Classical Hodgkin's lymphoma: past, present and future perspectives

Hodgkin's lymphoma treatment is a modern medical success story. Historically, staging involved invasive laparotomies, chemotherapy was highly emetogenic, and radiotherapy extensive. Cure was possible, but morbidity high. Now trials aim to maximize cure, minimize toxicity and introduce exciting targeted therapies.

In 1832, Thomas Hodgkin, a British pathologist, described seven patients who died with enlarged lymph nodes and splenomegaly (Hodgkin, 1832). He speculated that this may represent a primary disease process of these tissues rather than a reactive process. The first description of the microscopic appearance of the affected tissues occurred in the late 1800s. A curious giant bilobed cell was recognized as a hallmark of Hodgkin's lymphoma and named the Reed–Sternberg cell after its discovering pathologists (Sternberg, 1898; Reed, 1902). Historically, Hodgkin's lymphoma has been at the forefront of cancer medicine and provided a proof of principle that cancer could be cured.

In the 1950s, Hodgkin's lymphoma began to be cured with radiotherapy alone after pioneering work by Henry Kaplan, one of the first clinicians to use linear accelerators to deliver high energy, focused radiotherapy. Hodgkin's lymphoma proved to be responsive to single-agent chemotherapy in the 1940s and multi-agent chemotherapy in the 1960s (mechlorethamine, vincristine, procarbazine, prednisolone; MOPP), leading to 80% complete response rates with 68% remaining disease free at 10 years (DeVita et al, 1980).

The introduction of another regimen, ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) marked a step forward, improving survival and reducing toxic effects including infertility, second malignancies and myelosuppression when compared to MOPP (Canellos et al, 1992). Modern treatment of Hodgkin's lymphoma is now considered a major success story of modern haemato-oncology with early-stage disease being cured in 90%, and even 70–80% with advanced disease being cured. Given these excellent results, trials now focus on treatment de-escalation, individualizing treatment where possible to avoid late, potentially fatal side effects, and using targeted therapies.

Epidemiology and pathogenesis

Hodgkin's lymphoma is relatively rare across the entire population with an incidence of 2.7–2.8/100 000, but it is a relatively common cancer in young adults. It has a clear bimodal age distribution with peaks in those in their late 20s and those over 60 years of age. For many years, the nature of Hodgkin's disease was unclear. The cell of origin of the Reed–Sternberg cell was only elucidated about 13 years ago when micro-dissected cells were shown to have clonal rearrangement of immunoglobulin genes, confirming their B-cell origin (Marafioti et al, 2000). The demonstration of clonality resulted in a name change to Hodgkin's lymphoma. While the aetiology of Hodgkin's lymphoma remains unclear, there is a clear link with Epstein–Barr virus. The virus is found in Reed–Sternberg cells in 40% of cases of classical Hodgkin's lymphoma (Küppers, 2009). Indeed, primary Epstein–Barr virus infection results in a fourfold higher risk of developing Epstein–Barr virus-positive Hodgkin's lymphoma about 4 years after the infection (Hjalgrim et al, 2003).

Diagnosis and staging

Hodgkin's lymphoma presents as painless lymphadenopathy which is usually cervical or supraclavicular. Around half have a mediastinal mass which is normally asymptomatic but can cause dyspnoea, cough or rarely superior venal cava obstruction. B symptoms, defined as unexplained fevers over 38°C in the absence of infection, recurring and drenching night sweats and unexplained loss of >10% of body weight over the preceding 6 months, occur in 25% of cases. Other symptoms include pruritus (10–15%), alcohol-induced lymph node pain and rarely paraneoplastic icthyosis, cerebellar degeneration and nephrotic syndrome. Diagnosis is made by histological examination of an excision or core lymph node biopsy; a fine needle aspirate is insufficient.

Contrast-enhanced computed tomography of the neck, chest, abdomen and pelvis is essential for staging and negated the need for staging laparotomy and splenectomy, commonly performed in the 1970s. Recently, functional imaging with 18F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (*Figure 1*) has been combined with computed tomography. It has a strong evidence base for both accurate staging and assessing treatment response (Townsend and Linch, 2012).

Staging is based on the Ann Arbor staging system (*Table 1*). Despite being created over 40 years ago, it remains a useful prognostic tool and guides treatment strategy.

Dr Toby A Eyre *is Haematology Specialist Registrar,* **Dr Andrew J King** *is Haematology Specialist Registrar and* **Dr Graham P Collins** *is Haematology Consultant in the Department of Haematology, Cancer and Haematology Centre, Oxford University Hospitals NHS Trust, Oxford OX3 7LJ*

Correspondence to: Dr TA Eyre (toby.eyre@ouh.nhs.uk)

Bone marrow involvement occurs in 5–8%, and a staging bone marrow trephine used to be part of a standard work-up of new patients. However, involvement in early stage disease is less than 1% and given the accuracy of staging positron emission tomography-computed tomography, staging trephines are now considered obsolete.

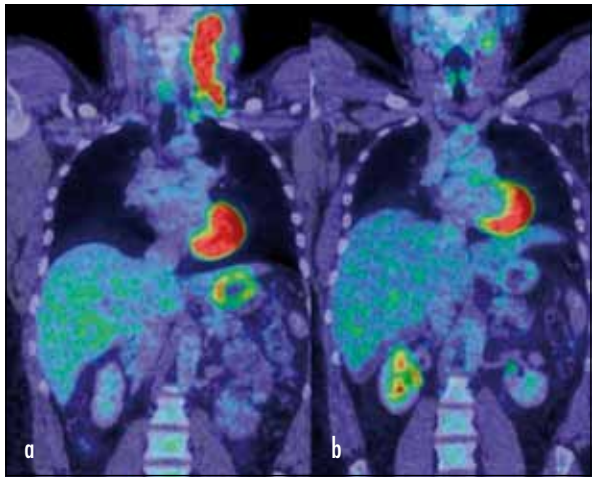
Pathology

Based upon the differences in the morphology, surface markers and composition of the cellular infiltrate, Hodgkin's lymphoma is subdivided into classical Hodgkin's lymphoma and nodular lymphocyte predominant Hodgkin's lymphoma. Nodular lymphocyte predominant Hodgkin's lymphoma accounts for 5% of cases and in some ways behaves more like an indolent non-Hodgkin's lymphoma. There is no international agreement on how to treat this condition. Some centres treat nodular lymphocyte predominant Hodgkin's lymphoma more like indolent non-Hodgkin's lymphoma whereas other units treat it in the same way as classical Hodgkin's lymphoma. This review focuses on classical Hodgkin's lymphoma.

Classical Hodgkin's lymphoma is further sub-divided into nodular sclerosis, mixed cellularity, lymphocyte-depleted and lymphocyte-rich sub-types. While these subdivisions are interesting, they do not affect management. The pathological hallmark of Hodgkin's lymphoma is the mononucleated Hodgkin cell and the multinucleated Reed–Sternberg cell. Classical Reed–Sternberg cells are large, have abundant, slightly basophilic cytoplasm and have at least two nuclear lobes or nuclei; Hodgkin cells have only one nucleus (*Figure 2*).

Hodgkin cells and Reed–Sternberg cells are positive for the cell surface marker CD30 in nearly all cases and for CD15 in the majority. They are usually negative for CD45. The malignant clone accounts for only 1–3% of tumour tissue with the majority of cells being a mixed infiltrate of eosinophils, plasma cells, and T lymphocytes (Küppers, 2009).

Figure 1. Early stage Hodgkin's lymphoma in the left cervical region as demonstrated by 18F-fluorodeoxyglucose and positron emission tomography computed tomography (a) before and (b) after four cycles of ABVD (adriamycin, bleomycin, vinblastine and darcarbazine).



Prognosis

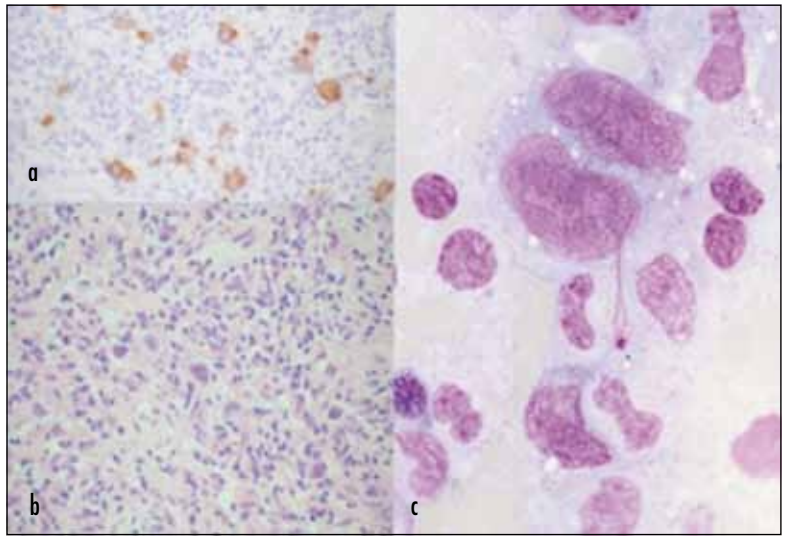
The prognosis for early stage disease (I–IIA) is uniformly excellent, with overall survival exceeding 90%. Patients with advanced stage disease (IIB–IV) can still expect to do well with an overall survival of 75–90% (Townsend and Linch, 2012).

In early stage disease, patients are classed as having favourable or unfavourable features (*Table 2*) and this guides treatment. In advanced stage, the international prognostic score (or Hasenclever score) has been used to predict prognosis (Hasenclever et al, 1998). This score is based on seven clinical and laboratory factors (*Table 3*) and when it was first developed, predicted accurately a

Table 1. The Ann Arbor staging system

Ann Arbor stage	
I	Involvement of one lymph node region or lymphoid structure
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph nodes on both side of the diaphragm
IV	Involvement of extranodal sites other than one contiguous or proximal extranodal site
Modifying features	
A	No symptoms
B	Unexplained fever >38°C in the absence of infection, drenching night sweats and unexplained loss of >10% of body weight over the preceding 6 months
X	Bulky disease (mediastinal mass larger than a third of thoracic diameter, or any nodal mass >10 cm in diameter)
E	Involvement of one contiguous or proximal extranodal site

Figure 2. a. CD30 immunohistochemical stain showed Reed–Sternberg and single-lobed Hodgkin's lymphoma cells in the bone marrow. b. Histological appearances of Hodgkin's lymphoma infiltrating the bone marrow. c. A Reed–Sternberg cell in a bone marrow aspirate.



5-year survival varying between 89% (for 0 factors) and 56% (≥5 factors). However, advances in treatment improved prognosis for all groups and the international prognostic score now has far less discriminatory power (Viviani et al, 2011).

It is likely that in the future, the response to treatment assessed by interim positron emission tomography will provide the most useful prognostic information rather than the currently used scores.

Management of the younger patient

In 2013, the overall cure rate for patients under 60 years of age is excellent. Patients are divided into early stage (I–II) and late stage (III–IV). The groups are managed quite differently.

Table 2. Prognostic factors, according to the European Organization for Research and Treatment of Cancer criteria

Favourable features	Unfavourable features
Stage I/II with <3 nodal involved areas	Stage II with >4 nodal involved areas
and age <50 years	or age >50 years
and mediastinal mass <1/3 of the thoracic diameter	Or mediastinal mass >1/3 of the thoracic diameter
and erythrocyte sedimentation rate <50 mm/hour without B symptoms	or erythrocyte sedimentation rate >50 mm/hour without B symptoms
or erythrocyte sedimentation rate <30 mm/hour with B symptoms	or erythrocyte sedimentation rate >30 mm/hour with B symptoms

from Brusamolino et al (2009)

Table 3. International prognostic score; one point for each factor

Age >45 years
Male sex
Serum albumin concentration <40 g/litre
Haemoglobin concentration <10^5 g/litre
Stage IV disease
Leucocytosis (≥15 x 10^9 white cells/litre)
Lymphopenia (<0.6 x 10^9 lymphocytes/litre or < 8% total white cell count)

from Hasenclever et al (1998)

Table 4. Important side effects of ABVD treatment

Chemotherapy	Important side effects
Adriamycin (doxorubicin)	Dose-dependent cardiotoxicity
Bleomycin	Pulmonary toxicity, exacerbated by smoking and granulocyte colony-stimulating factor injections
Vinblastine	Peripheral and autonomic neuropathy. Occasional dose adjustment required
Darcarbazine	Arm pain after infusion. Peripherally inserted central catheters lines are sometimes required

ABVD = adriamycin, bleomycin, vinblastine and darcarbazine

Early stage I–II

This encompasses a group with disease localized either above or below the diaphragm. These patients are further divided into two subgroups: the 'favourable' and 'unfavourable' (*Table 2*). Different study groups have different criteria defining risk. One example is that of the European Organization for Research and Treatment of Cancer described in *Table 2*.

These criteria have been used in clinical trials to risk stratify patients, in order to provide an appropriate risk-adapted, individualized treatment schedule. Combining involved field radiotherapy and combination chemotherapy (ABVD) is most commonly used in the UK and Europe for early stage disease. A series of large, multicentre trials have been performed with the aim of maximizing treatment overall response rates and overall survival, while minimizing toxicity.

Early stage I–II, favourable risk

Trials have focused on maintaining excellent cure rates, while attempting to de-escalate therapy. The landmark HD10 trial suggested that the standard of care is just two cycles of ABVD followed by 20 Gy involved field radiotherapy. Cure rates are excellent (>90%) and equivalent to four cycles of ABVD plus 30 Gy involved field radiotherapy (Engert et al, 2010). ABVD causes hair loss for many and myelosuppression with risk of infection. In addition, there are a number of specific drug effects (*Table 4*).

Early stage I–II, unfavourable risk

The HD11 trial (Eich et al, 2010) was a well-designed, large, randomized trial with four arms. Patients were randomized to four cycles of ABVD plus 20 Gy involved field radiotherapy, four cycles of ABVD plus 30 Gy involved field radiotherapy, four cycles of BEACOPP plus 20 Gy involved field radiotherapy or four cycles BEACOPP plus 30 Gy involved field radiotherapy. All groups had equivalent overall response rate and overall survival, apart from those who had four cycles of ABVD plus 20 Gy whose overall response rate was significantly worse. Most UK clinicians consider four cycles of ABVD plus 30 Gy to be the standard of care in this subgroup. There is still a lack of international consensus, with some clinicians favouring six cycles of ABVD with no involved field radiotherapy, and others using BEACOPP regimens.

Advanced stage: ABVD *vs* BEACOPP

Viviani et al (2011) compared six to eight cycles of ABVD with eight cycles of BEACOPP (four cycles of the dose-intense escalated regimen followed by four standard cycles in stage IIB–IV. BEACOPP (especially escalated BEACOPP) is intensive, and consists of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone. A total of 331 patients were randomized to ABVD or BEACOPP. Localized

radiotherapy as consolidation and autologous stem cell transplantation in those at relapse was permitted within the study. The trial found that the 7-year progression-free survival was 85% after BEACOPP and 73% after ABVD (P=0.004). More patients therefore required salvage treatment and an autologous stem cell transplant after ABVD, but the 7-year overall survival was not significantly different (89% (BEACOPP) *vs* 84% (ABVD), P=0.39). BEACOPP toxicity was significantly higher, with severe adverse events seen in 6%, compared with 1% if receiving ABVD. Similar results were confirmed in the HD2000 trial (Federico et al, 2009) and a Cochrane review (Bauer et al, 2011).

There is currently a lack of international consensus regarding the optimal first-line treatment for advanced stage Hodgkin's lymphoma. ABVD is favoured in the UK, some parts of Europe and the USA, whereas in Germany BEACOPP is first line. The much-needed trial that directly compares six cycles of ABVD with six cycles of escalated BEACOPP (considered the 'gold standard' by the German Hodgkin Study Group) has not been performed to date. The German Hodgkin Study Group HD15 study (Engert et al, 2012) found that six cycles of escalated BEACOPP is probably better than eight. Efficacy is similar but six cycles improves overall survival (91·9% *vs* 95·3%) by reducing acute toxicity and secondary cancers. The arguments for and against each regimen are shown in *Table 5*.

Radiotherapy

Radiotherapy is well known to increase the risk of so-called 'late effects', including breast cancer, lung cancer and heart disease. The trend over recent years is to minimize both the dose and the field size of radiotherapy in an attempt to minimize these risks. In early stage disease, a trial even suggested that omission of radiotherapy and administration of six courses of ABVD may result in improved overall survival because of a reduction in late effects (Meyer et al, 2011). However, this study used an outdated radiotherapy technique with far larger fields than would be used today. The current standard of care in early stage patients therefore remains combined modality treatment.

The use of radiotherapy following chemotherapy in advanced stage disease is controversial. Trials have attempted to answer questions about its use in positron emission tomography-positive lesions and residual bulk post-chemotherapy. The HD15 trial showed that when six cycles of escalated BEACOPP-based chemotherapy is used, consolidation radiotherapy can be omitted with no adverse outcomes in patients with a residual positron emission tomography-negative mass. This approach dramatically reduces the numbers requiring consolidation radiotherapy. Whether omission of radiotherapy based on positron emission tomography negativity after ABVD is safe remains unanswered although this practise is being increasingly adopted. Because the data are not available to suggest otherwise, most still advocate giving consolidation radiotherapy following ABVD to sites of bulk disease at presentation, or residual masses, regardless of positron emission tomography signal.

This approach is supported by the LY09 trial. Although this was a retrospective, non-randomized analysis, it demonstrated quite convincingly that in patients treated with ABVD, the progression-free survival (5-year 71% *vs* 86%) and overall survival (5-year 87% *vs* 93%) were significantly better across all prognostic groups in those that received consolidation radiotherapy (Johnson et al, 2010). Positron emission tomography assessments were not part of this study, however. Care must be taken to minimize pulmonary, thyroid and cardiac toxicity using involved field radiotherapy, especially given the risk of cardiac and pulmonary toxicity with anthracycline and bleomycin respectively in ABVD. Most radiation oncologists now are moving from involved field radiotherapy to involved site, which significantly reduces the field size.

Relapse, autologous transplantation and allogeneic transplantation

In young patients treated with ABVD, relapse is not uncommon, occurring in approximately 25% of advanced stage patients (Vivani et al, 2011). Further conventional chemotherapy has a minimal chance of producing a sustained remission and the standard of care currently is to use non-cross-reacting platinum-based chemotherapy culminating in high dose chemotherapy with an autologous stem cell transplant (Longo et al, 1992). No randomized controlled trials have compared the commonly used salvage regimens. DHAP (cisplatin, high-dose cytarabine and dexamethasone), ICE (ifosfamide, carboplatin, etoposide), and IGEV (ifosfamide, gemcitabine,

Table 5. The ABVD *vs* BEACOPP debate – for and against treatment approaches

For ABVD, against BEACOPP	ABVD is relatively non-toxic in young patients
	Low risk of infertility with ABVD, much higher risk with BEACOPP
	Less admissions with neutropenic sepsis with ABVD
	Equivalent overall survival if autologous stem cell transplantation is used as salvage in the small percentage that relapse after ABVD
	Higher risk of secondary myelodysplasia and/or acute myeloid leukaemia with BEACOPP
For BEACOPP, against ABVD	Significantly higher initial response rates
	Significantly lower relapse rates
	Less need for salvage therapy and autologous stem cell transplantation
	Predictable toxicity with BEACOPP
	Risk of secondary myelodysplasia and/or acute myeloid leukaemia in small percentage who receive an autologous stem cell transplant

ABVD = adriamycin, bleomycin, vinblastine and darcarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone

vinorelbine) are efficacious in re-inducing remission, and enhancing the collection of peripheral blood stem cells (Moskowitz et al, 2001; Josting et al, 2002; Santoro et al, 2007).

The British National Lymphoma Institute and European Group for Blood and Marrow Transplantation groups showed in two historical randomized trials that high-dose therapy using a BEAM (carmustine, etoposide, cytarabine, melphalan) autologous stem cell transplantation has superior 3-year event-free survival compared to dexa-mini-BEAM and mini-BEAM (Linch et al, 1993; Schmitz et al, 2002). Although these studies demonstrated no overall survival, this was probably because those patients progressing in the chemotherapy arm then crossed over to have high dose therapy. In carefully selected patients with good performance status, organ function and minimal comorbidities, BEAM autologous stem cell transplantation has become an excellent salvage, curable treatment. As one might expect, those that relapse early (less than 12 months) have inferior outcomes compared to late relapses.

Positron emission tomography may also have a role in prognosis at relapse, with those patients achieving positron emission tomography negativity pre-autologous stem cell transplantation having a superior outcome to those who remain positron emission tomography-positive (Moskowitz et al, 2012). Moreover, patients who relapse post BEAM autologous stem cell transplantation historically have a dismal prognosis (Martínez et al, 2013). The recent introduction of brentuximab and bendamustine (Corazzelli et al, 2013) in this setting has improved the chance of further disease control and subsequent allogeneic stem cell transplantation, using alemtuzumab-based conditioning in both sibling and unrelated donors (Peggs et al, 2007). There are no randomized trials in the setting, but undoubtedly some patients are cured with this approach.

Classical Hodgkin's lymphoma in older patients

Older patients (typically defined as those over 60 years in classical Hodgkin's lymphoma) have a poor survival. While partly explained by comorbidities, the toxic effects of treatment and the necessity for reduced treatment intensity, it also appears that the disease biology is different. Survival rates are disproportionately inferior when compared to the young (Brenner et al, 2008), being typically less than 50%. Older patients are under-represented in clinical trials and there are consequently limited good data on which to base management.

In the absence of comorbidities precluding anthracycline and bleomycin use, standard ABVD is recommended for patients younger than 70 years. In those with significant comorbidities or the elderly, non-bleomycin-containing regimens such as ChlVPP (chlorambucil, vinblastine, procarbazine, prednisolone) may be used although they are still associated with substantial toxicity. There is some evidence that AVD (bleomycin omitted to avoid lung toxicity) with granulocyte colony-stimulating factor support can produce reasonable outcomes (Canellos et al, 2004). Other options in those over 60 years include the VEPEMB (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone, and bleomycin) regimen as evaluated in the SHIELD study (Proctor et al, 2012). Although this option is not the gold standard treatment, this phase 2 study demonstrated that VEPEMB treatment results in reasonable disease control in early and advanced stage disease, with less pulmonary toxicity than ABVD. It is likely that brentuximab and bendamustine will soon influence treatment of classical Hodgkin's lymphoma in older patients and this is an important area for research in the future.

The future: maximizing cure, minimizing toxicity

Positron emission tomography-adapted approach

Positron emission tomography-computed tomography is an excellent staging modality in Hodgkin's lymphoma, and there are data to suggest its value as an early marker of treatment response and prognosis. Positron emission tomography positivity after two cycles of ABVD appears highly predictive of relapse and worse overall survival after a full six courses of the same chemotherapy, independent of the Hasenclever score (Gallamini et al, 2007). Positron emission tomography positivity pre-autologous stem cell transplantation has also been shown to be a powerful predictor of event-free survival. In the phase 2 study by Moskowitz et al (2012), those transplanted with a negative ^{18}F-FDG-positron emission tomography result after salvage had an event-free survival of >80% compared to 28.6% if the positron emission tomography remained positive (P<0.001).

This and other work has led to trials designed to modify treatment based on positron emission tomography results after two cycles of ABVD. In the UK, the RAPID and RATHL trials have fully recruited. The RAPID trial has asked whether non-bulky stage I–IIA patients who are positron emission tomography negative after three cycles can stop treatment and avoid involved field radiotherapy. Initial results suggest that this is indeed the case, although further follow up is required. The RATHL study is assessing whether bleomycin can be discontinued in IIB–IV patients who are positron emission tomography negative after two ABVD cycles. Positron emission tomography-positive patients are considered high risk and are therefore escalated to BEACOPP or escalated BEACOPP (physician's choice). The results of these studies are pending.

Brentuximab vedotin

Brentuximab vedotin is an exciting antibody-drug conjugate which links a monoclonal antibody to CD30

(expressed strongly on Hodgkin cells) to a microtubule toxin (monomethyl auristatin E) (*Figure 3*).

As a single agent it has displayed an excellent overall response rate 75% with complete response 34% in phase II (Younes et al, 2012) studies in relapsed, refractory Hodgkin's lymphoma post autologous stem cell transplantation. Given as a 3-weekly short intravenous infusion, it has a relatively non-toxic profile, with neutropenia and peripheral neuropathy its main side effects. In practice, it is currently used as a bridge to allogeneic stem cell transplantation and in the front line setting in clinical trials. The ECHELON-1 study is a multicentre, international randomized control trial that is currently recruiting stage III–IV patients. ABVD is being compared with AVD plus brentuximab. The aim is to improve overall response rate, overall survival and reduce toxicity by omitting bleomycin in the brentuximab arm. Its results in the first-line setting are eagerly awaited. **BJHM**

Images in Figure 2 *are used courtesy of www.bloodmed.com. The authors would like to thank Dr Caroline Watson, Oxford University NHS Trust for completion of* Figure 3.

Conflict of interest: Dr GP Collins has received honoraria for advisory work and as a speaker from Takeda Pharmaceutical Company; other authors: none.

Bauer K, Skoetz N, Monsef I, Engert A, Brillant C (2011) Comparison of chemotherapy including escalated BEACOPP versus chemotherapy including ABVD for patients with early unfavourable or advanced stage Hodgkin lymphoma. *Cochrane Database Syst Rev*: CD007941

Brenner H, Gondos A, Pulte D (2008) Ongoing improvement in long-term survival of patients with Hodgkin disease at all ages and recent catch-up of older patients. *Blood* **111**: 2977–83

Brusamolino E, Bacigalupo A, Barosi G et al (2009) Classical Hodgkin's lymphoma in adults: guidelines of the Italian Society of Hematology, the Italian Society of Experimental Hematology, and the Italian Group for Bone Marrow Transplantation on initial work-up, management, and follow-up. *Haematologica* **94**(4): 550–65

Canellos GP, Anderson JR, Propert KJ et al (1992) Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med* **327**(21): 1478–84

Canellos GP, Duggan D, Johnson J, Niedzwiecki D (2004) How important is bleomycin in the adriamycin + bleomycin + vinblastine + dacarbazine regimen? *J Clin Oncol* **22**(8): 1532–3

Corazzelli G, Angrilli F, D'Arco A et al (2013) Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. *Br J Haematol* **160**(2): 207–15

DeVita VT Jr, Simon RM, Hubbard SM et al (1980) Curability of advanced Hodgkin's disease with chemotherapy. Long-term follow-up of MOPP-treated patients at the National Cancer Institute. *Ann Intern Med* **92**(5): 587–95

Eich HT, Diehl V, Görgen H et al (2010) Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol* **28**(27): 4199–206

Engert A, Plütschow A, Eich HT et al (2010) Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med* **363**(7): 640–52

Engert A, Haverkamp H, Kobe C et al (2012) Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet* **379**(9828): 1791–9

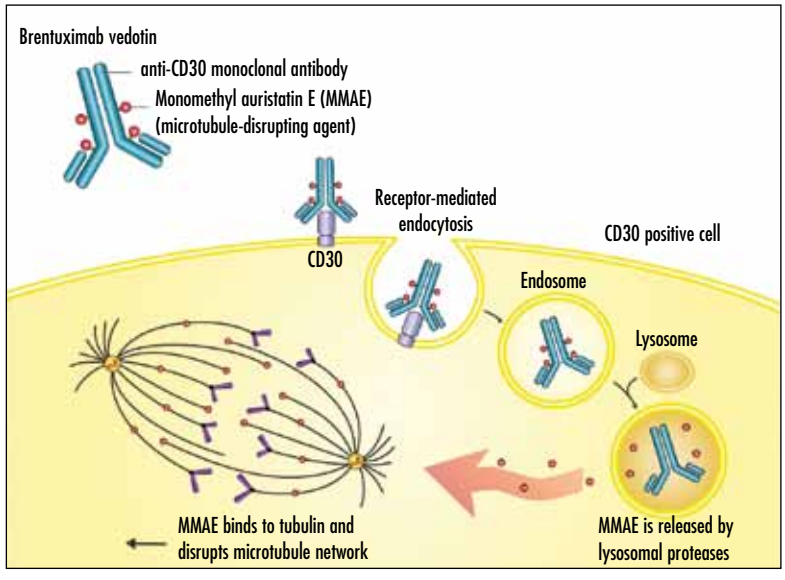
Federico M, Luminari S, Iannitto E et al (2009) ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. *J Clin Oncol* **27**(5): 805–11

Gallamini A, Hutchings M, Rigacci L et al (2007) Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *J Clin Oncol* **25**(24): 3746–52

Hasenclever D, Diehl V, Armitage JO (1998) A prognostic score for advanced Hodgkin's disease. *N Engl J Med* **339**: 1506–14

Hjalgrim H, Askling J, Rostgaard K et al (2003) Characteristics of Hodgkin's Lymphoma after Infectious Mononucleosis. *N Engl J Med* **349**(14): 1324–32

Figure 3. The mechanism of action of brentuximab vedotin.



KEY POINTS

- Hodgkin's lymphoma is a modern medical success story. It is a highly curable malignancy in those under 60 years of age but historically treatment led to acute and chronic toxicity. Cure was possible, but there was a high incidence of secondary cancers, along with cardiac, pulmonary and thyroid toxicity.
- International trials focused on reducing radiotherapy doses and fields, dose de-escalation in early stage disease while retaining high cure rates, and minimization of toxicity. ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) with involved field radiotherapy is the standard combined treatment approach.
- There is ongoing debate about AVBD vs escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone) first line for stage III/IV patients. Those relapsing after ABVD can often be salvaged using autologous stem cell transplantation. There is no overall survival advantage using either approach.
- Regardless of initial disease bulk, radiotherapy is safe to omit if the patient is positron emission tomography-negative after BEACOPP. It is currently unknown if the same holds true for ABVD.
- Positron emission tomography-computed tomography is an excellent staging tool, and its use as a prognostic marker is under investigation.
- Brentuximab vedotin is a new, exciting CD30 monoclonal antibody-drug conjugate currently in trials in the upfront setting following excellent results in the relapsed, refractory setting.

Hodgkin T (1832) On some morbid appearances of the absorbent glands and spleen. *Med Chir Trans* **17**: 69–97
Johnson PW, Sydes MR, Hancock BW, Cullen M, Radford JA, Stenning SP (2010) Consolidation radiotherapy in patients with advanced Hodgkin's lymphoma: survival data from the UKLG LY09 randomized controlled trial. *J Clin Oncol* **28**(20): 3352–9
Josting A, Rudolph C, Reiser M et al (2002) Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. *Ann Oncol* **13**(10): 1628–35
Küppers R (2009) Molecular biology of Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program* 491–6
Linch DC, Winfield D, Goldstone AH et al (1993) Dose intensification with autologous bone marrow transplantation in relapsed and resistant Hodgkin's disease. Results of a BNLI randomized trial. *Lancet* **341**(8852): 1051–4
Longo L, Duffey PL, Young RC et al (1992) Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: The low probability for cure. *J Clin Oncol* **10**(2): 210–18
Marafioti T, Hummel M, Foss HD et al (2000) Hodgkin and Reed-Sternberg cells represent an expansion of a single clone originating from a germinal center B-cell with functional immunoglobulin gene rearrangements but defective immunoglobulin transcription. *Blood* **95**(4): 1443–50
Martínez C, Canals C, Sarina B et al (2013) Identification of prognostic factors predicting outcome in Hodgkin's lymphoma patients relapsing after autologous stem cell transplantation. *Ann Oncol* **24**(9): 2430–4
Meyer R, Gospodarowicz MK, Connors JM et al (2011) ABVD alone versus radiation-based therapy in limited-stage Hodgkin's Lymphoma. *N Engl J Med* **366**(5): 399–408
Moskowitz CH, Nimer SD, Zelenetz AD et al (2001) A 2-step comprehensive high-dose chemo-radiotherapy second- line program for relapsed and refractory Hodgkin's disease: Analysis by intent to treat and development of a prognostic model. *Blood* **97**(3): 616–23
Moskowitz CH, Matasar MJ, Zelenetz AD et al (2012) Normalization of pre-ASCT FDG-PET with second line, non-cross-resistant chemotherapy programs improves event-free survival in patients with Hodgkin Lymphoma. *Blood* **119**(7): 1665–70
Peggs KS, Sureda A, Qian W et al (2007) Reduced-intensity conditioning for allogeneic haematopoietic stem cell transplantation in relapsed and refractory Hodgkin lymphoma: impact of alemtuzumab and donor lymphocyte infusions on long-term outcomes. *Br J Haematol* **139**(1): 70–80
Proctor SJ, Wilkinson J, Jones G et al (2012) Evaluation of treatment outcome in 175 patients with Hodgkin lymphoma aged 60 years or over: the SHIELD study. *Blood* **119**(25): 6005–15
Reed DM (1902) On pathological changes in Hodgkin's disease, with especial reference to its relation to tuberculosis. *Johns Hopkins Hosp Rep* **10**: 133–96
Santoro A, Magagnoli M, Spina M et al (2007) Ifosfamide, gemcitabine, and vinorelbine (IGEV): A new induction regimen for refractory and relapsed Hodgkin's lymphoma. *Haematologica* **92**(1): 35–41
Schmitz N, Pfistner B, Sextro M et al (2002) Aggressive conventional chemotherapy compared with high dose chemotherapy with autologous hemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet* **359**(9323): 2065–71
Sternberg C (1898) Über eine eigenartige unter dem Bilde der Pseudoleukämie verlaufende Tuberculose des lymphatischen Apparates. *Z Heilkunde* **19**: 21–90
Townsend W, Linch D (2012) Hodgkin's lymphoma in adults. *Lancet* **380**(9844): 836–47
Viviani S, Zinzani PL, Rambaldi A et al (2011) ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N Engl J Med* **365**(3): 203–12
Younes A, Gopal AK, Smith SE et al (2012) Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* **30**(18): 2183–9