(REVIEW ARTICLE)

Update on diagnosis and treatment of Chronic Lymphocytic Leukemia (CLL)

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Abstract

Chronic lymphocytic leukemia (CLL) defined by a minimum of 5x109/L monoclonal B cells in the blood, is the commonest leukemia found in adults western countries, affects more than 200000 people and is associated with approximately 4410 death in the USA annually. CLL is characterized by a progressive proliferation and accumulation of mature yet functionally incompetent lymphocytes. The disease typically occurs in elderly patients and has a highly variable clinical course. Leukemic transformation is initiated by specific genomic alterations that impair apoptosis of clonal B-cells.

Diagnosis: The diagnosis of chronic lymphocytic leukemia (CLL) requires the presence of more than or equal to 5×10^9/L B lymphocytes (5000/μL) in the peripheral blood for the duration of at least 3 months. Immunophenotyping of circulating B-lymphocytes, which identify a clonal B-cell population carrying the CD5 antigen, as well as typical B-cell markers are confirmatory test.

Prognosis: The two similar clinical staging systems, Binet and Rai stages, create prognostic information by using results of physical examination and blood counts. Various molecular biology markers also have prognostic value. Mutations of the *TP53* gene and x chromosome 17 chromosome (*del [17p]*) predict resistance to chemoimmunotherapy and a shorter time to progression, with most targeted therapies. A comprehensive, international prognostic score (CLL-IPI) integrates genetic, biological and clinical variables to identify distinct risk groups of CLL patients.

Therapy: Early-stage disease of CLL patients are followed up regularly, only patients with active or symptomatic disease or with advanced stages of Binet or Rai require treatment. When treatment is indicated, most patients with CLL have several options: a combination of obinutuzumab and venetoclax, ibrutinib monotherapy, or immunochemotherapy. In patients under 65 years of age who are physically fit (particularly if they have a mutated IGVH gene), immunochemotherapy with fludarabine, cyclophosphamide, and rituximab remains the standard of care because of its potential therapeutic potential. In case of relapse, the initial treatment can be repeated if the treatment-free period exceeds 3 years. And in case of early recurrence of the disease, treatment should be switched to an alternative regime. Patients with del(17p) or TP53 mutations are another high-risk group and should be treated with targeted drugs. Allogeneic SCT can be considered in patients with TP53 or del(17p) mutations or in patients on inhibitor therapy.

Keywords: CLL; Epidemiology; Diagnosis; Treatment; Prognosis; Relapsed therapy; Targeted therapy

1. Introduction

Chronic lymphocytic leukemia (CLL), is a typically slow-growing cancer which begins in lymphocytes in the bone marrow and extends into the blood. It is the proliferation and accumulation of lymphocytes (usually B cells) that are relatively unresponsive to antigenic stimuli. CLL is characterized by the clonal expansion and accumulation of mature

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CD5+ with the B-cell antigens CD19, CD20, and CD23. CD19+ and CD23+ B lymphocytes in the peripheral blood, bone marrow, and secondary lymphoid organs [1-4]. Each clone of leuke-mia cells is restricted to expression of either kappa or lambda immunoglobulin light chains. [5] CLL cells are phenotypically similar to antigen-experienced B cells and show gene expression profiles similar to memory B cells [6]. The cellular origin of CLL is still debated, but it is assumed that CLL cells originate either from unmutated mature CD5+ B cells or CD5+CD27+ post-germinal center B-cell subsets.

CLL is a disease predominantly of the older age group as the median age at initial diagnosis is 65-70 years and the male to female ratio 2:1. [7] Chronic lymphocytic leukemia is the most frequent type of leukemia in western countries. In the USA CLL estimated at 3.5 per 100,000 (male 5 female 2.5) [8]. in the UK estimate of 6.15 per 100,000 have been reported[9].

Immunophenotyping :In CLL cells co-express the surface antigen CD5 with the B-cell antigens CD19, CD20, and CD23. The levels of surface immunoglobulin, CD20, and CD79b are characteristically low compared to those found on normal B cells [10-11]. Each clone of leukemia cells is restricted to expression of either kappa or lambda immu-noglobulin light chains [10].

Approximately 70% to 80% of patients with CLL are asymptomatic at the time od diagnosis, and one third will never require treatment for CLL. The main feature of chronic lymphocytic leukemia is clonal proliferation and accumulation of mature, often CD5-positive, B cells in the lymph nodes, spleen, blood, and bone marrow [12]. An accurate and comprehensive description of the genetic landscape of CLL in large cohorts, showing that the disease often begins with the loss or addition of large amounts of chromosomal material (eg, 13q deletion, 11q deletion, trisomy 12), followed by additional mutations. The leukemia can be more aggressive [13].

Deletions in 11q22-q23, typically involve the ataxia telangiectasia (ATM) gene [14] which causes a genomic instability that prevent correct DNA-damage reparation, allow the accumulation of mutations and thus may contribute to CLL pathogenesis. Interestingly, the presence of a 17p or 11q deletion is associated with poor prognosis and predominates among advanced stages of the disease and among patients displaying unmutated VH genes, whereas the 13q deletion or a normal karyotype are associated with good prognosis, early disease and mutated VH genes.

Patients usually have a good performance status at diagnosis. Lymphadenopathy may be observed in approximately 80% of cases often with cervical and axillary lymph nodes bilaterally and symmetrically being affected. Splenomegaly is usually mild to moderate and is observed in approximately 50% of cases; hepatomegaly is less frequent. Anemia and thrombocytopenia may be observed in 15–30% of patients. immune thrombocytopenia (ITP), and immune neutropenia]. Lymphocytosis is always present, but the absolute number of lymphocytes is extremely variable. Morphological evaluation of a blood smear should show small mature lymphocytes with a narrow cytoplasm, a dense nucleus with partially aggregated chromatin, and the absence of visible nucleoli. CLL is defined by the presence of at least 5×10^9/L CD5+/CD23+ monoclonal B lymphocytes in peripheral blood (PB) for more than three months, with immunophenotyping of PB being sufficient for diagnosis.

The classical prognostic factors in CLL include clinical factors such as Rai stage, age, gender, and comorbid conditions as well as laboratory factors such as lymphocyte doubling time . Additional major prognostic indicators include CD38 expression, presence or absence of mutation in the variable heavy immunoglobin (IgVH), and specific cytogenetic abnormalities.

Many different drugs and drug combinations can be used as the first treatment for CLL. The options include monoclonal antibodies, target therapy and different combinations of these. The most common protocols are Chlorambucil and rituximab, FCR: fludarabine, cyclophosphamide, and rituximab, Bendamustine and rituximab, High-dose prednisone and rituximab, PCR: pentostatin, cyclophosphamide, and rituximab, Venetoclax alone, or with rituximab, Venetoclax and obinutuzumab , Alemtuzumab alone or with rituximab, Acalabrutinib , alone or with obinutuzumab , Ibrutinib, alone or with rituximab, Ibrutinib and obinutuzumab. It is now more important than ever to include patients with CLL in clinical protocols, in particular those with high-risk features and/or with refractory disease. If we all make an effort, we are confident that CLL will be a different disease with an improved outcome in 5–10 years from now.

2. Epidemiology

The annual incidence of CLL varies with the age and gender of the population. CLL is the most common type of leukemia in western countries, accounting for about 22% to 30% of all leukemias worldwide. While it is estimated at 3.5 per 100,000 in the US (males 5.0; females 2.5) [15], in the UK it is given as 6.15 per 100,000 [16]. In some Asian countries (eg, India, China, Japan), the percentage of CLL cases is much lower (4–10% of leukemias). [17-19] Despite this, these

countries have large populations, so the actual number of patients is likely to be similar. Global annual incidence ranges from <1 to 5.5 per 100,000 people, and males are more commonly affected than females. The incidence of CLL is approximately 4.2 cases per 100,000 people in the western world. [20] Caucasian populations have a significantly higher incidence compared to Japanese and Chinese populations, even in patients who immigrated to the United States, indicating that genetic influences are stronger than environmental factors in pathogenesis. The nature of this genetic predisposition is still unknown.

3. Clinical Features

The patients with chronic lymphocytic leukemia has diagnosed in an asymptomatic phase in 35 to 45 per cent in early 1975 to reach 55-65%. In symptomatic patients the most common features are symmetrical lymph node enlargement in most of the patients , loss of weight and symptoms and signs of anemia. An important complication in approximately 10% of cases is acquired haemolytic anaemia. [21] This is sometimes the first manifestation of chronic lymphatic leukaemia. It should be suspected when the degree of anaemia is in appropriately severe for the degree of lymph node and splenic enlargement, the degree of lymphocytosis, or when spherocytes or agglutination are present in the blood film[22]. A distinctive feature of the natural history of CLL is that neoplastic B lymphocytes accumulate over time. Therefore in all patients the occasional features are splenomegaly , hepatomegaly and hemorrhagic manifestation in patients with thrombocytopenia. The causes of thrombocytopenia are like ITP. This type of thrombocytopenia is respond to corticosteroid or splenectomy. Impaired platelet production due to hemopoietic tissue replacement by the diseases or from myelosuppressive effects of agents used for therapy of the disorder. Other manifestations like respiratory infections ,skin infiltration, tonsillar enlargement, nervous system manifestations , Bone or Joint pain, and disturbance of vision or hearing are late manifestations [23].

4. Blood Picture

Haemoglobin is normal in early stages to moderate or severely depressed values in advanced CLL. Anemia is usually normochromic and normocytic. When anaemia is due to haemolysis, it usually has the typical features of autoantibody-mediated red cell destruction, with spherocytosis, a positive Coomb's test, and a reticulocytosis. The typical features of CLL are leukocytosis, with lymphocytes count ranged from 50,000 to 200,000/μ.. Sometimes leukocytes are less than 10,000. 90% or more of the leukocytes are mature lymphocytes: CLL cells are typically small, with condensed nuclear chromatin, absent nucleoli, high nuclear to cytoplasmic ratio and round or ovoid nuclei. Nuclear clefts or folds are only seen in a minority of cells (Figure 1).

The morphology of some cases is atypical, with increased pleomorphism, occasional nucleoli and more abundant cytoplasm. Atypical morphology with an increased proportion of prolymphocytes is associated with cytogenetic abnormalities, most often trisomy 12 and del17p , progressive disease and refractoriness to therapy .
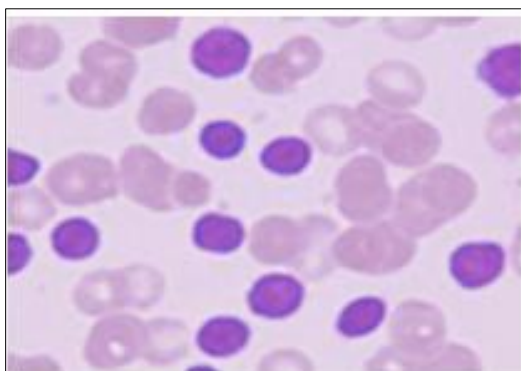

Figure 1 Chronic lymphocytic leukemia

Thrombocytopenia, with counts less than 50,000/μL is common. It is a feature of advanced stage. Serum Immunogbulin decreased in most CLL in late stages. It may fall to 0.3 to 0.4 g/dl and patient become more susceptible to all types of infection [22].

Richter syndrome (RS) is defined as the transformation of chronic lymphocytic leukemia (CLL) into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL). RS occurs in approximately 2% to 10% of CLL patients during the course of their disease, with a transformation rate of 0.5% to 1% per year[24].

5. Bone Marrow Aspiration and Biopsy

Usually are not necessary for making the diagnosis of CLL except in those aleukemic or subleukemic cases with no nodal or splenic involvement and few or no abnormal cells in the peripheral blood.

In marrow there is increase of lymphocytes and a corresponding reduction of megakaryocytes, myeloid precursors, and erythroid precursors. A bone marrow is only performed to assess marrow reserves and genetic analysis prior to therapy, and after treatment completion to assess response.

Chromosomal abnormalities are detected in more than 50% of patients with CLL and indicate a worse prognosis. The most frequently encountered is trisomy 12 (+ 12). Other cytogenetic abnormalities are 14q translocation.

In more than 90% of the cases, CLL lymphocytes express the CD5 antigen, which was formerly thought to be a T-cell antigen. Cells from most cases of B-CLL also expresses CD19, CD24, CD37 and CD21 antigen. About 60% of CLL are positive for CD23 but infrequently demonstrate positivity for CD22 [25].

CLL scoring systems have been devised to take into account some of these features and indicate the likelihood of a diagnosis of CLL based on the immunophenotypic characteristics (Table 1) [26, 27]. True CLL will have a score of 3 or more in 96% of cases. The assessment through scoring can be further strengthened by paying attention to intensity of CD20 expression. A proportion of CLL, 7–20% [28], will not show CD5 expression, but because of the multiple parameters used in scoring the diagnosis should still not be difficult. Some CLL cases show absent surface light chains and others show oligoclonal or biclonal expression [29], for example one kappa and one lambda restricted clone. These cases
should not be misinterpreted as polyclonal: the immunophenotype is otherwise that of CLL (CD5+ CD23+ CD79b-/dim CD20dim, FMC7-). Confirmation of clonality in those cases with absent surface light chains can be achieved by demonstrating cytoplasmic light chain restriction.

6. Cytogenetics

Standard cytogenetics using metaphase preparations are rarely useful in CLL as the cells are difficult to grow *in vitro*. Fluorescent *in situ* hybridization (FISH) studies (using fluorescent probes which align and hybridize with segments of the chromosome of interest), have identified a number of important abnormalities which assist in making a diagnosis in difficult cases but also carry prognostic significance (with del11q and del17p in particular, having an adverse outcome) (Table 2) [30]. The presence of such, together with IgVH gene mutation status, are important predictors of disease behaviour in early stage patients [31].

Table 1 The CLL scoring system

Antigen	Expression	Score
CD 5	Positive	1
CD23	Positive	1
FMC7	Negative	1
Surface Ig	Weak/dim	1
CD79b	Negative	1

Reproduced from Moreau et al. [6], with permission from American Society for Clinical Pathology

Important molecular markers include ZAP 70 and IgVH gene rearrangements. ZAP-70 is an intracellular protein that promulgates activation signals delivered to T lymphocytes and natural killer cells by their surface receptors for antigen [32]. It is rarely present in normal B cells but has been found in B cells from patients with CLL [33]. Patients with clones having few or no V-gene mutations or with many CD38+ or ZAP-70+ B cells had an aggressive, usually fatal course, whereas patients with mutated clones or few CD38+ or ZAP-70+ B cells had an indolent course [34].

Table 2 Cytogenetic aberrations and survival in CLL

Cytogenetic findings	Median survival (Months)
Normal	111
13q deletion	133
Trisomy12	114
11q deletion	79
17p deletion	32

Table 3 The RAI staging for chronic lymphocytic leukemia [11]

Stages	Characteristics	Survival
0	Peripheral blood lymphocytosis >15000/μL	>150 months
I	Lymphocytosis and lymphadenopathy	100 months
II	Hepatomegaly or splenomegaly or both	71 months
III	Anemia (<11g/dl or Hct <33%)	19 months
IV	Thrombocytopenia (platelets < 100,000/μL	19 months

Adapted from Rai KR, et al, Clinical staging of chronic Lymphocytic leukemia. Blood 1975; 46:219

The median survival of patients with chronic lymphocytic leukaemia was about nine years. Clinical stages, blood lymphocyte counts and morphology, bone marrow histopathological findings, serum lactate dehydrogenase, immunophenotyping ,and cytogenetic abnormalities are good predictors of survival [35-39] Table 3.

7. Treatment of Chronic Lymphoyctic Leukemia

The following parameters should be considered before recommending a treatment for CLL:

- The clinical stage of the disease
- The symptoms of the patient.
- The fitness and concomitant diseases of the patient, particular with regard to the potential organ toxicity of the newer, targeted agents.
- The genetic risk of the leukemia.
- The treatment situation (first versus second line, response versus nonresponse to the last treatment).

The CLL patients are staged according to Rai staging system. Most patients are managed supportively. Asymptomatic patient and those with early stages (0,I, II) may not be treated. 2/3 of patients respond to therapy with a single alkylating agent such as chlorambucil which may be used (20-30 mg/m^2 orally every 2-4 weeks; or in a daily dose of 2-5 mg/m^2 until WBCs stabilized. Patients with stage III and IV are treated with chlorambucil combined with prednisone (20-40mg/m^2/d) for one week every 2-3 weeks.

Prednisolone is effective in the treatment of autoimmune haemolysis or thrombocytopenia [40].

Purine Nucleoside Analogous: (E.g deoxycoformycin, 2-chlorodeoxy-adenosine, fludarabin) based on analogues of adenosine have recently become available for the treatment of CLL and low grade lymphomas. Fludarabine may be more effective as a single agent than chlorambucil. Fludarabine also useful in patients resist to chlorambucil (25-30 mg/m^2/day i.v for 45 days) repeated each month for 3-6 months [41].

Alternatively, they may be given CVP regimen (or R-CVP) every 3 weeks:

- Rituximab IV 375mg/m2 day 1 , Cyclophosphamide IV 750 mg/m2 day 1

- Vincristine IV 1.4 mg/m2(dose at 2 mg) day 1, Prednisone PO 100 mg, orally days 1-5. (if rituximab not available, give CVP at the same doses).

Current therapies of CLL include purine analogues (fludarabine and cladribine), monoclonal antibodies against CD20 (rituximab) and CD52 (alemtuzumab), radiation, and alkylating agents (chlorambucil and cyclophosphamide). FCR (Rituximab 375 mg/m² IV day 1, Fludarabine 25 mg/m² IV days 2–4, Cyclophosphamide 250 mg/m² IV over 1 hour days 2–4) have shown response rate of 30% to 60% in fludarabin-pretreated populations [42-43]. Alemtuzumab is showing increasing promise as a single or combined agent in refractory disease [44-45].

- Standard Bendamustine-Rituximab regimen; is Bendamustine IV 90 mg/m2 on days 1,2 and Rituximab IV 375 mg/m2 on day 1 are administered every 4 weeks for 4 cycles.
- Ibrutinib (Imbruvica) is a targeted drug that can be used to treat chronic lymphocytic leukemia (CLL). it is a bruton tyrosine kinase (BTK), is a critical enzyme in the B-cell receptor signalling pathway and is a novel therapeutic target in CLL approved for the treatment of patients with relapsed refractory chronic lymphocytic leukaemia (RR-CLL) [46-47].
- Idelalisib (Zydelig) is another targeted drug for CLL. It blocks a kinase protein called PI3K. This drug has been shown to help treat CLL after other treatments have been tried. The combination of idelalisib and rituximab, as compared with placebo and rituximab, significantly improved progression-free survival, response rate, and overall survival among patients with relapsed CLL who were less able to undergo chemotherapy[48].
- Venetoclax (Venclexta) is a selective drug that targets BCL-2, a protein in CLL cells had a manageable safety profile and induced substantial responses in patients with relapsed CLL or small lymphocytic lymphoma (SLL), including those with poor prognostic features [49].
- Acalabrutinib is a next-generation, irreversible BTKi approved for the treatment of CLL and small lymphocytic lymphoma with a shorter plasma half-life and greater selectivity for BTK compared with ibrutinib.[50] Acalabrutinib demonstrated superior progression-free survival (PFS) versus chemoimmunotherapy in phase III studies in patients with previously untreated (ELEVATE-TN) or relapsed or refractory (ASCEND) CLL, with toxicity-related treatment discontinuations in 9% and 11% of patients at the median follow-up of 28.3 and 16.1 months, respectively.
- Zanubrutinib; Like acalabrutinib, zanubrutinib is a second-generation, covalent BTK inhibitor with higher specificity and less off-target inhibition than ibrutinib. It was initially tested in a phase 1 study of various B cell malignancies.
- Obinutuzumab (GA101) is a novel type II, humanized, CD20 mAb that has been glycoengineered to reduce core fucosylation, conferring enhanced affinity for the human FcγRIIIa receptor on effector cells and, hence, enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). As a type II mAb, GA101 has lower capacity to relocalize CD20 into lipid rafts upon binding compared with type I antibodies and is a less potent in inducing complement-dependent cytotoxicity (CDC) but more potent in mediating homotypic cell adhesion and direct cell death. Subsequent clinical trials confirmed the high efficacy of obinutuzumab in CLL patients. The CLL11 trial demonstrated that obinutuzumab can induce considerable rates of MRD negativity in comorbid patients with durable remissions. Therefore, Ob-Clb is a current standard of care for previously untreated CLL patients with comorbidities.[51,52].
- Ofatumumab, a type I antibody like rituximab, is approved for treatment of patients with CLL refractory to fludarabine and alemtuzumab). In preclinical studies, ofatumumab was a more potent mediator of CDC than rituximab. Ofatumumab binds to a different epitope on CD20, involving both the small and large loops of CD20 [53-54].
- Lenalidomide proved to be effective in CLL as single agents or in combination with various chemo immunotherapeutic regimens. There were several concerns regarding toxicity, but modified protocols with low starting dose and gradual dose escalation suggest good tolerability. Lenalidomide might have a place in the first-line setting in older patients or as second-third line agent for patients treated with frontline chemoimmunotherapy. Currently, chemoimmunotherapy represents the standard first-line therapy for young and fit CLL patients, but patients who became refractory to fludarabine or carry deletion/mutation of TP53 and older or unfit patients could profit from alternative treatments, including, lenalidomide-based regimens [55].
- Pembrolizumab :Preclinical evidence suggested that the programmed death 1 (PD-1) pathway is critical for inhibiting the immune surveillance of CLL. Therefore, a phase 2 trial was performed with pembrolizumab, a humanized PD-1-blocking antibody, at a dose of 200 mg every 3 weeks in relapsed and transformed CLL [56].
- CART cells: An initial report using a lentiviral vector expressing a chimeric antigen receptor(CAR) with specificity for the B-cell antigen CD19, coupled with CD137 (a costimulatory receptor in T cells [4-1BB]) and CD3-zeta (a signal-transduction component of the T-cell antigen receptor) signaling domains showed a very impressive efficacy. A low dose (approximately 1.5×10^5 cells per kilogram of body weight) of autologous CAR-

modified T cells reinfused into a patient with refractory CLL expanded to a level that was more than 1000 times as high as the initial engraftment level in vivo, with delayed development of a tumor lysis syndrome and subsequent CR. [57].

Autologous and allogenic bone marrow transplantations are being explored as treatment options and promising treatment modalities [58].

Outcomes are improved by the addition of immunotherapy to combination chemotherapy for initial treatment in all subsets of treated patients.

Overall response rates between 75% and 90% and complete responses between 22% and 45% are expected in the current era, with more than 80% of treated patients alive at 3 years. Overall, 5-year survival has increased to 66% from 60% (P < .001) in the past 10 years [59] .

Table 4 CLL treatment

Stage	Del(17p)or TP53	Fitness	IGHV	Therapy
Inactive disease stage 0-II	Irrelevant	Irrelevant	Irrelevant	None
Active disease stage III-IV	Yes	Irrelevant	Irrelevant	Ibrutinib/acalabrutinib or Venetoclax+Obinutuzumab or Idelalisib-Rituximab
	No	Go go	M	FCR or Ibrutinib/Acalabrutinib or Venetoclax+Obinutuzumab
			U	Ibrutinib/acalabrutinib or Venetoclax+Obinutuzumab or FCR
		Slow go	M	Venetoclax+Obinutuzumab or Ibrutinib/acalabrutinib or chlorombucil -Obinutuzumab
			U	Venetoclax+Obinutuzumab or Ibrutinib/acalabrutinib + chlorombucil -Obinutuzumab
Refractory or Progress within 3 years		Go go		Change to venetoclax+rituximab, ibrutinib, or acalabrutinib.other options include: idelalisib+R, FA, FCR (after BR, Venetoclax, A-Dex, lenalidomide, BR after (FCR)
		Slow go		Change to: venetoclax+rituximab, ibrutinib or acalabrutinib. Other options include: idelalisib+R,A, FCR-lite, BR, lenalidomide(+R), Ofatumumab
Progress after 3 years		All		Repetition of IL therapy could be considered, but change to target therapy if chemotherapy previously given

The choice is entirely different in treatment-refractory CLL (as defined by an early relapse within 6 months after the last treatment), similar to relapsed cases with a chromosomal aberration *del(17p)*. By principle, the initial regimen should be changed since the second remission tends to be shorter and one of the potent second-line regimen should be selected. The following options exist:[60-62]

- Venetoclax in combination with rituximab for up to 2 years (or alone as a continuous therapy).
- BTK inhibitors (ibrutinib, acalabrutinib) alone or combined with venetoclax.
- Acalabrutinib combined with obinutuzumab.
- PI3K inhibitors (idelalisib and rituximab, duvelisib, umbralisib, etc.).
- Cellular therapies like CART cell therapy or allogeneic stem cell transplantation with curative intent.
- Alemtuzumab alone or in combination

8. Other Measures

Immunoglobulin replacement: e.g. 250-mg/kg month by intravenous infusion is useful for patients who have hypogammaglobulinemia and/ or recurrent infections and a poor IgG immune response to pneumococcal polysaccharide vaccination [63].

Prophylaxis against pneumocystis, herpes simplex virus, and varizella zoster virus, as well as a monitoring for CMV reactivation should be considered when treating CLL patients with these agents [64].

9. Prognostic factors

The classical prognostic factors in CLL include clinical factors such as Rai and Binet staging system are age, gender, and comorbid conditions as well as laboratory factors such as lymphocyte doubling time , serum markers including β2-microglobulin levels [65], thymidine kinase levels [66] and soluble CD23 levels [67] as well as cellular markers including CD38 [68] and ζ chain associated protein kinase 70 (ZAP70) [69], CD49d [70], chemokines CCL3 and CCL4, genetic parameters including mutational status of IGHV genes and cytogenetic aberrations [71].Also unfavorable prognostic factors are male gender, 65 years old, functional disorders due to medical comorbidities, late disease stage at the time of diagnosis, primary WBC over 35×10^9/l, lymphocyte doubling time < 6 months and diffuse histological pattern in the bone marrow infiltration [72]. Elevated levels of beta2-microglobulin, serum thymidine, and serum CD23 at diagnosis also lead to a poor prognosis [73].

10. Conclusion

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia that affects adults, accounting for about 22% to 30% of all leukemias worldwide. The median age of diagnosis is 70.The average 5-year survival rate following a diagnosis of chronic lymphocytic leukemia, or CLL, is between 50 and 80 percent, according to Healthline. Survival at the 10-year mark is around 34.8 percent for both CLL types. Advances in the understanding of CLL have amplified the clinical and prognostic relevance of genetic alterations, which have led to the emergence of novel targeted therapies and monoclonal antibodies. These new therapeutic agents have improved the outcomes of patients with CLL, including those with high-risk disease. The prognosis of CLL is affected by several factors. Advanced age, high blood levels of beta-2-microglobulin and deleted chromosomes 17 and 11 in the leukemic cells all contribute to a poor prognosis. People with CLL cells containing low levels of CD38 or ZAP-70 proteins or with a deletion on part of chromosome 13 have a better prognosis.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest.

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