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REVIEW

CHRONIC LYMPHOCYTIC LEUKAEMIA. MALIGNANT HEMOPATHY WITH MULTIPLE THERAPEUTIC OPTIONS

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Summary. Chronic lymphocytic leukemia is a chronic lymphoproliferative disorder, indolent but heterogeneous in evolution and difficult to predict. Beside cases whith long lasting evolution even without specific treatment, the clinical practice often faces cases with advanced stages, poor prognostic factors and high risk of disease progression in which choosing the best treatment tailored to each patients is a difficult task. Classical chemotherapy schemes have been effective but combining them with or shifting to new therapeutic agents, along with improved investigation techniques, led to a significant increase in the complete remission rates as well as improvement of survival, without risks of disease progression. During and after therapy, patients need to be thoroughly monitored, the detection of minimal residual disease increasing the chance to discover, early in the process, unresponsive cases or relapses. Complete clinical investigations and paraclinical tests, performed at the onset of disease have an important contribution for the selection of the best therapeutic option and moment of treatment initiation.
Key words: chronic lymphocytic leukaemia, prognosis factors, chemotherapy, treatment options

Chronic lymphocytic leukaemia (CLL) is a frequent malignant hemopathy, indolent in terms of clinical course but with an extremely heterogeneous evolution. While several cases have been mentioned with survival rates spanning over decades without the need of specific treatment, many patients experience a rapid progression of their disease from the moment of diagnosis, with an unfavourable response to chemotherapy. An essential risk factor for CLL development is the patient's medical history. Based on numerous CLL familial groups[1] were genetic analysis was possible, specialists noted that the age for CLL occurrence in the descendants of a known patient tends to decrease. According to a report released by National Cancer Institute Familial Registry, the average diagnostic age for familial cases was 58 years, 14 years below sporadic cases, this representing the only differentiation criterion[2]. Compared to non-family cases of CLL[3], in family cases the survival period was not significantly changed and the risk of aggressive transformation was not increased either. In most sporadic cases the average age is 60 years at the time of diagnosis, a consequence of the decrement in the immune response given by the process of aging. The disease occurs more often in men than in women; 10% of cases are present in adults below 40, while CLL cases in children are quite scarce[4]. CLL is the only leukaemia not associated with exposure to ionised radiation. Chemical or alky-lating agents lack an aetiological impact on CLL and environment factors hardly have a major influence on the pathogenesis. [5,6]. Although there is no substantial evidence on viruses' involvement in CLL's aetiology, the infection with a Human T-cell lymphotropic virus- Human T-cell Leukaemia/Lymphoma Virus (HTLV-I) - triggers, however, some rare forms of leukaemia, namely adult T-cell Leukemia/Lymphoma.

At the onset, most patient are asymptomatic, the disease being caught at a routine check-up during which lymphocytosis is detected in the peripheral blood as well as lymphadenopathies and mild splenomegaly. In more advanced stages symptoms may be: asthenia, fatigue, fever, night sweats, weight loss over a short amount of time, anaemia [7].

These accessible clinical and paraclinical signs grounded the two staging systems currently used - Rai and Binet staging [8,9] (Figure 1).

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The symptoms occur as a result of bone marrow and other tissues infiltration with malignant cells and the alteration of humoral and cellular immunity. CLL is

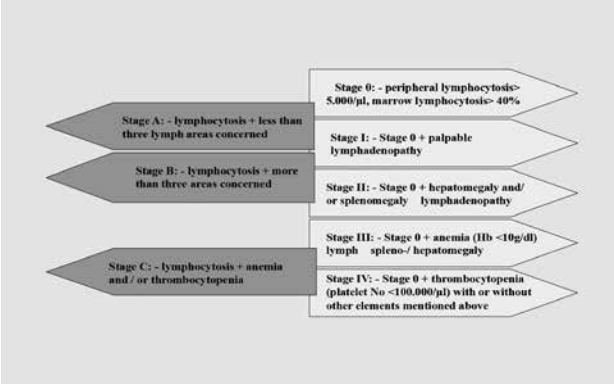

Figure 1. Rai and Binet staging of chronic lymphocytic leukaemia

defined by immunodeficiency, many patients presenting autoimmune disorders, especially haemolytic anemia and autoimmune thrombocytopenia. Other signs are susceptibility to recurrent viral infections (e.g. Herpes Zoster), bacterial infections (e.g. Pneumoccocus), fungal (e.g. Candida, Cryptococcus), with persistent evolution, complications and resistance to conventional therapy.[7]

In terms of treatment, several options have become available with the main purpose to obtain a complete, long term remission, thus increasing the survival chances for CLL patients. Together with standard treatments whose efficiency has been proved on decades, present clinical trials perform an extensive search for innovative methods to improve the therapeutic response. A series of classical prognosis factors was identified: advanced stages of disease, lymphocyte doubling time <12 months, initial absolute lymphocyte count > 50.000/mmc, abnormal karyotype. New factors for unfavourable evolution have also been established, in close connection with modern investigation techniques: thymidine kinase positivity, high levels of Beta 2-microglobulin, positive CD38, positive ZAP-70, IgVH mutation status, cytogenetic abnormalities (p53 mutations, trisomy 12 or 17p, 13q, 11q deletion)[7,10,11,12].

Identifying the factors that influence the clinical evolution is essential and in close relation to the purpose of therapy, namely to provide the best life quality and to treat only when the patient becomes symptomatic. The treatment's purpose is to obtain complete remission (CR), reduction of CLL cells from blood, bone marrow and lymph nodes, as much as possible. Remission is known in various forms: complete remission - undetectable CLL cells; minimal residual disease (MRD)- low CLL cell count, detectable only through highly sensitive tests (flow cytometry, molecular biology), partial remission (PR)- detectable CLL, but the CLL cell count in blood and bone marrow is low and the lymph nodes diminish.

Considering each case's particularities it is difficult to institute a standard first-line therapy, even less to agree on an optimal strategy. Hence, several strategies are in place: from "wait and watch" with a rigorous monitoring of symptoms, to the identification of high risk cases and early introduction of treatment - chemotherapy, immunotherapy, radiotherapy and stem cell transplant. Without bias for any of the abovementioned therapies, I will discuss briefly the specificity of the latter.

Monotherapy

Glucocorticoids are efficient as unique treatment for CLL in patients with haemolytic autoimmune anaemia, or autoimmune thrombocytopenia. In patients without autoimmune manifestations, glucocorticoids as single agents, can temporally control the diseases in about 10% of cases. They can function even for CLL patients with non-functional p53. Simultaneous therapy with H2 receptor antagonists and prophylactic antibiotherapy may decrease the risk of treatment complications[13, 14].

Alkylating agents - Chlorambucil: since it was first introduced in 1952, Chlorambucil has been the main alkylating agent used in CLL. Its oral administration renders it as a tolerable drug, without adverse events like: cystitis, alopecia or gastrointestinal disorders that can sometimes occur as a reaction to other alkylating agents. Myeloid and megakaryocytic series suffer little impact. In patients with advanced CLL, chlorambucil was administered for, at most, 6 months, in fixed dosage - 15mg/day until achievement of CR or stage 3 for toxicity. Some studies reported a higher complete or partial response rate (89,5%) compared to cyclophosphamide, doxorubicin, vincristine and prednisone treatment (CHOP) [15,16] but with the price of higher myelotoxicity related to long term use.

Bendamustine is another active agent for CLL. Trials on i.v. bendamustine administered for two consecutive days, every 4 weeks revealed a rate of overall response rates (ORR) varying from 56%-93% and CR rates from 7% to 29% in patients with relapsed or refractory CLL. [17]

Cyclophosphamide has a resembling activity as chlorambucil in CLL. Intermittent or simultaneous cyclophosphamide therapy predisposes at hemorrhagic cystitis, hence the recommendation is to administer it in a single dose, in the morning and the patients should be instructed to consume at least 2-3 liquids/day. [13,14,18].

Deoxyadenosine analogs. Fludarabine (2 fluoro-ara-AMP) is a fluorinated derivative of adenosine analogs, effective in CLL treatment. After i.v. or oral administration, the drug leads to complete or

partial hematologic response in a large percentage of patients. Several trials reported ORR asociated with fludarabine phosphate injection, of approximately 45%, of which 10% presented complete remission, in patients previously treated with different agents. Furthermore, the ORR rate of about 70% - 38% with CR - has been observed in patients who received fludarabine as first line regimen. Fludarabine, alone, seems to be more effective in patients with CLL than other combined chemotherapy regimens, as COP[13, 19].

Cladiribine (2-chloro deoxyadenosine) is a deoxyadenosine analog which, as fludarabine, has proven active in CLL. Specialists used various schemes with different doses and ways of administration that turned out to be. Monthly courses of i.v. cladiribine led to 40-60% ORR in patients previously treated with alkylating agents and even higher percentages in naive patients. In naïve CLL patients who received oral cladiribine, the ORR reached 75%. However, cladiribine treatment failed to improve the survival rate, the mean survival being around 9 months, while unresponsive patients have an average survival period of 4 months. As with fludarabine, patients with no favourable clinical response after two cladiribine cycles should benefit from alternative therapies in order to decrease the level of toxicity. [20,21,22]

Polychemotherapy

Chlorambucil - Prednisone. As first line treatment in CLL, chlorambucil, in or without glucocorticoid associacion , has been used, at large scale, achieving a longer disease free survival, even in advanced stages. The main controversy regarding the ORR is still open, especially in what concerns choosing a conservative treatment for patients with early stages of disease versus polychemotherapy associated or not with immunotherapy. These options in relation with prognostic factors are under continuous assessment and the main objective in studies that have been designed to investigate the new therapeutic agents efficacy [21,23].

Cyclophosphamide - Vincristine - Prednisone . The cyclophosphamide-vincristine-prednisone (CVP) combination showed an outcome improvement both in naive patients and in some cases with refractory CLL. Almost a quarter of patients obtain complete remission in the aftermath of this therapy. No significant differences in terms of survival have, so far, been observed either in patients treated with CVP or those who received chlorambucil and prednisone. However, the latter may reach a response after CVP regimen administration. Apparently CVP treatment has no advantage over deoxyadenosine analogs, as fludarabine. [24]

Cyclophosphamide - Doxorubicine - Vincristine - Prednisone. Adding doxorubicine in CVP regimen has represented a highly studied decision in patients with advanced CLL. In those cases where doxorubicin has been added, specialists noted that the survival rate expanded, on average, to over 4 years. Another interesting aspect highlighted by the studies was less significant role and benefit of vincristine within CHOP regimen, PR and ORR rates having been 64% and 75% in patients treated with CHOP, respectively 65% and 72% in those who received CVP [25].

Fludarabine - Cyclophosphamide (FC)
Fludarabine-Cyclophosphamide combination may lead to clinical favourable outcome- CR after 4-6 administrations, for 30-35% of naive patients. This response rate is superior to the fludarabine regimen as a unique agent, the ORR rate and median disease-free survival period, were significantly better than patients only treated with fludarabine. [26]

Recent therapeutic methods

Alemtuzumab is a specific human monoclonal antibody- CD52, a glycosylated protein, linked to the cell membrane by a glycosylphosphatidylinositol (GPI) anchor, present on most lymphocytes. It can induce mediated lysis, antibody dependant cell-mediated cytotoxicity and represents a direct lymphocyte inhibitor, including malignant B lymphocytes. Intravenously or subcutaneously administered it has a significant activity for the treatment of patients with recurrent or relapsed CLL. Among its essential features, one can count the capacity to annihilate CLL lymphocytes with 17q13 deletions which are, in general, resistant to standard therapy [27,28]. The drug's toxicity which occurs in most cases (~80%) consists of: shivers (90%), fever (85%), nausea (53%) and rash (33%). Except for the rash, the rest of these reactions usually decrease after the first administration. An important consequence of toxicity is immunosuppression, more than 50% of patients getting infections with opportunistic microorganisms (e.g. cytomegalovirus) during or after the treatment. [29,30]. As alemtuzumab seems to be the highest active drug in the process of blood and bone marrow leukemic cell destruction, which, usually are resistant to standard therapy, several studies have been performed in order to assess its use in consolidation therapy. [31,32,33].

Rituximab is a monoclonal CD20 antibody, initially used in follicular lymphoma. Although, compared to cells in the follicular lymphoma, CD20 is revealed at a lower level by B-cell lymphocytes in CLL, a series of clinical trials demonstrated that this monoclonal antibody is beneficial for CLL patients due to its role in inducing cellular apoptosis. [34,35,36]. When Rituximab is used as single agent it can induce PR in less than a third of patients. 1st or 2nd degree toxicity associated to the first administration appears in approximately 90% of cases, with frequent fever, shivers, nausea, vomiting, hypotension or dyspnoea. These manifestations are also subsequent to the increased white cell count, over 50x109/L at the time of

treatment initiation, when cytokine release syndrome may take place, as a result of TNF-α or interleukine-6 involment. Other adverse events are tumour lysis syndrome, drug induced neutropenia, disseminated intravascular coagulation (DIC). We can reduce difficulties related to treatment initiation by decreasing the rate of infusion and by first dose fraction, that is to say 100 mg Rituximab during the first day and the remaining of the dose, the following day. These reactions' severity and risk scale down with the following infusions. Prior to the initiation of rituximab therapy, reactivation of an underlying infection with hepatitis B or C virus should be considered. In these situations the physician should reassess the liver function and a simultaneous antiviral therapy is recommended. [37,38, 38].

Fludarabine - Rituximab. This combination is well tolerated, its efficacy being higher than treatment with Fludarabine alone. Patients treated with the two drugs may obtain CR in almost half of the cases. Associated toxicity resembles toxicity noticed in Fludarabine, as unique agent. In addition, the median disease-free survival period turned out longer as a consequence of immunochemotherapies associacion.

Fludarabine-Cyclophosphamoide-Rituximab treatment appears to have an elevated efficacy, accounting for CR in a quarter of the cases and ORR for 73% of relapsed patients after first line treatment. A higher response rate could be observed in naive patients, in what concerns the median disease-free survival, it was improved compared to those treated with FC. [40,41].

New therapeutic agents

In recent years, many clinical studies focused on finding new therapy options for relapsed or refractory CLL[42]. The following table counts the newest agents and their action mechanism, achieved during clinical trials. (Table I)

Autologus stem cell transplantation. Several studies focused on the benefits of large dose chemotherapy, followed by stem cells transplantation, recovered from CLL patients. Considering the high probability that acquired stem cells could contain leukemic cells, autologus stem cell transplantation is a complex issue, even for treated patients with minimal residual disease. Although specialists approached various techniques to remove unwanted leukemic cells, a small number of cases succeeded in achieving a complete answer for CLL patients, i.e. autologus stem cell transplantation prolonged the period of survival, with no signs of progression.

Allogenic stem cell transplantation. For young patients with a poor prognosis, allogenic stem cell transplantation represents an option. Aggressive therapy may eliminate leukemic cells which are undetectable to molecular techniques for clonal immunoglobulin gene rearrangement. A five year survival period can be attained in about 75% of cases, without additional therapy, while for approximately 25% of them, immunosuppressive therapy for graft versus host diseases is necessary. Results following allogenic transplant in patients with negative prognostic are encouraging, including for individuals with 17p deletion, but it is essential to undergo an initial thorough pre transplant assessment, with an estimation of the risk factors. [48,49,50].

Complementary therapies

Spleen Radiotherapy (RT), in 3-8 Gy doses, 1,5 Gy per fraction every 2 days is highly indicated for symptomatic splenomegaly. [51]. Nodal, local or generaliezed RT can help in voluminous, obstructive splenomegalies. Splenectomy represents an option for splenomegaly generating abdominal discomfort, splenic sequestration or refractory to treatment-symptomatic autoimmune hemolytic anaemia. [52,53]. Leukopheresis is recommended when increased leukocyte count can trigger hyperviscosity syndrome. 400mg/kg I.V. immunoglobulines, every 3 weeks can be safely used for severe hypogammaglobulinemia, in order to prevent infection complications. [54] Each of the strategies described above has its own use within the clinical practice, providing many alternatives. However the therapeutic course of a CLL case can often be challenging. Therefore, specialists must perform an initial assessment of prognosis factors, rigorous and regulate monitoring of patients, as well as a thorough selection of the best therapy options, at the right moment, in order to obtain a qualitative remission and a long period of survival, free of any event connected to the disease.

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Ibrutinib	• Previously known as: PCI-32765 • Potent and irreversible Bruton's tyronise kinase (BTK) inhibitor; oral administration. • It inhibits: Chemokynes, cytokines, signalling pathways mediated by microenvironment as well as ex vivo chemotaxis; • It reduces Ki67+ population and initiated apoptosis. [43,44] • It leads to several complete remissions and increase of survival period, even for cases of Richter's transformation or Bulky diseases [45,46,47]. • In naive patients: results are encouraging. On a 26 patients lot, aged <65, the survival period, without progression spanned to 15 months, in 96% of them. [47]. • Adverse events: nausea, fatigue, diarrhoea, rash, bleeding events- bruises. 3rd or 4th degree reactions: diarrhoea, hematologic infections and toxicity (anaemia and/or thrombocytopenia), with an average 10-13% rate of incidence. [45,46].
Ofatumumab	• Human monoclonal antibody- CD20 that binds to a different CD20 epitope. • Higher complement dependant cytotoxicity and antibody dependant cell mediated cytotoxicity, in pre clinical trials. • The antibody has been approved by FDA for treatment of refractory CLL patients to fludarabine and alemtuzumab.
Lenalidomide	• Immunomodulatory treatment promising in the area of salvage therapy for patients with relapsed/ refractory CLL.
Idelalisib (GS-1101, CAL-101)	• Known as GS-1101 or CAL-101, a specific Phosphoinositide 3-kinase inhibitor (P13K), with apoptotic activity against CLL leukemic cells.
Veltuzumab	• A IInd generation, humanized monoclonal antibody, anti-CD20 which can bind selectively and irreversibly to CD20 molecule. The antigen binding site is similar with Rituximab, but with improved binding avidity. Prolonged subcutaneous administration produced encouraging results in naive patients, with relapsed/refractory CLL and acceptable tolerability (degree: 3-4).
XmAb5574	• CD19 monoclonal antibodies are currently being considered for clinical applications. XmAb5574 is a human monoclonal antibody, anti-CD19 with increased binding avidity. During pre clinical trials, XmAb5574 exhibited antitumor activity, including direct cytotoxicity, antibody dependant and cellular phagocytosis against leukemic cells. Unlike other anti-CLL, monoclonal antibodies, XmAb5574 didn't display complement dependant cytotoxicity activity.
Navitoclax (ABT-263)	• Known as ABT-263. • It is an anti-apoptotic protein inhibitor, including Bcl-XL, Bcl-2 and Bcl-w with efficacy for patients with relapsed or refractory CLL.
TRU-016	• TRU-016 is a protein that targets CD37, present on normal and leukemic B cells. It has direct toxicity and antibody-dependant cellular cytotxicity against CLL, superior to Rituximab. TRU-016 and TRU-016 and Bendamustine have both been used in the management of relapsed CLL.
Alvespimycin (17-DMAG, KOS-1022)	• Alvespimycin, a synthetic derivate of the antibiotic geldanamycin is a heat shock protein 90 inhibitor. It has a regulatory activity on genes and proteins involved in the proliferation and survival of CLL cells.

Table I. New therapy agents in CLL treatment [42]