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 Moorman AV (2012). The clinical relevance of chromosomal and genomic abnormalities in B-cell precursor acute lymphoblastic leu- kaemia. Blood Rev, 26, 123–35. Pui CH, et al. (2015). Childhood acute lymphoblastic leukemia: pro- gress through collaboration. J Clin Oncol, 33, 2938–48. Soverini S, Bassan R, Lion T (2019). Treatment and monitoring of Philadelphia chromosome-positive leukemia patients: recent ad- vances and remaining challenges. J Hematol Oncol, 12, 39. van Dongen JJM, et al. (2015). Minimal residual disease diagnostics in acute lymphoblastic leukemia: need for sensitive, fast, and standard- ized technologies. Blood, 125, 3996–4009. Vora A, et al. (2013). Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by min- imal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol, 14, 199–209. Vora A, et al. (2014). Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. Lancet Oncol, 15, 809–18. 22.4.3 Hodgkin lymphoma Vijaya Raj Bhatt and James O. Armitage ESSENTIALS Hodgkin lymphoma is derived from a profoundly defective B cell, with the pathobiology, histology, and clinical features being both characteristic and distinct from non-Hodgkin lymphomas. Its cause is unknown. Incidence is about 3 per 100 000 per year in Western countries with a bimodal age distribution meaning that it is one of the commoner lymphomas of young people. Most cases are highly responsive to combination chemotherapy, with many patients being cured of their disease. Presentation and diagnosis Patients with Hodgkin lymphoma may present with lymphaden- opathy, a mediastinal (or other) mass, and systemic symptoms including weight loss, fever, and night sweats (B-symptoms). Workup requires staging with positron emission tomography (PET)-CT imaging, and biopsy. Classical Hodgkin lymphoma is defined by the presence of the binucleate Reed–Sternberg cell in an appropriate inflammatory histological context. These cells have a

characteristic immuno histochemical phenotype, showing CD15 and CD30 positivity, but being immunonegative for classical B-cell markers such as CD20. Additional histological subtypes have been defined, with the most clinically significant being lymphocyte-predominant Hodgkin lymphoma (with its differing clinical profile and management). Treatment and prognosis Patients with localized disease (Ann Arbor stage I or nonbulky stage II, without B-symptoms) may be treated with chemotherapy with or without radiotherapy. Those with more advanced-stage disease require combination chemotherapy, with radiotherapy to sites of initial bulk disease. While relapse is uncommon in patients with early-stage disease, some 20% of patients with advanced-stage dis- ease may need ‘salvage’ chemotherapy regimens for relapsed dis- ease, when the aim is to attain PET negativity before embarking on high-dose therapy with stem cell rescue. Since many patients have a good outcome, it is essential to min- imize the long-term sequelae of treatment, such as pulmonary fibrosis and the development of secondary cancers. Risk stratifi- cation, including through the use of PET-CT imaging, is a major focus of clinical trials in this area to determine optimal treatment strategies. Introduction Epidemiology and risk factors Unlike non-Hodgkin lymphoma, the incidence of Hodgkin lymphoma has been stable over the period 1950 to 2000, with about three new cases per 100 000 population/year in Western countries. Approximately 9000 new cases are diagnosed each year in the United States of America and 1800 in the United Kingdom. The condition displays a peculiar bimodal distribution of occurrence, with peaks in young adulthood and older age (Fig. 22.4.3.1). This dual peak has led some to propose that Hodgkin lymphoma actually represents two illnesses, with the earlier peak being related to an infectious aeti- ology and the latter representing a true malignancy, but there is little evidence to support this hypothesis. An association has been demonstrated between the occurrence of Hodgkin lymphoma and infection by the Epstein–Barr virus (EBV). Monoclonal or oligoclonal proliferation of EBV-infected cells is found in 20 to 40% of patients with Hodgkin lymphoma. 175 150 125 100 75 50 25 Number of cases 0–4 5–15 15–24 25–34 35–44 45–54 55–64 65–74 75–84 85+ Age groups Incidence: 3.29/100 000 males 2.07/100 000 females Females Males Fig. 22.4.3.1 Age distribution of Hodgkin lymphoma expressed as new cases registered in England and Wales in 1973.

5281 22.4.3 Hodgkin lymphoma Patients infected by HIV are at an increased risk for Hodgkin lymphoma in addition to non-Hodgkin lymphoma. The subtypes of Hodgkin lymphoma vary geographically and by age group. Patients in Western countries who develop Hodgkin lymphoma in young adulthood usually have the nodular scler- osis subtype. Patients from developing countries, elderly patients, and those infected with HIV, frequently have mixed cellularity or lymphocyte-depleted classical Hodgkin lymphoma. Hodgkin lymphoma is approximately 100 times more likely in an identical twin of an infected patient. Numerous instances of case clustering have been described. Although these might be taken as evidence of a genetic or infectious aetiology, the cause of Hodgkin lymphoma remains unknown. Pathology In 1832, Thomas Hodgkin of Guy’s Hospital, London, reported seven patients who died from a disorder involving lymph node and spleen enlargement. Then, early in the 20th century, Reed and Sternberg independently described the characteristic giant cells that now bear their name. The diagnosis of Hodgkin lymphoma - requires the identification of Reed–Sternberg cells in a charac- teristic cellular background. The World Health Organization (WHO) classification for Hodgkin lymphoma is presented in Box 22.4.3.1. Hodgkin lymphoma is unique in that the tumour cells constitute a minority of the total cellular population of involved lymph nodes. The tumour cell (i.e. the Reed–Sternberg cell) has been shown to be of B-cell origin. In the WHO classification, Hodgkin lymphoma is divided into classical Hodgkin lymphoma (95% of cases), and nodular lymphocyte-predominant Hodgkin lymphoma (5% of cases).

Classical Hodgkin lymphoma is sub- divided into nodular sclerosis, which is characterized by bands of fibrosis that are often visible to the naked eye; mixed cellularity, where a larger number of Reed–Sternberg cells in a mixed cel- lular background are typical; and lymphocyte-depletion Hodgkin lymphoma, which has either a large number of Reed–Sternberg cells and atypical mononuclear cells, or a background of diffuse fibrosis with occasional Reed–Sternberg cells. The diagnosis of lymphocyte-depletion Hodgkin lymphoma should always raise the possibility that an unusual diffuse large B-cell lymphoma is being confused with Hodgkin lymphoma. Although diffuse lymphocyte-rich (or predominant) Hodgkin lymphoma is listed as a diagnosis, in practice this is exceedingly rare. Most patients with lymphocyte-predominant Hodgkin lymphoma have the entity nodular lymphocyte-predominant Hodgkin lymphoma, which is a more indolent illness but usually treated in a manner similar to classical Hodgkin lymphoma. Pathobiology of lymphoma Increased understanding of the biology of the immune system has allowed the improved classification of lymphomas, and provided new prognostic information and new potential targets for therapy. Lymphomas are malignancies of lymphocytes in which the surface proteins involved in cell recognition and intracellular signalling are important in diagnosis, predicting clinical course, and therapy. Although the genetics of lymphomas are complicated, they too are beginning to be unravelled. Information gleaned from all these studies is likely to further change both the classification and therapy of the lymphomas. Immunology The recognition of new surface antigens has improved the ability to recognize specific subtypes of lymphoma. For example, dis- covery of the Ki-1 (CD30) antigen by investigators in Germany pro- vided a marker for the Reed–Sternberg cells in classical Hodgkin lymphoma. However, it was soon discovered that this antigen was found on the surface of cancers that were previously felt to be un- differentiated carcinomas and malignant histiocytosis. This obser- vation allowed the description of anaplastic large cell lymphoma as a diagnostic entity and, more importantly, allowed some patients with lymphoma to receive appropriate therapy. However, it is important to remember that not all cases of a particular type of lymphoma will have exactly the characteristic immunophenotype, and this does not invalidate the diagnosis. The Reed–Sternberg cells in classical Hodgkin lymphoma express CD15 and CD30 but downregulate B-cell markers including CD20. The Reed–Sternberg cells in nodular lymphocyte-predominant Hodgkin lymphoma express the leucocyte common antigen and other B-cell markers including CD20 but do not express CD15 and CD30 (Table 22.4.3.1). Genetics Clonal immunoglobulin gene rearrangement is observed in the Reed–Sternberg cells in essentially all cases of Hodgkin lymphoma. The presence of somatic hypermutation in the variable region of the immunoglobulin heavy chain genes indicates a germinal centre B- cell origin of the Reed–Sternberg cells. Deregulation of transcrip- tion factors including nuclear factor kappa-B (NF-κB) and Janus kinase/signal transducers and activators of transcription (JAK/ STAT) signalling pathway is associated with antiapoptotic changes and proliferation of the neoplastic cells. Neoplastic cells often dem- onstrate overexpression of p53, aneuploidy, and hypertetraploidy. Comparative genomic hybridization has highlighted recurrent gains on chromosomal arms 2p, 9p, and 12q and distinct high-level amplifications on chromosomal bands 4p16, 4q23 to q24, and 9p23 to p24. Gene expression profiling has demonstrated that Hodgkin Box 22.4.3.1 World Health Organization classification of Hodgkin lymphoma • Nodular lymphocyte-predominant Hodgkin lymphoma (5%) • Classical Hodgkin lymphoma (95%):

— Nodular sclerosis

— Mixed cellularity

— Lymphocyte depletion

— Lymphocyte rich Table 22.4.3.1 Immunological markers useful in the diagnosis of Hodgkin lymphoma Subtype Characteristic immunophenotype Classical Hodgkin lymphoma CD15+ CD20– CD30+ Nodular lymphocyte-predominant Hodgkin lymphoma CD15– CD20+ CD30–

section 22 Haematological disorders 5282 lymphoma resembles primary mediastinal lymphoma more closely than germinal centre B-cell-like diffuse large B-cell lymphoma. For example, the chromosome 9p region that contains regulators of T- cell responses, programmed death ligand (PDL)-1 and PDL2, is amp- lified in Hodgkin lymphoma and primary mediastinal lymphoma. More recently, flow-sorting and exome sequencing have revealed alterations in genes involved in antigen presentation, chromosome integrity, transcriptional regulation, and ubiquitination.
Clinical features Patients with classical Hodgkin lymphoma usually present with palpable nontender lymphadenopathy. In most patients, lymph nodes are discovered in the cervical, supraclavicular, and axillary regions. More than half the patients have mediastinal lymphaden- opathy at diagnosis, and symptoms from a large mediastinal mass such as superior vena cava obstruction are often the initial presenta- tion. Subdiaphragmatic presentation of Hodgkin lymphoma is un- usual, and more common in older men. Approximately one-third of patients with classical Hodgkin lymphoma present with systemic symptoms such as fevers, night sweats, pruritus, and/or weight loss. These systemic symptoms are believed to be the result of the release of cytokines by normal or malignant cells. Patients might present with cytopenia secondary to either bone marrow involvement or autoimmune destruction of the formed elements of the blood. Hodgkin lymphoma can present as a fever of unknown origin. This is more likely in older patients, those with mixed-cellularity or lymphocyte-depletion subtypes, and those who present with lymphoma below the diaphragm. Fevers associated with Hodgkin lymphoma occasionally persist for days to weeks, followed by afebrile periods, with subsequent reoccurrence of the fever. This pattern is known as Pel–Ebstein fever. Unusual presentations of Hodgkin lymphoma include severe and unexplained pruritus, cen- tral nervous system involvement, paraneoplastic cerebellar degen- eration, nephrotic syndrome, immune haemolytic anaemia and/or thrombocytopenia, hypercalcaemia, and pain in lymph nodes with alcohol ingestion. The possible presentations of lymphomas are so varied that the diagnosis should be considered in many patients, and not just those presenting with lymphadenopathy or splenomegaly. Diagnosis and evaluation The diagnosis of Hodgkin lymphoma is based on a review of an adequate biopsy by an expert haematopathologist. Fine needle as- piration or small biopsies should be avoided as the basis for diag- nosing lymphoma whenever possible. The differential diagnosis that the pathologist considers when diagnosing a lymphoma includes benign proliferations of lymphoid tissue, malignancies of myeloid cells, nonhaemopoietic malignancies, viral infections, and unusual disorders such as Castleman’s disease and giant lymph node hyper- plasia. Having tissue available for immunological studies and/or genetic studies will help to confirm the diagnosis. Once the diagnosis of a type of lymphoma has been established, a series of studies should be carried out to determine the stage of disease and to allow prognostication (Box 22.4.3.2). The anatomical spread of Hodgkin lymphoma is expressed as an Ann Arbor stage (Table 22.4.3.2). This staging system divides patients into those with lymphoma confined to one lymphatic site, multiple lymphatic sites on one side of the diaphragm, lymphatic involvement on both sides of the diaphragm, and those with bone marrow involvement, liver involvement, or other extensive extranodal lymphoma. The Ann Arbor stage also includes a suffix A or B indicating the absence (A) or presence (B) of unexplained fevers above 38°C, weight loss of

more than 10% of the body weight in the preceding 6 months, or drenching night sweats. Additional factors can also have an impact on a patient's response to therapy and survival. A revised classification includes stage II bulky lymphoma de- fined as a single nodal mass of 10 cm, or greater than a third of the transthoracic diameter at any level of thoracic vertebrae. Functional images, today obtained using fluorodeoxyglucose positron emission tomography (FDG-PET) scans, identify areas of abnormal glucose metabolism that are present in all patients with Hodgkin lymphoma. At the completion of therapy, repeat CT will often show only par- tial regression of mediastinal or retroperitoneal masses because of a sclerotic reaction to the tumour. In these patients, reversion of a previously abnormal PET scan to normal can confirm a complete Box 22.4.3.2 Staging evaluation for a new patient with lymphoma • Complete history and physical examination. • Haematological studies:

— Full blood count, erythrocyte sedimentation rate (ESR). • Chemistry studies to measure normal organ function:

— Serum creatinine, liver function studies, serum albumin.

— Serum lactate dehydrogenase. • Viral serology to include HIV, hepatitis B and C. • Imaging studies:

— Chest radiograph.

— PET/CT scan or contrast-enhanced CT of the neck, chest, ab- domen, and pelvis. • Bone marrow biopsy. • Pregnancy test in women of child-bearing age. • Fertility counselling. • Other studies as appropriate to evaluate specific complaints and to follow up abnormal results found from the studies previously listed:

— Not appropriate in all patients.

— At one time both bipedal lymphangiography and staging lapar- otomy were popular studies in evaluating new patients with Hodgkin's lymphoma, but they are now rarely—if ever—indicated. Newer imaging techniques have made clinical, as opposed to sur- gical, staging appropriate for essentially all patients. PET/CT is the current imaging modality of choice.

— Bone marrow biopsy may be omitted, particularly in early-stage lymphoma, if a PET is performed; this is because PET is highly sen- sitive in detecting marrow involvement by Hodgkin lymphoma.

— Other studies can be useful in particular situations. MRI studies are particularly useful in evaluating suspected bone or central ner- vous system sites of involvement. Cerebrospinal fluid cytology and flow cytometry may be necessary in evaluating suspected central nervous system sites of involvement. Hepatitis B serology should be performed if rituximab is being considered as a part of therapy in patients with nodular lymphocyte-predominant Hodgkin lymphoma, as the use of rituximab can increase the risk of hepatitis B reactivation. Echocardiography and pulmonary function tests are often performed before initiation of anthracycline and bleomycin respectively.

5283 metabolic response to therapy. Determining how much improve- ment in a PET scan was required to document a complete remis- sion limited the utility of this procedure until the development of the Deauville, or 5-point, score. This test takes advantage of the fact that there is always PET uptake in the blood pool of mediastinum and the liver, and the uptake in the liver is always greater than that in the mediastinum. The Deauville score is as follows: 1—no up- take consistent with the possible presence of lymphoma; 2—uptake in areas of previously known lymphoma, but less than the uptake in the mediastinum; 3—uptake in areas of previous or suspected lymphoma with an intensity between the mediastinum and the liver; 4—uptake in areas of previous or suspected lymphoma greater than the liver; and 5—new areas of lymphomatous involvement and/or a dramatic increase in the level of uptake in previous or suspected areas of lymphoma. In many trials, and increasingly in routine clin- ical practice, a score of 3 or less at the end of therapy is considered complete remission. Interim PET/CT scanning (i.e. early scans done after two cycles of therapy) is becoming increasingly widely used. Using interim PET/ CT it may be possible to escalate therapy in patients with a Deauville score greater than 3, or, potentially reduce therapy in patients who have responded favourably. So-called risk-adapted therapy is the subject of a number of current clinical trials. Nodular lymphocyte-predominant Hodgkin lymphoma, as noted previously, is a different clinical entity from classical Hodgkin lymphoma. These patients represent less than 5% of all patients found to have Hodgkin lymphoma. The evaluation of such pa- tients is carried out in a similar way to that for classical Hodgkin lymphoma. However, nodular lymphocyte-predominant Hodgkin lymphoma tends to follow a chronic, relapsing course and some- times transforms to diffuse large B-cell lymphoma. Prognostic factors The major factors determining treatment outcome for patients with Hodgkin lymphoma include the Ann Arbor stage, bulky lymphoma, the presence or absence of systemic symptoms, age, and gender. Patients with asymptomatic, localized lymphoma who are young and female have the best outlook. Histological subtypes do not ap- pear to have major independent prognostic significance. Patients with nodular sclerosing Hodgkin lymphoma are less likely to have adverse prognostic factors than those with mixed-cellularity or lymphocyte-depleted subtypes. The results of several laboratory studies can predict outcome in patients with Hodgkin lymphoma. Adverse results include anaemia, a greatly elevated ESR, a low al- bumin level, and a low lymphocyte count. The ESR is sometimes used to follow the course of patients with Hodgkin lymphoma as it reverts to normal with successful treatment. An International Prognostic Index for Hodgkin lymphoma has been developed (Table 22.4.3.3). This index uses seven adverse prognostic factors that determine the treatment outcome. These in- clude age of at least 45 years, stage IV, male sex, white cell count of at least 15 × 109/litre, lymphocyte count less than 0.6 × 109/litre or less than 8% of all white cells, albumin less than 40 g/litre, and haemoglobin less than 105 g/litre. The adverse prognostic factors present in an individual patient are summed. In a large study, pa- tients with no adverse prognostic factors had a 5-year freedom from progression of 84%, whereas for patients with five or more factors it was only 42%. The most important factor in predicting outcome for patients with Hodgkin lymphoma is their response to therapy. Patients who have a prompt, complete response to chemotherapy and/or radiotherapy have the best outlook and are most likely to be cured. Normalization of a PET scan after two cycles of chemotherapy (interim PET) may be used to omit radiotherapy in early-stage favourable disease or to deescalate therapy in advanced-stage disease. Patients who relapse after initial successful treatment for Hodgkin lymphoma can sometimes be effectively treated with further chemotherapy or radiotherapy. The chances for successful treatment depend, in part, on the duration of initial remission in addition to other prognostic factors present at relapse. Patients with a longer initial remission are more likely to be successfully retreated. Table 22.4.3.2 The Ann

Arbor staging system Stage Characteristics I 1 nodal site involved IE 1 site of localized extranodal involvement II 2 or more nodal sites involved, but only on 1 side of the diaphragm IIE 1 site of localized extranodal involvement plus regional nodes involved—all on 1 side of the diaphragm III Nodal involvement (i.e. spleen counts as a nodal site) on both sides of the diaphragm IV Bone marrow, liver, or other extensive extranodal involvement (e.g. multiple pulmonary nodules) A Absence of unexplained fever (i.e. >38°C), drenching night sweats, or weight loss (i.e. ≥10% in 6 months) B Presence of unexplained fever (i.e. >38°C), drenching night sweats, or weight loss (i.e. ≥10% in 6 months) Table 22.4.3.3 Prognostic factors for advanced Hodgkin lymphoma Adverse prognostic factors Age ≥45 years Stage IV Sex Male White blood count ≥15 x 109/litre Lymphocyte count <0.6 x 109/litre or <8% of all white cells Albumin <40 g/litre Haemoglobin <105 g/litre Outcome according to prognostic score Number of factors 5-year freedom from progression (%) 5-year overall survival (%) 0 84 89 1 77 90 2 67 81 3 60 78 4 51 61

> 5 42 56 22.4.3 Hodgkin lymphoma

section 22 Haematological disorders 5284 General principles of lymphoma treatment Types of treatment Those treatments effective in the management of patients with cancer include surgery, radiotherapy, cytotoxic chemotherapy, and a variety of new approaches developed through increasing under- standing of the biology of the immune system. The latter include cytokines, antibodies, and attempts to direct an immune reaction against cancer. As few patients with lymphoma have truly localized lymphoma, surgery has not been a major treatment modality. Since its utiliza- tion in medicine in the first part of the 20th century, radiotherapy has been a major treatment modality for patients with lymphoma, but is limited in its application by toxicity. Its curative potential de- pends upon being able to achieve a tumouricidal dose (typically 30– 40 Gy) without irreversibly injuring normal organs. Thus, the site of involvement by a lymphoma, as well as the number of sites involved, can limit the effectiveness of this treatment, since toxicity increases with the volume of tissue irradiated. Cure rates are often higher when chemotherapy precedes the radiation. Cytotoxic chemotherapeutic agents were first discovered in the 1940s when mechlorethamine (i.e. the nitrogen mustard gas used in warfare), and subsequently methotrexate, were found to cause regressions in immune system malignancies. A wide variety of agents have since been shown to be able to cause lymphoma regression in many patients with lymph- omas. Unfortunately, early studies showed that regressions induced by single agents were almost invariably followed by regrowth of the tumour and eventual death of the patient. In an attempt to cir- cumvent this, combinations of chemotherapeutic agents were first utilized in the 1960s and early 1970s. The drugs were combined by attempting to choose agents with different mechanisms of action and nonoverlapping toxicities to allow the administration of doses that were near to the maximum tolerated dose with an individual agent. In both childhood acute leukaemia and Hodgkin lymphoma, this approach was validated by the cure of a significant number of patients. Today, several combination chemotherapy regimens with acceptable toxicity have been shown to be effective and are widely used worldwide (Table 22.4.3.4). Increasing knowledge of the immune system has further led to the recognition that a number of biologically active molecules can cause regression of lymphomas and, in some cases, impact survival. The first such agent to be widely used was interferon-α, which has some activity in both non-Hodgkin lymphoma and Hodgkin lymphoma. The ability to produce monoclonal antibodies has provided new therapeutic molecules.

Rituximab, which targets the CD20 antigen, has been shown to be active in a variety of B-cell lymphomas including nodular lymphocyte-predominant Hodgkin lymphoma. The antibody conjugate brentuximab vedotin has shown signifi- cant responses in CD30-expressing tumours including Hodgkin lymphoma. Very high doses of cytotoxic chemotherapeutic agents with or without radiotherapy and biologically active molecules have been utilized in the treatment of patients with lymphomas as part of the haematopoietic stem cell transplantation procedure. This involves the administration of very high doses of antilymphoma therapy in an attempt to overcome presumed treatment resistance. Patients are rescued from the toxicity of treatment by the reinfusion of haemo- poietic stem cells. The patient's own haemopoietic stem cells (an au- tologous transplant) or those from another individual with identical Table 22.4.3.4 Popular combination chemotherapy regimens used in treating patients with Hodgkin lymphoma Regimen Drug Dose (mg/m2) Route Schedule ABVD Doxorubicin 25 IV D1 and 15 28-day cycles Bleomycin 10 unit/m2 IV D1 and 15 Vinblastine 6 IV D1 and 15 Dacarbazine 375 IV D1 and 15 Stanford V Doxorubicin 25 IV D1 and 15 28-day cycles Vinblastine 6 IV D1 and 15 Mechlorethamine 6 IV D1 Vincristine 1.4 IV D8 and 22 Bleomycin 5 unit/m2 IV D8 and 22 Etoposide 60 IV D15 and 16 Prednisone 40 PO Every other day, taper D15
of cycle 2 or 3 BEACOPP (escalated)a Doxorubicin 35 IV D1 21-day cycles Cyclophosphamide 1250 IV D1 Etoposide 200 IV D1–3 Prednisone 40 PO D1–14 Procarbazine 100 PO D1–7 Bleomycin 10 unit/m2 IV D8 Vincristine 1.4 IV D8 D, day(s); IV, intravenously; PO, orally. a Baseline BEACOPP has lower doses of doxorubicin (25 mg/m2), cyclophosphamide (650 mg/m2), and etoposide (100 mg/m2).

5285 HLA genes (an allogeneic transplant) can be utilized. Cells for this procedure can be obtained from either bone marrow or peripheral blood. Autologous transplantation has been widely used for patients with lymphoma and shown to be able to cure patients with relapsed Hodgkin lymphoma. Allogeneic transplantation, while apparently curative, has a higher mortality rate and is reserved for younger, fitter patients with multiply relapsed lymphoma or after failure of autologous transplant. General strategy of treatment A number of factors need to be taken into account when formu- lating a treatment recommendation for a patient with lymphoma (Box 22.4.3.3). This decision should be made in conjunction with the patient, and requires good judgement in addition to technical knowledge. The aggressiveness of the treatment that is finally chosen will often depend upon the physician's interpretation of the chances for cure. More toxicity is likely to be acceptable if the goal is cure ra- ther than palliation. For most patients, the goal of therapy is to achieve a complete remission. This implies the disappearance of all symptoms and ob- jective evidence of lymphoma. In practice, a complete remission is documented by repeating all abnormal staging studies after sev- eral cycles of therapy or at the completion of the planned therapy. Documentation of complete remission is important. Patients who achieve a complete remission have a chance for cure; those who do not achieve a complete remission with initial therapy will often go directly to second-line treatments. Patients who fail to be cured with initial therapy, either because they do not achieve an initial remission or because they relapse from remission, are candidates for what has been termed 'salvage therapy'. These second-line regimens can cause tumour regression in most patients with lymphoma and can occasionally produce long-term, lymphoma-free survival. However, for most patients, the only curative approach in this setting is haematopoietic stem cell transplantation. The toxicity of haematopoietic stem cell transplantation limits its use to patients under 70 to 75 years of age, who have a good perform- ance status, without serious compromise of major organ function; and to patients who do not have

bulky/chemotherapy-refractory lymphoma. Primary therapy Patients with localized Hodgkin lymphoma (i.e. stage I or nonbulky stage II) are usually treated with combined chemotherapy and radiotherapy or chemotherapy alone. To minimize late compli- cations, limiting the radiation dose and field size are increasingly utilized. When radiotherapy alone is utilized, a dose of 30 to 36 Gy is usually administered in fractions of 1.75 to 2.00 Gy daily to known sites of involvement and frequently to adjacent lymph node- bearing areas. However, radiotherapy alone is now rarely used ex- cept in nodular lymphocyte-predominant Hodgkin lymphoma and possibly as a palliative care approach in relapsed or refrac- tory Hodgkin lymphoma in unfit patients. When radiotherapy is used as a consolidation therapy after chemotherapy, a dose of 20 to 36 Gy is usually administered. Although 90% of patients who achieve a complete metabolic response following chemotherapy will remain in remission at 3 years, there remains an additional benefit for involved nodal irradiation in further reducing the risk of relapse in some trials. Combined modality treatment will, however, increase the risk of secondary malignancies and, if the mediastinum is involved, of cardiovascular disease. It is hoped that the reduction in radiation field using modern radiotherapy techniques should help minimize these concerns. In very low-risk, early-stage patients, the German Hodgkin Group have shown it is possible to achieve excellent outcomes with two courses of chemo- therapy (ABVD) followed by low-dose (20 Gy) nodal irradiation. In patients with higher-risk disease (based on the number of nodal sites and prognostic markers discussed previously), three or four courses of chemotherapy followed by radiotherapy remains the standard of care. In routine clinical practice, it seems reasonable to individualize treatment decisions based on the outcome of interim scanning and the risks and benefits of consolidative radiotherapy in consultation with the patient. Patients with otherwise localized Hodgkin lymphoma who pre- sent with a large mediastinal mass pose special therapeutic problems. A large mediastinal mass is often defined as one with a maximum diameter greater than one-third of the maximum thoracic diameter. Treatment with radiotherapy alone, or chemotherapy alone, is as- sociated with a high relapse rate. Large mediastinal masses are one indication for combined-modality therapy. Patients who present with B-symptoms or stage III or IV lymphoma are best treated initially with a combination chemo- therapy regimen. If complete remission is documented after com- pleting a course of chemotherapy, the majority of patients will be cured. Patients who have large masses often receive adjuvant radio- therapy to the sites of previous bulky lymphoma after completing the chemotherapy regimen. The most popular regimen for treating Hodgkin lymphoma is currently ABVD (Table 22.4.3.4). ABVD has been shown to be equivalent to more complicated regimens that include the same drugs plus alkylating agents, and superior to alkylator-based regimens alone. Other treatment regimens in- clude BEACOPP and Stanford V. BEACOPP involves higher doses of drugs given in a very dose-intensive fashion, while the drugs are administered weekly for 12 weeks in the Stanford V regimen. Excellent results have been reported with both of these approaches. Comparative studies of the Stanford V regimen and ABVD have found them to be of equivalent efficacy but the simplicity of the ABVD regimen has made it the most popular. Box 22.4.3.3 Factors to consider in therapy for a patient with lymphoma • Specific type of lymphoma • Age • Performance status • Presence of other lymphomas • Stage • Systemic symptoms • Pace of lymphoma • Potential side effects • Likelihood of cure • Patient’s concerns about specific treatments • Convenience • Patient’s immediate and long-term goals • Quality of life 22.4.3 Hodgkin lymphoma

 The BEACOPP regimen is very intensive and associated with a high rate of side effects. It cannot be given safely to older patients. However, it appears to have a higher durable remission rate in younger patients than ABVD. One study from Europe

compared BEACOPP with ABVD. The study demonstrated improved initial tumour control with BEACOPP but no difference in the overall survival between these two approaches. Patients who failed initial therapy underwent autologous stem cell transplantation. BEACOPP is associated with infertility and the risk of treatment-related leu- kaemia. These potential risks need to be balanced against its excel- lent cure rate in younger patients. Risk-adapted strategies using interim PET/CT are being increasing used allowing escalation of therapy is those patients failing to achieve remission after two courses of therapy. Other in- vestigators start with a more intensive regimen and deescalate once an early response has been achieved. Elderly, pregnant, and HIV-positive patients pose special thera- peutic problems. In Hodgkin lymphoma, elderly patients have a much worse prognosis: patients over 60 years of age at the time of diagnosis have a survival rate less than half that of younger patients. Elderly patients with localized lymphoma seem to benefit from radiotherapy in a manner comparable to younger patients. However, older patients tolerate aggressive chemotherapy regimens much less well and, even if the drugs can be administered, older patients have a higher relapse rate. Since it occurs frequently in young adults, Hodgkin lymphoma is sometimes diagnosed in pregnant women. Exposure to PET or CT scanning should be avoided in pregnancy. Alternative imaging modalities may include ultrasonography, magnetic resonance imaging (MRI) and chest radiography with the use of an abdom- inal shield. It is now clear that Hodgkin lymphoma can be treated with chemotherapy at any point during pregnancy with a chance of a good treatment outcome and a surviving infant. However, the risks are higher in the first trimester. Most physicians would favour delaying therapy past the first trimester, if possible. Beyond the first trimester, the risks of chemotherapy to the fetus seem to less than originally feared and ABVD appears to be a safe regimen with outcomes comparable between pregnant and nonpregnant women with Hodgkin lymphoma. The decision to defer chemotherapy until after delivery is a reasonable strategy in patients with lower- risk disease providing careful monitoring with MRI is performed. Pregnant patients should not be treated with radiotherapy. If the decision is made to treat a pregnant patient with chemotherapy, it must be remembered that the fetus will be myelosuppressed in a manner similar to the mother, and this must be taken into account when planning delivery of the baby. The risk of classical Hodgkin lymphoma and non-Hodgkin lymphoma is significantly elevated in HIV-positive patients. Unlike non-Hodgkin lymphoma, the risk of Hodgkin lymphoma is not re- duced with the use of antiretroviral therapy. HIV-positive patients with Hodgkin lymphoma should be managed in consultation with an infectious lymphoma specialist with expertise in antiretroviral therapy. Early initiation of antiretroviral therapy and attention to drug interactions are important. Otherwise, HIV-positive patients should be managed similarly to those without HIV infection. The presence of HIV is not a contraindication for autologous transplant- ation. With aggressive treatment, the outcomes of HIV-positive pa- tients are largely comparable to those without. The optimal treatment for nodular lymphocyte-predominant Hodgkin lymphoma is unclear. Some clinicians favour no initial therapy in asymptomatic patients. However, involved-field radio- therapy, or a brief course of chemotherapy plus radiation, can produce durable remissions in some patients with this subtype of Hodgkin lymphoma. Rituximab is an active agent in nodular lymphocyte-predominant Hodgkin lymphoma. The clinician must be alert for transformation to diffuse large B-cell lymphoma. Treatment of relapse Approximately 25 to 35% of patients treated with chemotherapy for stage III or IV Hodgkin lymphoma will suffer a relapse after achieving a remission, and a few patients will fail to enter initial complete remission. Patients who fail to attain complete remis- sion or who relapse within one year of completing therapy have a poor prognosis with further standard chemotherapy. Autologous haematopoietic stem cell transplantation can be curative in 25 to 50% of such patients,

and is the treatment of choice. Patients who have an initial remission of longer than one year pose a more com- plicated therapeutic problem. These patients are likely to achieve a second remission with a standard chemotherapy regimen. However, long-term follow-up has demonstrated that most of these remissions are not durable, and many physicians would rec- ommend autologous haematopoietic stem cell transplantation to such patients. The occasional patient with a localized relapse after chemotherapy can sometimes be cured with radiotherapy. Two new drugs are active in patients with relapsed Hodgkin lymphoma and are likely to make a major impact in second-line therapy and, probably, incorporation into primary therapy. These include brentuximab vedotin, and anti-programmed death (PD)- 1 antibodies, nivolumab and pembrolizumab. It is increasingly clear that Hodgkin lymphoma cells, and some of the cells in the tumour microenvironment, can express PDL-1. When this inter- acts with PD-1 on activated T cells, the cells are ‘shut off’ and are prevented from killing Reed–Sternberg cells. Initial studies with brentuximab vedotin as well as anti-PD-1 antibodies suggest a very high response rate in patients who failed chemotherapy and stem cell transplantation, and some of the responses are ongoing after many months. The use of brentuximab vedotin as a consoli- dation therapy after autologous transplantation significantly im- proves lymphoma control. The eventual place of these agents in the treatment of Hodgkin lymphoma will become apparent over the next few years. Other single agent drugs available for treatment of relapsed Hodgkin lymphoma include everolimus, lenalidomide, and bendamustine. Treatment complications The treatment of Hodgkin lymphoma is associated with both short- term and long-term complications. Prominent short-term compli- cations include hair loss, emesis, fatigue, anaemia, and infection due to chemotherapy-induced neutropenia. Hair loss is usually transient. Emesis can be prevented in almost all patients by using 5-hydroxytryptamine antagonists. Anaemia and fatigue do not usu- ally limit the administration of therapy. Chemotherapy-induced neutropenia is a major problem, and neutropenic fever needs to be managed aggressively with intravenous antibiotics after cultures are obtained. Even so, treatment for Hodgkin lymphoma is adminis- tered entirely on an outpatient basis.

5287 Delayed toxicity from the treatment of Hodgkin lymphoma has become a major problem for young patients who are cured of the lymphoma and have been followed for extended periods. In fact, for patients with good-prognosis Hodgkin lymphoma, long-term com- plications might lead to a higher mortality rate than the Hodgkin lymphoma itself. Most of the serious complications of radiotherapy appear after long follow-up. In the first few months after treatment, some pa- tients will develop an electric shock sensation down the spine and into the legs on flexion of the neck. This represents Lhermitte’s syn- drome and needs to be recognized so that further evaluation can be avoided. It is usually transient. In some patients, delayed pul- monary fibrosis or cardiac injuries are associated with thoracic radiotherapy. Modern radiotherapy techniques have minimized the risk of these problems, but accelerated coronary artery disease is a significant problem and leads to a number of treatment-related deaths. Follow-up of these patients should emphasize reducing risk factors for coronary artery disease. The major delayed problem with radiotherapy is the development of secondary cancers. This risk be- gins to appear beyond 10 years after therapy, and by 20 years after therapy leads to a significant number of deaths. Patients treated with thoracic radiotherapy for Hodgkin lymphoma should be strongly encouraged not to smoke, to reduce the risk of lung cancer. Young women, who have received chest or axillary radiotherapy between the ages of 10 and 30 years should have screening mammography and breast MRI instituted 8 to 10 years after completing treatment or at the age of 40 years. Patients who receive radiotherapy to the neck have a high risk of developing subsequent hypothyroidism. Follow-up in such pa- tients should include periodic quantitation of their thyrotropin levels to anticipate this problem. Some

patients treated with ei- ther radiotherapy or chemotherapy will develop herpes zoster. This diagnosis does not necessarily signify a relapse of Hodgkin lymphoma. Long-term problems associated with chemotherapy include treatment-related leukaemia, infertility, and aseptic necrosis of bone. Infertility is most likely in patients who receive alkylating agent-containing regimens. In women, the risks of infertility are age related. Women over 30 years of age are much more likely to be permanently infertile than those under 30 years. However, in any patient, resumption of fertility is possible and the patient should be aware of this. Infertility is less of a problem in patients who re- ceive the ABVD regimen. Men who wish to retain fertility should be offered semen storage and women should be offered egg storage. Treatment-related leukaemia is most frequent in patients who receive chemotherapy regimens containing alkylating agents and who are treated on more than one occasion. Young patients treated with only one chemotherapy sequence are unlikely to develop leu- kaemia. The incidence of leukaemia rises dramatically in patients over 40 years of age, and in those who receive alkylating agents on more than one occasion. Leukaemia is unusual in patients treated with ABVD. The combination of chemotherapy and radiotherapy seems to increase the risk of leukaemia. The leukaemias that occur in this setting usually present with myelodysplasia and typic- ally have genetic abnormalities involving chromosomes 5, 7, and 8. Etoposide can lead to the development of acute leukaemia that involves abnormalities on chromosome 11 without a preceding myelodysplasia. Patients who receive corticosteroid treatment as part of a com- bination therapy are at risk for aseptic necrosis of the femoral heads, and those who develop hip pain on follow-up should be evaluated for this possibility. FURTHER READING Advani RH, et al. (2015). Randomized phase III trial comparing ABVD plus radiotherapy with the Stanford V regimen in patients with stages I or II locally extensive, bulky mediastinal Hodgkin lymphoma: a subset analysis of the North American Intergroup E2496 Trial. J Clin Oncol, 33, 1936–42. Advani RH, Hoppe RT (2013). How I treat nodular lymphocyte pre- dominant Hodgkin lymphoma. Blood, 122, 4182–8. Ansell SM, et al. (2015). PD-1 blockade with nivolumab in relapsed or refractory Hodgkin lymphoma. N Engl J Med, 372, 311–19. Armitage JO (2010). Early-stage Hodgkin lymphoma. N Engl J Med, 363, 653–62. Barrington SF, et al. (2014). Role of imaging in the staging and re- sponse assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol, 32, 3048–58. Cheson BD, et al. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol, 32, 3059–68. Gordon LI, et al. (2013). Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordin- ated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol, 31, 684–91. Hasenclever D, Diehl V (1998). A prognostic score for advanced Hodgkin lymphoma. International prognostic factors project on ad- vanced Hodgkin lymphoma. N Engl J Med, 339, 1506–14. Hutchings M, et al. (2014). In vivo treatment sensitivity testing with positron emission tomography/computed tomography after one cycle of chemotherapy for Hodgkin lymphoma. J Clin Oncol, 32, 2705–11. Moskowitz CH, et al. (2015). Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet, 385, 1853–62. Radford J, et al. (2015). Results of a trial of PET-directed therapy for early-stage Hodgkin lymphoma. N Engl J Med, 372, 1598–607. Viviani S, et al. (2011). ABVD versus BEACOPP for Hodgkin lymphoma when high- dose salvage is planned. N Engl J Med, 365, 203–12. 22.4.3 Hodgkin lymphoma

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