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Infectious Diseases and Clinical Complications During Treatment in CLL

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1. Introduction

Infectious complications continue to be one of the major causes of morbidity and mortality in patients with chronic lymphocytic leukemia (CLL). The pathogenesis of infections in these patients is multifactorial (Wadhwa & Morrison, 2006). Predisposition to infection in CLL is mediated through various abnormalities including both the immune defects inherent in the primary disease (impairment in humoral and cellular immunity) and in the further immunosuppression related to management of CLL (Morra et al., 1999). Increased infectious events may arise from the multiple courses of immunosuppressive therapy and progressive deterioration of a patient's immune system over the course of disease (Elter et al., 2009). Hypogammaglobulinemia is an important predisposing factor for infection in patients with early-stage disease and for those treated with conventional alkylating agents (Wadhwa & Morrison, 2006). It is probably the most important immune defect increases the risk of severe bacterial infections and its frequency and severity has direct relationship with the duration of the disease (Morra, et al., 1999). The majority of disease-specific complications in CLL, notably infection and autoimmunity, relate to the underlying alterations in immune function. Both cellular and humoral immunity are impaired with qualitative and quantitative defects in B cells, T cells, NK cells, neutrophils and the monocyte/macrophage lineage. Virtually all patients have reduced immunoglobulin levels, even in early stages, and this is associated with an increased frequency and severity of infection (Dearden, 2008). The immunodeficiency chiefly manifests as hypogammaglobulinaemia but involves all elements of the immune system. It is caused by the interpolation of tumor cells among immunological cells and mediated by bi-directional cell contact and secretion of cytokines, which both sustain and invigorate the tumor and suppress immunity. CLL treatment generally makes the immunodeficiency worse (Hamblin & Hamblin, 2008). The proportion of patients treated with purine analogs and monoclonal antibodies such as rituximab and alemtuzumab is increasing. As a result of this therapy, these patients often experience profound and sustained T-cell immunodeficiency. Consequently, the spectrum of organisms causing infections in these patients is changing from common bacterial organisms to less common opportunistic pathogens such as *Pneumocystis*, *Listeria*, mycobacteria, herpesviruses and *Candida* (Wadhwa & Morrison, 2006). The early recognition of infections as well as prophylactic administration of appropriate antibiotics has been the mainstay of managing infections in

patients with CLL. Hopefully, increasing understanding of the molecular events underlying the neoplastic change in CLL will lead to more targeted and less immunosuppressive therapeutic modalities (Ravandi & O'Brien S, 2006).

2. Infectious diseases in chronic lymphocytic leukemia

Patients with lymphoid malignancies such as chronic lymphocytic leukemia are at increased risk for infectious morbidity and mortality. Defects in cell-mediated immunity appear to be a major predisposing factor in these patients. An expanding spectrum of pathogens associated with lymphocytopenia and depletion of CD4 has been described in the setting of therapy with purine analogs. Infectious diseases in chronic lymphocytic leukemia are categorized as bacterial, viral, fungal and parasitic infection. CLL is characterized by progressive defects in humoral- and cell-mediated immunity. These defects are manifested as a propensity to develop infections with encapsulated, and less frequently, with gram-negative enteric bacteria. In addition, reactivation of viruses such as herpesvirus is not uncommon. Treatment of the disease exacerbates immunosuppression by depleting immune effectors and broadening the spectrum of potentially offending pathogens (Wierda, 2003). Neutrophil count, serum immunoglobulin G level and granulocyte chemotaxis are predicting factors of susceptibility to infections. Phagocytosis and intracellular killing of granulocytes are intact in patients with CLL (Itälä et al, 1996, 1998). Over the past decade, the introduction of nucleoside analogs and monoclonal antibodies into the treatment of patients with CLL has resulted in higher rates and longer duration of response. This is a significant step towards achieving the ultimate goal of disease-eradication and improved survival. A continuing problem, however, is the susceptibility of these patients to infections. Profound dysregulation of the host immune system in patients with CLL and its impact on the clinical course of the disease are well established. A number of investigators have sought to identify the mechanisms underlying this innate immune dysfunction, which is further exacerbated by the actions of the potent therapeutic agents (Ravandi & O'Brien S, 2006). A characteristic spectrum of infectious complications has been described for specific treatment agents. With chlorambucil, most infections are bacterial in origin, caused by common Gram-positive and -negative organisms. Recurrent infections are a hallmark, with the respiratory tract being the most common site of infection. The pathogenesis of infection with the purine analogues is related to the quantitative and qualitative T-cell abnormalities induced by these agents. Risk factors for infection identified in patients treated with fludarabine include advanced-stage disease, prior CLL therapy, response to therapy, elevated serum creatinine, hemoglobin < 12 g/dl, and decreased serum IgG. As compared with patients receiving chlorambucil, patients receiving fludarabine have more major infections and herpes virus infections. However, Pneumocystis, Aspergillus, and cytomegalovirus (CMV) infections are uncommon. The use of alemtuzumab is complicated by frequent opportunistic infections. CMV reactivation is especially problematic, occurring in 10%-25% of patients (Morrison, 2009). The humanized, anti-CD52 monoclonal antibody alemtuzumab has shown notable activity for both untreated and fludarabine-refractory CLL. The antibody not only targets malignant cells but also affects normal, healthy immune cells. The cumulative effects of the malignancy and successive courses of treatments adversely impinge on a patient's defense response to certain bacterial, fungal, and viral infections (Elter et al., 2009). Severe lymphopenia is one of the most profound hematologic effects of alemtuzumab, often predisposing patients to infectious complications such as herpes simplex virus,

cytomegalovirus, and *Pneumocystis jirovecii* pneumonia. Opportunistic infections secondary to mycobacterial sources have been documented less frequently (Saadeh & Srkalovic, 2008).

2.1 Bacterial infection

Patients with chronic lymphocytic leukemia are at an increased risk for infections with bacteria which require complement for opsonization (Heath & Cheson, 1985). Patients with chronic leukemias typically are affected by infections due to the underlying hematologic condition, particularly hypogammaglobulinemia in CLL patients. With active treatment, particularly those agents that cause defects in cell-mediated immunity, the incidence of opportunistic infections increases although endogenous bacterial, mycobacterial, and fungal infections also occur (Young, 2011). These defects are manifested as a propensity to develop infections with encapsulated bacteria, and less frequently, with gram-negative enteric bacteria. Bacterial pneumonia, urinary tract infection, sepsis, meningitis, typhlitis or neutropenic enterocolitis and soft tissue infections are common infections occur in CLL patients with bacterial source (Perkins et al., 2002). *Staphylococcus* spp., *Streptococcus* spp. (especially *Streptococcus pneumoniae*) *Enterococcus* spp., *Enterobacteriaceae*, *Hemophilus influenzae*, *Pseudomonas* spp. (especially *Pseudomonas aeruginosa*), *Listeria monocytogenes*, *Nocardia*, *Vibrio vulnificus* etc. are bacteria that cause infection in CLL patients (Travade et al, 1986; Barton & Ratard, 2006). Infections are one of the most important causes of mortality in CLL patients, and *Streptococcus pneumoniae* has been considered the most important single pathogen in this group (Sinisalo et al., 2007). In a survey on CLL patients with pneumonia, *Pneumococcus* was the most frequent agent followed by *Pseudomonas aeruginosa*, *Pneumocystis carinii* and *Aspergillus fumigatus*. (Batlle et al., 2001).

2.2 Epstein-Bar virus infection

Epstein-Barr virus (EBV) is a gammaherpesvirus which infects greater than 90% of the world population. Infection is nonsymptomatic in healthy individuals, but has been associated with a number of lymphoproliferative disorders when accompanied by immunosuppression. Like all herpesviruses, EBV has both latent and lytic replication programs, which allows it to evade immune clearance and persist for the lifetime of the host (Bajaj et al., 2001). The most common primary symptoms of EBV infection are fever, skin eruption, lymphadenopathy, hepatosplenomegaly, eyelid edema, pharyngitis, cardiac arrhythmia and arthralgia (Li et al. 2004; C. Berger 2003). EBV can cause meningoencephalitis or central nervous system tumor-like lesion in immunocompromised patient (Khalil et al., 2008; Turkulov et al., 1999). This virus plays an important role in the etiology of nasopharyngeal carcinoma, adenocarcinoma of the parotid glands, gastric carcinoma, Burkitt's lymphoma and lymphoproliferative syndromes (Zahorodnia, 2011). EBV is pathogenically associated with a well defined group of lymphoid and epithelial tumors in which the virus directly drives transformation of infected cells. Recent evidence however indicates that this virus may infect a subpopulation of tumor cells in patients with chronic lymphocytic leukemia (Dordević, 2006). As one the most important clinical presentation of EBV and other herpesviruses is central nervous system (CNS) involvement; Rapid, sensitive and economical detection and identification of human herpesviruses as

causative agents of CNS infections is clinically important. The traditional methods for the detection of herpesviruses in CNS infections all suffer from limitations. Polymerase chain reaction (PCR) is the best laboratory test. Multiplex nested consensus PCR provide a rapid, sensitive and economical method for detection of viral infections and is applicable to small volumes of CSF samples (Tafreshi, 2005). The spectrum of drugs active against EBV remains very limited. Gancyclovir and acyclovir are used in medical practice. The search of new compounds active against EBV remains necessary (Zahorodnia, 2011).

2.3 Cytomegalovirus infection

Human cytomegalovirus (CMV) is one of herpesviruses that commonly infect humans. Advances in molecular virology coupled with improvements in diagnostic methods and treatment options have vastly improved ability to manage CMV infection, but many uncertainties remain, including the mechanisms of persistence and pathogenesis and its hypothesized roles in a variety of human illnesses (Boeckh & Geballe, 2011). It is a recognized cause of morbidity and mortality in immunocompromised individuals (Emery, 2001). Primary infection with CMV is followed by persistence of the virus in a latent form. During life, the virus can reactivate, resulting in renewed shedding of the virus or development of disease. Significant progress has been made in detecting CMV, but in the immunocompromised patients, establishing the diagnosis of CMV infection can still be problematic (Vancíková & Dvorák, 2001).

Cellular immune responses are important against virus infections (Sester et al, 2002). CMV infection causes significant morbidity and mortality in the setting of immunodeficiency (Ozdemir et al, 2002). It can cause serious clinical complications in eye (retinitis), lung, central nervous system and other organs in immunocompromised individuals (Bronke et al, 2005; Reeves et al, 2005). For diagnosis the most sensitive molecular amplification methods such as PCR should be used. Treatment of infection depends mainly on the immune status of the host (Vancíková & Dvorák, 2001). The availability of sensitive diagnostic tests such as pp65 antigenemia has made the early diagnosis of CMV possible (Kusne et al, 1999). CMV should be suspected as a cause of pneumonia in immunocompromised patients and diagnosis may require invasive procedures bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) may be required for diagnosis of CMV pneumonitis. (Yadegarynia et al, 2009). In immunocompetent patients only symptomatic treatment is recommended, while in immunocompromised patients antiviral therapy should be used. The most commonly used antiviral agents are: ganciclovir, foscarnet, cidofovir, valganciclovir and valaciclovir (Vancíková & Dvorák, 2001). Although it remains rare, ganciclovir-resistant CMV disease is increasingly seen in clinical practice, potentially fostered by the prolonged use of antiviral agents in high-risk patients. Treatment of drug-resistant CMV is currently non-standardized and may include foscarnet, cidofovir, CMV hyperimmune globulins or leflunomide (Eid & Razonable, 2010).

2.4 Herpes simplex virus infection

Herpes simplex viruses type 1 and 2 (HSV-1 and HSV-2) are alpha herpes viruses. Humans are the only natural host and they can be transmitted through oral or genital secretions. These viruses are ubiquitous all over the world, with different percentage rates (Dordević,

2006). They can infect both skin and nerves and develop latent infection within the dorsal root and trigeminal ganglia. Infection with these viruses is common and causes a wide range of clinical syndromes (Midak-Siewirska et al, 2010). HSV infections range in severity from common cutaneous outbreaks to life-threatening central nervous system and deep organ involvement (Higgins et al 1999). Atypical clinical manifestations of HSV may occur in immunocompromised patients. HSV-2 infection is responsible for significant neurological morbidity, perhaps more than any other virus (JR. Berger et al, 2008). Herpes esophagitis is common in immunosuppressed patients, but has rarely been reported in immunocompetent individuals, in whom it appears to be a self-limited illness (Canalejo Castrillero et al, 2010). Pneumonia, hepatitis, gastrointestinal involvement and disseminated infection may occur in immunocompromised patients (Longerich et al, 2005; Medlicott et al, 2005; Massler et al, 2011). Multiple herpes virus co-infection (HSV and EBV) may occur in patients with chronic lymphocytic leukemia (Mercadal et al, 2006). HSV infections have a severe and rapidly progressive course especially in immunocompromised patients, leading to significant morbidity and mortality. Therefore, rapid and reliable laboratory diagnosis of HSV infections is important for initiation of early antiviral therapy. PCR, direct fluorescein antibody (DFA) methods and cell culture are used for diagnosis (Cordes et al, 2011). There is evidence that acyclovir is effective for preventing and treating HSV infections. There is no evidence that valaciclovir is more effective than acyclovir, or that a high dose of valaciclovir is better than a low dose (Nolan, 2009). Antiviral-resistant herpes virus infection has become a great concern for immunocompromised patients (Shiota et al, 2011).

2.5 Hepatitis B virus infection

Recent studies emphasize the risk of hepatitis B virus (HBV) reactivation among patients with hematologic malignancies of B lineage, in which HBV has been recently hypothesized to play a pathogenetic role. Occult HBV infection is significantly more prevalent among patients with CLL and may contribute to the susceptibility of patients with CLL to HBV reactivation, whether exposed or not to biological agents (Rossi et al, 2009). Chemotherapy-induced HBV reactivation is a serious problem in chronic HBV carriers with hematologic malignancies. In Yağci's study all patients with chronic lymphocytic leukemia experienced chemotherapy-induced HBV reactivation regardless of the chemotherapy regimen. CLL patients who are HBV carriers are at significant risk of chemotherapy-induced HBV reactivation (Yağci et al, 2006). Reactivation of HBV in HBsAg-positive patients is a well-documented complication of cytotoxic or immunosuppressive therapy and has also been observed after treatment with rituximab (Heider et al, 2004). Patients may be treated with lamivudine or lamivudine plus adefovir dipivoxil combination therapy to control viral replication and allow for long-term anti-cancer chemotherapy (Cortelezzi et al, 2006). lamivudine is highly effective in inhibiting HBV proliferation and can be used to prevent HBV flare-up during chemotherapy in patients with positive HBs antigen (Heider et al, 2004).

2.6 Fungal infection

Opportunistic fungal infection may occur in patient with CLL. *Candida* and *Aspergillus* are common fungi. Invasive *Candida* infections are important causes of morbidity and mortality in immunocompromised patients. The cornerstone of diagnosis remains the detection of the

organism by culture with identification of the isolate at the species level; in vitro susceptibility testing is mandatory for invasive isolates. Options for initial therapy of candidaemia and other invasive *Candida* infections in non-granulocytopenic patients include fluconazole or one of the three approved echinocandin compounds; liposomal amphotericin B. Voriconazole are secondary alternatives. In granulocytopenic patients, an echinocandin or liposomal amphotericin B is recommended as initial therapy. Indwelling central venous catheters serve as a main source of infection independent of the pathogenesis of candidaemia and should be removed whenever feasible. Dose reduction or discontinuation of pre-existing immunosuppressive treatment (particularly glucocorticosteroids) should be performed. Ophthalmoscopy is recommended prior to the discontinuation of antifungal chemotherapy to rule out endophthalmitis or chorioretinitis (Ruhnke et al, 2011).

Morbidity and mortality caused by invasive *Aspergillus* infections are increasing. This is because of the higher number of patients with malignancies treated with intensive immunosuppressive therapy regimens as well as their improved survival from formerly fatal bacterial infections. Clinical diagnosis is based on radiologic findings and non-culture based diagnostic techniques such as galactomannan or DNA detection in blood or bronchoalveolar lavage samples. Most promising outcomes can be expected in patients at high risk for aspergillosis in whom antifungal treatment has been started pre-emptively, backed up by laboratory and imaging findings. The gold standard of systemic antifungal treatment is voriconazole, which has been proved to be significantly superior to conventional amphotericin B and has led to a profound improvement of survival rates in patients with cerebral aspergillosis. Liposomal amphotericin B at standard dosages appears to be a suitable alternative for primary treatment, while caspofungin, amphotericin B lipid complex or posaconazole have shown partial or complete response in patients who had been refractory to or intolerant of primary antifungal therapy. Combination therapy with two antifungal compounds may be a promising future strategy for first-line treatment (Maschmeyer et al, 2007).

Cryptococcus neoformans is an important fungal pathogen of immunocompromised individuals. Lung and CNS are two important organs involved by *Cryptococcus neoformans* (Price et al, 2011). Diagnosis is based on direct microscopic examination of India ink preparations and PCR (Ndiaye et al, 2011; Sidrim et al, 2010; Mseddi et al, 2011). Amphotericin B and flucytosine is used for treatment (Thalla et al, 2009). Histoplasmosis (Van Koeveeringe & Brouwer, 2010), fusariosis (Campo et al, 2010) and other uncommon fungal infection may be seen in immunocompromised patients.

2.7 *Pneumocystis jirovecii* infection

Pneumocystis jirovecii pneumonia (formerly *Pneumocystis carinii* pneumonia) occurs frequently in patients with immunodeficiency (Otaibachi et al, 2007). *Pneumocystis carinii* pneumonia (PCP) in patients with chronic lymphocytic leukaemia (CLL) who have not been treated with fludarabine are rare, although clinically relevant CD4 T-cell depletion can occur in longstanding CLL without prior treatment with purine analogues (Vavricka et al, 2004). It is associated with a wide spectrum of clinical presentations (Gal et al, 2002). The most frequent symptoms are: fever, dyspnea, non-productive cough, thoracic pain, chills and severe hypoxaemia (Pagano et al, 2002). For diagnosis of PCP bronchoalveolar lavage (BAL) cytology and transbronchial lung biopsy (TBLB) may be required (Bijur et al, 1996). Because *Pneumocystis* cannot be cultured, diagnosis relies on detection of the organism by

colorimetric or immunofluorescent stains or by polymerase chain reaction. Trimethoprim-sulfamethoxazole is the preferred drug regimen for both treatment and prevention of PCP, although a number of alternatives are also available. Corticosteroids are an important adjunct for hypoxemic patients (Kovacs et al, 1994).

2.8 Mycobacterium avium complex infection

Mycobacterium avium complex (MAC) primarily causes respiratory infection in patients with underlying lung disease or disseminated disease in immunocompromised patients (Azzam et al, 2009). MAC is clinically important since it can cause severe infections in immunocompromised individuals (Rodrigues et al, 2009). Severe lymphopenia is one of the most profound hematologic effects of alemtuzumab, often predisposing patients to infectious complications such as herpes simplex virus, cytomegalovirus, and Pneumocystis jirovecii pneumonia. Opportunistic infections secondary to mycobacterial sources like mycobacterium avium complex have been documented less frequently (Saadeh & Srkalovic, 2008). A diagnosis requires a high index of suspicion in patients with immunocompromised status who present with prolonged fever, with or without organ-specific symptoms and signs. Therefore, clinical specimens must be sent for mycobacterial cultures for a definite diagnosis (Saritsiri et al, 2006). Microscopic evaluation, culture and PCR may be necessary for diagnosis (Haas et al, 1998). Combination of clarithromycin, rifabutin and ethambutol has proven to be the most efficacious therapy and therefore it is considered as standard therapy for disseminated MAC infection. Clarithromycin, rifabutin and azithromycin given as primary prophylaxis can diminish the risk of disseminated MAC infection (Fätkenheuer et al, 1998).

2.9 Adenovirus infection

Adenovirus infections are widespread in society and are occasionally associated with severe, but rarely with life-threatening, disease in otherwise healthy individuals. In contrast, adenovirus infections present a real threat to immunocompromised individuals and can result in disseminated and fatal disease (Andersson et al, 2010). It is an important cause of morbidity and mortality in the immunocompromised host (Gavin & Katz, 2002). Adenovirus infection has been reported following alemtuzumab treatment in CLL patients (Martin et al, 2006). There is no formally approved treatment of adenovirus infections today, and existing antiviral agents evaluated for their antiadenoviral effect give inconsistent results (Andersson et al, 2010). ribavirin and cidofovir are used for treatment of adenovirus infection (Gavin & Katz, 2002).

2.10 Other microorganism infection

Other opportunistic and non-opportunistic organisms like toxoplasmosis, tuberculosis, non tuberculosis mycobacteria, herpes zoster infection, etc may infect CLL patients (Herrero et al, 1995; Mehta et al, 1997; Juliusson & Liliemark, 1996; Krebs et al, 2000)

3. Management

3.1 Diagnosis

Appropriate diagnosis is important for treatment. Different diagnostic methods may be needed to achieve diagnosis. Culture (blood, urine, sputum, etc.), search for antigens

(*Legionella pneumophila* serogroup 1, galactomannan, and *Streptococcus pneumonia*), CSF analysis, radiologic modality (x-ray, CT scan, MRI, etc.), bronchoscopy, endoscopy, tissue biopsy and other diagnostic test may be used to find the etiologic agents (Batlle et al., 2001; Krebs et al, 2000).

3.2 Treatment

Appropriate antibacterial, antiviral and anti fungal treatment can be life saving (for specific treatment of each microorganism see above). Immunoglobulins are an important component of host defense against infections. They also play a central role in immune regulation. A wide spectrum of human diseases is associated with decreased or abnormal regulation of immunoglobulin levels. Recently intravenous (IV) preparations of immunoglobulin have become available for clinical studies. There are already substantial data indicating a useful role for IV immunoglobulin in patients with primary hypogammaglobulinemia, neonates predisposed to group B streptococcal infections, individuals with ITP, children with Kawasaki disease, bone marrow transplant patients predisposed to CMV infections and in individuals with CLL (Berkman et al, 1988). Intravenous immunoglobulin (IVIg) replacement therapy reduces the number of bacterial infections in CLL patients. However, due to the complexity of immunodeficiency in CLL and the cost-effectiveness of replacement therapy, it is important to identify patients who are likely to benefit from the treatment and to investigate which dose should be used. Low dose of gammaglobulin intravenously can restore normal serum IgG levels in hypogammaglobulinaemic B-CLL patients, and leads to a decreased number of febrile episodes and admissions to hospital due infections (Jurlander et al, 1994, 1995). IVIG has been shown to be a useful prophylactic therapy against infections (Gamm et al, 1994). Granulocyte colony stimulating factor (G-CSF) supplementation may improve the rate of infectious complications by reducing the duration of drug-induced neutropenia (Südhoff et al, 1997). It can be used safely and effectively in CLL-patients with severe bacterial infections to restore neutropenia (Hollander et al, 1991). Granulocyte macrophage colony stimulating factor (GM-CSF) is also effective in improving CLL associated chronic neutropenia and also enhances impaired granulocyte chemiluminescence. Thus, GM-CSF could be helpful for giving chemotherapy without neutropenic delays and for prophylaxis of infectious complications in CLL patients (Itälä et al, 1996, 1998).

3.3 Prophylaxis

Patients with advanced disease who receive cytotoxic therapy may benefit from antibacterial prophylaxis. Risk of infection can potentially be reduced by administration of intravenous immunoglobulin and use of prophylactic antibiotics for individuals who are at high risk (5). Treatments of CLL enhance the risk of myelosuppression and infection, so these patients may need antibiotic, antiviral, and antimycotic prophylaxis during and after their administration (Todisco, 2009). Antimicrobial prophylaxis, particularly anti-*Pneumocystis* prophylaxis, may be indicated in selected patients (Young, 2011). Consideration of primary prophylaxis against *M. avium* complex infections in aggressively treated patients with advanced B-CLL or other clinical indications may be warranted (Saadeh & Srkalovic, 2008). Some investigators recommend routine antibacterial and antiviral prophylaxis during and after purine nucleoside analogues treatment (Perkins et al.,

2002). An understanding of the patients at highest risk and duration of risk are important in developing recommendations for empirical management, antimicrobial prophylaxis and targeted surveillance (Thursky et al, 2006).

3.4 Vaccination

Routine vaccination should be maintained in CLL patients and vaccination early in the course of treatment may result in improve protection (Young, 2011). Antibody response rates to vaccine antigens are lower in patients with CLL compared to normal host. However, if the vaccine has been administered at an early stage of the disease and before starting chemotherapy and the development of hypogammaglobulinaemia, a significant vaccination response to antigens will be obtained in almost 40% of the CLL patients. Early administration of vaccine may be beneficial in CLL patients (Sinisalo et al., 2007). Bacterial polysaccharide vaccines would seem to be ineffective in antibody formation in patients with CLL. However, protein and conjugate vaccines appear to be more immunogenic and their responses may be further enhanced with ranitidine adjuvant treatment (Sinisalo et al, 2003). Response rate to *Haemophilus influenzae* type b (Hib) conjugate vaccine among adult and elderly patients with chronic lymphocytic leukaemia was 43% in Sinsalo's study (Sinsalo et al, 2002). It is recommended to vaccinate CLL patients with *S. pneumoniae* and *Haemophilus influenzae* type b (Hib) vaccines as soon as the diagnosis of CLL is made, early in the course of the disease with determination of post-vaccination antibody levels (Hartkamp et al, 2001). Antibody production after vaccination against common pathogen in CLL patients may improve by treatment histamine type-2 receptor blockade such as ranitidine (Jurlander et al, 1994, 1995). Influenza vaccination is recommended for patients with B-cell CLL however immune response to influenza vaccination appears to be poor (Van der Velden et al, 1995). New well-designed investigations are needed to develop appropriate vaccination strategies and evaluate vaccination efficacy in infection morbidity and mortality in CLL (Sinisalo et al, 2003).

4. Conclusion

Infectious complications are leading causes of morbidity and mortality in CLL patients. High index of suspicious and using appropriate diagnostic methods, treatment and prophylaxis can enhance survival of patients.

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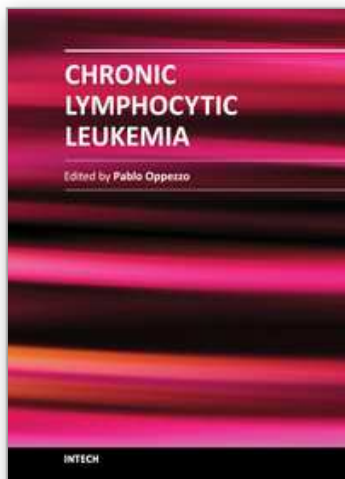
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B-cell chronic lymphocytic leukemia (CLL) is considered a single disease with extremely variable course, and survival rates ranging from months to decades. It is clear that clinical heterogeneity reflects biologic diversity with at least two major subtypes in terms of cellular proliferation, clinical aggressiveness and prognosis. As CLL progresses, abnormal hematopoiesis results in pancytopenia and decreased immunoglobulin production, followed by nonspecific symptoms such as fatigue or malaise. A cure is usually not possible, and delayed treatment (until symptoms develop) is aimed at lengthening life and decreasing symptoms. Researchers are playing a lead role in investigating CLL's cause and the role of genetics in the pathogenesis of this disorder. Research programs are dedicated towards understanding the basic mechanisms underlying CLL with the hope of improving treatment options.

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