

Immune Response and Immunotherapy in Chronic Lymphocytic Leukemia

Leticia Huergo-Zapico¹, Ana P. Gonzalez-Rodríguez², Juan Contesti³,
Azahara Fernández-Guizán¹, Andrea Acebes Huerta¹,
Alejandro López-Soto¹ and Segundo Gonzalez¹

¹*Functional Biology Department, Instituto Universitario Oncológico del Principado de Asturias (IUOPA), University of Oviedo, Oviedo,*

²*Hematology Department, Hospital Universitario Central de Asturias, Oviedo*

³*Hematology Department, Hospital Cabueñe, Gijón, Spain*

1. Introduction

The contribution of the immune system to the pathogenesis of chronic lymphocytic leukemia (CLL) is receiving increasing attention in recent years. This interest has been supported by population studies, which have shown the increase of cancer risk in immunodeficient individuals (Grulich *et al.*, 2007; Smyth *et al.*, 2006; Swann *et al.*, 2007), and experimental studies, which have shown that deficiencies in key immunological molecules and cells increase the susceptibility to develop several types of solid tumors and hematological malignancies (Smyth *et al.*, 2006; Swann *et al.*, 2007). Additionally, the interest in the study of tumor immunology has been boosted by the increasing use of immunotherapy in the treatment of cancer, particularly in CLL. In this chapter, we review the role of the immune system in the elimination of CLL, the mechanisms that leukemia cells use to evade the immune response, and finally, we analyze the basis of the use of immunotherapy in the treatment of CLL patients.

2. Immune surveillance of cancer

The immune system is able to prevent cancer development by eliminating cancer cells prior to tumors becoming clinically detectable or by attenuating tumor growth and progression (Smyth *et al.*, 2006; Swann *et al.*, 2009). Both T cells and Natural Killer (NK) cells play a critical role in cancer immune surveillance (**Figure 1**). T cells are able to recognize tumor antigens, which differentiate cancer cells from their nontransformed counterparts. Several tumor antigens have been described such as mutation of oncogenic proteins (e.g. p53), over-expressed cellular antigens (such as HER-2), viral antigens, differentiation antigens and aberrantly expressed antigens (Smyth *et al.*, 2006; Swann *et al.*, 2007). Cytotoxic CD8 T cells and helper CD4 T cells may recognize transformed cells bearing these tumor antigens presented as peptides by MHC class I and class II molecules, respectively.

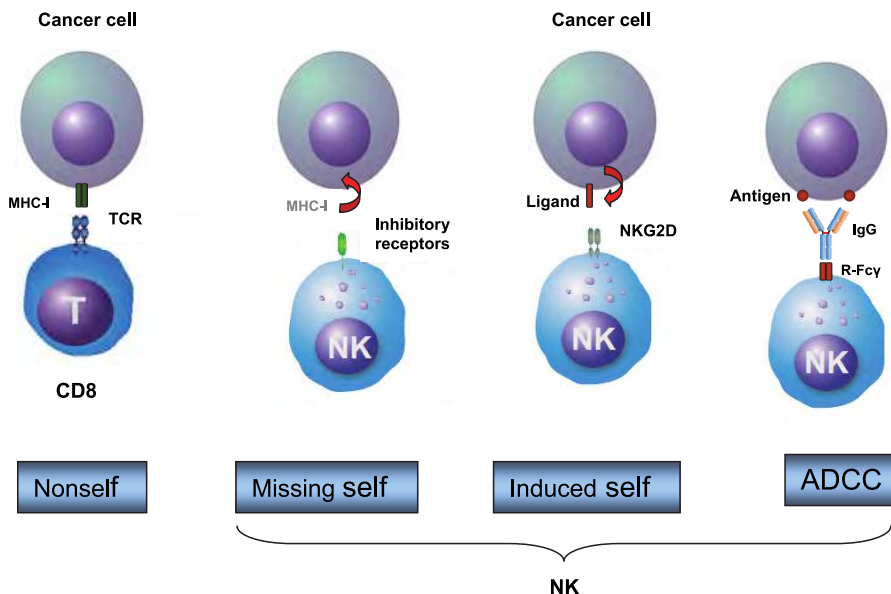


Fig. 1. Mechanisms of cancer immune surveillance. T Cell Receptor (TCR) expressed by CD8 T cells is able to recognize tumor antigens presented as peptides by the Major Histocompatibility Complex class I proteins (MHC-I) (nonself recognition). NK cells use several mechanisms to recognize tumor cells. NK cells use inhibitory receptors to differentiate "self" from "missing self". The impairment of MHC class I expression observed in some tumor cells impairs the recognition by CD8 T cells. Nevertheless, MHC class I molecules have an inhibitory effect on the activation of NK cells. Consequently, the lack of expression of MHC class I molecules (*missing self*) promotes the activation of NK cells and the lysis of the target cell. NK cells also express activating receptors, such as NKG2D, which is able to recognize several ligands induced in transformed cells (*induced self*). NK cells also express the Fc γ RIII receptor (also named CD16), which is able to recognize tumor cells that have been bound by specific IgG antibodies. This mechanism of recognition is termed Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC).

NK cells do not directly recognize tumor antigens, but instead, they recognize changes in cells caused by transformation. Several mechanisms of cancer recognition by NK cells have been described (Gonzalez *et al.*, 2011). NK cells use a set of inhibitory receptors, such as killer cell immunoglobulin-like receptors (KIRs), to differentiate and eliminate cancer cells that lack MHC class I expression ("missing self" recognition) (Figure 1) (Gonzalez *et al.*, 2011). NK cells also express activating receptors which recognize stress-induced molecules expressed on tumor cells ("induced self" recognition). The activating receptor NKG2D plays a pivotal role in the immune response against cancer. This receptor is expressed by NK cells, $\gamma\delta$ T cells and CD8 T cells, and recognizes several tumor-associated ligands named MICA, MICB and ULBP1-5 molecules. NKG2D ligands are restrictedly expressed in healthy cells, but they are induced in stressed and transformed cells, allowing the elimination of these cells by the immune system (Das *et al.*, 2001; Raulet *et al.*, 2003; Bauer *et al.*, 1999; Lopez-Larrea *et al.*, 2008; Bahram *et al.*, 1994; Cosman *et al.*, 2001; González *et al.*, 2008; Guerra *et al.*, 2008).

al., 2008). NK cells may also lyse target cells that have been bound by specific IgG antibodies. They are able to recognize the Fc region of the antibody through Fc γ RIII receptor (also named CD16). This mechanism of recognition is termed Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) and it is an important mechanism of action against tumors of therapeutic monoclonal antibodies, such as rituximab and alemtuzumab (Figure 1). These mechanisms of anti-tumor immune response may protect the host in the early stages of tumor initiation; however during cancer progression, tumors develop a plethora of mechanisms of immune evasion. Consequently, the anti-tumor response is ineffective in advanced tumors (Smyth *et al.*, 2006; Swann *et al.*, 2007).

3. Immune surveillance of chronic lymphocytic leukemia

There is little information related to the role of the immune response in the early stages of CLL progression. Nevertheless, it has widely been reported that the amounts of CD8 and CD4 T cells and NK cells are significantly elevated at diagnosis of the disease. The expansion of cytotoxic CD8 T cells is higher than CD4 T cells, and many CLL patients showed an inversion of CD4/CD8 ratio (Gonzalez-Rodriguez *et al.*, 2010). Similar expansions of immune cells have been observed in other hematological malignancies and this increase of immune cells has been associated with a better prognosis of patients. Thus, higher absolute lymphocyte count predicts higher survival in lymphoma, acute myeloblastic leukemia and myeloma (Cox *et al.*, 2008; Siddiqui *et al.*, 2006; Porrata *et al.*, 2007, 2009; Ray-Coquard *et al.*, 2009; De Angulo *et al.*, 2008; Behl *et al.* 2006, 2007; Ege *et al.*, 2008). NK cell count has also been associated with clinical outcome in patients with diffuse large B-cell lymphoma (Plonquet *et al.*, 2007). The expansion of immune cells observed in CLL and in other hematological malignancies may be compared to the expansion of tumor infiltrating lymphocytes in epithelial tumors. In several types of cancer, the presence of tumor infiltrating lymphocytes, mainly NK and CD8 T cells, has also been associated with the anti-tumor response and was found to be a better predictor of patient survival than traditional histopathological methods used to stage tumors (Dunn *et al.*, 2004; Clemente *et al.*, 1996; Scanlan *et al.*, 2004; Rollins *et al.*, 2006; Moore OS *et al.*, 1949; Clark *et al.*, 1969; Pagès *et al.*, 2005)

In agreement with an anti-tumor role of the immune system, the expansion of NK and T cells has been associated with the time to treatment in CLL (Palmer *et al.*, 2008). Furthermore, the relative numbers of CD8 and CD4 T cells at diagnosis are independent predictors for survival, and higher CD8 count is associated with significantly higher median time of survival of CLL patients (Gonzalez-Rodriguez *et al.*, 2010). This suggests that the expansion of immune cells observed at diagnosis of CLL patients may be due, at least in part, to the expansion of anti-tumor immune cells. However, the analysis of the functionality of these cells is still lacking. Early studies showed that the expanded CD8 T cells have an activated phenotype and cytotoxic function and appear to have restricted clonality, which were originally interpreted as evidence of an autologous T cell response against leukemia cells. Furthermore, a subset of $\gamma\delta$ T cells with anti-tumor activity is one type of the immune cells expanded in CLL patients (Poggi *et al.*, 2004). These T cells express the activating receptor NKG2D, which is able to mediate the lysis of CLL cells expressing NKG2D ligands ("induced self" recognition) (Figure 1). Leukemia cells from most patients lack NKG2D ligands expression and are highly resistant to NK cell-mediated lysis, but NKG2D ligands

expression may be induced in leukemia cells by treatment with trans-retinoic acid or histone deacetylases (HDACs) inhibitors, rendering leukemia cells susceptible to lysis by immune cells (Kato et al., 2007; Del Giudice et al., 2009). The expansion of $\gamma\delta$ T cells has been associated with a better prognosis of CLL patients, supporting the hypothesis that the increase of T cells observed at diagnosis of CLL patients may be due, at least in part, to the expansion of anti-tumor T cells.

The activation of the immune system in CLL patients has not only been associated with improved prognosis, but also with tumor regression. The natural history of stage A disease is generally indolent or only slowly progressive. However, it is less known that CLL may undergo spontaneous regression (Del Giudice et al., 2009). There are no data about the functional role of the immune system in these remissions; however the activation of immune system has been associated with spontaneous remissions in other types of cancers (Smyth et al., 2006; Swann et al., 2007). This suggests that the activation of the anti-tumor immune response may have a significant impact on the progression of CLL, however further analyses about the functionality of immune cells in CLL are clearly warranted.

The role of immune system in CLL is further highlighted by the analysis of cancer risk in immunodeficient individuals. However, the deficiency of CD8 T cells is not compatible with life and most of the studies about the role of other immune deficiencies on cancer susceptibility are nonpopulation-based and of small sample size, making difficult to draw definite conclusions. Nevertheless, primary immune deficiency patients have been associated with a marked increased risk of cancer. Some types of cancers appear to be associated with specific forms of immunodeficiency including stomach cancer with common variable immune deficiency (CVID) (Kinlen et al., 1985; Mellemkjaer et al., 2002), leukemia with ataxia-telangiectasia (Morrell et al., 1986), and nonmelanocytic skin cancer with cartilage-hair hypoplasia (Taskinen et al., 2008). In a recent population-based study, the association of antibody deficiency with an increasing risk of leukemia, non-Hodgkin lymphoma and gastric cancer has been described (Vajdic et al., 2010). In agreement with clinical data, deficiencies in T cells and NK cells have also been associated with increased susceptibility of cancer in a diversity of experimental models of cancer (Smyth et al., 2006; Swann et al., 2007).

Nevertheless, the most compelling evidence about the potential role of the immune system in the pathogenesis of CLL is the increasing use of immunotherapy in the treatment of this disease. This highlights the capacity of the activation of the immune system to eliminate CLL cells and the potential role of immune system to cure this disease. Thus, the therapeutic effect of allogeneic hematopoietic stem cell transplantation in CLL relies on the ability of the immune cells of the graft to recognize and eliminate leukemia cells (Mehta et al., 1996; Ritgen et al., 2008). Similarly, the therapeutic use of immunomodulatory drugs, such as lenalidomide, is not directly based on a cytotoxic effect on CLL cells, but instead, lenalidomide exerts its therapeutic effect through the stimulation of the immune system.

4. Immune defects in chronic lymphocytic leukemia patients

In spite of the existence of compelling evidences about the ability of the immune system to eliminate nascent tumors, when the immune system is unable to eliminate all cancer cells, it sculpts or edits the phenotype of cancer cells, eliminating the most immunogenic ones and selecting the less immunogenic tumor cells, which are able to evade or suppress the immune

response. The consequence of this process, named cancer immunoediting, is the development of numerous mechanisms of immune evasion and immune suppression in advanced tumors (Smyth et al., 2006; Swann et al., 2007). Accordingly, there is a progressive acquisition of a wide variety of immune defects in the course of the progression of CLL. As a result, patients progressively acquire a immunodeficiency status, which increases the incidence of opportunistic infections and the development of secondary neoplasias (Hamblin et al., 2008). The corollary of immune defects also includes the development of several autoimmune reactions. CLL patients have a 5-10% risk of development of an autoimmune complication, which primarily cause cytopenia (Zent et al., 2010). The most common autoimmune disease affecting CLL patients is hemolytic anemia, with a lower frequency of immune thrombocytopenia and pure red blood cell aplasia and only rarely, autoimmune granulocytopenia.

Practically all components of the immune system are impaired in CLL patients. The most obvious and well-known immune defect is hypogammaglobulinemia, which is present in up to 85% of patients (Hamblin *et al.*, 1987). Hypogammaglobulinemia is observed in other lymphoid malignancies, but the impairment of the humoral immune response is far greater in CLL. The clinical consequence of hypogammaglobulinemia is the increase of susceptibility of CLL patients to infection with extracellular bacteria, commonly affecting respiratory tract, skin and urinary tract, and the reactivation of some latent virus infections, mainly belonging to *Herpesviridae* family.

The defects in the humoral immunity are accompanied by several abnormalities in the cellular immune response, including quantitative and qualitative alterations of NK cells, CD4 and CD8 T cells, dendritic cells, neutrophils, monocytes and cytokines. The activity of NK cells against leukemia cells is frequently reduced and lymphoid neoplasms are quite resistant to NK cell-mediated cytotoxicity (Foa et al., 1984; Jewell et al., 1992; Kato et al., 2007). All effector mechanisms of NK cells analyzed are impaired in some degree in advanced CLL patients (Katrinakis et al., 1996; Caligaris-Cappio et al., 1999; Wierda et al., 1999). A partial down-regulation of MHC class I molecules, which allow leukemic cells to escape from cytotoxic T cell attack, has been reported (Demaret et al., 2004). However, the "missing self" recognition by NK cells (**Figure 1**) is limited in CLL by the aberrant expression of HLA-G in leukemia cells. HLA-G is a non classical MHC class I molecule that is physiologically expressed on fetal derived placental cells. Classical MHC class I molecules (HLA-A, -B and -C) are not expressed in fetal placental cells, but HLA-G inhibits NK cells activation against placental cells by interacting with several inhibitory receptors expressed by NK cells and cytotoxic T lymphocytes. Likewise, the aberrant expression of HLA-G on leukemia cells impairs the anti-leukemia immune response mediated by these cells. Accordingly, the expression of HLA-G on leukemia cells correlated with progression free survival and the level of immunosuppression of CLL patients (Nüchel et al., 2005; Erikci et al., 2009).

There are also defects on the expression of NKG2D and its ligands in CLL (Gasser et al., 2005; Groh et al., 1996, 1999; Diefenbach et al., 2001; Cerwenka et al., 2001; González et al., 2006). The expression of NKG2D ligands in leukemia cells is low or absent in most of patients, which confers them with a high resistance to lysis by immune cells (Poggi et al., 2004). Furthermore, leukemia cells may also counter the anti-tumor activity of NKG2D by shedding some of its soluble ligands. Serum levels of soluble MICA, MICB and ULBP2 are significantly increased in

CLL patients and are associated with a poor treatment-free survival (Nückel et al., 2010). The shedding of soluble MICA has been described in many types of cancer and elevated levels of soluble MICA correlated with advanced stage tumors, metastasis and poor prognosis (Salih et al. 2002, 2003; Raffaghello et al., 2004; Rebmann et al., 2007), because soluble MICA impairs the recognition of cancer cells by immune cells and suppress the immune response (Groh et al., 2002, 2006). Of relevance, some of the immune defects observed in CLL patients may be reversible. For instance, leukemia cells which express low levels of NKG2D ligands may be rendered susceptible to immune cells when are treated with trans-retinoic acid or histone deacetylase inhibitors inhibitors, which restored the expression of NKG2D ligands on leukemia cells (Salih et al., 2002). This clearly suggests that therapeutic approaches that can bypass the immune evasion mechanisms of CLL patients may have therapeutic application in this disease.

T cell function is also impaired in CLL. There are defects on antigen presentation (Cantwell et al., 1997), T cell activation, in differentiation and function of CD4 T cells and defects in the cytotoxic activity of CD8 cells that are caused by direct contact with leukemia cells (Gorgun et al., 2005; Rossi et al., 1996; Junevik et al., 2007; Mackus et al., 2003). Regulatory T cells, a specialized subpopulation of T cells which suppresses the activation of the immune system and thereby maintains tolerance to self antigens, are increased in number in CLL and this increase is more significantly in most advanced patients (Beyer *et al.*, 2006). It is not yet clear whether inhibitory T cells may promote the tolerance of leukemia cells by the immune system and may contribute to the immune deficiency. Nevertheless, it is noticeable that this population is exquisitely sensitive to treatment with fludarabine. It has been proposed that the elimination of these inhibitory T cells might be one of the mechanisms that favors the development of autoimmune hemolytic anemia after treatment of CLL patients with fludarabine (Hamblin *et al.*, 2006).

The defects of cellular immunity observed in CLL increase the susceptibility of patients to virus infections, opportunistic infections and second malignancies, and may contribute to impair the anti-leukemia immune response. Additionally, the use of chemotherapy agents may complicate the clinical course of CLL since may exacerbate the pre-existing immunodeficiency. Nevertheless, the development of drugs and therapeutic strategies that can either bypass immune evasion mechanisms or rescue immune suppressor pathways may significantly benefit CLL patients. Thus, the increasing understanding of the molecular and cellular events underlying the immune dysfunction in CLL is of key importance in the development of novel immune-based therapies.

5. Immunotherapy

CLL is generally considered as an incurable disease, but it frequently progresses slowly. Early-stage CLL is, in general, not treated since there are no clear evidences that early therapeutic intervention improves survival time or quality of life. Instead, the disease is monitored over time to detect changes in disease progression. Determining when to start the treatment and by what means is often difficult. The National Cancer Institute Working Group has issued guidelines for treatment (Cheson et al., 1996; Hallek et al., 1996).

Until recently, chemotherapy has been the keystone of treatment of CLL. Alkylating agents have been considered the first line in the treatment of CLL patients for a long time. They can

induce complete responses, but it is not considered curative. Chlorambucil slows disease progression, but does not prolong survival (Dighiero et al., 1998; Eichhorst et al., 2006; Hallek, 2010) (Figure 2). The purine analogue fludarabine was shown to give superior response rates to chlorambucil as primary therapy (Steurer et al., 2006; Rai et al., 2000), but there are no evidences that the early use of fludarabine improves overall survival. Treatment combinations of Fludarabine with the alkylating agent Cyclophosphamide (FC) result in higher response rates, in longer median progression-free survival and longer treatment-free survival than single agents (Maloney et al., 1999). Thus far, no difference in median overall survival has been observed.

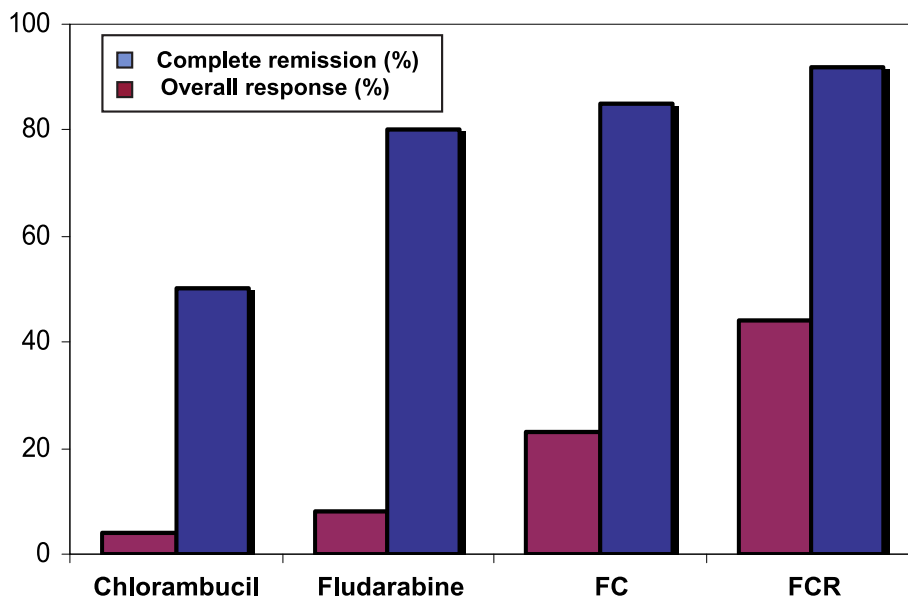


Fig. 2. Chronic lymphocytic leukemia therapy. The figure shows rates of complete remissions and overall response in CLL first line treatment. (F=Fludarabine, C=Cyclophosphamide, R= Rituximab).

In spite of the fact that chemotherapy provides benefits for CLL patients, it is palliative, and treated patients frequently develop recurrent disease. Likewise treatment induces myelosuppression and selection of chemotherapy resistant clones. Additionally, it can worsen immune function, increasing the immunodeficiency status of CLL patients. Prognosis for patients treated with chemotherapy regimens remains poor, prompting the development of new targeted agents. In line with this idea, the activation of the immune system to fight against CLL cells has opened new vistas in the treatment of CLL. Immunotherapy may potentially provide curative treatment and some immunotherapeutic approaches may mitigate disease complications caused by the defects of the immune system observed in CLL patients. In this sense, monoclonal antibodies, allogeneic hematopoietic stem cell transplantation and immunomodulatory drugs have successfully been used in the treatment of CLL. Immune-based therapy represents an exciting mode of treatment since it may be able to eliminate leukemia cells without myelosuppression.

5.1 Monoclonal antibodies

Monoclonal antibodies have the ability to target specific antigens expressed preferentially on the surface of malignant cells. Due to their specificity, the therapeutic efficacy of monoclonal antibodies is not generally associated with a high non-specific toxicity. Thus, they are increasingly being used in the treatment of hematological malignancies and solid tumors. In CLL, the use of **rituximab**, a chimeric murine/human monoclonal antibody directed against CD20, has improved the treatment of patients. Unlike other B cells antigens, CD20 is neither shedded nor internalized in resting normal B cells. Therefore it is an ideal target for antibody-based therapy in mature B cell malignancies. Rituximab treatment induces a significant reduction in B cell count within 3 days followed by a slow recovery over 9-12 months (Maloney et al., 1997; Onrust et al., 1999). The mechanism of B cell killing has not completely been elucidated, but rituximab acts through Antibody-Dependent Cell-Mediated Cytotoxicity, complement-mediated cytotoxicity, the activation of macrophages, and direct apoptosis of leukemia cells both caspase dependent and independent (Jagłowski et al., 2010) (Figure 3).

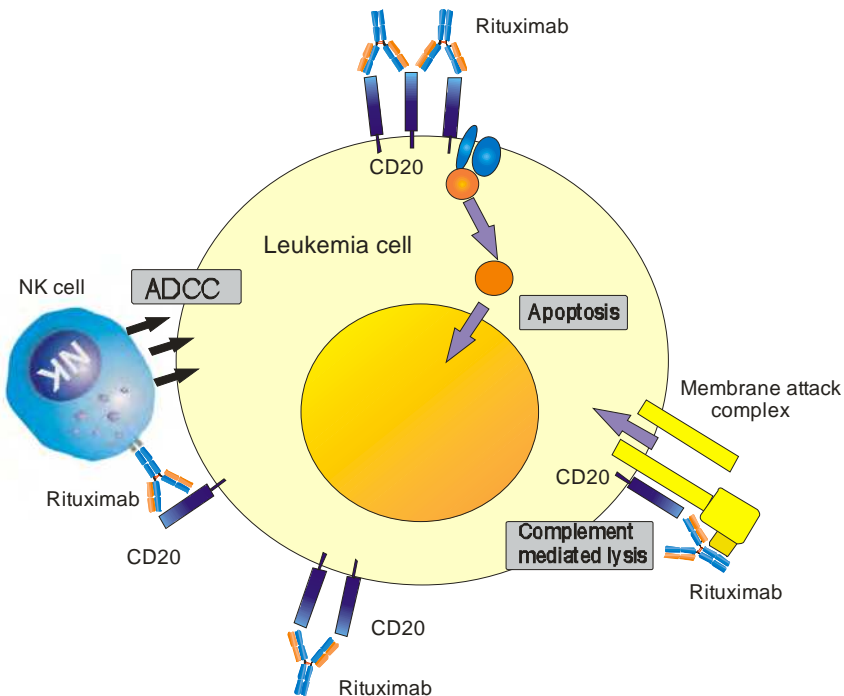


Fig. 3. Mechanism of action of rituximab. Rituximab is a monoclonal antibody directed against CD20 antigen, which is expressed on the surface of B cells. The recognition of the Fc portion of rituximab through the Fc γ RIII receptor mediates the lysis of leukemia cells by NK cells; a process named Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC). The Fc portion of rituximab also induces the activation of the classical pathway of complement. The activation of complement cascade forms a transmembrane channel, which causes the osmotic lysis of the leukemia cell. Rituximab may also cause a direct apoptosis of CD20 cells.

The efficacy of rituximab monotherapy in CLL is lower than in other B cell malignancies. The resistance to rituximab is frequently associated with a low CD20 expression. Nevertheless, the addition of rituximab to chemotherapy has proven to be very efficacious therapy for CLL. Treatment combinations of Fludarabine, Cyclophosphamide and Rituximab (FCR) obtain the highest response, but they are not still considered curative (Byrd et al., 2005; Tam et al., 2008; Wierda et al., 2005) (**Figure 2**). FCR therapy shows superiority for response rates and progression-free survival when compared to FC chemotherapy (Hallek et al., 2009; Robak et al., 2008), and it is becoming the first-line choice for younger patients (Casak et al., 2011). Additionally, rituximab represents one of the most active therapies for the treatment of autoimmune complications of CLL not responding to initial steroid treatment. The use of monoclonal antibodies for purging of leukemia cells *ex vivo* also improves the results of autologous stem cell transplantation (Gribben et al., 2005; Montillo et al., 2006).

The therapeutic efficacy of rituximab is minimally hampered by non-specific toxicity; however it has been associated with adverse events such as immunosuppression, reactivation of latent virus and infusion-related. Combination with chemotherapy may be associated with more profound immunosuppression. Management of these adverse events is a critical component of the treatment strategy for CLL since they can greatly affect the quality of life of patients and the ability to tolerate this therapy.

Alemtuzumab, a CD52-target humanized monoclonal antibody, has demonstrated benefits in the treatment of CLL patients (Gribben et al., 2009). CD52 is a protein highly expressed on both normal and malignant lymphocytes (B and T cells) and it is also found in other immune cells such as monocytes, macrophages and eosinophils; but it is not expressed on hematopoietic progenitors. The administration of alemtuzumab results in a severe lymphopenia with a reduction in both B and T cells, but it also affects other healthy CD52-expressing immune cells, which likely exacerbate the pre-existing immunodeficiency. After treatment, there is a slow recovery of immune cells, except for B cells, which remain at low level at 18 months. Alemtuzumab acts through Antibody-Dependent Cell-Mediated Cytotoxicity (Crowe et al., 1992) (**Figure 1**), complement-mediated cytotoxicity (Golay et al., 2004; Zent et al., 2004), and induces direct cell death through a mechanism that is independent of p53 status and caspase activation (Mone et al., 2006), and is effective in patients with deletion (17p)(13.1).

A significant difference between the efficacy of alemtuzumab and rituximab is based on the fact that the level of CD52 expression in normal and malignant B cells is far greater than the level of CD20 expression in CLL cells. The high expression of CD52 may contribute to the improved clinical activity of alemtuzumab as a single-agent compared to rituximab in CLL (Ashraf et al., 2007). Alemtuzumab is currently approved for first-line treatment of CLL, and it is a good option for symptomatic patients, previously untreated patients and relapsed patients with poor prognostic features (Keating et al., 2002; Osterborg et al., 1996; Lundin et al., 2002; Hillmen et al., 2007).

New monoclonal antibodies directed against CD20, such as ofatumumab and GA101, have been developed. **Ofatumumab** and rituximab bind to different epitopes, and, in theory, ofatumumab has greater capacity of activation of complement-dependent cytotoxicity than rituximab (Teeling et al., 2004). *In vitro* studies have demonstrated that ofatumumab is

significantly more effective than rituximab at lysing CLL cells and B cell lines, especially those with low CD20 copy numbers. It is currently approved for treating CLL patients who are refractory to fludarabine and alemtuzumab.

The novel third generation humanized monoclonal antibody **GA101** also binds with high affinity to CD20, and as a result it promotes greater induction of Antibody-Dependent Cell-Mediated Cytotoxicity (Jagłowski et al., 2010) and induces more efficient NK cell activation than rituximab (Bologna et al., 2011). The development of new monoclonal antibodies is probably the best demonstration of the therapeutic efficacy that these agents have obtained in CLL and other hematological malignancies.

5.2 Hematopoietic stem cell transplantation

About 20% of patients who need treatment develop an aggressive disease despite early institution of intensive chemotherapy. Efforts to develop curative treatment for these CLL patients have focused on autologous and allogeneic hematopoietic stem cell transplantation (Dreger et al., 2009). Both approaches show some methodological similarities, but the bases of both treatments are significantly different. Most patients may achieve a complete molecular response followed by **autologous stem cell transplantation**, a lower-risk form of treatment using the patient's own blood cells, which restores the hematopoietic system after an intensive chemotherapy regimen. The increase of the dose chemotherapy regimen is the base of the efficacy of autografting, and consequently, it is not an immune-based therapy. This therapy is not curative and subsequent clinical progression is inevitable (Provan et al., 1996; Milligan et al., 2005). The results of a phase 3 randomized European Group for Blood and Marrow Transplantation trial of autologous stem cell transplantation show the reduction of the risk of progression of CLL by more than 50%, but it does not have an effect on overall survival (Michallet et al., 2011), and it is particularly concerning the high incidence of myelodysplastic syndrome (9-12%) (Kharfan-Dabaja et al., 2007). Therefore, it is necessary to look for other solutions of treatment in this disease different from the chemotherapy and to move toward alternative non-chemotherapy-based treatment approaches.

Allogeneic stem cell transplantation offers a chance of definite cure of CLL, but is only feasible in a minority of patients. The basis of therapeutic response of allogeneic stem cell transplantation relies on the ability of immune cells of the graft to recognize and eliminate leukemia cells, a process known as graft-versus-leukemia effect (GvL) (Mehta et al., 1996; Ritgen et al., 2008) (**Figure 4**). Thus, allogeneic stem cell transplantation is a cellular-based immunotherapy completely different from autografting. The immunology of allogeneic stem cell transplantation is different from other types of transplants, such as heart or kidney transplants, because the graft, in addition to stem cells, contains and generates mature immune cells including T cells, NK cells and dendritic cells. These cells repopulate the recipient's immune system, restoring the response to infections and eliminating leukemia cells. The donor immune cells exert its graft-versus-leukemia effect through T cell-mediated alloreaction against the histocompatibility antigens displayed on leukemia cells. However, as histocompatibility antigens are shared by all cells of individual, recipient tissues may also be attacked by donor's immune system causing graft-versus-host-disease (GvHD) (rejection), a life-threatening condition. For this reason, matching donor and recipient HLA molecules is crucial to minimize graft-versus-host-disease. Mismatches in HLA-A, -B, -C and HLA class II alleles are significant risk factors for graft-versus-host-disease. Due to the

high number of HLA alleles is quite difficult to find a HLA-matched unrelated donor, but nearly 25% of siblings share both HLA haplotypes, because all HLA genes are closely linked in a small region of chromosome 6, known as Major Histocompatibility Complex (MHC). However, even in HLA-matched recipient and donor, graft-versus-host-disease may occur due to minor histocompatibility antigens, which are derived from differences between donor and recipient in other polymorphic genes different from HLA, differences in the level of expression of proteins or are derived from genome differences between male and female (such as H-Y antigens encoded by Y chromosome, which is absent in females).

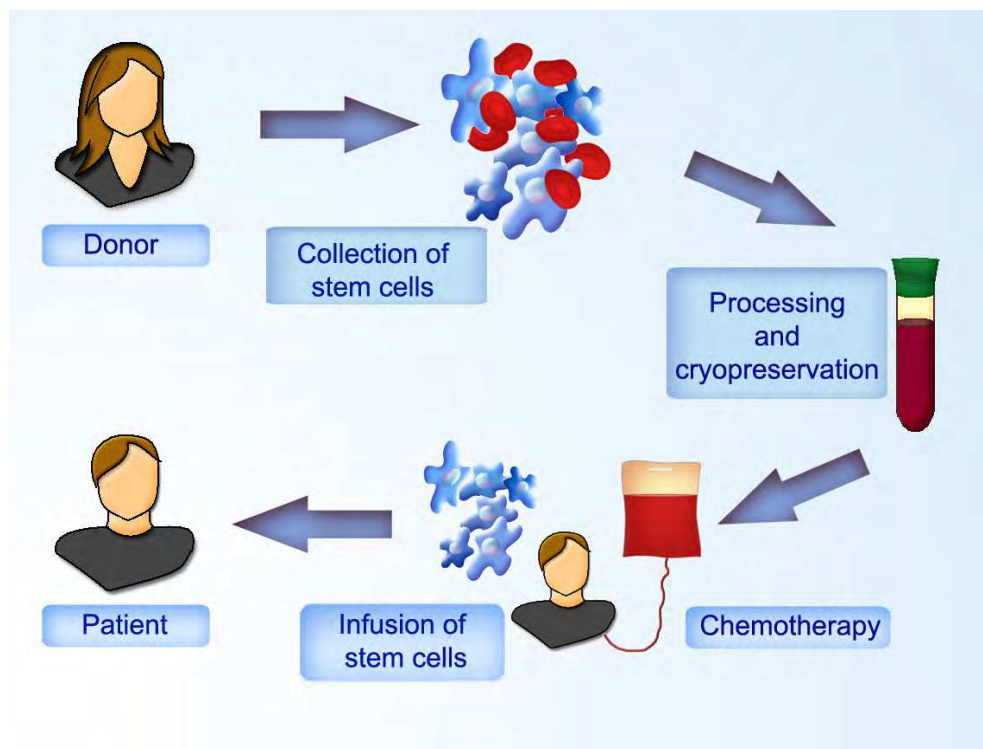


Fig. 4. Allogeneic stem cell transplantation. Hematopoietic stem cells are collected from the bone marrow or blood of the donor. Bone marrow or blood is taken to the processing laboratory where stem cells are concentrated and may be frozen (cryopreservation). High dose chemotherapy and/or radiation are given to the patient. To restore the patient's immune system, thawed or fresh stem cells are infused into the patient. The donor immune cells eliminate leukemia cells (graft-versus-leukemia) through a T cell-mediated alloreaction against patient's histocompatibility antigens displayed on leukemia cells.

If a HLA-matched sibling is not available, the use of unrelated umbilical blood units or an unrelated matched donor are viable options. Umbilical blood units offer the advantage that a higher number of mismatches in HLA antigens does not preclude transplant feasibility since naïve T cells in cord blood are less able to cause graft-versus-host-disease than mature donor T cells in bone marrow or peripheral blood, however graft-versus-leukemia is also

less intense. Family donors, who matched a HLA haplotype, but fully mismatched the other (“haploidentical”) is another option to obtain hemopoietic stem cells. The haploidentical transplant recipients have high risk of T-cell mediated graft-versus-host-disease (Velardi et al., 2010). This is controlled by an extensive immunosuppressive intensity in the conditioning regimen and extensive T cell depletion of the graft to prevent graft-versus-host-disease. The immune suppression and the depletion of T cells might be expected to result in weak or no graft-versus-leukemia effect, as it is conventionally achieved through T cell-mediated alloreactivity directed against recipient’s histocompatibility antigens. Surprisingly, another immune cell influences the outcome of allogeneic stem cell transplantation in a favorable way. In these transplants, NK cell-mediated alloreactivity may control leukemia relapse without causing graft-versus-host-disease. This alloreaction is due to the fact that NK cells express specific inhibitory receptors, such as KIR or CD94/NKG2, for groups of HLA class I alleles. Inhibitory receptors and HLA class I genes structure individual NK cell repertoires during development. To establish a self-tolerance, each individual selects NK cells carrying inhibitory receptor combinations for their self HLA class I molecules. NK cells from those individuals that express inhibitory receptors for a HLA class I group, which is absent on allogeneic transplants, sense the missing expression of their self HLA class I molecules and mediate alloreactions against leukemia cells by “missing self” recognition (Figure 1).

Several nonrandomized prospective trials have demonstrated the potential efficacy of allogeneic stem cell transplantation in CLL; however even with reduced-intensity conditioning allogeneic stem cell transplantation is associated with significant morbidity and mortality. Nevertheless, it is a reasonable treatment option for poor-risk CLL patients. Allogeneic stem cell transplantation can overcome treatment resistance of poor-risk CLL defined as purine analogue refractoriness, early relapse after purine analogue combination therapy or autologous stem cell transplantation, and CLL with p53 deletion/mutation requiring treatment (Dreger et al., 2007). Nonmyeloablative allogeneic stem cell transplantation resulted in sustained remissions and prolonged survival in patients who had chemotherapy-refractory CLL (Sorrer et al., 2008) and in high risk patients (Schetelig et al., 2008). Myeloablative allogeneic stem cell transplantation consistently results in a plateau in survival after 1 year, and the development of undetectable minimal residual disease (Pavletic et al., 2005). Evidence for graft-versus-leukemia in CLL can result in a complete and durable suppression of the leukemic clone (Ritgen et al., 2008; Rondón et al., 1996; Dreger et al., 2005; Farina et al., 2009; Sorror et al., 2005; Gribben et al., 2005). A prospective clinical trial is currently being performed in patients with high-risk CLL. This trial will finish in 2012 and will probably give us some guidance when and how to use allogeneic stem cell transplantation in poor-risk CLL.

In summary, there is convincing evidence that allogeneic stem cell transplantation can provide long-term disease control and possibly cure in selected patients with CLL, including those with a biologically highly unfavorable risk profile. Even patients who relapsed after allogeneic transplant may achieve durable remission following **donor lymphocyte infusion** without further chemotherapy or radiation chemotherapy (Hoogendoorn et al., 2007; Schetelig et al., 2003; Delgado et al., 2006; Marina et al., 2010). This further highlights the capacity of the donor-derived immunity in eradicating tumors (Marina et al., 2010).

5.3 Immune modulating drugs

Lenalidomide is a new immunomodulatory drug used in the treatment of CLL that is receiving considerable interest. It is a small molecular analog of thalidomide that was originally selected based on its ability to effectively inhibit tumor necrosis factor α (TNF- α) production. The mechanism of action of lenalidomide is complex and not yet fully understood. In CLL, lenalidomide has not a direct anti-tumor effect by inducing of apoptosis, but it has a significant anti-angiogenic and immune effects. It represents an exciting drug since it is able to eliminate CLL cells without immunosuppression.

Lenalidomide is clinically used in combination with dexamethasone in patients with multiple myeloma who have received prior therapy, in myelodysplastic syndrome, and in addition, there are current clinical trials analyzing the therapeutic effect of this drug in other types of cancers. In CLL, lenalidomide is clinically effective as a single agent in relapsed and refractory patients (Ferrajoli et al., 2008 ; Chanan-Khan et al., 2006), and ongoing trials are demonstrating that lenalidomide is clinically active as first-line CLL therapy (Chen et al., 2010). The responses achieved with lenalidomide are durable, even in patients with high-risk disease, with poor risk cytogenetics and with high-risk cytogenetics [del(11q)(q22.3) or del(17p)(p13.1)] (Sher et al., 2010).

The immunomodulatory mechanism of action of lenalidomide in CLL is poorly understood. Lenalidomide improves the humoral and cellular immune response of CLL patients (Figure 5). Lenalidomide treatment is associated with a significant increase in immunoglobulin

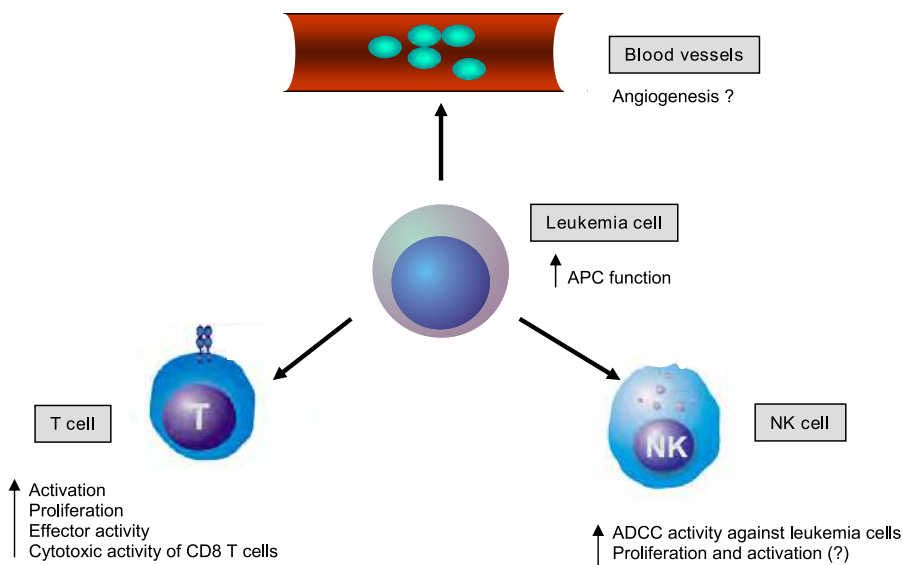


Fig. 5. Mechanism of action of lenalidomide in chronic lymphocytic leukemia. Lenalidomide does not have a direct cytotoxic effect on leukemia cells. Lenalidomide favors antigen presentation, activation, proliferation and functional activity of T cells. It also enhances Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) against rituximab-exposed leukemia cells. Other effects on angiogenic status remain to be elucidated.

levels. For instance, IgG levels were normalized in 7 out of 12 (58%) CLL patients with hypogammaglobulinemia (Badoux et al., 2009). Lenalidomide enhances antigen presentation to T cells (Aue et al., 2009; Chanan-Khan et al., 2006) and increases proliferation, activation and effector activity of T cells, which as mentioned before is impaired in CLL patients (Ramsay et al., 2008). Thalidomide and lenalidomide also have a significant immunomodulatory effect on NK cells. In some experimental models, the antitumor effect of lenalidomide was mediated by NK cell stimulation (Awan et al., 2010). There is little information about the effect of lenalidomide on NK cells *in vivo*. Nevertheless, lenalidomide treatment increased the number of NK cells in CLL patients and increased Antibody-Dependent Cell-Mediated Cytotoxicity against leukemia cells (Wu et al., 2008). Lenalidomide induces a unique and previously uncharacterized immune response called tumor flare reaction associated with immune mediated antitumor response. Tumor flare reaction with lenalidomide appears to be disease-specific to CLL, may reflect clinical manifestation of tumor cell activation and correlates with clinical response (Chanan-Khan et al., 2010). Combination of lenalidomide with rituximab may act synergistically if the timing and sequencing strategies are optimized. An exciting new therapeutic strategy may be targeting tumor cell with chemotherapy or monoclonal antibodies and the microenvironment with lenalidomide (Ramsay et al., 2009).

6. Conclusion

In spite of the existence of little information about the role of the immune system in the pathogenesis of CLL, the current data clearly support the hypothesis that the activation of the anti-tumor immune response, particularly in the early stages of the disease, may have a significant impact on tumor progression. However, CLL patients progressively acquire a wide variety of immune evasion mechanisms. As a result, patients acquire a progressive immunodeficiency status, which increases the incidence of opportunistic infections and the development of secondary neoplasias. Chemotherapy has been the keystone of treatment of CLL, but it is palliative and may worsen the immunodeficiency status of patients. Nevertheless, the development of drugs and therapeutic strategies that can either bypass the immune evasion mechanisms or rescue immune suppressor pathways may significantly benefit CLL patients. Thus, immunotherapy may provide curative treatment and may mitigate disease complications caused by the defects of the immune system observed in CLL patients. In this sense, monoclonal antibodies, allogeneic hematopoietic stem cell transplantation and immunomodulatory drugs have successfully been used in the treatment of CLL. Immune-based therapy represents an exciting mode of treatment since it may be able to eliminate leukemia cells without inducing immune suppression. The elucidation of the molecular and cellular events underlying the immune dysfunction in CLL is of key importance to further develop novel immune-based therapies. It is presumably that a deeper knowledge of the immune response in CLL may open new frontiers in the treatment of these patients.

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8. References

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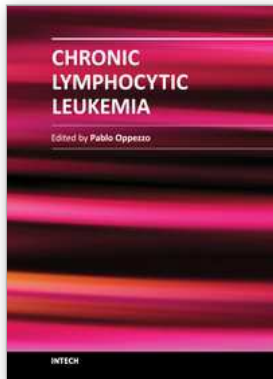
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B-cell chronic lymphocytic leukemia (CLL) is considered a single disease with extremely variable course, and survival rates ranging from months to decades. It is clear that clinical heterogeneity reflects biologic diversity with at least two major 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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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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