Diagnosis and management of complications of chronic lymphocytic leukemia/small lymphocytic lymphoma

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Abstract

Chronic lymphocytic leukemia (CLL) causes early-onset immune dysregulation increasing the risk of infection, second malignancies, and autoimmune complications by poorly understood mechanisms. Targeted therapy has improved therapeutic outcomes but persistent immune deficiency remains an unresolved problem. Severe infections (20/100 patient-years) cause or contribute to over 35% of CLL-related deaths. Most identified infections are bacterial (~70%) with the commonest blood isolates being *Escherichia coli, Streptococcus pneumoniae,* and *Staphylococcus* aureus. Viral infections (~25%) are disproportionately caused by Herpes viruses and influenza. Most common infection sites are lower respiratory tract, skin, and urogenital tract. CLL patients have an increased risk (~2-fold) of second malignancies with the commonest being squamous and basal cell skin cancer, melanoma, and lung cancer. There is a significantly increased risk of additional clonal and non-clonal non-Hodgkin lymphomas and Hodgkin lymphoma. Autoimmune cytopenias affect ~10% of CLL patients causing anemia (hemolysis and red cell aplasia), thrombocytopenia, and neutropenia. Nonhematological autoimmune complications are rare. Management of these complications requires a comprehensive multidisciplinary approach including education, preventative medicine, active monitoring, and early diagnosis and treatment. Research to better understand CLL-related immune defects and determine how to reverse them is essential for improved clinical care.

Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) is the most prevalent lymphoid malignancy in Europe [1] and North America [2] and causes considerable morbidity and mortality. CLL is associated with early onset and often profound immune dysregulation that increases the risk of infection, second malignancies, and autoimmune complications [3–5]. The incidence and prevalence of these complications are likely to increase because of population aging and the ongoing development of more effective but still noncurative therapies resulting in longer survival.

Immune dysfunction effecting both the adaptive and innate immune responses occurs early in the course of CLL and high-count monoclonal B-cell lymphocytosis (MBL) [6–8]. The mechanism by which CLL induces immune dysfunction is poorly understood. T cell dysfunction in CLL is characterized by abnormal CD4:CD8 effector ratios, skewed helper T cell profiles (e.g., increased Th2:Th1), impaired immune synapse formation, and reduced proliferative and cytotoxic activities characteristic of T cell exhaustion [8–11]. Humoral immune defects include skewed memory B and plasma cell populations that correlate with hypogammaglobulinemia [12, 13]. Innate immune defects include altered monocyte and macrophage immunophenotypes with increased circulating "immunosuppressive" (CD14+/HLA-DR$^{neg-low}$) cells [14, 15]. CLL also causes impaired neutrophil function and decreases serum complement levels [7].

Treatment of progressive CLL with chemoimmunotherapy causes short-term exacerbation of CLL immunosuppression and subsequent immune recovery, even in patients with a large reduction of CLL disease burden, is limited resulting in long-term immune compromise [16]. Treatment with targeted therapy has less initial detrimental effect on immune competence compared to chemoimmunotherapy but there is currently no evidence of substantial recovery of immune competence in responding patients. Ibrutinib has been reported to reverse some CLL-induced immune changes. Studies have shown increased T cell activity, reversal of the exhaustion phenotype and Th1 skewing, and reduced expression of immunosuppressive molecules (CD200, BTLA, and IL-10) but the role of inhibition of BTK versus off-target ibrutinib effects (e.g., on T cell TEK family kinase ITK) is still unclear [17–19]. Studies of chimeric antigen receptor (CAR) T cell products, bispecific antibody targeted T cells, and MHC-independent gamma/delta+ T cells, have also pointed toward the ability of ibrutinib to promote T cell activation by off-target TEC protein kinase inhibition in the short-term [18, 20–22]. In contrast, the more specific BTK inhibitor acalabrutinib does not appear to have the same effects as ibrutinib on T cell subsets [19]. The availability of targeted therapy has greatly improved the outcome for many patients with CLL, but we are still not able to correct CLL-induced immune deficiency [23]. A better understanding of the complex effects of CLL on immune function will required to achieve the important goal of immune reconstitution.

Infection

Historically, major infections were reported to occur at least once in more than 50% of CLL patients and to cause or contributed to 30%–

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50% of deaths [24, 25]. Some of the more contemporary data from clinical trials could be biased by selective eligibility and enrollment of patients that are younger and fitter than the average of the CLL population [26, 27]. The risk and consequences of infections in CLL patients could also be changing because of the increasing use of less toxic and more effective targeted therapy [28] that have decreased the rate of serious infections following initiation of therapy [29]. With increased CLL patient survival, the lifetime risk of infections is increasing and complications not recognized as severe adverse effects by standardized criteria (e.g., shingles associated neuropathic pain) are causing more morbidity. The overall burden of infection in CLL patients is likely to remain a problem in the foreseeable future.

A recently published single-center observational study reported on a population of CLL patients during the transition period from chemoimmunotherapy to targeted therapy. Severe infections requiring inpatient admission or intravenous antimicrobial therapy had an incidence rate (IR) of 20/100 person-years and less severe infections occurred at a rate of 70/100 person-years [3]. The most common sites of severe infections were lower respiratory tract (IR 8/100 person-years), skin (IR 3/100 person-years), and urogenital tract (2/100 person-years). The causative organism could be determined in 38% of patients with the majority being bacterial (27% of all infections) followed by viral (7%) and fungal (4%). Fifteen (38%) of 40 deaths during the study were attributable to infections. In treatment naive patients multivariate analysis showed that the risk of infection was increased in patients with more advanced clinical stage at diagnosis and with increased time from diagnosis. Patients requiring treatment for CLL had increased risk of infection with the highest risks on patients treated with purine analoges or alemtuzumab. Patients treated with ibrutinib had higher risk of infection compared to treatment naive patients.

Patient with CLL are reported to have a propensity to infection with encapsulated bacteria. A Danish study reported on 317 positive blood cultures in 3,822 patients, which occurred at a rate of 15.5 per 1,000 patient-years in treatment naive and 62.3 per 1,000 patient-years in treated patients. The most commonly isolated bacteria were *Escherichia coli* (24%), *Streptococcus pneumoniae* (10%) and *Staphylococcus aureus* (9%) and 28% of patients died within 30 days of their positive blood culture [30].

Herpes virus reactivations and infections are increased in both patients with treatment naive and treated CLL. Varicella zoster is an important complication with both localized dermatome-restricted infections (shingles) and disseminated varicella. Shingles has been reported at rate of 3.1/100 patient-years with most (90%) being considered minor infections (grade <3) but with the potential to cause serious long-term neuropathy [3]. Disseminated varicella zoster is a rare but serious complication of CLL and its treatment [31].

Herpes simplex reactivation can cause serious complications in patients with CLL. Treatment naive patients have an increased rate of reactivation and this risk is significantly increased by immunosuppressive therapy [32]. Of particular concern is systemic dissemination causing severe illness. CLL patients also appear to have an increased risk of herpes simplex adenitis that can be clinically indistinguishable from transformation to diffuse large B-cell lymphoma (DLBCL) [33, 34]. Fortunately, this condition is usually rapidly responsive to anti-viral therapy.

Cytomegalovirus (CMV) reactivation can occur in treatment naive CLL patients, and the risk is increased in patients receiving highly immunosuppressive therapy and especially alemtuzumab [32]. Serious morbidity and mortality from CMV reactivation in high-risk CLL patients can be decreased by monitoring for CMV viremia and treating positive patients.

There is increasing data on the infectious complications in patients treated with targeted therapy. The 5-year follow-up data from studies of ibrutinib monotherapy in both treatment naive patients and relapsed/refractory (R/R) CLL showed a cumulative rate of grade 3 or higher infections of 42% at 3 years and 48% at 5 years with more cases in patients with R/R disease [35]. The most common infections were pneumonia, cellulitis, and sepsis. There have been concerns that ibrutinib could increase the risk of fungal infections in patients with CLL. Although atypical pneumonia caused by Pneumocystis jirovecci pneumonia (PJP) was reported in CLL patients on ibrutinib therapy, these infections were either asymptomatic (detected by routine CT scans) or caused only minor symptoms and responded to oral therapy [36]. PCP prophylaxis is currently not recommended [37]. Aspergillus infections could be a concern for patients treated with ibrutinib in combination with corticosteroids or with other additional causes of immunocompromise [38]. Reactivation of herpes virus infections and hepatitis B are rare in patients on ibrutinib monotherapy [29].

In contrast to ibrutinib, rates of infectious complications for CLL appear to be increased by regimens including idelalisib. Combination therapy clinical trials including idelalisib were halted by the Federal Drug Administration and European Drug Agency because of concerns for excess toxicity including increased rates of PJP and CMV infections [29]. There are limited data on the effect of duvelisib and umbralisib on risk of infection in CLL patients.

Management

Management of infection in CLL patients requires education of patients and care givers to respond rapidly to evidence of infection, appropriate vaccination, and prophylactic antimicrobial and immunoglobulin replacement therapy, and rapid recognition and aggressive treatment of serious infections by health care providers.

Vaccination

CLL patients should not get live vaccines but could benefit from inactive vaccines despite the generally poorer immune responses than in people without CLL. The pneumococcal conjugate vaccine (PCV) response rate is ~40% in early-stage CLL patients and protection can persist for more than 5 years [39]. The 23-valent pneumococcal polysaccharide vaccine (PPV23) generates poorer responses in CLL patients [39, 40] but is still considered protective and is recommended every 5 years [30]. The annual influenza vaccine is recommended for all CLL patients despite decreased efficacy [30] and limited data suggest that vaccine responses are not decreased by ibrutinib therapy [41].

Immunoglobulin replacement therapy

CLL is characterized by hypogammaglobulinemia that can worsen with progression of disease and treatment [13]. A series of randomized trials with short follow-up done in the 1980s and 1990s showed that intravenous immunoglobulin (IVIG) replacement therapy decreased the incidence of bacterial infections in CLL patients with hypogammaglobulinemia or a history of recurrent infections but did not significantly alter overall survival [13]. There are no validated criteria for use of immunoglobulin replacement therapy but consensus opinions include recommendations of supplementation in patients with hypogammaglobulinemia and two or more infections requiring antibiotics in 1 year [30].

Second Malignancies

Patients with CLL have an increased risk of second malignancies that can be the most common cause of death in some populations [5, 42]. A recently published report from the Swedish national CLL cohort included over 18,000 patients showed a 2-fold overall increase risk of a second cancer [43].

Skin cancer

The most common nonhematological malignancies in CLL patients involve the skin with an increase in relative risk for invasive nonmelanoma skin cancer of 24.5 for in situ and 7.6 for invasive nonmelanoma skin cancer, and an increased relative risk of melanoma of 3.2 [43].

Nonmelanoma skin cancer

CLL patients have an increased risk of both basal cell and squamous cell carcinoma that are likely to be more aggressive and can be metastatic [44]. There is also an increased risk of the rarer Kaposi sarcoma (relative risk 6.8) [43].

Melanoma

A recently published study of a single institution cohort showed that 18 (4%) of 470 patients seen over 16 years had 22 melanomas [45]. Compared to a matched CLL population from the U.S. Surveillance, Epidemiology, and End Results (SEER) database, the standardized ratio of invasive melanoma was significantly increased at 6.3 (95% CI 3.5–10.6) [45]. Most of the melanomas (77%) were diagnosed during recommended regular skin evaluation, only 12% of melanomas were advanced stage, and 45% of patients were CLL treatment naïve [45].

Other Nonhematological Cancers

Large population-based studies of CLL patients show a significantly higher risk of malignancies of the lungs, kidneys, colon, thyroid, salivary glands, head and neck, and central nervous system, renal cell, and Merkel cell carcinoma and sarcoma [42, 43].

Hematological malignancies

Second lymphoid malignancies: Patients with CLL have a significantly increased risk of additional non-Hodgkin lymphoma (relative risk 3.1) and Hodgkin lymphoma (relative risk 7.1) [43]. These second malignancies can be clonally related to their CLL or represent de-novo lymphoid disease.

Diffuse large B cell lymphoma (DLBCL) also known as classical Richter syndrome [46] occurs in 2%–8% of patients with CLL [46]. These DLBCL can arise in CLL patients by transformation of a CLL cell (80%) or a de novo event resulting in a clonally unrelated disease (20%) [47]. The risk of transformation to DLBCL in CLL patients is significantly increased in patients with TP53 disruption and NOTCH1 mutation [47]. Diagnosis of DLBCL in patients with CLL can be challenging. DLBCL needs to be distinguished from clonal evolution of CLL to a more aggressive disease histologically different from DLBCL and characterized by larger and more rapidly dividing cells in enlarged nodal proliferation centers. This discrete histological entity can occur spontaneously or during treatment with targeted therapy [46, 48]. In addition, patients with an established diagnosis of CLL can have an increasing number of circulating prolymphocytes over time, which is often associated with acquired TP53 defects and MYC translocations [49, 50]. Although this condition has previously been described as "prolymphocytic transformation," it is not a discrete disease entity and clearly different from primary B-cell prolymphocytic leukemia [46].

Diagnosis of Richters syndrome in patients with CLL can be difficult. The negative predictive value of [18]FDG PET/CT scans is over 97% for DLBCL in CLL patients and this imaging modality is also useful in selecting the most appropriate site for biopsy when highly FDG avid tissue is found [47]. Definitive diagnosis of DLBCL requires excision biopsy of a lymph node or large excision biopsy of involved tissue [51]. In patients with a diagnosis of DLBCL, VDJ rearrangement analysis or IGHV sequencing is then required to distinguish between DLBCL clonally related to the patients CLL and a clonally unrelated de novo DLBCL. Clonally related DLBCL has a gene expression profile distinct from de-novo DLBCL [47], no established treatment options and poor prognosis (median survival < 1 year) [41, 46]. The less common clonally unrelated DLBCL have similar biology and outcome to DLBCL arising in patients with no pre-existing lymphoid malignancy [46].

Hodgkin lymphoma occurs in <1% of CLL patients [46]. There is limited data on optimal treatment and median survival of 4 years is shorter than de-novo classical Hodgkin lymphoma [47].

Myeloid malignancies: Studies of large populations of CLL patients have not shown an increase in incidence of acute myelogenous leukemia [42]. However, combination chemotherapy including purine analoges and alkylating agents could increase the risk of treatment-related myelodysplastic syndrome/acute myeloid leukemia [52].

Management

Patients and their care providers need to be educated about risk prevention and monitoring. Patients should avoid ultraviolet irradiation by wearing protective clothing and using effective sunscreens. Patients are advised to do monthly skin checks and be

followed by a dermatologist at least annually. Patients should avoid other known carcinogens and especially tobacco and excessive alcohol. Patients and their families should be educated about the clinical manifestations of CLL transformation.

Autoimmune diseases

Patient with CLL have a significant increase in the rate of autoimmune cytopenias. CLL is not associated with an increased risk of the more common nonhematological autoimmune diseases [53]. Autoimmune cytopenias include autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), pure red blood cell aplasia (PRBCA), and autoimmune neutropenia. In >90% of patients, AIHA and ITP are caused by high-affinity polyclonal IgG produced by nonmalignant B cells implying a loss of self-tolerance by an as yet undefined mechanism [54]. A minority of patients have AIHA or ITP caused by monoclonal autoantibodies synthesized by the CLL cells. PRBC and autoimmune neutropenia can be caused by humoral or cellular (T-cell-mediated) cytotoxicity [54].

Autoimmune cytopenia can occur at any time in the course of CLL and in 25% of cases can precede or be concomitant with CLL [4]. Autoimmune cytopenia does not have the same adverse prognostic significance as bone marrow failure [4, 55–60]. This important clinical distinction is now recognized in the IWCLL recommendations for evaluation and treatment of progressive CLL [61]. However autoimmune cytopenia can be a serious and even fatal complication of CLL [62].

Autoimmune cytopenia incidence in CLL patients is ~0.5% per year [62] and causes ~25% of non-iatrogenic cytopenia [4]. AIHA (55%) is the most common presentation followed by ITP (47%), PRBCA (12%), and autoimmune neutropenia (4%). More than 10% of patients have more than one cytopenia with the most common being Evans syndrome (AIHA and ITP) [62].

CLL patients are at increased risk of paraneoplastic pemphigus [44], glomerulonephritis [63], and angioedema caused by C1q inhibitor deficiency [64]. CLL patients also have an increased risk of exaggerated arthropod reactions especially after mosquito bites that can lead to loss of skin integrity and serious skin infections [3, 44].

Management

Appropriate management of autoimmune cytopenia requires an accurate assessment of etiology by examination of the bone marrow. Concomitant extensive bone marrow involvement by CLL

(bone marrow index <15%) suggests a "complex" etiology requiring treatment for both the autoimmune cytopenia and progressive CLL. In contrast, patients with adequate bone marrow reserve have "simple" autoimmune cytopenia and do not require CLL directed therapy [4, 65]. Effective therapies for AIHA and ITP include corticosteroids, rituximab, and alkylating agents and PRBCA and autoimmune neutropenia can be responsive to cyclosporine and corticosteroids [66, 67]. Ibrutinib therapy does not appear to be associated with an increased risk of autoimmune disease and the drug has been used in the therapy of patients with CLL with generally good outcomes and can decrease the duration of immunosuppressive therapy [68-71].

Conclusion

CLL is a complex medical disease affecting the hematopoietic and immune systems resulting in complicating pathologies that cause considerable morbidity and mortality. Improving patient outcome requires preventative education and interventions, and active monitoring for early recognition and management of complications. This requires a team comprising the patients and their caregivers and dedicated health care providers. Research efforts should focus on better definition of the immune deficits induced by CLL and methods to restore immune competence in patients responsive to therapy.

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The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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