Metadata of the chapter that will be visualized online

Chapter Title	The Clinical Presentation of CLL	
Copyright Year	2019	
Copyright Holder	Springer Nature Switzerland AG	
Corresponding Author	Family Name	**Catovsky**
	Particle	
	Given Name	**Daniel**
	Suffix	
	Division	Division of Molecular Pathology
	Organization/University	The Institute of Cancer Research
	Address	London, UK
	Email	daniel.catovsky@icr.ac.uk
Author	Family Name	**Else**
	Particle	
	Given Name	**Monica**
	Suffix	
	Division	Division of Molecular Pathology
	Organization/University	The Institute of Cancer Research
	Address	London, UK
	Email	monica.else@icr.ac.uk
Author	Family Name	**Oscier**
	Particle	
	Given Name	**David**
	Suffix	
	Division	Department of Molecular Pathology
	Organization/University	Royal Bournemouth Hospital
	Address	Bournemouth, UK

Abstract	This chapter deals with the basic demographics and presents features of CLL and how to assess patients once a diagnosis has been made. CLL is predominantly a disease of the elderly with a preponderance of male patients. New evidence suggests that there are variations in gender incidence according to the clinical status of patients, with a higher male:female ratio in the groups with worse prognosis. Full blood counts and a physical examination are the basis of the existing staging systems of Rai and Binet. Establishing the patient's clinical stage sets the scene for the frequency of follow-up, the possible need for therapy and the need for cytogenetic and molecular investigations. Examination of blood films is still important, to identify the presence of prolymphocytes and to consider alternative diagnostic possibilities. In addition, biochemical tests such as beta-2 microglobulin and lactate dehydrogenase are a valuable part of the prognostic evaluation. Patients may need support to deal with the psychological and quality of life issues arising from their disease.
Keywords (separated by " - ")	CLL - Incidence - Clinical presentation - Second malignancies - Age at diagnosis - Gender - Rai stage - Binet stage

The Clinical Presentation of CLL

3

Daniel Catovsky, Monica Else, and David Oscier

3.1 Introduction

CLL is predominantly a disease of the elderly and has a variable clinical presentation and subsequent evolution. Clinical features and laboratory investigations are important for making decisions about patient management and for predicting outcomes, which are very variable in this disease.

There has been a lot of progress in the last decade in our understanding of the factors that determine the clinical evolution of CLL as well as its pathogenesis and molecular genetics. Still, patient-related criteria, such as symptoms and physical signs and simple blood tests, are the backbone for the clinical staging and management planning.

3.2 Demographics

3.2.1 Incidence

The incidence of CLL in the USA and Western Europe is between 4 and 5 per 100,000 persons per year equating to a lifetime risk of developing CLL of 0.6 in the USA (2011–2013 data) [1] and 1/155 men and 1/260 women in England (2013–2014 data) [2]. There are marked racial differences in the incidence of CLL; it is five- to tenfold lower in Asians compared to those of European descent [3].

Epidemiological surveys have shown that CLL has one of the highest familial risks of any cancer, with an 8.5-fold increased risk among first-degree relatives of developing CLL and a 1.9-fold risk of developing other B-cell chronic lymphoproliferative disorders, especially lymphoplasmacytic lymphoma and hairy cell leukaemia [4, 5]. Genome-wide association studies have identified over 30 single nucleotide polymorphisms (SNPs) mapping in, or close to, genes with roles in B-cell biology [6].

3.2.2 Age Distribution

There is a slight discrepancy in the literature concerning the median age of CLL patients at diagnosis. In most registries, this is between 70 and 72 years [1]. In patients entered into clinical trials, the median age is lower. This may be because few elderly patients have been entered into treatment trials in the past, often due to exclusion criteria which debar patients who are older or who have conditions which are commoner in the elderly, such as organ dysfunction or other malignancies. Recent trials cater specifically for more elderly patients with the use of less

D. Catovsky (✉) · M. Else
Division of Molecular Pathology, The Institute of Cancer Research, London, UK
e-mail: daniel.catovsky@icr.ac.uk; monica.else@icr.ac.uk

D. Oscier
Department of Molecular Pathology, Royal Bournemouth Hospital, Bournemouth, UK

M. Hallek et al. (eds.), *Chronic Lymphocytic Leukemia*, Hematologic Malignancies,
https://doi.org/10.1007/978-3-030-11392-6_3

toxic oral agents, obviating the need for multiple hospital visits and in-patient care. Other reasons for the younger age of patients entered into trials may be that disease requiring treatment is diagnosed earlier than more benign disease, or that CLL may have a more benign clinical course in the elderly, resulting in later diagnosis. In studies running in the UK between 1979 and 2004, comprising a total of 3120 patients, the median age of patients randomised into treatment trials was 65 years, whilst in those entered into observational studies of stage A patients the median was 67 years. The age distribution of these two groups is shown in Fig. 3.1 where it can be seen that the observational studies had a higher proportion of patients in the older age bands.

Similarly, the median age of the 3472 patients included in the CLL International Prognostic Index (CLL-IPI) [7] was 61 years, because the majority derived from randomised trials, whilst in the Danish National CLL registry, in which 80% were Binet Stage A patients, the median age was 70 years [8]. Only 7% of patients in the UK clinical trials depicted in Fig. 3.1 were aged <50 years, the youngest patients being 31 years old.

The relevance of age is that it remains an important predictor of overall survival (OS), as illustrated in Fig. 3.2. It is one of the five independently significant variables contributing to the CLL-IPI prognostic index [7].

3.2.3 Gender

It has long been recognised that twice as many men as women develop CLL, with a male:female ratio of 2:1. However, data from the UK trials [9] and a review of the literature show that the male:female ratio varies with the stage of the disease. In the condition preceding CLL, known as monoclonal B-cell lymphocytosis, the male:female ratio is 1:1. The ratio increases in the early stages of the disease, namely Rai Stage 0 and Binet Stage A, and increases again above 2:1 in patients needing treatment (Table 3.1).

Confirmation of the evidence that men more frequently develop progressive CLL comes from an analysis of cases included in the CLL-IPI study [7]. When patients from two large data sets are distributed according to the four CLL-IPI risk categories, the male:female ratio increases threefold in the higher risk cases (Table 3.2). This supports the concept that women have a more benign form of CLL and respond better to therapy, including chemoimmunotherapy, than men [9, 10]. The corollary is that CLL in men runs a more aggressive course. Our evidence showed that there are several reasons for this difference, of which the most important is perhaps the prevalence of biological markers of good prognosis in women [9]. As a result, the OS in all the UK CLL trials was better in women than in men, as also was progression-free survival (PFS), which was measured in the LRF CLL4 trial [9]. These results were confirmed in the German data derived from chemoimmunotherapy trials [10]. In the CLL-IPI study, women had a better median OS than men, 124 vs. 84 months respectively, with the proportion surviving at 5 and 10 years being significantly better ($p < 0.0001$) [7].

3.3 Clinical Features

3.3.1 Presentation

The commonest presenting features of CLL are fatigue, infections, particularly bacterial infections of the respiratory tract, and lymphadenopathy. Other symptoms may be involuntary weight loss or unexplained fever. The incidence of these features has fallen in recent decades and over 80% of cases are now diagnosed with early asymptomatic disease based on the finding of a lymphocytosis in a blood count performed for an incidental reason [11]. Such asymptomatic cases have early CLL (Rai Stage 0 or Binet Stage A) and only need to be followed for the first few months to confirm the diagnosis, ascertain features of progression and decide on the clinical staging (see below). Features that become more frequent during the course of the disease, and especially following treatment, include opportunistic infections, psychological problems and second malignancies.

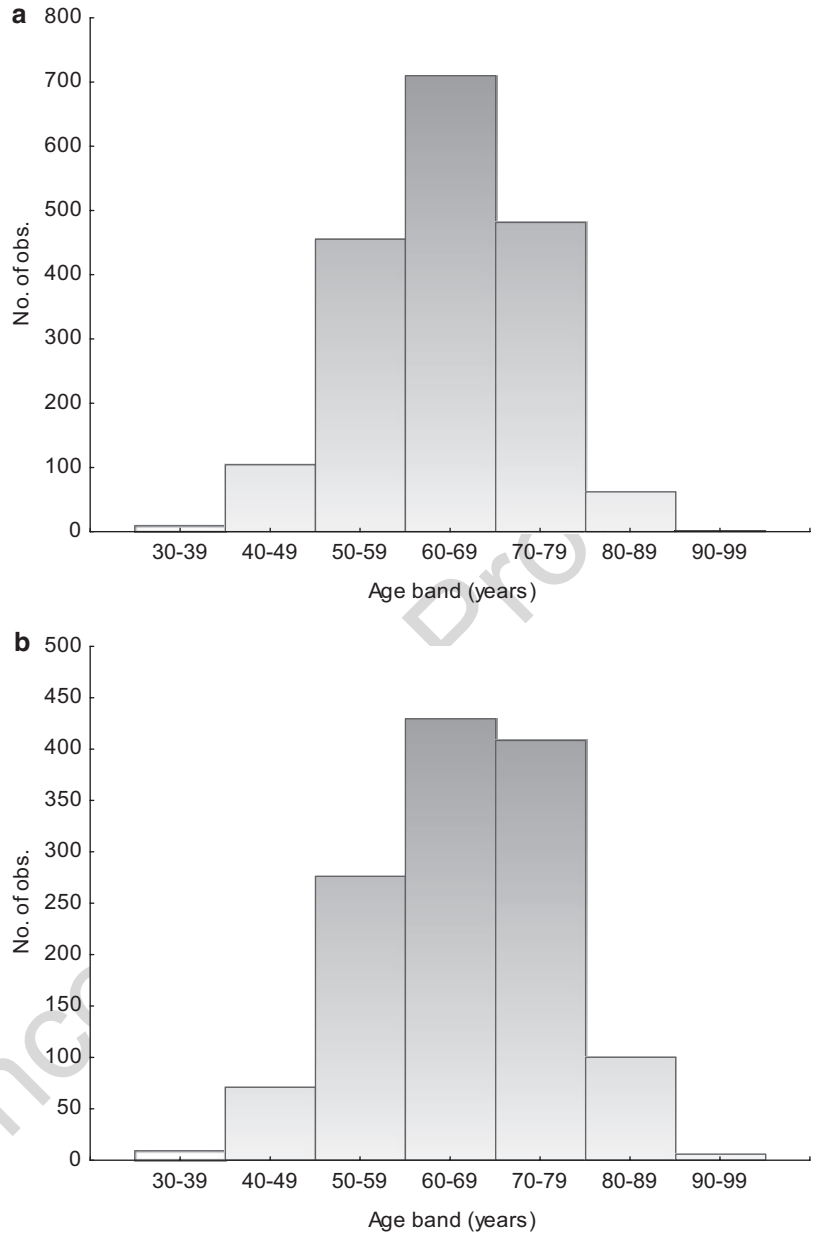

Fig. 3.1 UK CLL trials: histograms showing the age bands of patients at study entry. (**a**) Randomised patients in the UK CLL trials 1–4 ($n = 1821$). (**b**) Registration-only patients (observational studies) ($n = 1299$)

Clinical features are often classified based on whether they are patient-, disease- or treatment-related, and whether disease-related features reflect tumour burden or the immune dysfunction that accompanies CLL. In practice, many symptoms have a number of possible causes and, in an individual patient, are often multifactorial. For example, fatigue may be a consequence of increased cytokine production, anaemia caused by marrow suppression or red cell autoantibodies, or depression.

For patients, particularly the elderly, who are considered for treatment and/or entry into clinical trials, it is always important to assess comorbidities and performance status, as a higher disease burden and greater number of comorbidities correlate with a worse OS [12] (see also chapters …).

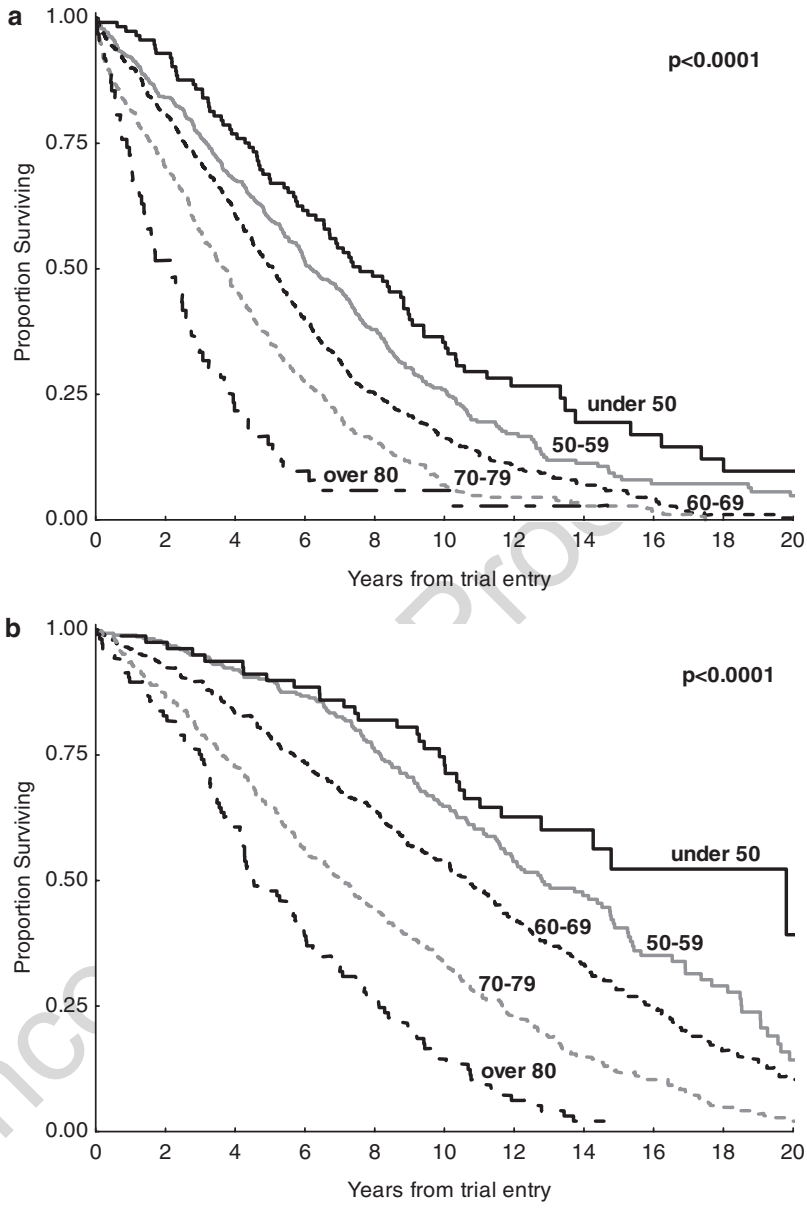

Fig. 3.2 UK CLL trials: overall survival from trial entry by age band (years). (**a**) Randomised patients in the UK CLL trials 1–4 ($n = 1821$). (**b**) Registration-only patients (observational studies) ($n = 1299$)

Table 3.1 Male:female ratios according to clinical status

	No. of patients	Male:female ratio
Monoclonal B-cell lymphocytosis [9]	996	1.1: 1
Stage A/0—literature [9]	1816	1.3: 1
Stage A—UK trials [9]	1299	1.5: 1
Danish national registry [8][a]	3023	1.5: 1
Clinical trials—literature [9]	2399	2.7: 1
UK randomised trials [9]	1821	2.7: 1
German CLL study group [10][b]	1078	2.7: 1

[a]This study applied the International Prognostic Index (CLL-IPI) in a population-based cohort. The majority (79%) were stage A

[b]Chemoimmunotherapy trials

Table 3.2 Male:female ratios according to the CLL-IPI[a]

Risk groups (score)	Main data set $N = 1799$	Training data set $N = 1214$
Low risk (0–1)	1.74	1.56
Intermediate risk (2–3)	2.37	2.22
High risk (4–6)	3.03	3.16
Very high risk (7–10)	4.43	3.77

[a]J Bahlo, personal communication of data from patients included in a study by the CLL International Prognostic Index (CLL-IPI) working group (2016) [7]

3.3.2 Lymphoid Involvement

Enlarged lymph nodes, usually >1 cm in diameter, are painless, largely symmetrical and may involve the neck (anterior or posterior triangle and/or supraclavicular region), axillae and the inguinal region, including superficial femoral nodes. Lymphadenopathy in these three areas is used for staging purposes together with splenomegaly and hepatomegaly [13, 14]. It is important to be aware that an enlarged liver may have other causes such as congestive heart failure. A palpable spleen below the left costal margin is often associated with palpable nodes but in <5% of cases may be the only physical finding. Abdominal fullness and/or discomfort in the left hypocondrium may indicate splenomegaly. In younger male patients, significantly enlarged nodes may be associated with 11q deletion by cytogenetic (fluorescence in situ hybridisation—FISH) analysis.

3.3.3 Extramedullary Features

Clinical and/or laboratory abnormalities of many non-haematological organs or systems such as neurological symptoms or renal dysfunction are common in CLL. These may be related to infections, autoimmune or inflammatory disorders, treatment toxicity or unrelated morbidities, but another important cause, which it is important not to overlook, is extramedullary involvement by CLL. A Medline search of cases reported between 1975 and 2012 identified 192 such cases [15]. The most commonly reported sites were: skin (33%), central nervous system (CNS) (27%), gastrointestinal (GI) tract (14%), genito-urinary/gynaecological (10%), lung (5%) and ocular (5%). Survival from the diagnosis of extramedullary disease varied with the site of involvement and was worst for CNS disease. Diagnosis may be straightforward if there is a solid mass to biopsy, but can be more difficult if there is diffuse tissue infiltration with small lymphocytes. The latter is a common post-mortem finding in the absence of clinically significant ante-mortem organ dysfunction. Similarly, the sensitivity of cerebrospinal fluid (CSF) analysis to detect CNS involvement by CLL in a single centre study was 89% but the specificity was only 42%, reflecting the frequency of CLL cells in the CSF in other neurological conditions affecting patients with CLL [16]. The incidence of extramedullary disease is difficult to ascertain as it is frequently reported in the form of single case reports or small series. The German CLL Study Group analysed the disease status of patients at the time of entry into three first-line chemo or chemoimmunotherapy trials [17]. Extramedullary disease, excluding CNS involvement, was found in 3.6% of patients with the commonest sites being lung/pleural effusion, GI tract and skin.

A physical examination of the patient should include careful examination of the skin for signs of pallor, purpura or skin lumps representing CLL infiltration, although these are uncommon at clinical presentation.

3.3.4 Constitutional Symptoms

Symptoms such as fatigue, night sweats, weight loss, disturbed sleep and low grade fever in the absence of an alternative cause are features of progressive CLL, and their sudden onset in conjunction with rapidly enlarging lymph nodes may signal disease transformation. Indications for treatment in the current IWCLL guidelines [18] include severe and persistent constitutional symptoms, but a minority of mostly early stage patients with less severe symptoms may nevertheless suffer an impaired quality of life. Based on the association between constitutional symptoms and raised levels of circulating cytokines, and the finding of activated *JAK2/STAT3* signalling in CLL, a phase II trial of the *JAK1/JAK2* inhibitor, ruxolitinib, in patients with no

indication for systemic CLL therapy, showed a reduction in constitutional symptoms in the majority of patients [19].

3.3.5 Second Malignancies

Since the 1970s, numerous studies have documented an increased risk of second malignancies in patients with CLL compared to an age-matched general population and have speculated on the role of disease- or therapy-related immunosuppression and therapy-related carcinogenesis as contributory factors. Standardised incidence ratios for all second malignancies, and for specific solid tumours, primary haematological malignancies and Richter's transformation, vary among series, reflecting differences in demographics, treatment exposure and duration of follow-up [20–22]. The increasing incidence of second tumours as a cause of death in CLL, and the negative impact of CLL on the management of some second tumours, highlights the importance of identifying and screening those CLL patients most at risk of second tumours. Risk factors for solid and haematological malignancies in patients treated with first-line alkylating agents, purine analogues and/or rituximab include age, male gender, comorbidities and at least one subsequent treatment. Risk factors for skin cancers are a prior history of skin cancer and "poor risk" CLL at diagnosis, as defined by the CLL-IPI index [22–24].

3.4 Laboratory Investigations

3.4.1 Full Blood Count

The main finding of the initial tests is evidence of lymphocytosis with at least 5×10^9/L clonal B-cells by light chain restriction (either kappa or lambda) required for diagnosis [18].

CLL lymphocytes are small, with a rim of cytoplasm and a characteristic clumped nuclear chromatin without a visible nucleolus. Smear cells, or Gumprecht nuclear shadows, in blood films are also a typical feature of CLL and not seen in other disorders evolving with lymphocytosis. Larger cells with a prominent nucleolus (prolymphocytes) are always seen in blood films, usually <5% (Fig. 3.3).

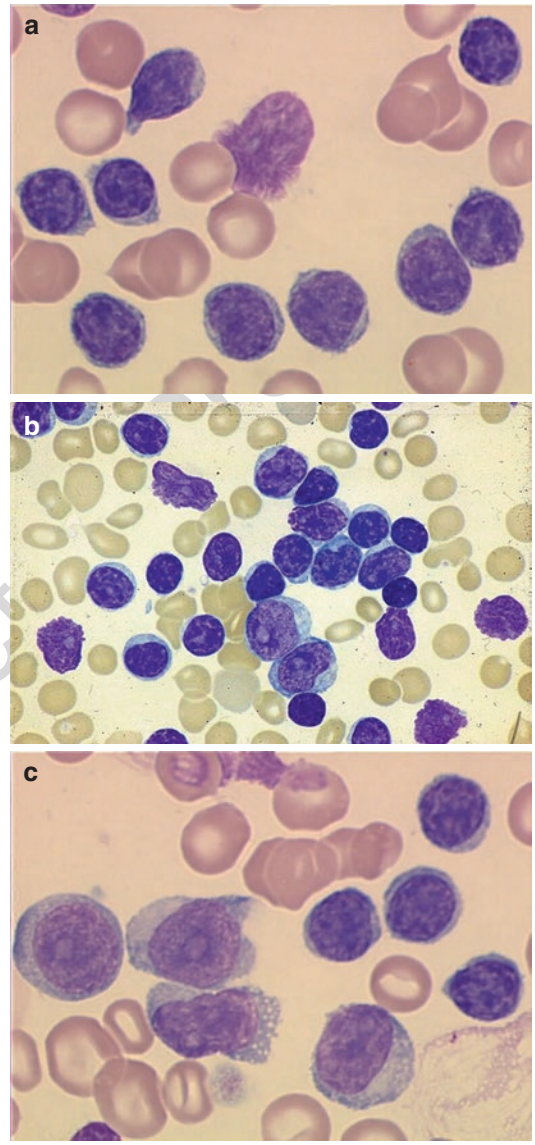

Fig. 3.3 CLL blood films. (**a**) Typical CLL. All the cells are small lymphocytes and there is a single smear cell (reproduced from Oscier et al. 2016 [25], courtesy of BJH). (**b**) Typical CLL with mostly small lymphocytes; there are two prolymphocytes in the lower half and a few smear cells. (**c**) Typical CLL/PL (defined as CLL cases with 11–55% circulating prolymphocytes). There is a mixture of prolymphocytes and typical CLL lymphocytes (reproduced from Oscier et al. 2016 [25], courtesy of BJH)

In an analysis of the morphology of peripheral blood films of over 500 patients entered in the LRF CLL4 trial, the majority (86%) had <10% prolymphocytes [25]. The finding of more than 10% prolymphocytes in the remaining 14% of patients was associated with a shorter PFS and OS and correlated with the presence of *NOTCH1* mutations, absence of 13q deletions, higher CD38 expression and unmutated *IGHV* genes, all associated with poor prognosis [25]. Therefore, a careful examination of blood films is important to trigger other investigations and to evaluate features of clinical progression.

Two other features of the blood count, the haemoglobin level and the platelet count, are necessary to define cytopenias and are an integral part of the staging systems [13, 14] (see Sect. 3.5). A raised reticulocyte count together with anaemia is suggestive of autoimmune haemolytic anaemia (AHA), whilst a very low or absent reticulocyte count together with anaemia suggests pure red cell aplasia (PRCA).

Lymphocyte counts are one of the best indicators of disease progression. It is important to assess the lymphocyte doubling time (LDT) in asymptomatic patients presenting in early stage CLL with no other features of disease progression. Lymphocyte counts need to be repeated initially every 2–4 weeks to calculate the LDT. The counts can be plotted in a semi-logarithmic chart to document an exponential increase as a straight line or can be determined by linear regression extrapolation to calculate the LDT. An LDT of <12 months has been considered evidence of progression, though the IWCLL guidelines have now recommended a shorter period of 6 months. When the lymphocyte count is artificially raised by factors such as infections, or treatment with corticosteroids or the new kinase small molecule inhibitors, this is not considered as evidence of progression.

3.4.2 Other Blood Tests

Biochemical screening is necessary to assess renal and liver function prior to therapy and as part of the total clinical evaluation on presentation.

Beta-2 microglobulin (B2M), a single chain part of the major histocompatibility complex class I proteins, has become an important prognostic marker associated independently with PFS and OS. A level >3.5 mg/L is associated with poor prognosis in the CLL-IPI risk assessment [7]. B2M is cleared by glomerular filtration and catabolised in the proximal renal tubule and therefore it also increases when the renal function is impaired. See also Chap. 4.

Serum lactate dehydrogenase (LDH), a marker of cell turnover, also correlates with disease activity and worse prognosis. In the CLL-IPI study, half the cases had levels >250 U/L and, in univariate analysis, they had a worse outcome than those with levels below 250 U/L, with a median OS of 80 and 124 months, respectively ($p < 0.0001$). However, in multivariate analysis, LDH did not qualify as an independent factor in the CLL-IPI prognostic index [7]. Another recent report described an association between LDH and PFS in patients with trisomy 12. One third of the 222 patients tested had LDH levels above normal and had a significantly shorter PFS than those with normal LDH [26]. High levels of both LDH and B2M have also been reported in cases with expanded proliferation centres in tissue biopsies and progressive CLL [27].

Serum immunoglobulins (Igs) are generally decreased in CLL, and the low levels may be largely responsible for the high frequency of respiratory infections. Serum Igs tend to decrease with disease progression. Small monoclonal bands, usually IgM, are seen in c.10% of cases. There is no evidence that the serum Igs or the monoclonal bands have prognostic connotations.

A direct antiglobulin test (DAT), or Coombs test, is a useful baseline investigation as it may predict the development of AHA after treatment. In the LRF CLL4 trial, 14% of patients had a positive DAT test at entry and this correctly predicted the development of AHA in one out of three patients, whilst a DAT negative test was >90% correct in predicting that patients would not subsequently develop AHA. The incidence of AHA in that trial was 10%, similar to the incidence reported in the literature. DAT positivity in that trial correlated with Binet stage C and a

higher B2M at presentation [28]. After therapy, there was a higher incidence of AHA when chlorambucil (12%) or fludarabine alone (11%) was given than when fludarabine was combined with cyclophosphamide (5%). This confirms that the more effective treatments may reduce the incidence of AHA, as is also seen when anti-CD20 monoclonal antibodies are used. In the German CLL11 trial, there was a clear trend towards a lower incidence of AHA after treatment with chlorambucil combined with either rituximab or obinutuzumab compared with chlorambucil alone (GCLLSG, personal communication). The use of the BTK inhibitor ibrutinib may also significantly reduce the risk of secondary AHA [29]. In fact, when ibrutinib in combination with immunosuppressive therapy is given to patients with active AHA, this may result in the eventual resolution of this complication. For more details, see also Chap. 9.

3.4.3 Bone Marrow (BM) Examination

Although a BM examination is not a diagnostic requirement [18], it is an important baseline investigation for patients who are considered for treatment. More than 30% of a BM aspirate consists of lymphocytes. A trephine biopsy is more useful than an aspirate to assess cellularity and to identify patterns of infiltration, which tend to correlate with disease burden. Biopsy patterns are interstitial, nodular, mixed nodular and interstitial, or diffuse. The latter reflects heavy BM infiltration with no fatty spaces and correlates with cytopenias and disease burden. The value of a BM test at presentation is fourfold:

1. To assess the nature or cause of cytopenias, particularly in Binet Stage C (or Rai III-IV), for example by showing abundant megakaryocytes in immune thrombocytopenic purpura (ITP), or absence of erythroid precursors in PRCA, complicating the CLL;
2. To help distinguish CLL from other B lymphoproliferative disorders in difficult cases, for example by identifying paratrabecular deposits which are characteristic of follicular lymphoma, or by showing proliferation centres which are unique to CLL;
3. To serve as a baseline from which to assess treatment response. A BM biopsy is essential to document complete remission (CR) [18];
4. To assess prognosis according to the pattern of infiltration described above.

3.4.4 Imaging Tests

A routine chest X-ray is often performed at presentation. It is a useful baseline measure and it may detect pre-existing lung pathology or hilar lymphadenopathy.

Computed tomography (CT) scans of abdomen and pelvis are important to detect enlarged para-aortic nodes and other organ enlargement. Although this information is not required for staging, it is a necessary comparator for later treatment follow-up.

A Spanish group performed routine abdominal CT scans in 140 patients presenting with Rai Stage 0 and found detectable enlarged lymph nodes in 27% [30]. This finding correlated with a greater degree of BM infiltration, shorter LDT and a shorter time to progression and to the need for treatment than in those with a normal CT scan. There was no difference in OS between the two groups. The IWCLL Guidelines do not recommend routine CT scans in patients with Binet stage A or Rai stage 0 as it is important to avoid unnecessary radiation exposure. It can be argued that clinical progression can be detected by other means. Nevertheless, the IWCLL guidelines suggest that clinical studies evaluating the use of CT scans in CLL should be encouraged [18]. The result of a CT scan does not alter staging but it is required as a baseline for patients entered into treatment trials.

Abdominal ultrasounds are less invasive but less useful for detecting abdominal nodes. They may however be used to give a precise measure of the size of the spleen and liver, particularly if enlargement is palpable during physical examination.

3.4.5 Cytogenetics/Molecular Investigations

Tests may be carried out to determine *IGHV* mutation status and to detect cytogenetic abnormalities such as *TP53* deletion/mutation, 11q deletion and trisomy 12. Whilst the results may help to predict the clinical course, it should be emphasised that the indication for treatment does not depend on any of these tests [18]. These important prognostic factors are discussed more fully in Chap. 4.

3.5 Clinical Staging

There are two historical but still highly relevant staging systems for CLL, that of Rai [13] and Binet [14], which have been used for several decades. They are simple to use and rely only on the full blood count and physical examination.

After making a diagnosis, the first task of a physician is to decide on the patient's disease stage. This will guide the initial action plan and further investigations.

There are subtle differences between the Rai and Binet staging, even though the original Rai staging has now been simplified from 5 to 3 risk groups [31] (Table 3.3). One difference is the threshold for the haemoglobin level which defines the more advanced cases: 110 g/L in Rai (high risk, formerly III) and 100 g/L for Binet stage C. Binet stage A includes patients with some minimal organomegaly (up to two sites), whilst Rai low risk (formerly stage 0) is restricted to patients without any palpable nodes.

On a historical note, it is worth recalling that after the first International Workshop on CLL (IWCLL) meeting in Paris in 1979 the group proposed to integrate both systems as A (0, I, II), B (I, II) and C (III, IV) [32]. This idea was reiterated in a position paper in 1989 [33]. Despite these publications, the integrated proposal was never implemented in practice, presumably as it was deemed too complex. Clinicians in the USA continue to use the Rai staging and those in Europe the Binet staging. In fact, since both have three stages, consequent differences in patient management are likely to be minimal.

One major issue with both systems is that in patients with early CLL (Rai 0, Binet A) it is difficult to predict the subsequent evolution. In this context, it is interesting to quote from the IWCLL position paper of 1989 [33]: "*Each system has advantages and disadvantages. The Rai system has a precedent, is easily understood, and identifies a subset of patients (stage 0) unlikely, in most instances, to require therapy or to die from chronic lymphocytic leukemia. The disadvantages of the system are the number of disease*

Table 3.3 Clinical staging systems

		Haemoglobin g/L	Platelets × 10^9/L
Rai staging [13, 30][a]	*Lymph nodes/spleen/liver*		
Low risk (formerly stage 0)	Not palpable	≥110	≥100
Intermediate risk (formerly stages I and II)	Palpable nodes and/or spleen and/or liver enlargement	≥110	≥100
High risk (formerly stages III and IV)	Palpable or not	<110 and/or <100	
Binet staging [14]	*Areas of involvement*[b]		
A	0, 1 or 2	≥100	≥100
B	3 or more	≥100	≥100
C	Palpable or not	<100 and/or <100	

[a]Update

[b]Five areas are considered: head and neck, including Waldeyer's ring; axillae; groin, including superficial femorals; palpable spleen; liver (clinically enlarged)

stages (five) and its failure to distinguish different prognostic groups in some studies. The Binet system is a better discriminator of prognosis and is more easily applied to clinical trials and therapeutic strategies (three stages). The Binet system does not identify patients who would be assigned to the Rai stage 0 subset. Also, both systems fail to consider adequately the dynamic nature of the disease. It is reasonable to use either staging system;"…. "*Some variables not included in either system such as the lymphocyte count or its doubling time, bone marrow histologic patterns, and other variables may provide useful supplementary prognostic criteria.*"

There was an earlier study by the French group which attempted to refine the prognostic value of Binet stage A. Cases with a haemoglobin level ≥120 g/L and a lymphocyte count <30 × 10^9/L were distinguished from those with a haemoglobin level <120 g/L and/or a lymphocyte count ≥30 × 10^9/L. There was a significant difference in prognosis between these two groups in the 309 patients studied, with the first group having better OS at 5 years and slower disease progression [34]. This finding was confirmed with data from the MRC CLL1 trial in 606 pts [35].

In the UK clinical trials, the Binet system was used for identifying a subset of patients, "stage A-progressive", as a group requiring treatment. We defined this group by the presence of at least one of the following: a persistent rise in lymphocyte count with doubling time <12 months; a downward trend in haemoglobin or platelets, or both; more than 50% increase in the size of liver, spleen or lymph nodes, or appearance of these signs if not previously present; constitutional symptoms attributable to the disease [36]. In the LRF CLL4 trial, the features which most commonly defined stage A-progressive were a short lymphocyte doubling time and an increase in organomegaly. The clinical justification for defining stage A-progressive as a separate group, meeting the criteria for trial entry, is illustrated in Fig. 3.4, in which the combined data from two large clinical trials (MRC CLL3 and LRF CLL4) show no difference in OS between Stage A-progressive and Stage B.

One important point when staging a patient as Binet C (or Rai high risk, formerly III or IV) is to establish the cause of the cytopenia: either heavy/diffuse BM involvement or an autoimmune process. The former reflects disease burden, whilst the latter may reflect AHA, ITP or the rare PRCA, due to autoantibodies. Data from a large retrospective study at the Mayo Clinic, comprising 1750 CLL patients of whom 24% had cytopenia, showed that 75% of cytopenias were due to BM failure, and 25% due to one of the autoimmune

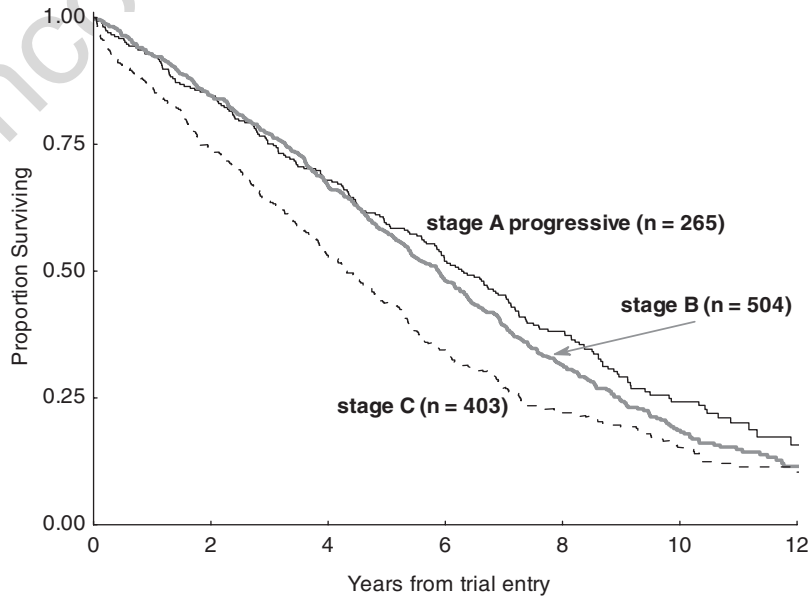

Fig. 3.4 UK trials MRC CLL3 and LRF CLL4: overall survival from trial entry by Binet stage. Log rank test: B vs. A progressive, not significant; B vs. C, $p = 0.0005$; C vs. A progressive, $p < 0.0001$

diseases. The main finding was that those due to autoimmune disease had a significantly better OS than those due to BM burden by CLL [37].

The CLL-IPI prognostic scoring system includes stage as one of the five prognostic criteria by integrating Rai I-IV and Binet B/C, with a score of 1. In contrast, high serum B2M and unmutated *IGHV* genes score 2 each and *TP53* mutation/deletion scores 4 [7] (see Chap. 4).

When dealing with elderly patients it is always necessary to exclude other causes of anaemia, such as iron or folate deficiency, another malignancy, or renal failure. Some of these may be easily corrected with the appropriate haematinics before deciding that the patient needs specific treatment for CLL.

3.6 The Patient's Perspective

Patients may present with quality of life impairment, due in large part to fatigue, with or without anaemia. This may impact adversely their ability to undertake their normal roles and activities [38]. In addition, susceptibility to infections may constrain social and family life. In this context, stage A patients and their families often suffer emotional stress, finding it difficult to accept why, after a diagnosis as serious as leukaemia, treatment is being withheld [39]. They may find it helpful to receive a leaflet explaining why their prognosis is better without treatment and also guidance about what steps they themselves can take to improve their general health and wellbeing. Patients requiring treatment can be reassured that achieving a sustained remission is likely to allow them to return to normal living [38].

References

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, et al., editors. SEER cancer statistics review, 1975–2013. Bethesda: National Cancer Institute; 2016. https://seer.cancer.gov/statfacts/html/clyl.html.
2. Lifetime risk estimates calculated by the Statistical Information Team at Cancer Research UK. Based on data provided by the Office of National Statistics, ISD Scotland, the Welsh Cancer Intelligence and Surveillance Unit and the Northern Ireland Cancer Registry, on request. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-cll/incidence.
3. Yang SM, Li JY, Gale RP, Huang XJ. The mystery of chronic lymphocytic leukemia (CLL): why is it absent in Asians and what does this tell us about etiology, pathogenesis and biology? Blood Rev. 2015;29:205–13.
4. Liang XS, Caporaso N, McMaster ML, Ng D, Landgren O, Yeager M, et al. Common genetic variants in candidate genes and risk of familial lymphoid malignancies. Br J Haematol. 2009;146:418–23.
5. Cerhan JR, Slager SL. Familial predisposition and genetic risk factors for lymphoma. Blood. 2015;126:2265–73.
6. Law PJ, Berndt SI, Speedy HE, Camp NJ, Sava GP, Skibola CF, et al. Genome-wide association analysis implicates dysregulation of immunity genes in chronic lymphocytic leukaemia. Nat Commun. 2017;8:14175.
7. International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol. 2016;17:779–90.
8. Da Cunha-Bang C, Christiansen I, Niemann CU. The CLL-IPI applied in a population-based cohort. Blood. 2016;128:2181–3.
9. Catovsky D, Wade R, Else M. The clinical significance of patients' sex in chronic lymphocytic leukemia. Haematologica. 2014;99:1088–94.
10. Al-Sawaf O, Robrecht S, Bahlo J, Fink AM, Cramer P, von Tresckow J, et al. Impact of gender on outcome after chemoimmunotherapy in patients with chronic lymphocytic leukemia: a meta-analysis by the German CLL study group. Leukemia. 2017;31(10):2251–3. https://doi.org/10.1038/leu.2017.221.
11. Abrisqueta P, Pereira A, Rozman C, Aymerich M, Giné E, Moreno C, et al. Improving survival in patients with chronic lymphocytic leukemia (1980-2008): the Hospital Clinic of Barcelona experience. Blood. 2009;114:2044–50.
12. Stauder R, Eichhorst B, Hamaker ME, Kaplanov K, Morrison VA, Österborg A, et al. Management of chronic lymphocytic leukemia (CLL) in the elderly: a position paper from an international Society of Geriatric Oncology (SIOG) Task Force. Ann Oncol. 2017;28(2):218–27. https://doi.org/10.1093/annonc/mdw547.
13. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46:219–34.
14. Binet JL, Auquier A, Dighiero G, Chastang C, Piguet H, Goasguen J, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981;48:198–206.
15. Ratterman M, Kruczek K, Sulo S, Shanafelt TD, Kay NE, Nabhan C. Extramedullary chronic lymphocytic leukemia: systematic analysis of cases reported between 1975 and 2012. Leuk Res. 2014;38:299–303.

16. Strati P, Uhm JH, Kaufmann TJ, Nabhan C, Parikh SA, Hanson CA, et al. Prevalence and characteristics of central nervous system involvement by chronic lymphocytic leukemia. Haematologica. 2016;101:458–65.
17. Cramer P, Bahlo J, Eichhorst B, Fischer K, Hallek M. Extramedullary manifestations of chronic lymphocytic leukaemia are not unusual. Leuk Res. 2014;38:284–5.
18. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111:5446–56.
19. Jain P, Keating M, Renner S, Cleeland C, Xuelin H, Gonzalez GN, et al. Ruxolitinib for symptom control in patients with chronic lymphocytic leukaemia: a single-group, phase 2 trial. Lancet Haematol. 2017;4:e67–74.
20. Hisada M, Biggar RJ, Greene MH, Fraumeni JF Jr, Travis LB. Solid tumors after chronic lymphocytic leukemia. Blood. 2001;98:1979–81.
21. Tsimberidou AM, Wen S, McLaughlin P, O'Brien S, Wierda WG, Lerner S, et al. Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. J Clin Oncol. 2009;27:904–10.
22. Maurer C, Langerbeins P, Bahlo J, Cramer P, Fink AM, Pflug N, et al. Effect of first-line treatment on second primary malignancies and Richter's transformation in patients with CLL. Leukemia. 2016;30:2019–25.
23. Solomon BM, Rabe KG, Slager SL, Brewer JD, Cerhan JR, Shanafelt TD. Overall and cancer-specific survival of patients with breast, colon, kidney, and lung cancers with and without chronic lymphocytic leukemia: a SEER population-based study. J Clin Oncol. 2013;31:930–7.
24. Kleinstern G, Rishi A, Achenbach SJ, Chaffee KR, Kay NE, Shanafelt TD, et al. Skin cancers among chronic lymphocytic leukemia (CLL) patients - the effect of UV radiation and CLL clinical characteristics. Blood. 2016;128:4772.
25. Oscier D, Else M, Matutes E, Morilla R, Strefford JC, Catovsky D. The morphology of CLL revisited: the clinical significance of prolymphocytes and correlations with prognostic/molecular markers in the LRF CLL4 trial. Br J Haematol. 2016;174:767–75.
26. Autore F, Strati P, Innocenti I, Corrente F, Trentin L, Cortelezzi A, et al. LDH levels predict progression-free survival in treatment-NaÏVe patients with trisomy 12 chronic lymphocytic leukemia. Blood. 2016;128:3211. Abstract.
27. Giné E, Martinez A, Villamor N, López-Guillermo A, Camos M, Martinez D, et al. Expanded and highly active proliferation centers identify a histological subtype of chronic lymphocytic leukemia ("accelerated" chronic lymphocytic leukemia) with aggressive clinical behavior. Haematologica. 2010;95:1526–33.
28. Dearden C, Wade R, Else M, Richards S, Milligan D, Hamblin T, et al. The prognostic significance of a positive direct antiglobulin test in chronic lymphocytic leukemia: a beneficial effect of the combination of fludarabine and cyclophosphamide on the incidence of hemolytic anemia. Blood. 2008;111:1820–6.
29. Rogers KA, Ruppert AS, Bingman A, Andritsos LA, Awan FT, Blum KA, et al. Incidence and description of autoimmune cytopenias during treatment with ibrutinib for chronic lymphocytic leukemia. Leukemia. 2016;30:346–50.
30. Muntañola A, Bosch F, Arguis P, Arellano-Rodrigo E, Ayuso C, Giné E, et al. Abdominal computed tomography predicts progression in patients with Rai stage 0 chronic lymphocytic leukemia. J Clin Oncol. 2007;25:1576–80.
31. Rai KR. A critical analysis of staging in CLL. In: Gale RP, Rai KR, editors. Chronic lymphocytic leukemia: recent progress and future directions. New York: Alan R. Liss; 1987. p. 253–64.
32. Binet J-L, Catovsky D, Chandra P, Dighiero G, Montserrat E, Rai KR, et al. Chronic lymphocytic leukaemia: proposals for a revised prognostic staging system. Br J Haematol. 1981;48:365–7.
33. International Workshop on Chronic Lymphocytic Leukemia. Chronic lymphocytic leukemia: recommendations for diagnosis, staging, and response criteria. Ann Intern Med. 1989;110:236–8.
34. French Cooperative Group on Chronic Lymphocytic Leukaemia. Natural history of stage A chronic lymphocytic leukaemia untreated patients. Br J Haematol. 1990;76:45–57.
35. Binet J-L, Catovsky D, Chastang C, Dighiero G, Fooks J, Galton DAG, et al. Workshop: prognostic features of early CLL. Lancet. 1989;334:968–9.
36. Catovsky D, Richards S, Matutes E, Oscier D, Dyer MJ, Bezares RF, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. Lancet. 2007;370:230–9.
37. Zent CS, Ding W, Schwager SM, Reinalda MS, Hoyer JD, Jelinek DF, et al. The prognostic significance of cytopenia in chronic lymphocytic leukaemia/small lymphocytic lymphoma. Br J Haematol. 2008;141:615–21.
38. Else M, Cocks K, Crofts S, Wade R, Richards SM, Catovsky D, et al. Quality of life in chronic lymphocytic leukemia: 5-year results from the multicenter randomized LRF CLL4 trial. Leuk Lymphoma. 2012;53:1289–98.
39. Shanafelt TD, Bowen D, Venkat C, Slager SL, Zent CS, Kay NE, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. Br J Haematol. 2007;139:255–64.

Author Queries

Chapter No.: 3 0004271563

Queries	Details Required	Author's Response
AU1	Please check and confirm if the affiliations are presented correctly.	
AU2	Please check the hierarchy of the section headings and confirm if correct.	
AU3	Please check the presentation of figures and their captions, and correct if necessary.	
AU4	Please check the occurrence "(See also chapters …)" at the end of the paragraph starting "For patients, particularly …", and provide the corresponding chapter numbers to include.	