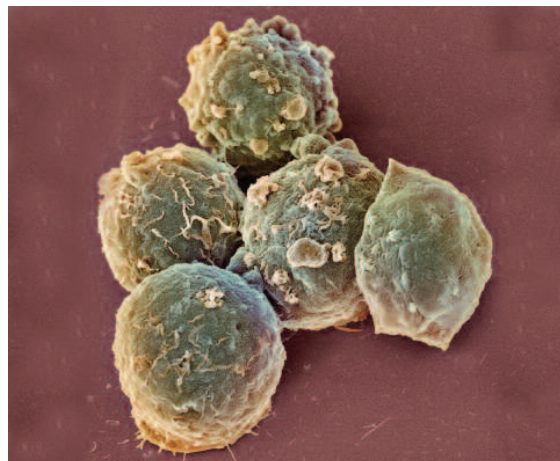


Lymphatic malignancies

— Hodgkin's lymphoma

By David Thomson, MRPharmS

Hodgkin's lymphoma, a malignancy of the lymph nodes, liver and spleen, is characterised by the occurrence of two nuclei in Reed-Sternberg cells. This article outlines the aetiology, pathology, clinical features and treatment of the disease



Coloured scanning electron micrograph (SEM) of lymphoma cancer cells grown in culture

STEVE GOSCHMISNER/SPL

There are around 1,400 patients diagnosed with new cases of Hodgkin's lymphoma each year in the UK, accounting for one in 190 cases of all cancers. There are two peaks in the age-specific incidence of the disease, one in young people aged 15–29 and another in older adults aged 60–79. Incidence rates in the UK declined in the late 1970s, but since the mid-1980s, they have remained unchanged at about three per 100,000 in males and two per 100,000 in females.¹

Because the disease is uncommon and survival rates are good, there are only 300 deaths from Hodgkin's lymphoma in the UK each year. Mortality rates reflect the much better survival of young adults — the rates increase with increasing age, most rapidly after 55 years of age and peak at 80–84 years. Since the early 1970s there have been large decreases in the death rates for the disease, with mortality rates falling by around 3–5 per cent in each decade since then. The biggest falls in mortality have been seen in young and middle-aged adults, with the smallest in those over 65.

Prognosis for patients with Hodgkin's disease is improving. The five-year survival rate for patients diagnosed in England between 1996–1999 was 80 per cent. The data show that survival rates fall by around 8 per cent between five and 10 years after diagnosis. There are large differences in Hodgkin's lym-

phoma survival rates by age: five year survival in patients aged 15–49 is 87 per cent in men and 92 per cent in women, compared with 27 per cent and 32 per cent, respectively, in those over 70.

Aetiology

New insights have been gained into Hodgkin's lymphoma, yet it remains a malignancy of unknown aetiology. The Epstein-Barr virus which can cause glandular fever, however, has been shown to play an important role in Hodgkin's lymphoma tumourgenesis, accounting for about 50 per cent of all cases. Hodgkin's lymphoma is almost 100 times as likely in an identical twin of a diagnosed patient, but for non-identical twins there is no increased risk. This raises the question of whether a faulty gene is involved.² Patients who have reduced immunity, such as those with AIDS, or taking immunosuppressants after an organ transplant, may have a slightly increased risk of developing Hodgkin's lymphoma.

Pathology

Microscopically, diagnosis of Hodgkin's lymphoma is based on the finding of binucleate Reed-Sternberg cells. Hodgkin's disease is most often found in the lymph nodes, the liver and the spleen though it may also rarely be found in the lungs, skin, central nervous system or bone marrow. Cells such as lymphocytes, neutrophils and fibroblasts may

also be found infiltrating the node or affected organ.

Hodgkin's lymphoma is divided into two distinct categories.³ Nodular lymphocyte-predominant Hodgkin's lymphoma is uncommon, representing around 5 per cent of all cases. The more common form, classical Hodgkin's lymphoma, is divided into four histological subclassifications (Panel 1, p346). Of these subtypes, nodular sclerosing classical Hodgkin's lymphoma is the most common. All of these types of classical Hodgkin's lymphoma are treated in the same way.

Clinical presentation

Most patients present with a painless swelling of the lymph nodes in the neck, chest, armpit, abdomen or groin. If lymph nodes in the chest are involved patients may present with a cough or breathlessness — indeed mediastinal masses may be found after routine chest radiography. Fatigue, fever, weight loss and night sweats (known as B symptoms and characteristic of lymphoma) may be present. Itching of the area, which may be worse after alcohol, is another potential symptom.

Massive lymphadenopathy can occur and may have consequences as a result of local pressure, although in general lymphomas tend to grow around structures rather than directly invade them. In the mediastinum, dysphagia and superior vena cava obstruction can occur. In the abdomen, renal failure due to ureteric obstruction and lower limb oedema due to pelvic node enlargement may be seen.

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— Staging and prognosis

The staging of Hodgkin's lymphoma follows the four stage Cotswolds modification of the Ann Arbor classification system (Panel 2).⁴

Disease stage and the presence of B-cell symptoms are the two major factors that allow stratification of patients with Hodgkin's lymphoma. It has recently been accepted that bulky disease (defined in Panel 2) is also a prognostic factor. The classification of Hodgkin's lymphoma therefore tends to follow the traditional early stage (I–IIA or B) and advanced stage (III–IV or I–IIB with bulky disease) definitions. Within the early stage group several features have been identified which indicate a worse prognosis in stage I and II disease, thus allowing stratification of these patients (Panel 3, p349).⁵

In advanced disease, the international prognostic score (IPS) has been developed which identifies seven factors which individually reduce progression rates by around 8 per cent (Panel 4, p349).⁶ However, stratification of patients on the basis of the IPS score is still experimental, with a number of trials attempting to tailor treatment strategies based on the IPS score. The division of Hodgkin's lymphoma into early stage and advanced stage is therefore common practice.

— Early stage disease

Extended field irradiation alone was traditionally the treatment of choice for early-stage favourable Hodgkin's lymphoma. However, due to high relapse rates (about 25–30 per cent) and fatal long-term effects (secondary malignancies or cardiac toxicity), this approach is now thought to be unacceptable by many. Risk of relapse can be reduced by combined treatment with chemotherapy and radiotherapy. The combined approach allows the use of shorter courses of chemotherapy and of more restricted radiotherapy, which reduces the toxic effects. Due to the low rate of deaths in this patient group, evidence showing that the combined modality approach improves a patient's survival is lacking.⁷

Panel 1: World Health Organization classification of Hodgkin's lymphoma

- Nodular lymphocyte-predominant Hodgkin's lymphoma
- Classical Hodgkin's lymphoma
 - Nodular sclerosis classical Hodgkin's lymphoma
 - Mixed cellularity classical Hodgkin's lymphoma
 - Lymphocyte-rich classical Hodgkin's lymphoma
 - Lymphocyte-depleted classical Hodgkin's lymphoma

In unfavourable risk disease, four cycles of chemotherapy have been shown to be as effective as six, and involved-field radiation (only known disease areas are treated) as effective as subtotal nodal irradiation (a wider area including the spleen is treated).⁸ Overall survival rates at six years were 90 per cent for this poor-risk patient group. Four year event-free survival rates of 99 per cent have been shown for three cycles of chemotherapy plus involved field radiotherapy in patients with favourable risk disease.⁹ The combined modality approach was also found to be more effective than subtotal nodal irradiation alone.

A number of chemotherapy regimens are used in the treatment of Hodgkin's lymphoma (Panel 5, p351). It is generally accepted that in this patient group short courses of chemotherapy are adequate. In the UK three cycles of combination chemotherapy (usually ABVD) plus involved-field radiotherapy is considered standard therapy for favourable risk early-stage disease. Ongoing studies are attempting to reduce the long-term complications of treatment without increasing mortality by varying the intensity of irradiation and chemotherapy and by omitting radiation.^{10,11}

— Advanced stage disease

The introduction of the MOPP drug regimen in the 1960s was a major step forward in the treatment of advanced Hodgkin's lymphoma and achieved a 50 per cent cure rate.¹² Over the next few years a number of modifi-

cations were made to the regimen, with chlorambucil or cyclophosphamide in place of chlormethine, which maintained its efficacy but possibly reduced the gastrointestinal and neurological toxic effects.^{13,14} With the MOPP and MOPP-like regimens, around 15–30 per cent of patients did not reach complete remission and only 50 per cent of patients would be cured.¹⁵ This led to the introduction of the ABVD regimen: initially as salvage therapy for patients failing MOPP and then later as first-line treatment. The drugs in the ABVD regimen are less likely to cause infertility and secondary leukaemia than those in MOPP (ie, MOPP induces infertility in almost all men).^{16–17}

A trial of patients with advanced Hodgkin's lymphoma compared MOPP, ABVD, and alternating MOPP/ABVD without additive radiotherapy and showed that ABVD and MOPP/ABVD were equally effective.¹⁸ A long-term follow-up of this study over 15 years showed 45–50 per cent progression-free survival and 65 per cent overall survival for both regimens. ABVD has the advantage of a low incidence of long-term toxic effects — and in combination with radiotherapy presents a 3 per cent lifetime risk of patients developing acute leukaemia.¹⁹ There is a low incidence of toxic effects with the ABVD regimen, but there are cardiotoxicity and pulmonary side-effects with long courses. ABVD has been accepted as the gold standard chemotherapy used in the combined modality treatment of advanced Hodgkin's lymphoma.²⁰

Panel 2: Cotswolds modification of the Ann Arbor staging of Hodgkin's lymphoma

Stage

- I** Involvement of a single lymph-node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring [area including the pharynx and tonsils]) or involvement of a single extra-lymphatic site
- II** Involvement of two or more lymph-node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localised contiguous involvement of only one extra-nodal organ or site and lymph node region(s) on the same side of the diaphragm. The number of anatomical regions involved should be indicated by a subscript (eg, II₃).
- III** Involvement of lymph node regions on both sides of the diaphragm, which may also be accompanied by involvement of the spleen (III_S) or by localised contiguous involvement of only one extra-nodal organ site (III_E), or both (III_{SE})

- III1** With or without involvement of splenic, hilar, celiac or portal nodes
- III2** With involvement of para-aortic, iliac and mesenteric nodes

- IV** Diffuse or disseminated involvement of one or more extra-nodal organs or tissues, with or without associated lymph node involvement

Modifying features

- A** No symptoms
- B** Fever (temperature >38C), drenching night sweats, unexplained loss of more than 10 per cent of body weight within the previous six months
- X** Bulky disease (a widening of the mediastinum by more than one third or the presence of nodal mass with a maximum dimension greater than 10cm)
- E** Involvement of single extra-nodal site that is contiguous or proximal to the known nodal site

Dose intensified chemotherapy regimens Over the past decade, encouraging results have been achieved with a number of alternative regimens. The Stanford V regimen consists of seven drugs which are given for 12 weeks with radiotherapy. The five-year failure-free survival rate for this regimen is 89 per cent and overall survival rate is 96 per cent.²¹ These results have led to a number of ongoing randomised trials comparing the Stanford V regimen with ABVD.

A number of trials were carried out in the early 1990s to find out whether increasing dose intensity could improve the outcome for patients with advanced disease. A German trial compared COPP/ABVD, baseline BEACOPP and increasing doses of BEACOPP in patients with advanced Hodgkin's lymphoma.²² The freedom from treatment failure at five years was 87 per cent for escalated BEACOPP, 76 per cent for baseline BEACOPP, and 69 per cent for COPP/ABVD. There was also a significant difference in overall survival between COPP/ABVD and escalated BEACOPP. Final conclusions about this regimen will only be available after longer follow-up as the data also indicated that there may be an increased incidence of acute myeloid leukaemia and myelodysplastic syndrome in patients receiving the escalated BEACOPP regimen. Trials are under way to compare the escalated BEACOPP regimen with ABVD alone.

Trials are also ongoing on a "time intensified" BEACOPP baseline regimen given at 14 day intervals, with granulocyte colony stimulating factor support for advanced Hodgkin's disease (BEACOPP-14). This regimen was developed as a method of achieving the high

efficacy of the escalated BEACOPP regimen without the increased toxicity.²³ The initial results are promising and this approach is being investigated further.

Hodgkin's lymphoma, therefore, is becoming a highly curable disease and as a result treatment-associated adverse effects — especially infertility and impaired quality of life — have become more important issues. Around 80 per cent of men treated with escalated BEACOPP become sterile, but in comparison patients who receive ABVD tend not to have sterility problems. It is for these reasons that ABVD, with or without radiotherapy, remains the gold standard treatment of advanced Hodgkin's lymphoma, while studies continue to compare the Stanford V, escalated BEACOPP and ABVD regimens. Studies are also under way to assess whether intensive regimens should be reserved for high-risk patients.

Radiotherapy in advanced Hodgkin's lymphoma

The possible benefits of adding radiotherapy to chemotherapy and the delayed toxicity of radiotherapy after anthracycline drugs are important issues influencing treatment decisions in advanced stage Hodgkin's lymphoma. The results of a number of trials suggest that radiotherapy may give no advantage compared with extra chemotherapy²⁴ and indeed may, due to long-term toxic effects, reduce survival.²⁵ Despite these conclusions, both the Stanford V and escalated BEACOPP regimens have used radiotherapy in most patients with good results.

Primary progressive and relapsed disease

Patients with refractory or relapsed disease have a variety of treatment options. Standard chemotherapy is the treatment of choice for patients who relapse after initial radiotherapy for early-stage disease and the survival of these patients is comparable to that of patients receiving initial chemotherapy for advanced-stage disease. Options for patients

who have relapsed after initial chemotherapy include salvage radiotherapy, salvage chemotherapy, high-dose chemotherapy with autologous stem-cell support (where stem cells are taken from the patient and returned after the chemotherapy has been administered) and, in some cases, allogeneic stem-cell transplant (stem cells donated by another person).

The success of salvage treatment has been shown to be influenced by the length of remission after initial chemotherapy.²⁶ Therefore disease can be classified as primary progressive Hodgkin's lymphoma (patients who never achieved a complete remission), early relapse (within 12 months of complete remission) and late relapse (after more than 12 months of complete remission). Survival rates are poor in patients with primary progressive disease, but improve in those with early or late relapse who have shown a 20-year survival rate of 11 per cent and 22 per cent, respectively.²⁷

Most patients with a relapse will require systemic treatment, but if the disease is localised, radiotherapy may be used. Results with standard dose chemotherapy have been good in late relapsers but have been poor in patients with primary progressive or early relapsed disease.²⁸

High-dose chemotherapy with autologous stem-cell transplants in relapsed Hodgkin's lymphoma has only become an established treatment over the past 25 years. Recent improvements in this treatment modality have led to around 40–50 per cent of transplanted relapsed or resistant disease patients being alive at five years.²⁹ High-dose chemotherapy is usually preceded by standard dose chemotherapy to reduce disease bulk and determine whether the disease will be sensitive to chemotherapy.

In a British National Lymphoma Investigation trial, patients with relapsed or refractory disease were treated with conventional dose mini-BEAM or high-dose BEAM with autologous stem-cell transplant.³⁰ Event-free survival was significantly better in the group receiving high-dose BEAM and similar results have been reported by other groups.³¹ These results have led to high-dose chemotherapy and autologous stem cell transplantation being used widely for patients under 65 years of age who fail first-line chemotherapy.

It is not clear whether allogeneic transplantation in patients with Hodgkin's lymphoma is of benefit. High transplant-related mortality has been reported, but it has also been suggested that patients who do survive have a reduced relapse rate.³² This suggests that there is a positive effect and interest is focusing on the use of less toxic non-meloablative allogeneic transplants in this setting.

Complications of treatment

Radiotherapy Wide-field irradiation can cause long-term side effects, eg, irradiation of

Panel 3: Prognosis and risk factors in localised disease*

- Early stage favourable
 - Cotswold stage (CS) I-II without risk factors (supradiaphragmatic)
- Early stage unfavourable (intermediate)
 - CS I-II with ≥ 1 risk factors (supradiaphragmatic)
- Advanced stage
 - CS III-IV

Risk factors

- Large mediastinal mass
- Age ≥ 50 years
- Elevated erythrocyte sedimentation rate ≥ 50mm/h without B symptoms or ≥ 30mm/h with B symptoms
- ≥ 4 involved regions

*As defined by the European Cancer Research Organisation

Panel 4: International prognostic score for advanced disease

Negative prognostic factors

- Age over 45 years
- Male sex
- Serum albumin less than 40g/L
- Haemoglobin concentration less than 10.5g/dL
- Stage IV disease
- Leucocytosis (white-cell count greater than or equal to $15 \times 10^9/L$)
- Lymphopenia (lymphocyte count less than $0.6 \times 10^9/L$ or less than 8 per cent of the total white cell count)

the neck causes hypothyroidism and, if administered during puberty, possible thyroid cancer. Mediastinal irradiation has been shown to cause pneumonitis and lung fibrosis as well as pericarditis. Sterility may be a result of irradiation of the pelvis, and in women it can also cause amenorrhoea.

Chemotherapy The acute toxicity of chemotherapy causes nausea and vomiting, alopecia and bone marrow suppression. Neutropenic sepsis is a potential hazard of any chemotherapy drug. The use of the vinca alkaloids can lead to peripheral neuropathy. Doxorubicin has specific dose-related cardiotoxic effects and bleomycin can cause lung damage at high doses. Neither of these effects will be expected in standard treatment schedules but may become a potential hazard in patients requiring retreatment.

The anthracycline-containing regimens, such as ABVD, have the advantage of preserving fertility whereas after MOPP type regimens most patients are sterile, with men being more sensitive than women.

There is increasing concern regarding the incidence of secondary malignancies in patients who are cured of their Hodgkin's lymphoma. The incidence increases over time with over 15 per cent of patients who have survived for 20 years or more affected. In the early years acute myeloid leukaemia and non-

Hodgkin's lymphoma is more common, and this is especially true in patients who have had disease with a remitting and relapsing course, as they tend to receive more alkylating agents. The major problem appears to be an increasing risk of solid tumours in later years. The greatest incidence is in those patients receiving both radiotherapy and chemotherapy, while the risk for those receiving radiotherapy alone appears much lower. It is thought that the newer anthracycline-containing regimens may be safer in this respect.

Infertility arises after irradiation of the gonads and after the use of certain chemotherapy agents such as procarbazine and the alkylating agents.

— Novel treatments

Immunotherapy The CD30 antigen is expressed at high levels on Reed-Sternberg cells and therefore has become a potential target for immunotherapy. There are several studies aimed at targeting cell surface molecules such as CD30 or CD20 in Hodgkin's lymphoma, bringing about their effect via a number of mechanisms including antibody-dependent cellular cytotoxicity. Agents being tested currently in phase I trials are MDX-060³³ and SGN-30,³⁴ although early results show modest efficacy for these agents when given alone.

Bortezomib Bortezomib (Velcade) was approved recently for the treatment of relapsed and refractory multiple myeloma. Bortezomib is a proteasome inhibitor and as a result may prove to be of benefit in the treatment of Hodgkin's lymphoma. Nuclear factor κ B (NF- κ B) is frequently activated in the Reed/Sternberg cells and the proteasome inhibitors prevent the degradation of I κ B which in turn keeps the liberation of NF- κ B at a low level.³⁵ Trials are now under way investigating this agent.

Gemcitabine Gemcitabine is among the most promising traditional type of chemotherapeutic agent currently under investigation. In a small series of heavily treated patients, an overall response rate of approximately 50 per cent was found with 10–20 per cent complete responses.³⁶ Even more encouragingly, the combination of gemcitabine with cisplatin and a corticosteroid was found to give an overall response rate higher than 75 per cent.³⁷

— Conclusion

The treatment of Hodgkin's lymphoma continues to improve, and with such improvements, the avoidance of delayed side effects becomes more important. Less intensive initial therapy cures fewer

Panel 5: Chemotherapy regimens frequently used to treat patients with Hodgkin's lymphoma

Chemotherapy regimen name	Drug and dose	Route	Cycle schedule (days)	Cycle length
■ MOPP	Chlormethine 6mg/m ²	iv	Days 1 and 8	28 days
	Vincristine 1.4mg/m ²	iv	Days 1 and 8	
	Procarbazine 100mg/m ²	po	Days 1–14	
	Prednisolone 40mg/m ²	po	Days 1–14	
■ ABVD	Doxorubicin 25mg/m ²	iv	Days 1 and 15	28 days
	Bleomycin 10,000units/m ²	iv	Days 1 and 15	
	Vinblastine 6mg/m ²	iv	Days 1 and 15	
	Dacarbazine 375mg/m ²	iv	Days 1 and 15	
■ StanfordV	Chlormethine 6mg/m ²	iv	Weeks 1, 5, and 9	12 weeks
	Doxorubicin 25mg/m ²	iv	Weeks 1, 3, 5, 7, 9 and 11	
	Vinblastine 6mg/m ²	iv	Weeks 1, 3, 5, 7, 9 and 11	
	Prednisolone 40mg/m ²	po	Weeks 1–9, then taper weeks 10–13	
	Vincristine 1.4mg/m ²	iv	Weeks 2, 4, 6, 8, 10 and 12	
	Bleomycin 5,000units/m ²	iv	Weeks 2, 4, 6, 8, 10 and 12	
	Etoposide 60mg/m ²	iv	Two consecutive days, weeks 3, 7 and 11	
■ COPP	Cyclophosphamide 650mg/m ²	iv	Days 1 and 8	28 days
	Vincristine 1.4mg/m ²	iv	Days 1 and 8	
	Procarbazine 100mg/m ²	po	Days 1–10	
	Prednisolone 40mg/m ²	po	Days 1–14	
■ BEACOPP	Bleomycin 10mg/m ²	iv	Day 8	21 days
	Etoposide 100mg/m ²	iv	Days 1–3	
	Doxorubicin 25mg/m ²	iv	Day 1	
	Cyclophosphamide 650mg/m ²	iv	Day 1	
	Vincristine 1.4mg/m ²	iv	Day 8	
	Procarbazine 100mg/m ²	po	Days 1–7	
	Prednisolone 40mg/m ²	po	Days 1–14	
■ BEACOPP escalated	Bleomycin 10mg/m ²	iv	Day 8	21 days
	Etoposide 200mg/m ²	iv	Days 1–3	
	Doxorubicin 35mg/m ²	iv	Day 1	
	Cyclophosphamide 1,250mg/m ²	iv	Day 1	
	Vincristine 1.4mg/m ²	iv	Day 8	
	Procarbazine 100mg/m ²	po	Days 1–7	
	Prednisolone 40mg/m ²	po	Days 1–14	
■ BEACOPP 14 day	Bleomycin 10mg/m ²	iv	Day 8	14 days
	Etoposide 100mg/m ²	iv	Days 1–3	
	Doxorubicin 25mg/m ²	iv	Day 1	
	Cyclophosphamide 650mg/m ²	iv	Day 1	
	Vincristine 1.4mg/m ²	iv	Day 8	
	Procarbazine 100mg/m ²	po	Days 1–7	
	Prednisolone 40mg/m ²	po	Days 1–14	
	Granulocyte-colony stimulating factor	sc	Day 8 onwards	
■ mini-BEAM	Carmustine 60mg/m ²	iv	Day 1	Single course
	Cytarabine 100mg/m ²	iv	Twice daily days 2–5	
	Etoposide 75mg/m ²	iv	Days 2–5	
	Melphalan 30mg/m ²	iv	Day 6	
■ BEAM	Carmustine 300mg/m ²	iv	Day 1	Single course
	Cytarabine 200mg/m ²	iv	Twice daily days 2–5	
	Etoposide 200mg/m ²	iv	Days 2–5	
	Melphalan 140mg/m ²	iv	Day 6	

patients, but treatment failures can be salvaged by subsequently more intensive treatment. The choice of therapy is therefore dependent on the balancing of side effects with efficacy.

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