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section 22 Haematological disorders 5302 The Non-Hodgkin’s Lymphoma Classification Project (1997). A clinical evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin’s Lymphoma. Blood, 89, 3909–18. Vose JM, Armitage JO, Weisenburger D (2008). International per- ipheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J ClinOncol, 26, 4124–30. 22.4.5 Chronic lymphocytic leukaemia Clive S. Zent and Aaron Polliack ESSENTIALS Chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma is the most prevalent lymphoid neoplasm in Europe and North America. The ‘cell of origin’ is a mature B lymphocyte with a re- arranged immunoglobulin gene. CLL cells express modest amounts of surface immunoglobulin, and are characterized by defective apoptosis. The cause of CLL is unknown. Clinical features Most patients show no specific clinical features of disease and are diagnosed during evaluation of an incidental finding of peripheral blood lymphocytosis, lymphadenopathy, or splenomegaly. A small percentage of patients (<10%) present with symptomatic disease re- sulting from (1) tissue accumulation of lymphocytes such as disfig- uring lymphadenopathy, splenomegaly with abdominal discomfort, profound fatigue, drenching night sweats, weight loss, and fever; or (2) manifestations of marrow failure with cytopenias including an- aemia and thrombocytopenia. All CLL patients have an increased risk of infection, autoimmune cytopenias, and second haemato- logical (e.g. diffuse large B-cell lymphoma) and nonhaematological malignancies. Diagnosis and clinical staging Diagnosis is usually made by analysis of the immunophenotype of the monoclonal circulating cells in the peripheral blood. In patients with the small lymphocytic variant of CLL without a detectable cir- culating monoclonal B-cell population, the diagnosis is made using tissue from the bone marrow, lymph nodes, or spleen. Current diagnostic criteria have an arbitrary requirement for (1) a mono- clonal B-lymphocyte count greater than 5 × 109/litre, or (2) clinic- ally detectable lymphadenopathy of at least 1 cm in diameter, or (3) organomegaly, or (4) over 30% bone marrow involvement by CLL cells. Staging is

based on both clinical examination and blood count evaluation. Treatment and prognosis Treatment—there is no standard curative therapy and patients should not be treated until they have progressive and symptom- atic disease or develop anaemia or thrombocytopenia due to bone marrow failure. If a decision is made to treat, then the best initial treatment should be given, based on evaluation of the patient's dis- ease characteristics with specific attention to the integrity of TP53 (coding for p53) and patient fitness. Treatment options include chemoimmunotherapy combining purine analogues, alkylating agents, and anti-CD20 monoclonal antibodies, targeted small mol- ecules inhibiting tyrosine kinases in the B-cell receptor pathway and BCL-2, and entry into clinical trials of experimental therapies including immune modulating drugs. Prognosis—this is highly variable and depends on the clinical stage of disease, intrinsic biological characteristics of the CLL cells, the gen- eral health and performance status of the patient, and type of treat- ment. The median survival at diagnosis is in excess of 10 years but varies considerably depending on CLL biology and patient fitness. Many patients with CLL who are appropriately managed can expect good quality and duration of survival. Introduction The mature lymphocytic leukaemias were historically defined by light microscopic cell morphology and this category included a wide range of disorders derived from different classes of lympho- cytes. Subsequent major advances and improvements in the under- standing of lymphocyte biology resulted in the development of better diagnostic methodologies. These methods are now routinely used for more accurate diagnosis of CLL, in clinical management decisions, and during the period of subsequent patient follow-up. Individual disorders can now be more accurately defined and diag- nosed, at both cellular and molecular levels. The majority of patients with mature lymphocytic leukaemias in Europe and North America have chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma. The other less frequently encountered entities, which always need to be considered in the differential diagnosis of CLL, include the leukaemic phase of B-, T-, and natural killer (NK) cell lymphomas, prolymphocytic leukaemias, and the nonclassified chronic lymphoproliferative disorders. This chapter concentrates on CLL, with only limited reference to these rarer malignancies of mature lymphocytes. CLL, the most prevalent of these lymphoid neoplasms in Europe and North America, is a distinct B-cell ma- lignancy. This lymphoid malignancy has a protean clinical presen- tation, marked variation in the rate of disease progression, and a rapidly increasing number of effective treatment options. The first and major challenge to the practitioner who encounters a case of this nature is to make an accurate diagnosis, recognize the significance of prognostic factors, as well as the indications for treatment, and to be aware of how to manage the many potential complications of the disease. Although CLL is incurable with standard therapy and will eventually cause major morbidity and possibly mortality in most pa- tients, good medical care can improve the quality of life and prolong longevity for most patients. Historical perspective The mature lymphocytic leukaemias were first recognized in the latter half of the 19th century. The subsequent recognition of the piv- otal role of lymphocytes in the immune system led to the discovery

 and recognition of the different T, B, and NK subsets. This infor- mation has now been combined with a better understanding of lymphocyte biology, in order to develop newer more appropriate classifications of lymphoid malignancies. The current World Health Organization (WHO) classification is based on the presumptive normal counterpart of the neoplastic cells and in this scheme, CLL is considered to be a distinct malignancy of a mature B lymphocyte. The clinical presentation of CLL has changed dramatically during the past few decades as the widespread use of automated cell ana- lysers, providing rapid and accurate blood

lymphocyte counts, in- creased the incidental finding of lymphocytosis. In patients with persistent lymphocytosis, these cells can be characterized by flow cytometers in clinical pathology laboratories. This is a sensitive and specific method of diagnosing CLL and is now used routinely. Among populations with access to these technologies, most patients with CLL are accordingly diagnosed at an earlier stage with asymp- tomatic disease while considerably fewer cases present with symp- tomatic disease. CLL and small lymphocytic lymphoma, previously considered to be different diseases, were subsequently found to have the same immunophenotype and pathophysiology and are now considered to be variants of the same disease in the WHO classification. Clinical presentation of the disease with predominance of adenopathy as op- posed to high circulating numbers of leukaemic cells is likely to re- flect differences in CLL cell trafficking and does not appear to have major biological or clinical significance. In the last three decades, there has been a marked improvement in the availability of more treatment options for patients with pro- gressive CLL. Therapy with single-agent alkylators was superseded by chemoimmunotherapy combining purine analogues, alkyl- ating agents, and lymphocyte-targeting monoclonal antibodies. Subsequent developments have led to therapies using targeted small molecule inhibitors of the B-cell receptor pathway and BCL-2 that are highly effective in the management of high-risk and relapsed/ refractory CLL. These therapies have resulted in better and more durable responses to therapy, associated with longer disease-free periods and increased overall survival together with improved quality of life for these patients. Aetiology, genetics, pathogenesis, and pathology The aetiology of CLL remains essentially unknown. CLL is familial in about 5 to 10% of patients who have first-degree relatives with CLL or other B-cell lymphoproliferative disorders. Additional evi- dence for a genetic predisposition for CLL is the marked ethnic variation in the incidence of the disease, which remains relatively unchanged after large population migrations. The highest incidence rates of CLL are in patients of European descent, with a substantially lower risk in people of South East Asian ancestry. The specific gen- etic defects in susceptible patients have not yet been clearly defined. The role of environmental factors in the aetiology of CLL is also poorly understood. Epidemiological studies have raised concerns about the increased risk in patients with exposure to industrial and agricultural chemicals but radiation exposure is not an established risk factor. The current model of B-cell lymphoid malignancies assumes that distinct diseases evolve from malignant transformation of lymphocytes at a specific stage of maturation. Although the ‘cell of origin’ of CLL is not yet fully defined, there is a body of increasing data showing that the physiological counterpart of CLL cells is the mature CD5+ B cells (B1 compartment) which comprises only a small fraction of normal B cells in adults. This cell is a mature B lymphocyte that has rearranged its immunoglobulin gene but ex- presses only small amounts of detectable surface immunoglobulin. These CD5+ B-CLL cells are also capable of undergoing somatic hypermutation in response to antigen stimulation. CLL cells have a low proliferation rate (0.1–1% per day) and ac- cumulate largely because of defective apoptosis which is a major mechanism in this disease. However, the fundamental defect in apoptosis is as yet undefined. CLL cells have disrupted BCL2 gene family expression with higher levels of intracellular antiapoptotic proteins (especially BCL-2, MCL1, and XIAP) and lower levels of proapoptotic proteins, and the mechanisms underlying these cel- lular changes are now being actively investigated. CLL cells are characterized by several recurrent genetic defects, which are likely to be events that occur after the CLL cell becomes malignant and are generally found in subclones of the neoplastic cell population. Clonal evolution with development of additional subclones bearing new mutations is characteristic of CLL. These genetic lesions include interstitial deletions of chromosome band 17p13 (loss of one allele of TP53 coding for p53), dysfunctional mu- tations of TP53, interstitial

deletions of 11q22 (loss of one allele of ATM, a critical DNA damage-sensing protein in the DNA damage repair pathway), dysfunctional mutations of ATM and SF3B1, and activating mutations of NOTCH1. However the most frequently re- current chromosomal defect in CLL detected by the commonly used interphase fluorescent in situ hybridization (FISH) assay is intersti- tial deletion of 13q14 resulting in the loss of the microRNA genes MIR15A and MIR16-1 which negatively regulate BCL-2 synthesis. CLL cells are identified by immunophenotyping of membrane proteins in a light chain restricted (predominant expression of either the κ or λ immunoglobulin light chains) monoclonal B-cell popula- tion. The characteristic immunophenotype of the CLL clone includes the expression of CD19 (pan-B-cell marker), and co-expression of CD5, CD23, CD20 (dim), CD79b (dim), and light chain (dim). CLL cells grow in proliferation centres in the lymphoid tissue and less frequently in the bone marrow. Mature cells can accumulate in the bone marrow, lymph nodes, and spleen, and traffic between these sites via the blood and lymphatics. CLL cells are often found in vis- cera, serosal fluids, and cerebrospinal fluid, even in early-stage CLL, and can infiltrate any site of inflammation. Pathological effects of CLL cells can be both direct and indirect. The most common direct effects of accumulation of CLL cells are lymphadenopathy, splenomegaly, hepatomegaly, and bone marrow failure. Lymphadenopathy is an early event in disease progression followed by splenomegaly and hepatomegaly, and bone marrow in- volvement resulting in cytopenia is usually a late event. In contrast, the indirect effects of CLL are less predictable, and their mechan- isms are not well understood. Patients with CLL have an early-onset defect in humoral immunity characterized by decreased produc- tion of antibodies and a restricted antibody repertoire. This results in decreased antibody levels and increased rates of infection espe- cially with encapsulated bacteria. T-cell function is better preserved in early-stage disease despite a skewed T-cell repertoire. However, T-cell function can be considerably compromised with disease

 progression and particularly after toxic treatments such as purine analogues which also affect T cells. CLL patients have an increased risk (c.5%) of developing autoimmune cytopenias during the course of their disease. These can present as autoimmune haemolytic an- aemia (AIHA), immune thrombocytopenia (ITP), pure red blood cell aplasia (PRCA), or rarely autoimmune granulocytopenia. In addition, CLL is associated with a marked increase in the risk of developing second malignancies of the haematopoietic tissue, solid organs, and skin. The most common second haematological ma- lignancy is diffuse large B-cell lymphoma (DLBCL) (Richter syn- drome), which is often, but not always, clonally related to the CLL. The most common nonhaematological malignancies are squamous and basal cell carcinomas and melanoma, which can behave in an aggressive and rapidly progressive manner. The risk of most other common cancers is also increased. The reason for this association of second malignancies is unknown, but defective immune surveil- lance could be a risk factor. Epidemiology CLL is the most prevalent lymphoid malignancy in Europe and North America, with a lower prevalence in Africa and the lowest prevalence in the Far East. In most patients with access to modern medical care, CLL is an incidental diagnosis made during investi- gation of leucocytosis and lymphocytosis and these patients usually have early-stage asymptomatic disease. CLL is very rare in patients under the age of 30, and the median age at diagnosis is about 72 years with a 2:1 male to female predom- inance. In the past, most patients with CLL died of the disease or its complications. However, the improvements in understanding the disease complications and availability of more targeted therapies could change this in the near future. The improvement in diagnostic methods in recent years has re- sulted in an increased recognition of small monoclonal B-cell popula- tions (< 5 × 109/litre), which usually have a CLL immunophenotype, in patients who may have normal

lymphocyte counts and no other evidence of CLL. This monoclonal B-cell lymphocytosis (MBL) increases in prevalence with age and can be detected in 3 to 5% of Europeans over the age of 65 years. The natural history of MBL is not yet completely defined, but retrospective data suggest that only a very small minority of people with MBL without lymphocytosis or lymphadenopathy will progress to CLL or other clinically relevant lymphoid malignancies. Prevention There are no known preventive measures to decrease the risk of CLL. Clinical features CLL has a highly variable clinical presentation and course. Most pa- tients have an incidental diagnosis on investigation of lymphocytosis without any overt clinical features of disease. These patients should have as complete an evaluation of the prognostic biological charac- teristics of their disease as possible. Although no treatment is indi- cated outside of clinical trials, this information is still very important for the planning of subsequent care and to allow these individuals to adjust to their new diagnosis. The clinical manifestations of CLL can be a direct consequence of the tumour burden itself or be due to the indirect effects of the CLL cells. The rate of progression of CLL is highly variable and only a minority of patients have rapidly progressive disease requiring treat- ment for symptoms or cytopenia within a few years of diagnosis. In contrast, about 20 to 30% of patients will never require treatment for their CLL. Progressive adenopathy can cause disfigurement and some abdominal distension and discomfort while also occasion- ally causing obstruction of the ureters or other viscera. Progressive splenomegaly can cause abdominal discomfort in the left upper quadrant, abdominal distension, and early satiety due to pressure on the stomach. Rare splenic infarcts can cause severe abdominal pain. Anaemia is usually the first manifestation of bone marrow failure caused by progressive infiltration by CLL cells and often followed by the development of thrombocytopenia. However, the differential diagnosis of both anaemia and thrombocytopenia in patients with cytopenia includes AIHA, ITP, PRCA, and other unrelated causes. The lymphocyte count can increase to very high levels in patients with CLL, but complications of extreme lymphocytosis are extremely rare. In patients with progressive disease, increased tumour burden can be associated with severe fatigue, drenching night sweats, fever, and weight loss. These clinical features need to be carefully investi- gated to ensure that they are due to CLL rather than other medical conditions. Immune dysfunction associated with CLL causes both immuno- suppression and an increased risk of autoimmune cytopenia. Due to the early suppression of humoral immunity, patients are at high risk of infections with encapsulated bacteria, which can cause severe infections. Further deterioration of immune function including T- cell-mediated immunity increases the risk of viral reactivation and opportunistic infections as the disease progresses or after therapies that decrease the general immune status. Autoimmune complications of CLL usually cause cytopenia. The most common problems are AIHA and PRCA resulting in symp- tomatic anaemia, and ITP which may cause bleeding. These abnor- malities need to be carefully distinguished from cytopenias due to varying degrees of bone marrow failure, which bear a poorer prog- nosis and often require very different therapy. Second malignancies are markedly increased in CLL. The most common second lymphoid malignancy is DLBCL (Richter syn- drome), which can cause dramatic weight loss, night sweats, fevers, and rapid increases in the size of lymph nodes. Differential diagnosis The differential diagnosis of CLL depends on the disease pres- entation. Most patients present with sustained lymphocytosis. The differential diagnosis then includes benign aetiologies as- sociated with lymphocytosis, which is sometimes atypical mor- phologically, and other lymphoid malignancies in the leukaemic phase (Fig. 22.4.5.1). Benign lymphocytosis is usually caused by

22.4.5 Chronic lymphocytic leukaemia 5305 chronic infections (e.g. hepatitis C). The other lymphoid malig- nancies that most frequently present with lymphocytosis of mature small lymphocytes are the leukaemic phase of other B-cell-derived lymphoid neoplasms such as mantle cell, marginal zone, fol- licular, and lymphoplasmacytic lymphoma, hairy cell leukaemia, prolymphocytic leukaemia, and the unclassified chronic B-cell lymphoproliferative disorders. In patients presenting with lymph- adenopathy and splenomegaly, the differential diagnosis includes a wide range of benign and malignant causes, and when malignant peripheral blood lymphocytes are not available for analysis, a bone marrow or lymph node biopsy, or even splenectomy may be re- quired to establish the diagnosis. Clinical investigation CLL is most easily diagnosed by analysis of the immunophenotype of the malignant cells from the blood. In rare patients without a detectable monoclonal B-cell population in the peripheral blood, lymphocytes from the bone marrow, lymph nodes, or spleen can be examined. Staging is based on a clinical examination and blood count evaluation and does not require imaging studies or a bone marrow study (Box 22.4.5.1). Bone marrow examination is re- quired to investigate the cause of cytopenias and is done prior to initiation of therapy by many physicians to exclude other causes of cytopenia and to determine tumour burden. Imaging studies are not required routinely in all patients, and their use should be limited to investigating specific clinical concerns. However, an increasing number of treating physicians perform CT scans before starting specific therapy as a baseline study to facilitate evaluation of the eventual therapeutic outcome. The only real indication for the use of positron emission tomography (PET)-CT in patients with CLL is clinical concern that a patient could have other con- comitant malignancies including DLBCL or infection. Evaluation of established prognostic factors is important and is detailed in the section on staging CLL. Criteria for diagnosis The CLL cell typically coexpresses the B-cell surface antigen CD19 with CD5 and CD23 and has low levels of expression of surface im- munoglobulin (and CD79b) and CD20. These characteristics are used for diagnosis by flow cytometric or immunohistochemical techniques. Interphase FISH examination of CLL cells with an IGH probe is very useful for excluding mantle cell lymphoma with its characteristic t(11;14). The current criteria for diagnosis of CLL re- quire a B-cell lymphocytosis greater than 5 × 109/litre, clinically de- tectable adenopathy (at least 1 cm in diameter), organomegaly, or greater than 30% bone marrow involvement by CLL cells. Staging CLL The clinical staging systems for CLL are based on readily avail- able clinical data. The widely used Rai and Binet classifications use Lymphocytosis (mature cells) Polyclonal Monoclonal - light chain restriction - TCR analysis - NK cell markers T cell NK cell B cell Leukaemic phase of lymphoma - mantle cell - marginal zone - lymphoplasmacytic - other
Hairy cell leukaemia Chronic lymphocytic leukaemia/small lymphocytic lymphoma
Chronic B cell lymphoproliferative disease (not otherwise specified) Fig. 22.4.5.1 Evaluation of chronic lymphocytosis. TCR, T-cell receptor. Box 22.4.5.1 Clinical staging of CLL Rai classification 0 Lymphocytosis I Lymphocytosis and lymphadenopathy II Lymphocytosis and palpable liver or spleen enlargement III Lymphocytosis and anaemia (haemoglobin <110 g/litre) IV Lymphocytosis and thrombocytopenia (platelets <100 × 109/litre) Modified Rai classification Low risk Stage 0 Intermediate risk Stages I–II High risk Stages III–IV Binet classification A Lymphocytosis and lymphadenopathy in less than three areasa B Lymphocytosis and lymphadenopathy in three or more areasa C Anaemia (<100 g/litre) and/or thrombocytopenia (<100 × 109/litre) a Areas are cervical, axillary, and inguinal nodes (unilateral or bilateral), liver, and spleen (n = 5).

 clinical examination and the complete blood count to determine tumour burden (Box 22.4.5.1). These simple methods are very ef- fective at identifying

patients with advanced-stage disease who have a poorer prognosis. However, clinical staging using the Rai or Binet classifications does not provide any information on the risk of dis- ease progression in the majority of patients who are diagnosed with early- to intermediate-stage CLL. Improvements in the diagnosis and management of CLL in the past few decades have increased the utility of determining prog- nosis at diagnosis in earlier-stage disease. This information can be very useful to health care providers as well as patients in planning medical care. There has been impressive progress in defining mo- lecular determinants of risk in CLL patients. These are direct meas- urements of critical biological parameters in the malignant CLL cells rather than indirect measures of tumour progression. The best- studied novel parameters are immunoglobulin mutation sequence analysis (somatic hypermutation status of IGHV), specific chromo- somal defects detected by using interphase FISH, expression of the intracellular protein ZAP-70, and surface membrane protein CD38 (Table 22.4.5.1). IGHV mutation (≥2% difference from germline sequence) has been shown to be associated with a significantly better survival in multiple analyses. FISH analysis is currently the most useful available clinical method of chromosome analysis in CLL and usually includes probes for detection of deletions at chromosome bands 13q14, 11q22, and 17p13, trisomy 12 (12+), and abnormal- ities involving 14q32 (IGH locus). Deletion of 17p13 (17p13−) re- sulting in loss of one allele of TP53 coding for p53 is associated with a shorter time to initial treatment, response duration and overall sur- vival. Deletion of 11q22 (11q22−), resulting in loss of one allele of the ATM gene, is more commonly encountered in younger patients and associated with more aggressive disease, bulky adenopathy, and a poorer prognosis. Patients with 12+ or no detected abnormality have an intermediate prognosis and patients with only deletion of 13q14 (13q14−) generally have the least aggressive disease. Targeted sequencing approaches have also substantially improved the ability to evaluate risk of progression and poor prognosis at diagnosis or later in the course of CLL. Patients with impaired DNA damage responses caused by ac- quired mutations have a very high risk of disease progression, poor response to chemotherapy using DNA-damaging drugs (purine analogues and alkylating agents), and a worse prognosis with chemoimmunotherapy and BCR pathway inhibitor therapies. The best validated poor prognostic genetic mutations are dysfunctional mutations of TP53, ATM, and SF3B1 and activating mutations of NOTCH1. ZAP-70 is an intracellular signalling molecule expressed at a high level by T lymphocytes but only in a small minority of normal B cells. ZAP-70 expression (≥20% positive cells measured by flow cytometry on peripheral blood CLL cells) was originally predicted to be a surrogate marker for unmutated IGHV status and although this predictive capability of ZAP-70 measurement was sub- sequently found to be limited, ZAP-70 expression is still regarded as an independent marker of poor prognosis in CLL. Unfortunately, the assay for ZAP-70 expression is technically demanding and poorly reproducible, which limits its routine clinical application. CD38 is a cell membrane protein of uncertain function expressed by mature B cells and plasma cells. Expression of CD38 by at least 30% of CLL cells is an independent predictor of poor prognosis, but the CD38 expression can change during the course of the disease, and there is still no true consensus on the clinical application of this parameter. Additional biological markers of prognosis in early-stage CLL in- clude serum β2-microglobulin, soluble CD23, thymidine kinase, and the percentage of smudge cells seen on the peripheral smear (low numbers predict for poorer prognosis). The challenge in the future is to combine a selection of these factors and other markers of prog- nosis into a practical prognostic formulation that will be easy to use and accessible to most patients with CLL. Treatment Currently, there is no standard curative therapy for CLL. Patients should not be treated until they have progressive and symptom- atic disease or develop anaemia or thrombocytopenia due to bone marrow failure. In this regard, early treatment of all patients has

not been shown to be of benefit and could even be detrimental to some patients. Initial treatment Patients are treated for progressive disease as defined by the International Workshop for CLL (IWCLL) modification of the 1996 National Cancer Center Working Group criteria published in 2008. The recommended criteria for treatment of patients for CLL are symptoms attributable to CLL (severe fatigue, drenching night sweats, fever, >10% weight loss, discomfort from lymphaden- opathy or splenomegaly), rapidly progressive disease based on in- creases in adenopathy and organomegaly, and bone marrow failure manifesting as anaemia (haemoglobin <110 g/litre) or thrombo- cytopenia (platelets <100 × 109/litre). Optimal initial therapy for CLL depends on the biology of the dis- ease (and especially TP53 analysis) and the patient's comorbidities
Table 22.4.5.1 Molecular prognostic factors and risk of disease progression in early-stage CLL Low risk Intermediate risk High risk Very high risk FISH Gene sequencing 13q14− as sole abnormality Nil, 12+ 11q22− NOTCH1 mutation SF3B1 mutation ATM mutation 17p13− TP53 mutation IGHV mutation Mutated (≥2%) except for VH3-21 Unmutated, VH3-21 mutated ZAP-70 (≥20%) Negative Positive CD38 (≥30%) Negative Positive FISH, fluorescent in situ hybridization.

 and functional status (fitness). For fit patients with progressive CLL without a known defect in p53 function, the current 'standard of care' initial therapy is chemoimmunotherapy combining a purine analogue and anti-CD20 monoclonal antibody. The purine ana- logues (fludarabine, pentostatin, and cladribine) in use since the late 1980s, achieve higher response rates, a longer duration of response, and better overall survival than alkylating agents such as chloram- bucil. Multiple randomized phase III studies have shown better out- comes with the combination of fludarabine and cyclophosphamide compared to fludarabine alone. Therapy of CLL has been further improved by the introduction of the therapeutic anti-CD20 mono- clonal antibodies such as rituximab. Although rituximab has limited efficacy as a single agent, the addition of this monoclonal antibody has been shown, in a randomized phase III trial, to improve both responses and survival of CLL patients treated with fludarabine and cyclophosphamide. These chemoimmunotherapy regimens usually induce a high response rate (>90%) with complete response rates ranging from 40 to 60% and median durations of response of about 3 to 5 years. Less fit patients, and especially those who are older with associated comorbidities, are less likely to tolerate purine analogue-containing chemoimmunotherapy. In this population, chemoimmunotherapy with an alkylating agent (e.g. chlorambucil or bendamustine) and an anti-CD20 monoclonal antibody (rituximab, ofatumumab, or obinutuzumab) is tolerated better and can achieve high response rates and even improved overall survival. Monotherapy and sup- portive care are also reasonable options in an even frailer subgroup of older patients. Patients with progressive CLL and a defective p53-mediated DNA damage repair pathway (17p13−, TP53 mutations) have a poor re- sponse to purine analogue-based therapy. In this patient popula- tion, targeted therapy with tyrosine kinase inhibitors has markedly improved treatment outcome. The current available agents include the irreversible Bruton's tyrosine kinase (BTK) inhibitor ibrutinib and the phosphatidylinositol-4,5-bisphosphate-3-kinase catalytic subunit delta (PI3Kδ) idelalisib. These drugs inhibit B-cell receptor pathway signalling, causing CLL cells to stop growing and to migrate from the lymphoid tissues into the peripheral circulation. Ibrutinib and idelalisib are highly effective in the management of patients with very high-risk CLL (purine analogue refractory, TP53 dysfunc- tional) and their use as monotherapy (ibrutinib) and in combination with anti-CD20 monoclonal antibodies (idelalisib) has become the standard of care for these patient populations. Relapsed and refractory disease Patients with progressive disease after initial primary therapy usu- ally do not require treatment until they once again fulfil the standard criteria for initiating

treatment. Patients with CLL treated initially with chemoimmunotherapy who had a response lasting for at least 2 years and have no evidence of acquisition of TP53 dysfunc- tion, can be considered for retreatment with the same or similar chemoimmunotherapy regimen they received as frontline therapy. However, patients with initial treatment failure, earlier progression, or clonal evolution with development of TP53 dysfunction, should be treated with ibrutinib monotherapy, idelalisib, and rituximab, or be considered for a clinical trial. Ongoing and recently completed clinical trials have shown promising results for therapy of this popu- lation of CLL patients with the BCL-2 inhibitor venetoclax and a new BTK inhibitor acalabrutinib. Furthermore, there is consider- able ongoing research on additional novel small molecule inhibitor therapies in CLL and the repertoire of treatment options is likely to continue to increase in the near future. However, none of the currently available therapies is likely to be curative, so the role of immunotherapy for those patients who respond less well to these treatments is still under investigation. Potential options include immune-modulatory therapy with drugs that disrupt the PD1 pathway and novel methods to re-establish immune surveillance against CLL cells, including the use of chimeric antigen receptor T cells directed against CLL cell antigens such as CD19 (CART-19). Transplantation Allogeneic stem cell transplantation can induce a therapeutic graft-versus-leukaemia effect and is potentially curative in CLL. Myeloablative allogeneic transplantation is, however, associated with very high treatment-related mortality (30–40%) largely due to infection, and is thus of limited value in patients with CLL. However, reduced-intensity conditioning allogeneic transplantation has a lower initial morbidity and mortality and can be considered as an option for younger fit patients with purine analogue refractory dis- ease or TP53 and p53 pathway dysfunction who have achieved a low CLL tumour burden on initial therapy. High-dose chemotherapy with autologous stem cell support has no proven role in the man- agement of CLL. Management of complications of CLL Autoimmune cytopenia is responsible for about 20% of anaemia and thrombocytopenia seen in patients with CLL. In those cases without a large CLL tumour burden, treatment should first be directed at the autoimmune cytopenia. The initial management of severe anaemia or thrombocytopenia is usually therapy with corticosteroids but may also require the use of intravenous immunoglobulin (IVIG). Patients with ITP may benefit from splenectomy, but those with AIHA are less likely to improve after this procedure. Many patients with AIHA and ITP will also respond well and benefit from the use of anti-CD20 monoclonal antibody therapy; however, because about half of the cases of PRBCA involve a cellular immunity-mediated mechanism, anti-CD20 monoclonal antibody therapy is less likely to be effective treatment for this entity. Management of more advanced-stage CLL complicated by autoimmune cytopenia requires regimens that are used in the treatment of both the autoimmune disorder and the underlying CLL. Effective regimens for this include the combination of alkylating agents, corticosteroids, and rituximab, and ibrutinib. Purine analogue-containing regimens should not be used in patients with active autoimmune cytopenia, because in some instances they can themselves induce autoimmune haemolysis. Infection is the most common direct cause of death in CLL. Even patients with early-stage CLL have increased susceptibility to in- fections with encapsulated bacteria which can progress rapidly and prove fatal. Patients are also at an increased risk of developing sinus- itis and other respiratory tract infections and should be educated about this risk and advised to seek early medical evaluation for all fe- brile illnesses. With subsequent disease progression and continuing therapy against CLL, more severe defects in cellular immunity de- velop, and individual patients become more susceptible to viral and opportunistic infections. In this regard, patients must again be edu- cated about the need for early antimicrobial treatment in the event

section 22 Haematological disorders 5308 of infection. Prophylactic treatment of patients with monthly IVIG does decrease the risk of bacterial infection but has not been shown to improve overall survival. Furthermore IVIG therapy is expensive and tedious for the individual concerned; nevertheless, it is used routinely in most centres for a selected subpopulation of patients with low immunoglobulin levels and recurrent serious bacterial in- fections. Use of prophylactic antiviral therapy in patients with recur- rent herpes zoster and herpes simplex infections can be beneficial and should be considered in patients receiving therapy with purine analogues. Vaccination against influenza and pneumococcus is less effective than in immunocompetent subjects but may still be useful and is indicated routinely. Second malignancies Patients with CLL need to be followed carefully for the develop- ment of second malignancies. This includes providing the patient with information about the symptoms of transformation to DLBCL including being aware of the significance of drenching night sweats, fever, and involuntary weight loss. DLBCL (Richter's syndrome) is most frequently related to clonal evolution of the original CLL cells and when evident generally has a poor prognosis. In a minority of pa- tients with CLL (about 20%), DLBCL can occur as a de novo second malignancy, which may then be more responsive to conventional therapy used for DLBCL. In this respect, genetic testing to determine the clonal relationship between coexistent CLL and DLBCL has clin- ical utility. Patients with CLL also need to be informed about the high risk of developing skin cancers (squamous and basal cell carcinomas and melanoma). They need to be educated about skin care including avoidance of sun damage, and should be carefully observed for the development of skin cancers, which should be treated aggressively when detected. An important measure to decrease the risk of other secondary cancers is the cessation of smoking. Careful routine checks for malignancy should be advised and can be beneficial. Quality of life A diagnosis of incurable CLL is stressful for the patient. This emo- tional burden is exacerbated by a number of factors including the lack of effective early intervention, the need for a prolonged ob- servation period before treatment (active monitoring or watchful waiting), and the current lack of curative therapy for this disease. Measures that could be taken for alleviating this problem include placing an emphasis on the importance of active monitoring for early detection and management of potential complications, gaining additional general knowledge on CLL, encouraging simple and frank discussions on the disease and its standard complications, and recognition and greater awareness on the part of treating physicians regarding the validity of the patient's concerns and fear of the future. Prognosis The prognosis of patients with CLL is highly variable and depends on the clinical stage of disease, biological characteristics of the leu- kaemic cells, the presence or absence of associated comorbidities, and the degree of patient fitness. In previous years, patients with advanced-stage disease generally had a poor prognosis with a me- dian survival of approximately 6 years, but recent data suggest that this has been considerably improved by the introduction of newer targeted therapies. In contrast, patients with early-stage CLL have a wider variation of overall survival with the lowest risk cohort (mutated IGHV, 13q14 deletion as the sole abnormality on FISH analysis, negative ZAP-70 and low CD38 expression, and absence of mutations of TP53, ATM, NOTCH1, and SF3B1) likely to have a median survival that is not significantly different to age and sex matched populations without CLL. Areas of uncertainty or controversy Biology Topics of active research aimed at resolving some uncertain issues include defining the normal counterpart of the CLL cell, investiga- tion of the possible causes of CLL, and defining the role of genetic susceptibility to the disease. Prognostic markers Evaluation of the biology of the CLL cell is the key to risk stratifi- cation, individualized patient management, and more successful therapy. Recent studies have identified putative driver mutations in CLL that include previously defined pathways and extend this concept to additional intracellular pathways.

The pathways affected by driver mutations include DNA damage response (e.g. p53, ATM), NOTCH signalling, RNA and ribosomal processing (e.g. SF3B1, XPO1), BCR signalling (e.g. BRAF, IRF4), inflammatory pathways (BIRC3, MYD88), and chromatin modification (e.g. HIST1H1E). Ongoing studies are likely to better define these pathways and their associated defects leading to the development of better prognostic and predictive markers in CLL and the identification of future therapeutic targets. Treatment The current standard of care is still to treat patients with CLL only when they have progressive disease causing clinical problems. Frontline treatment for most patients has improved considerably with the intro- duction of chemoimmunotherapy. The current challenge is to deter- mine the role of the novel oral targeted nonchemotherapy agents in the frontline/primary treatment of progressive CLL in patients without TP53 dysfunction. Recent data suggest that ibrutinib could be suitable initial therapy for older (≥65 years old) patients. A number of large phase III clinical trials have showed a clear benefit for ibrutinib +/− rituximab over standard immunochemotherapy. Recently the com- bination of ibrutinib with venetoclax, the novel BCL2 inhibitor, has shown high remission rates of almost 90% in high risk older patients with CLL. Longer follow-up will be necessary to understand long term toxicity, but it is likely that ibrutinib and newer BTK inhibitors will re- place previous chemotherapy regimens. Treatment of relapsed/refrac- tory CLL has improved considerably with the introduction of targeted therapies and patients are living longer with less adverse effects of treat- ment. However, CLL still remains an incurable malignancy. Likely future developments Biology Determining the genetic basis of monoclonal B-cell lymphocytosis and the factors responsible for the subsequent development of CLL

 could provide useful data in disease prevention. Identification of the cell of origin of CLL will provide a baseline for determining which characteristics of CLL are disease specific and provide additional targets for treatment. Better definition of the effects of CLL on both innate and adaptive immunity will improve our understanding of the acquired immunodeficiency associated with CLL and improve management of infections, autoimmune disease and possible pre- vention of second malignancies and especially the process of trans- formation to DLBCL (Richter syndrome). Treatment Ongoing use of molecular prognostic and predictive markers will improve individualized prognosis at diagnosis and approaches to treatment that should be more effective and less toxic. An improved understanding of the driver mutations and molecular pathology of CLL will result in the development of more and improved targeted therapies. This will no doubt lead to the design of further novel multidrug regimens that will target the different critical pathways in CLL cells that may contribute to the eventual elimination of the malignant CLL clone. The development of chimeric antigen receptor therapy via manipulation of autologous T cells targeting CD19 cells is the first step to be taken in developing effective immunotherapy for CLL. These therapies could prevent recurrence of disease in patients with a low tumour burden after initial frontline therapy and increase the chances for long-term disease-free survival. Better understanding of the acquired immune deficiency in CLL patients could also help to develop interventions to repair the immune system and prevent the inevitable complications of immune dysfunction including infection, autoimmune complications, and second malignancies. FURTHER READING Binet JL, et al. (1981). A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer, 48, 198–205. Brewer JD, Habermann TM, Shanafelt TD (2014). Lymphoma- associated skin cancer: incidence, natural history, and clinical man- agement. Int J Dermatol, 53, 267–74. Burger JA, et al. (2015). Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med, 373, 2425–37. Byrd JC, et al. (2015). Three-year follow-up of treatment-naive and previously treated patients with CLL and

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