We are IntechOpen, the world's leading publisher of Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Infectious Diseases and Clinical Complications During Treatment in CLL

Farhad Abbasi

Bushehr University of Medical Sciences

Iran

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 osponization (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 Streptoccoccus pneumonia) Enterococcus spp., Enterobacteriaceae, Hemophillus influenza, 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 fumigates. (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, gasterointestinal 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 Koeveringe & Brouwer, 2010), fusariosis (Campo et al, 2010) and other uncommon fungal infection may be seen in immunocomromised patients.

2.7 Pnemocystis jirovecii infection

Pneumocystis jiroveci pneumonia (formerly Pneumocystis carinii pneumonia) occurs frequently in patients with immunodeficiency (Otahbachi et al, 2007). Pneumocystis carinii pneumonia (PCP) in patients with chronic lymphocytic leukaemia (CLL) who have not been treated with fludarabin 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 toxoplamosis, 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.), broncoscopy, 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.

5. Acknowledgment

6. References

Andersson EK, Strand M, Edlund K, Lindman K, Enquist PA, Spjut S, Allard A, Elofsson M, Mei YF, Wadell G. (2010). Small-molecule screening using a whole-cell viral replication reporter gene assay identifies 2-{[2-(benzoylamino)benzoyl]amino}-benzoic acid as a novel antiadenoviral compound. *Antimicrob Agents Chemother.* Vol.54, No.9, (September 2010), pp.3871-7, ISSN 0066-4804

Azzam HC, Gahunia MK, Sae-Tia S, Santoro J. (2009). Mycobacterium avium-avium-associated typhlitis mimicking appendicitis in an immunocompetent host. *Am J Med Sci.* Vol.337, No.3, *(*March 2009), pp. 218-20, ISSN 0002-9629

Bajaj BG, Murakami M, Robertson ES. (2001). Molecular biology of EBV in relationship to AIDS-associated oncogenesis. *Cancer Treat Res.* Vol.133, *(*2001), pp. 141-62, ISSN 0927-3042

Barton JC, Ratard RC. (2006).Vibrio vulnificus bacteremia associated with chronic lymphocytic leukemia, hypogammaglobulinemia, and hepatic cirrhosis: relation to host and exposure factors in 252 V. vulnificus infections reported in Louisiana. *Am J Med Sci.* Vol.332, No.4, *(*October 2006), pp. 216-20, ISSN 0002-9629

Batlle M, Ribera JM, Oriol A, Rodríguez L, Cirauqui B, Xicoy B, Grau J, Feliu J, Flores A, Millá F. (2001). Pneumonia in patients with chronic lymphocytic leukemia. Study of 30 episodes. *Med Clin (Barc).* Vol.116, No.19, *(*May 2001), pp. 738-40, ISSN 0025-7753

Berger C. Infectious mononucleosis. *Ther Umsch.* Vol.60, No.10, *(*October 2003), pp. 625-30, ISSN 0040-5930

Berger JR, Houff S. (2008). Neurological complications of herpes simplex virus type 2 infection. *Arch Neurol.* Vol.65, No.5, *(*May 2008), pp. 596-600. ISSN 0003-9942

Berkman SA, Lee ML, Gale RP. (1988). Clinical uses of intravenous immunoglobulins. *Semin Hematol.* Vol.25, No. 2, *(*April 1988), pp. 140-58, 0037-1963

Bijur S, Menon L, Iyer E, Deshpande J, Sivaraman A, Vaideeswar P, Mahashur AA. (1996). Pneumocystis carinii pneumonia in human immunodeficiency virus infected patients in Bombay: diagnosed by bronchoalveolar lavage cytology and transbronchial lung biopsy. *Indian J Chest Dis Allied Sci.* Vol.38, No.4, *(*October-December 1996), pp. 227-33, ISSN 0377-9343

Boeckh M, Geballe AP. (2011). Cytomegalovirus: pathogen, paradigm, and puzzle. *J Clin Invest.* Vol.121, No.5, *(*May 2011), pp. 1673-80, ISSN 0021-9738

Bronke C, Palmer NM, Jansen CA, Westerlaken GH, Polstra AM, Reiss P, Bakker M, Miedema F, Tesselaar K, van Baarle D. (2005). Dynamics of cytomegalovirus (CMV)-specific T cells in HIV-1-infected individuals progressing to AIDS with CMV end-organ disease. *J Infect Dis.* Vol.191, No.6, *(*March 2005), pp. 873-80, ISSN 1553-6203

Campo M, Lewis RE, Kontoyiannis DP. (2010). Invasive fusariosis in patients with hematologic malignancies at a cancer center: 1998-2009. *J Infect.* Vol.60, No.5, *(*May 2010), pp. 331-7, ISSN 1553-6203

Canalejo Castrillero E, García Durán F, Cabello N, García Martínez J. (2010). Herpes esophagitis in healthy adults and adolescents: report of 3 cases and review of the literature. *Medicine (Baltimore).* Vol.89, No.4, *(*July 2010), pp. 204-10, ISSN 0025-7974

Cordes C, Tiemann M, Tiemann K, Knappe D, Hoffmann M, Gottschlich S. (2011). Epstein-Barr virus-associated diffuse large B-cell lymphoma of the hypopharynx. *B-ENT.* Vol.7, No.1, *(*2011), pp. 43-6, ISSN 1781-782X

Cortelezzi A, Viganò M, Zilioli VR, Fantini NN, Pasquini MC, Deliliers GL, Colombo M, Lampertico P. (2006). Adefovir added to lamivudine for hepatitis B recurrent infection in refractory B-cell chronic lymphocytic leukemia on prolonged therapy with Campath-1H. *J Clin Virol.*Vol.35, No.4, *(*April 2006), pp. 467-9, ISSN 1386-6532

Dearden C. *(*2008). Disease-specific complications of chronic lymphocytic leukemia. *Hematology Am Soc Hematol Educ Program.* *(* 2008), pp.450-6, ISSN 1520-4391

Dordević H. (2006). Serological response to herpes simplex virus type 1 and 2 infection among women of reproductive age. *Med Pregl.* Vol.59, No.11-12, (November-December 2006), pp. 591-7, ISSN 0025-8105

Eid AJ, Razonable RR. (2010). New developments in the management of cytomegalovirus infection after solid organ transplantation. *Drugs.* Vol.70, No.8, (Fall 2009), pp. 965-81, ISSN 0012-6667

Elter T, Vehreschild JJ, Gribben J, Cornely OA, Engert A & Hallek M. (2009). Management of infections in patients with chronic lymphocytic leukemia treated with alemtuzumab. *Ann Hematol.* Vol.88, No.2, (February 2009), pp.121-32, ISSN 0939-5555

Emery VC.(2001). Investigation of CMV disease in immunocompromised patients. *J Clin Pathol.* Vol.54, No.2, (February 2001), pp. 84-8, ISSN 0021-9746

Fätkenheuer G, Salzberger B, Diehl V. (1998). Disseminated infection with Mycobacterium avium complex (MAC) in HIV infection. *Med Klin (Munich).* Vol.93, No.6, (Jun 1998), pp. 360-4, ISSN 0723-5003

Gal AA, Plummer AL, Langston AA, Mansour KA. Gal AA, Plummer AL, Langston AA, Mansour KA. *Pathol Res Pract.* Vol.198, No.8, (2002), pp. 553-8, ISSN 0344-0338

Gamm H, Huber C, Chapel H, Lee M, Ries F, Dicato MA. (19994). Intravenous immune globulin in chronic lymphocytic leukaemia. *Clin Exp Immunol.* Vol.97, No. Suppl 1, (July 1994), pp. 17-20, ISSN 0009-9104

Gavin PJ, Katz BZ. (2002). Intravenous ribavirin treatment for severe adenovirus disease in immunocompromised children. *Pediatrics.* Vol.110, No.1, (July 2002), pp.9, ISSN 0031-4005

Haas WH, Amthor B, Engelmann G, Rimek D, Bremer HJ. (1998). Preoperative diagnosis of Mycobacterium avium lymphadenitis in two immunocompetent children by polymerase chain reaction of gastric aspirates. *Pediatr Infect Dis J.* Vol.17, No.11, (November 1998), pp. 1016-20, ISSN 0891-3668

Hamblin AD & Hamblin TJ. (2008). The immunodeficiency of chronic lymphocytic leukaemia. *Br Med Bull.* Vol.47, No.1, (2008), pp. 49-62, ISSN 0007-1420

Hartkamp A, Mulder AH, Rijkers GT, van Velzen-Blad H, Biesma DH. (2001). Antibody responses to pneumococcal and haemophilus vaccinations in patients with B-cell chronic lymphocytic leukaemia. *Vaccine.* Vol.19, No. (13-14), (February 2001), pp. 1671-7, ISSN 0264-410X

Heath ME, Cheson BD. (1985). Defective complement activity in chronic lymphocytic leukemia. *Am J Hematol.* Vol.19, No.1, (May 1985), pp. 63-73, ISSN 0361-8609.

Heider U, Fleissner C, Zavrski I, Jakob C, Dietzel T, Eucker J, Ockenga J, Possinger K, Sezer O. (2004). Treatment of refractory chronic lymphocytic leukemia with Campath-1H in combination with lamivudine in chronic hepatitis B infection. *Eur J Haematol.* Vol.72, No.1, (January 2004), pp. 64-6, ISSN 0902-4441

Herrero M, Cabrera JR, Briz M, Forés R, Díez JL, Regidor C, Sanjuán I, Fernández MN. (1995). Treatment with fludarabine of chronic refractory lymphoid leukemia. *Sangre (Barc).* Vol.40, No.2, (April 1995), pp. 115-9, ISSN 0036-3634

Higgins JP, Warnke RA. (1999). Herpes lymphadenitis in association with chronic lymphocytic leukemia. *Cancer.* Vol.86, No.7, (October 1999), pp. 1210-5. ISSN 0008-5472.

Hollander AA, Kluin-Nelemans HC, Haak HR, Stern AC, Willemze R, Fibbe WE. (1991). Correction of neutropenia associated with chronic lymphocytic leukaemia following treatment with granulocyte-macrophage colony-stimulating factor. Ann Hematol. Vol.62, No. 1, (February 1991), pp. 32-4, ISSN 0939-5555

Itälä M, Vainio O, Remes K.(1996). Functional abnormalities in granulocytes predict susceptibility to bacterial infections in chronic lymphocytic leukaemia. *Eur J Haematol.* Vol.57, No.1, (July 1996), pp. 46-53, ISSN 0902-4441

Itälä M, Pelliniemi TT, Remes K, Vanhatalo S, Vainio O. (1998). Long-term treatment with GM-CSF in patients with chronic lymphocytic leukemia and recurrent neutropenic infections. *Leuk Lymphoma.* Vol.32, No. (1-2), (December 1998), pp. 165-74. ISSN 1042-8194

Juliusson G, Liliemark J. (1996). Long-term survival following cladribine (2-chlorodeoxyadenosine) therapy in previously treated patients with chronic lymphocytic leukemia. *Ann Oncol.* Vol.7, No. 4, (April 1996), pp. 373-9, ISSN 0923-7534

Jurlander J, Geisler CH, Hansen MM. (1994). Treatment of hypogammaglobulinaemia in chronic lymphocytic leukaemia by low-dose intravenous gammaglobulin. *Eur J Haematol.* Vol.53, No. 2, (August 1994), pp. 114-8, ISSN 0902-4441

Jurlander J, de Nully Brown P, Skov PS, Henrichsen J, Heron I, Obel N, Mortensen BT, Hansen MM, Geisler CH, Nielsen HJ. (1995). Improved vaccination response during ranitidine treatment, and increased plasma histamine concentrations, in patients with B cell chronic lymphocytic leukemia. *Leukemia.* Vol.9, No. 11, (November 1995), pp. 1902-9, ISSN 0887-6924

Khalil M, Enzinger C, Wallner-Blazek M, Scarpatetti M, Barth A, Horn S, Reiter G. (2008). Epstein-Barr virus encephalitis presenting with a tumor-like lesion in an immunosuppressed transplant recipient. *J Neurovirol.* Vol.14, No.6, (October 2008), pp. 574-8, ISSN 1355-0284

Kovacs JA, Masur H. Evolving health effects of Pneumocystis: one hundred years of progress in diagnosis and treatment. *Schweiz Med Wochenschr.* Vol.124, No.(1-2), (Jun 1994), pp. 73-8, ISSN 0036-7672

Krebs T, Zimmerli S, Bodmer T, Lämmle B. (2000). Mycobacterium genavense infection in a patient with long-standing chronic lymphocytic leukaemia. *J Intern Med.* Vol.248, No. 4, (October 2000), pp. 343-8, ISSN 0954-6820

Kusne S, Shapiro R, Fung J. (1999). Prevention and treatment of cytomegalovirus infection in organ transplant recipients. *Transpl Infect Dis.* Vol.1, No.3, (September 1999), pp. 187-203, ISSN 1398-2273

Li ZY, Lou JG, Chen J. (2004). Analysis of primary symptoms and disease spectrum in Epstein-Barr virus infected children. *Zhonghua Er Ke Za Zhi.* Vol.42, No.1, (Jane 2004), pp. 20-2, ISSN 0578-1310

Longerich T, Eisenbach C, Penzel R, Kremer T, Flechtenmacher C, Helmke B, Encke J, Kraus T, Schirmacher P. (2005).Recurrent herpes simplex virus hepatitis after liver retransplantation despite acyclovir therapy. *Liver Transpl.* Vol.11, No.10, (October 2005), pp. 1289-94. ISSN 1527-6465

Martin SI, Marty FM, Fiumara K, Treon SP, Gribben JG, Baden LR. (2006). Infectious complications associated with alemtuzumab use for lymphoproliferative disorders. *Clin Infect Dis.* Vol.43, No.1, (July 2006), pp. 16-24, ISSN 1058-4838

Maschmeyer G, Haas A, Cornely OA. (2007). Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. *Drugs.* Vol.67, No.11, (2007), pp. 1567-601, ISSN 0012-6667

Massler A, Kolodkin-Gal D, Meir K, Khalaileh A, Falk H, Izhar U, Shufaro Y, Panet A. (2011). Infant lungs are preferentially infected by adenovirus and herpes simplex virus type 1 vectors: role of the tissue mesenchymal cells. *J Gene Med.* Vol.13, No.2, (February 2011), pp.101-13, ISSN 1099-498X

Medlicott SA, Falck VG, Laupland KB, Akbari M, Beck PL. (2005). Herpes simplex virus type II infection of ileum mesothelium: a case report and review of the literature. *Can J Gastroenterol.* Vol.19, No.6, (Jun 2005), pp. 367-71. ISSN 0835-7900

Mehta J, Powles R, Singhal S, Riley U, Treleaven J, Catovsky D. (1997). Antimicrobial prophylaxis to prevent opportunistic infections in patients with chronic lymphocytic leukemia after allogeneic blood or marrow transplantation. *Leuk Lymphoma.* Vol.26, No. (1-2), (June 1997), pp. 83-8. ISSN 1042-8194

Mercadal S, Martinez A, Nomdedeu B, Rozman M, Gaya A, Salamero O, Campo E. (2011). Herpes simplex and Epstein-Barr virus lymphadenitis in a patient with chronic lymphocytic leukemia treated with fludarabine. *Eur J Haematol.* Vol.77, No.5, (November 2006), pp. 442-4, ISSN 0902-4441

Midak-Siewirska A, Karabin K, Chudzik E, Dzieciatkowski T, Przybylski M, Majewska A, Łuczak M, Młynarczyk G. (2010).Application of real-time PCR assay for investigating the presence of herpes simplex virus type 1 DNA. *Med Dosw Mikrobiol.* Vol.62, No.1, (2010), pp. 85-92, ISSN 0025-8601

Morra E, Nosari A& Montillo M. (2006). Infectious complications of chronic lymphocytic leukemia. *Hematol Cell Ther.* Vol.41, No.4, (Agust 2006), pp.145-51, ISSN 1269-3286

Morrison VA. (2009). Infectious complications in patients with chronic lymphocytic leukemia: pathogenesis, spectrum of infection, and approaches to prophylaxis. *Clin Lymphoma Myeloma.* Vol.9, No.5, (October 2009), pp. 365-70, ISSN 1938-0712

Mseddi F, Sellami A, Sellami H, Cheikhrouhou F, Makni F, Ayadi A. (2011). Two new media Pinus halepensis seed agar and blackberry agar for rapid identification of Cryptococcus neoformans. *Mycoses.* Vol.54, No.4, (July 2011), pp. 350-3, ISSN 0933-7407

Ndiaye M, Diagne NR, Seck LB, Sow AD, Sène MS, Diop AG, Sow HD, Ndiaye MM.(2011). Cryptococcal meningitis in children: description of 3 cases. *Med Trop (Mars).* Vol.71, No.2, (April 2011), pp. 176-8, ISSN 0025-682X

Nolan A. (209). Interventions for prevention and treatment of herpes simplex virus in cancer patients. *Evid Based Dent.* Vol.10, No.4, (2009), pp. 116-7, ISSN 1462-0049

Otahbachi M, Nugent K, Buscemi D. (2007). Granulomatous Pneumocystis jiroveci Pneumonia in a patient with chronic lymphocytic leukemia: a literature review and hypothesis on pathogenesis. *Am J Med Sci.* Vol.333, No.2, (February 2007), pp. 131-5. ISSN 0002-9629

Ozdemir E, St John LS, Gillespie G, Rowland-Jones S, Champlin RE, Molldrem JJ, Komanduri KV. (2002). Cytomegalovirus reactivation following allogeneic stem cell transplantation is associated with the presence of dysfunctional antigen-specific CD8+ T cells. *Blood.* Vol.100, No.1, (November 2002), pp. 3690-7, ISSN *0006-4971*

Pagano L, Fianchi L, Mele L, Girmenia C, Offidani M, Ricci P, Mitra ME, Picardi M, Caramatti C, Piccaluga P, Nosari A, Buelli M, Allione B, Cortelezzi A, Fabbiano F, Milone G, Invernizzi R, Martino B, Masini L, Todeschini G, Cappucci MA, Russo D, Corvatta L, Martino P, Del Favero A. (2002). Pneumocystis carinii pneumonia in patients with malignant haematological diseases: 10 years' experience of infection in GIMEMA centres. *Br J Haematol.* Vol.117, No.2, (May 2002), pp. 379-86, ISSN 1365-2141

Perkins JG, Flynn JM, Howard RS, Byrd JC. (2002). Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma: implications for clinical trials in this patient population. *Cancer.* Vol.94, No.7, (April 2002), pp. 2033-9, ISSN 0008-5472.

Price MS, Betancourt-Quiroz M, Price JL, Toffaletti DL, Vora H, Hu G, Kronstad JW, Perfect JR. (2007) . Cryptococcus neoformans Requires a Functional Glycolytic Pathway for Disease but Not Persistence in the Host. *MBio.* Vol.2, No.3, (Jun 2011), pp. 103-11, ISSN 2150-7511

Ravandi F & O'Brien S. (2006). Immune defects in patients with chronic lymphocytic leukemia. *Cancer Immunol Immunother.* Vol.55, No.2, (February 2006), pp. 197-209, ISSN 0340-7004

Reeves M, Sissons P, Sinclair J. (2005). Reactivation of human cytomegalovirus in dendritic cells. *Discov Med.* Vol.5, No.26, (April 2005), pp. 170-4, ISSN 1539-6509

Rodrigues L, Sampaio D, Couto I, Machado D, Kern WV, Amaral L, Viveiros M. (2009). The role of efflux pumps in macrolide resistance in Mycobacterium avium complex. *Int J Antimicrob Agents.* Vol.34, No.6, (December 2009), pp. 529-33, ISSN 0924-8579

Rossi D, Sala L, Minisini R, Fabris C, Falleti E, Cerri M, Burlone ME, Toniutto P, Gaidano G, Pirisi M. (2009). Occult hepatitis B virus infection of peripheral blood mononuclear cells among treatment-naive patients with chronic lymphocytic leukemia. *Leuk Lymphoma.* Vol.50, No.4, (April 2009), pp.604-11, ISSN 1042-8194

Ruhnke M, Rickerts V, Cornely OA, Buchheidt D, Glöckner A, Heinz W, Höhl R, Horré R, Karthaus M, Kujath P, Willinger B, Presterl E, Rath P, Ritter J, Glasmacher A, Lass-Flörl C, Groll AH. (2011). Diagnosis and therapy of Candida infections: joint recommendations of the German Speaking Mycological Society and the Paul-Ehrlich-Society for Chemotherapy. *Mycoses.* Vol.54, No.4, (July 2011), pp. 279-310, ISSN 0933-7407

Saadeh CE, Srkalovic G. (2008). Mycobacterium avium complex infection after alemtuzumab therapy for chronic lymphocytic leukemia. *Pharmacotherapy.* Vol.28, No.2, (February 2008), pp. 281-4, ISSN 0277-0008

Saritsiri S, Udomsantisook N, Suankratay C. (2006). Nontuberculous mycobacterial infections in King Chulalongkorn Memorial Hospital. J Med Assoc Thai. Vol.89, No.12, (December 2006), pp. 2035-46, ISSN 0125-2208

Sester M, Sester U, Gärtner BC, Girndt M, Meyerhans A, Köhler H.(2002). Dominance of virus-specific CD8 T cells in human primary cytomegalovirus infection. *J Am Soc Nephrol.* Vol.13, No.10, (October 2002), pp. 2577-84, ISSN 1046-6673

Shiota T, Lixin W, Takayama-Ito M, Iizuka I, Ogata M, Tsuji M, Nishimura H, Taniguchi S, Morikawa S, Kurane I, Mizuguchi M, Saijo M. (2011). Expression of herpes simplex virus type 1 recombinant thymidine kinase and its application to a rapid antiviral sensitivity assay. *Antiviral Res.* Vol.91, No.2, (Jun 2011), pp. 142-149, ISSN 0166-3542

Sidrim JJ, Costa AK, Cordeiro RA, Brilhante RS, Moura FE, Castelo-Branco DS, Neto MP, Rocha MF. (2010). Molecular methods for the diagnosis and characterization of Cryptococcus: a review. *Can J Microbiol.* Vol.56, No.6, (Jun 2010), pp. 445-58, ISSN 0008-4166

Sinisalo M, Aittoniemi J, Käyhty H, Vilpo J. (2003). Vaccination against infections in chronic lymphocytic leukemia. *Leuk Lymphoma.* Vol.44, No. 4, (April 2003), pp. 649-52. ISSN 1042-8194

Sinsalo M, Aittoniemi J, Käyhty H, Vilpo J. (2002). Haemophilus influenzae type b (Hib) antibody concentrations and vaccination responses in patients with chronic lymphocytic leukaemia: predicting factors for response. *Leuk Lymphoma.* Vol.43, No. 10, (October 2002), pp. 1967-9. ISSN 1042-8194

Sinisalo M, Vilpo J, Taurio J, Aittoniemi J. (2007). Antibody response to 7-valent conjugated pneumococcal vaccine in patients with chronic lymphocytic leukaemia. *Vaccine.* Vol.*26*, No.*1*, (December 2007), pp. 82-7, ISSN **0264-410X**

Südhoff T, Arning M, Schneider W. (1997). Prophylactic strategies to meet infectious complications in fludarabine-treated CLL. *Leukemia.* Vol.11, No. Suppl 2, (April 1997), pp. 38-41, ISSN 0887-6924

Tafreshi NK, Sadeghizadeh M, Amini-Bavil-Olyaee S, Ahadi AM, Jahanzad I, Roostaee MH. (2005). Development of a multiplex nested consensus PCR for detection and identification of major human herpesviruses in CNS infections. *J Clin Virol.* Vol.32, No.4, (April 2005), pp. 318-24, ISSN1386-6532

Thalla R, Kim D, Venkat KK, Parasuraman R. (2009). Sequestration of active Cryptococcus neoformans infection in the parathyroid gland despite prolonged therapy in a renal transplant recipient. *Transpl Infect Dis.* Vol.11, No.4, (August 2009), pp. 349-52, ISSN 1398-2273

Thursky KA, Worth LJ, Seymour JF, Miles Prince H, Slavin MA. (2006). Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab. *Br J Haematol.* Vol.132, No. 1, (January 2006), pp. 3-12, ISSN 0902-4441

Todisco M. (2009). Chronic lymphocytic leukemia: long-lasting remission with combination of cyclophosphamide, somatostatin, bromocriptine, retinoids, melatonin, and ACTH. *Cancer Biother Radiopharm.* Vol.24, No. 3, (June 2009), pp. 353-5, ISSN 1084-9785

Travade P, Dusart JD, Cavaroc M, Beytout J, Rey M. (1986). Severe infections associated with chronic lymphoid leukemia. 159 infectious episodes in 60 patients. *Presse Med.* Vol.15, No.34, (October 1986), pp. 1715-8, ISSN **0755-4982**

Turkulov V, Madle-Samardzija N, Brkić S. (1999). Meningoencephalitis as the only manifestation of Epstein-Barr virus infection. *Med Pregl.* Vol.52, No.(9-10), (September 1999), pp. 391-3, ISSN 0025-8105

Vancíková Z, Dvorák P.(2001). Cytomegalovirus infection in immunocompetent and immunocompromised individuals-a review. *Curr Drug Targets Immune Endocr Metabol Disord. 2001* Vol.1, No.2, (February 2001), pp. 179-87, ISSN 1568-0088

Van der Velden AM, Mulder AH, Hartkamp A, Diepersloot RJ, van Velzen-Blad H, Biesma DH. (1995). Influenza virus vaccination and booster in B-cell chronic lymphocytic leukaemia patients. *Eur J Intern Med.* Vol.12, No. 5, (September 1995), pp. 420-424, ISSN 0953-6205

Van Koeveringe MP, Brouwer RE. (2010). Histoplasma capsulatum reactivation with haemophagocytic syndrome in a patient with chronic lymphocytic leukaemia. *Neth J Med.* Vol.6*8*, No.1*2*, *(*December *2010*), pp. 418-21, ISSN 0300-2977

Vavricka SR, Halter J, Hechelhammer L, Himmelmann A. (2004). Pneumocystis carinii pneumonia in chronic lymphocytic leukaemia. *Postgrad Med J.* Vol.80, No.942, *(*April 2004), pp. 236-8, ISSN 0022-3859

Wadhwa PD & Morrison VA. (2006). Infectious complications of chronic lymphocytic leukemia. *Semin Oncol.* Vol.33, No.2, *(*April 2006), pp. 240-9, ISSN 0093-7754

Wierda WG.(2003). Immunologic monitoring in chronic lymphocytic leukemia. *Curr Oncol Rep.* Vol.5, No.5, *(*September 2003), pp. 419-25, ISSN 1523-3790

Yadegarynia D, Abbasi F, Haghighi M, Korooni Fardkhani S, Yadegarynia S. Pneumonitis due to cytomegalovirus in an immunocompromised patient. *Iranian Journal of Clinical Infectious Disease* Vol.4, No.4, *(*Fall 2009), pp. 238-240, ISSN 1735-5109

Yağci M, Acar K, Sucak GT, Aki Z, Bozdayi G, Haznedar R. (2006). A prospective study on chemotherapy-induced hepatitis B virus reactivation in chronic HBs Ag carriers with hematologic malignancies and pre-emptive therapy with nucleoside analogues. *Leuk Lymphoma.* Vol.47, No.8, *(*August 2006), pp. 1608-12, ISSN 1042-8194

Young JA. (2011). Epidemiology and management of infectious complications of contemporary management of chronic leukemias. (2011). *Infect Disord Drug Targets.* Vol.11, No.1, *(*February 2011), pp. 3-10, ISSN 1871-5265

Zahorodnia SD, Nesterova NV, Danylenko VP, Bukhtiarova TA, Baranova HV, Holovan' AV. (2011). Effect of isonicotinic acid derivates on reproduction of Epstein-Barr virus. *Mikrobiol Z.* Vol.73, No.2, *(*March-April 2011), pp. 65-72, ISSN 1028-0987
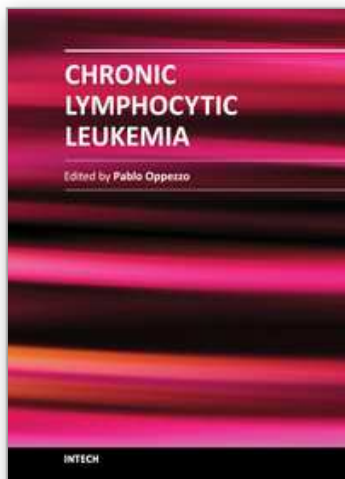
Chronic Lymphocytic Leukemia

Edited by Dr. Pablo Oppezzo

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 pancitopenia 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.

INTECH
open science | open minds