 63 % in advanced disease (stage IIB, III and IV). No poor prognostic factors were identified on multivariate testing. The most common grade 3/4 toxicity was neutropenia (53 %). Our study confirms the excellent prognosis and manageable toxicity in HL patients receiving ABVD in phase III studies are reflected in patients treated in routine clinical practice in the modern era.

Keywords Hodgkin lymphoma · ABVD · Chemotherapy · Toxicity · Survival

Introduction

Hodgkin lymphoma (HL) is an uncommon lymphoma with approximately 560 new cases of classical HL diagnosed annually in Australia [1, 2]. The advent of multi-agent chemotherapy and improved approaches to radiation therapy have led to HL being one of the most curable malignancies with long-term survival rates above 90 % in early-stage disease [3]. However, a proportion of patients, particularly those with poor prognosis advanced disease, often relapse and ultimately succumb to disease [4]. The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was introduced in the mid-1970s as treatment for HL and has remained a first-line standard of care for patients with newly diagnosed HL in many countries although the optimum number of cycles and use of radiotherapy in conjunction with ABVD is still disputed [5]. Whilst ABVD has been evaluated in large-scale, phase III studies, it is uncertain whether these results are reproduced outside the context of clinical trials. This study aims to assess survival outcomes and toxicity from ABVD, for the first time, in an Australian cohort of HL.

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Methods

Patients aged ≥16 years with a diagnosis of HL who received ABVD chemotherapy between November 1999 and December 2014 were identified from an electronic pharmacy database across three large metropolitan centres. All information was obtained from patient records. Baseline data collected included gender, age, histopathological subtype, date of diagnosis, baseline computed tomography (CT) and positron emission tomography (PET) staging, bone marrow involvement, B symptoms and baseline biochemistry including erythrocyte sedimentation rate (ESR). Early disease was defined as stage IA, IB, IIA and stage II with unknown B symptoms which was encompassable in a single radiotherapy field. Patients with stage IIB, III and IV disease were considered to have advanced disease and treated with the advanced disease protocol at our institutions. Early disease was not routinely categorised into favourable and unfavourable disease as this stratification does not alter management at our institutions. The International Prognostic Score (IPS) was calculated where possible in advanced disease [6]. Treatment details including the number of cycles of ABVD, whether involved field radiotherapy was given, granulocyte colony stimulating factor (GCSF) use, dose reductions, dose delays and toxicity were documented along with details of disease relapse and survival. Dose reduction was defined as a documented, clinician-intended cessation or dose reduction of any drug by any amount whilst dose delay was a delay of any duration due to toxicity. Any toxicity documented in patient notes was recorded in addition to abnormal biochemistry and haematology results and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) where possible. The study was approved by the institutional review boards of the hospitals involved.

Statistical considerations

The primary endpoint of the study was overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response rate (ORR) and toxicity from ABVD. Lymphocyte-predominant subtype was included in toxicity analysis but excluded from OS and PFS analysis, as were patients with insufficient information regarding disease status at last known follow-up. Fisher's exact test was used to compare CR rates for statistical significance; factors analysed in univariate analysis included age (<45 versus ≥45 years), B symptoms (present versus absent), ESR ≥upper limit of normal local laboratory range (yes versus no), disease status (early stage versus advanced stage), dose delay (yes versus no), dose reduction (yes versus no) and in advanced disease, bone marrow involvement (yes versus no) and IPS (<4 versus ≥4); differences were considered significant if p values were <0.05 (two-sided). All statistically significant univariate results were assessed by multivariate analysis.

OS was measured from the date of diagnosis until death from any cause. Subjects alive were censored at date last followed up. PFS was measured from the date of diagnosis until disease progression, relapse or death from any cause. Those without disease progression at last date of follow-up were censored. Survival functions were estimated using the Kaplan-Meier method with calculation of median and five-year OS and EFS and compared using the log-rank test. The 2007 International Working Group revised response criteria was used for response assessment [7]. PET was used to stage patients and assess response at the end of treatment; however, no management was changed according to on-treatment PET results (i.e. no PET-adaptive therapy was performed).

Results

Overall, 189 eligible patients were identified between November 1999 and December 2014 (Fig. 1). Baseline characteristics and treatment details are summarised in Table 1. Both contrast-enhanced CT and PET/CT were performed at baseline in 128 patients; 8 of whom had staging increased by PET/CT assessment in comparison to contrast-enhanced CT. Eighty-one patients received adjunct radiotherapy with chemotherapy.

Data were available to evaluate response to treatment in 165 patients (Table 2). The ORR was 95 % with CR in 89 %; CR was confirmed by PET in 91 %. The CR rate was significantly lower in advanced disease compared with early disease (83 versus 97 %, $p<0.01$). A lower CR rate was associated with B symptoms (82 versus 95 %, $p=0.03$) but not with bone marrow involvement in advanced disease patients. Advanced age ($p=0.17$) and high IPS ($p=0.8$) in advanced disease did not predict for inferior CR rates.

One hundred and sixty patients were eligible for survival analysis. Median follow-up for OS and PFS was 44 months (range 1–175 months) and 37 months (1–173 months), respectively. The estimated five-year OS and PFS in the 160 patients were 91 and 71 %, respectively (Fig. 2a).

Five-year OS was 93 % (95 % CI, 76–98) in patients with early disease and 89 % (95 % CI, 78–95) in advanced disease ($p=0.09$; Fig. 2b). On univariate analysis, a statistically significant inferior OS was associated with age ≥45 years (five-year OS 84 versus 94 % for age <45, $p<0.01$); however, the presence of B symptoms (90 versus 94 %, $p=0.09$) and elevated ESR (89 versus 100 %, $p=0.14$) was not statistically significant. In the advanced disease cohort, an inferior five-year OS was associated with an IPS ≥4 (71 versus 100 %, $p<0.01$), bone marrow involvement (69 versus 90 %, $p<0.01$) and any dose change during treatment, being either delay, reduction or both (75 versus 93 %, $p<0.01$; Table 3).

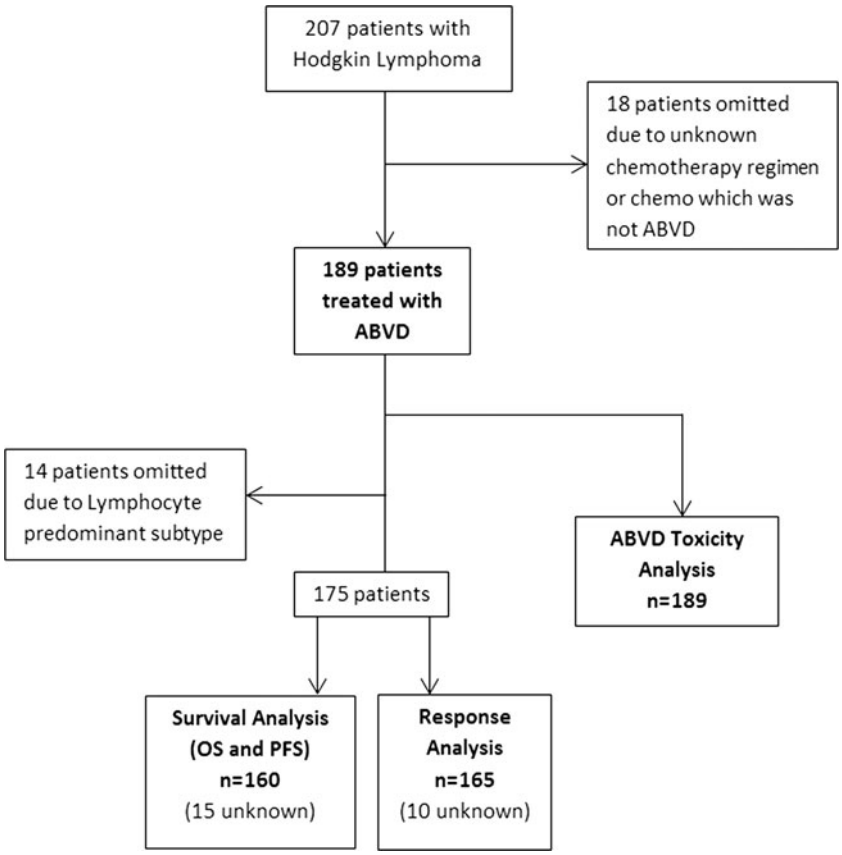

Fig. 1 Summary of patient selection. *ABVD* doxorubicin, bleomycin, vinblastine dacarbazine; *OS* overall survival; *PFS* progression-free survival

However, none of these factors predicted for worse outcomes on multivariate analysis.

In contrast to OS, the five-year PFS was significantly inferior in advanced disease compared with early disease (63 versus 84 %, $p < 0.01$; Fig. 2c). On univariate analysis, an elevated ESR (63 versus 94 %, $p = 0.04$) and presence of B symptoms (61 versus 87 %, $p < 0.01$) at presentation were also associated with an inferior PFS. In advanced disease, five-year PFS was worse in patients with an IPS ≥4 (35 versus 82 %, $p < 0.01$), bone marrow involvement (8 versus 69 %, $p < 0.01$) and any dose change (54 versus 81 %, $p = 0.05$). However, none of these were statistically significant on multivariate testing. Age did not predict for inferior PFS (61 % in patients aged ≥45 years versus 75 % in age <45, $p = 0.09$).

In total, 8 patients with early disease (8 %) and 25 patients with advanced disease (15 %) had either primary progressive or relapsed disease; 12 of these patients had an initial partial response or primary progressive disease with 21 patients in initial CR relapsing at a later date. The median time-to-relapse following first-line treatment in patients with early disease was 13 months (3–39 months) compared to 15 months (range 2–43 months) in advanced disease. In the patients in PR at completion of ABVD, four were monitored with no further treatment required (three advanced disease, one early stage disease) and six patients progressed and proceeded to subsequent salvage chemotherapy plus autologous stem cell transplant (ASCT) (five advanced stage, one early stage disease). Fourteen of the 22 patients who relapsed/progressed following an initial CR to ABVD proceeded to salvage chemotherapy plus ASCT. Eighteen of 22 patients who received ASCT had CR (64 %) however 2 patients subsequently relapsed and died. Of the 19 patients (11 %) who had partial response or primary progressive disease following ABVD, 14 proceeded to salvage chemotherapy plus ASCT.

Toxicity analysis was conducted on 189 patients (Table 3) although not all patients were completely evaluable. Mild anaemia was the most common toxicity overall, but neutropenia was the most common grade 3–4 toxicity (53 %), with similar rates in early (53 %; 40/76) and advanced disease (54 %; 49/91). Forty-six percent of all patients received GCSF support. Only one septic death occurred in the context of febrile neutropenia. Thirteen percent of evaluable patients (21/157) had dose reduction, 11 % (18/162) had a dose delay and 8 % (11/132) had both. The most common reasons for dose delay were febrile neutropenia (12/29) and pulmonary toxicity (9/29). The most common reason for dose reduction was pulmonary toxicity (20/32), followed by febrile neutropenia (7/32). Amongst the 25 patients who had pulmonary toxicity, 23 patients had either dose reduction or delay and 10 patients went on to have radiotherapy. All pulmonary

Table 1 Baseline patient characteristics

Baseline characteristics (%)	
$n = 189$ (%)	
Age, years	
Median (range)	32 (17–79)
≥45 (%)	47 (25)
Gender (%)	
Male	96 (51)
Female	93 (49)
HL subtype	
NS	148 (78)
MC	13 (7)
LP	14 (7)
Unclassified	14 (7)
Stage at diagnosis	
I	20 (11)
II	107 (57)
III	30 (16)
IV	30 (16)
Unknown	2 (1)
Disease status	
Early disease	85 (45)
Advanced disease	102 (54)
Unknown	2 (1)
B symptoms	
Yes	69 (37)
No	89 (47)
Unknown	31 (16)
Bone marrow involvement in advanced disease	
Yes	14 (8)
No	67 (65)
Unknown/not recorded	21 (28)
Hasenclever score in advanced disease ($n = 96$)	
0	4 (4)
1	11 (11)
2	18 (19)
3	21 (22)
4	18 (19)
5+	12 (13)
Insufficient data to calculate	12 (13)
Chemotherapy	
ABVD	180 (95)
AVD	7 (4)
modified ABVD	2 (1)
Early disease	
≤4 cycles ABVD	51 (60)
5–6 cycles ABVD	32 (38)
Unknown	2
Advanced disease	
≤4 cycles of ABVD	13 (13)
5–6 cycles of ABVD	88 (86)
Unknown	1
Radiotherapy + ABVD (81/189)	
4 cycles of ABVD	55 (29)
≥6 cycles of ABVD	26 (14)

NS nodular-sclerosing, *MC* mixed cellularity, *LP* lymphocyte-predominant

toxicity occurred during or immediately following chemotherapy; no clinically significant pulmonary toxicity was diagnosed after radiotherapy delivery. Nineteen patients developed peripheral neuropathy but only four subsequently had a dose reduction of vinblastine. There was no documented grade 3 or 4 cardiac toxicity. Two patients (1 %) developed subsequent malignancies; both were early-stage colorectal cancer.

Twelve of the 160 evaluable patients died: eight from HL (primary disease progression in five and subsequent to relapse in three), one neutropenic sepsis and three from transplant-related toxicities (one sepsis, two graft versus host disease). No deaths occurred from cardiac disease, pulmonary toxicity or second malignancies. Of note, five of the deaths occurred >5 years following initial diagnosis—including two of the transplant-related deaths and three disease-related following multiple lines of therapy.

Discussion

ABVD has been the accepted standard of care for first-line treatment of HL for at least three decades in many regions of the world [5, 8]. Outcomes have improved over time, presumably due to better supportive care measures, more accurate staging and response assessment with functional imaging and increased options for relapsed disease [3]. The standard regimen for most patients in Australia is 2–4 cycles of ABVD + IFRT for early-disease HL, and 6 cycles of ABVD in advanced disease. BEACOPP is an alternative, particularly for patients under 60 years of age, which offers improved disease control rates compared to ABVD at a cost of increased acute and late toxicity with conflicting data on overall survival benefit, largely due to the late effects of BEACOPP and lack of studies using overall survival as the primary endpoint [9–13]. Several studies have reported improved progression-free survival with BEACOPP compared to ABVD and ABVD-like regimens; however, with longer follow-up, this may differ. In the 10-year follow-up of the German HD9 study, overall survival was superior with escalated BEACOPP compared to COPP-ABVD; however, both arms had similar rates of secondary malignancy (5–6 %) and COPP-ABVD is known to have increased toxicity compared to ABVD alone with no proven equivalent efficacy, hence is not a current standard [12]. In the only long-term follow-up of a study comparing BEACOPP to ABVD alone, there was no difference in PFS or OS at 10 years between the two regimens, which is likely due to the low rate of second malignancies in the ABVD arm (0.9 % compared to 6.7 % with BEACOPP) and the success of salvage treatment in the higher proportion of ABVD patients who relapsed [13]. A meta-analysis, which recently concluded that 6 cycles of escalated BEACOPP significantly improve OS compared with ABVD 'and other regimens', did not use individual patient data and included only

Table 2 Treatment outcomes

	Complete response *n* (%)	Partial response *n* (%)	Overall response rate *n* (%)	Progressive disease *n* (%)
All patients *n* = 165	147 (89)	11 (7)	158 (96)	8 (4)
Early stage *n* = 73	71 (97)	2 (3)	73 (100)	0
Advanced stage *n* = 92	76 (83)	8 (9)	84 (92)	8 (9)
PET response *n* = 147	133 (90)	9 (6)		5 (4)
Early stage *n* = 67	65 (97)	2 (3)	67 (100)	0
Advanced stage *n* = 80	68 (85)	7 (9)	75 (94)	5 (6)

PET positron emission tomography

one study that randomised patients to 6 cycles of escalated BEACOPP which recruited patients 5–10 years after those recruiting patients to ABVD/ABVD-like regimens with only 4 years median follow-up [14]. Based on these large published reports, in line with most centres in the USA and UK, the three institutions in this study use ABVD as the main first-line regimen. Despite ABVD being a longstanding upfront therapy, this is the first Australian study, to our knowledge, to assess survival outcomes and toxicity in a cohort of HL patients and one of the largest to review the use of ABVD in the routine clinical setting outside the context of a trial.

The varying definitions of early and advanced disease are problematic in directly comparing the outcomes in our study with published results from a trial setting [15]. Moreover, differences in outcome may reflect discrepancies in fitness and age between trial and non-trial patient populations, the former being subject to the bias from fulfilling trial eligibility criteria. With these obvious caveats, the five-year OS in our study in both early and advanced disease is comparable with published trials [3, 16–19].

Recognising that our early-stage patients have not been categorised into favourable versus unfavourable disease, with respect to PFS, in the early disease cohort, the 5-year PFS of 84 % (95 % CI, 70–92) is numerically lower than both the early favourable disease patients in the German HD10 study receiving four cycles of ABVD and 30 Gy radiotherapy (94 %; 95 % CI, 90–96) and the early unfavourable patients in the HD14 study (89 %; 95 % CI, 86–92) [16, 20].

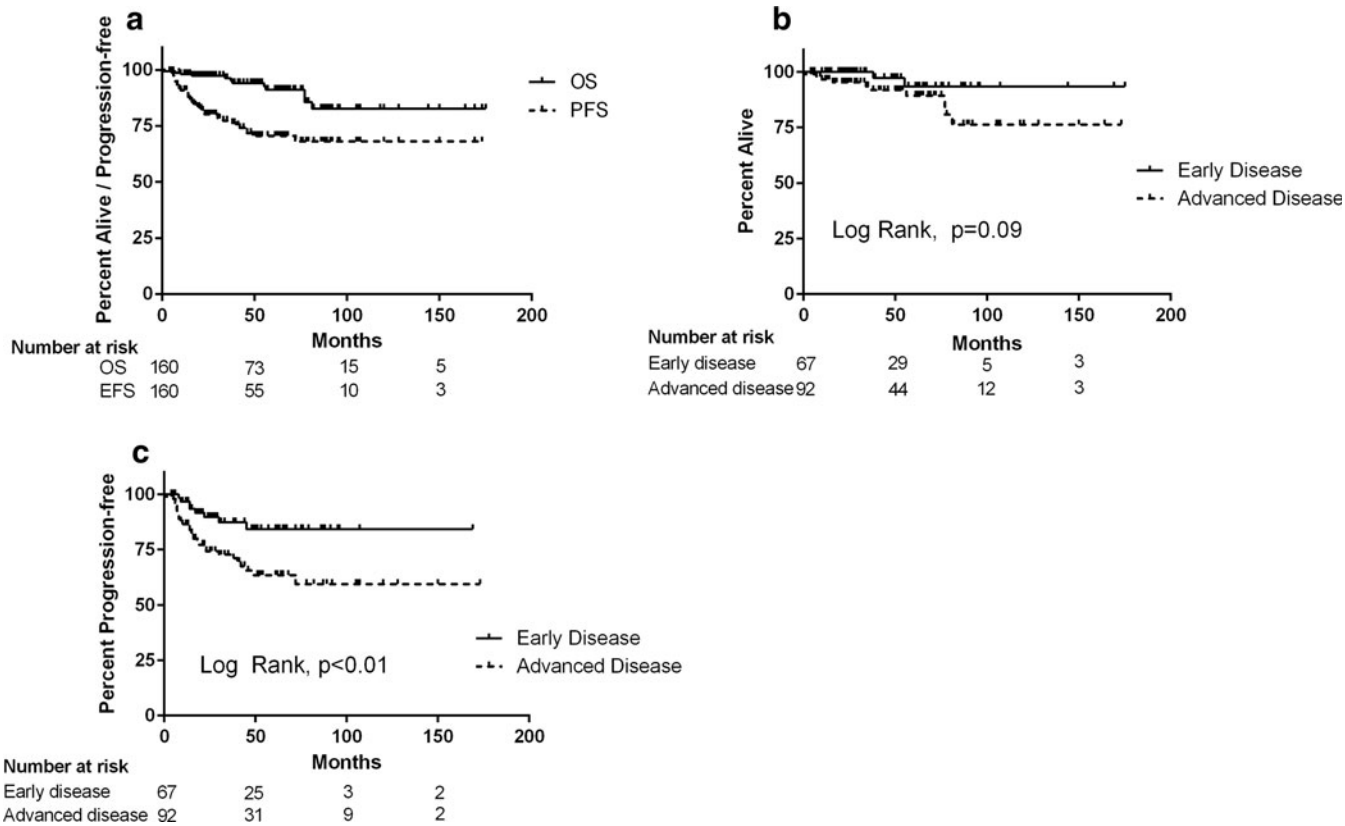

Fig. 2 Survival. **a** Overall and progression-free survival. **b** Overall survival according to stage. **c** Progression-free survival according to stage

Table 3 Toxicity analysis

Acute toxicity, $n = 189$	All grades n/evaluable patients[a] (%)	Grade 3 or 4 n/evaluable patients[a] (%)
Anaemia	135/169 (80)	6/169 (4)
Thrombocytopenia	31/170 (18)	6/170 (4)
Neutropenia	128/168 (76)	89/168 (53)
GCSF support	78/168 (46)	
Febrile neutropenia	20/160 (13)	
Renal impairment	4/150 (3)	0
Non-neutropenic infection[b]	42/158 (27)	N/A
Lung toxicity[b]	25/172 (15)	N/A
Cycles ≤3	22/172 (13)	
Cycles >3	3/172 (2)	
Neuropathy[b]	19/155 (12)	N/A
Nausea or vomiting[b]	105/157 (7)	N/A
Stomatitis[b]	34/154 (22)	N/A

(%) is the percentage of those who had documentation of presence or absence of relevant toxicity

[a] Evaluable patients = number of patients able to be assessed for this toxicity

[b] Unable to be graded so only recorded as 'all grades'

In advanced disease, the five-year PFS of 63 % (95 % CI, 51–74) also appears numerically lower than those in published randomised studies, which range from 71–76 %. All confidence intervals quoted overlap with that in our analysis [9, 18, 19, 21]. Our inclusion of patients who would have been trial-ineligible may be a factor contributing to the lower PFS, as similarly illustrated by a recent retrospective series from Slovenia in 314 HL patients with advanced disease which reported comparable five-year OS (76 %) to published trials but lower five-year PFS (62 %) respectively [22].

One of the study objectives was to determine the rates of toxicity with ABVD in a clinical setting and the decisions made by physicians relating to dose reductions or delays. Reporting of toxicity in retrospective studies relies on consistent, detailed documentation and, therefore, our rates of adverse events are potentially under-represented; however, we used results of investigations where possible to minimise this bias. The main haematological toxicity was grade 3–4 neutropenia, with the incidence of 53 % comparable with observed rates in other studies in advanced disease [10]. However the 53 % grade 3–4 neutropenia in our early-disease population was considerably higher than the 23 % reported in two other studies of early disease [16, 20]. This disparity could be attributed to reluctance to dose modify or delay in clinical care and/or the practice at one of our centres of only administering GCSF in patients who experience febrile neutropenia. Despite the rate of GCSF use (46 %) being considerably lower than in some other studies (75 %) [18], few neutropenic patients in our cohort developed infectious sequelae.

Pulmonary toxicity of any grade occurred in 15 % with the majority occurring in the first 3 cycles and resulting in dose reductions/delays of bleomycin in 23 of the 25 patients. Due to the retrospective nature of the study, it was not possible to accurately grade the severity of lung toxicity, but the rates we report are similar to the reported 10–21 % pulmonary toxicity of any grade in published studies [17, 18]. Of note, all diagnoses of pulmonary toxicity were made during or immediately following chemotherapy delivery, before any radiotherapy was delivered so it can be assumed all lung toxicity in our cohort was due to bleomycin. No serious cardiac complications or deaths from second malignancies occurred, although we note that follow-up is currently inadequate to fully assess this.

A limitation to determining the specific reasons for dose delay or reduction was the co-existence of multiple toxicities. In this study, patients with advanced disease who also had dose delay and/or reduction had poorer outcomes, but this did not reach statistical significance on multivariate analysis, suggesting other confounding factors potentially contribute to this in our population. A much larger study of the patients recruited to HD12 and HD15 trials [23] showed no difference in outcomes associated with dose reductions of bleomycin and vincristine. Bleomycin was the most commonly omitted or reduced drug in our cohort, followed by vinblastine; however, in elderly patients recruited to another study, dose intensity of less than 65 % was associated with inferior survival [24].

In conclusion, our study confirms the excellent overall survival and acceptable toxicity of first-line ABVD chemotherapy in patients with HL and is consistent with reports from large phase III studies. Improvements in outcome may occur with better selection of patients for more intensive therapies using PET-directed approaches and newer molecular characterisation techniques, and modifications to combination chemotherapies such as ABVD and the alternative regimen

escalated BEACOPP. The potential use of non-bleomycin regimens in the elderly [25] and replacement of bleomycin with brentuximab vedotin, an antibody drug conjugate targeting CD30, is currently under investigation in both early [26] and advanced disease [27], although these are yet to be proven superior to ABVD or BEACOPP in a randomised phase III trial. Incorporation of programmed cell death 1 monoclonal antibodies [28], reduced irradiation doses and new radiotherapy techniques including involved nodal irradiation may also result in reductions in relapse and long-term toxicity, respectively. However, in the interim, based on our results, we continue to favour ABVD chemotherapy at our institutions for the majority of HL patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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