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REVIEW ARTICLE

Chronic Lymphocytic Leukemia: Inception to Cure: Are We There?

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Abstract There have been remarkable advances in our understanding of the biology and therapeutics of chronic lymphocytic leukemia. B cell receptor signaling and microenvironment in CLL biology have been the most modern areas of research. In CLL therapeutics, we have come a long way from alkylating agents to chemo-immunotherapy. Despite this there remain significant lacunae in the disease biology that has hindered our quest to achieve the ultimate in CLL: Cure. This review aims to summarize the past, present and future in the biology and treatment of CLL.

Keywords Chronic lymphocytic leukemia · Biology · Treatment · Review

Introduction

Cinderella of All Leukemias

For decades chronic lymphocytic leukemia (CLL) received little attention. Largely because it has a prolonged course, many persons afflicted by CLL live a relatively normal life and eventually die of causes unrelated to CLL. Despite this seemingly unexciting background, the task of understanding pathogenesis and designing new therapies in CLL has challenged and fascinated clinical investigators almost continuously over the past half century. The reason for this fascination is the extreme variability in the clinical course of patients with CLL. Currently CLL is receiving increasing attention from biologists and clinicians. Characteristics of this disease have helped to define relationships between antigenic stimulation and malignant transformation as well as shed light on association of lymphoid tumors and autoimmunity. CLL is a good model for studying basic and translational research pertaining to investigations and treatment of B cell chronic lymphoproliferative disorders. The factors that make CLL a good model for research are its high population prevalence, ease of accessibility of malignant cells for study and that most patients being asymptomatic have long disease specific survival. Therefore CLL has been called as the "Cinderella" of all leukemias [1].

Ontogenesis in CLL

Antigen-activated naive B-cells differentiate into centroblasts. These introduce somatic hyper mutations (SHM) to increase affinity to antigen; into the immunoglobulin variable segment (IgV) gene during the clonal expansion in the dark zone of the germinal center of lymph nodes. This is a T cell dependent process. A parallel T cell independent process bypassing IgV hyper mutation (unmutated) also exists. Centroblasts then differentiate into centrocytes and move to the light zone. Here B cells with improved antigen-binding are selected. A subset of centrocytes finally differentiates into memory/marginal zone B cells or plasma cells. The germinal centre reaction involves the risk of oncogenic transformation at several steps of differentiation, resulting in the development of different lymphoma subtypes. The cell of origin in CLL is presumed to be a memory/marginal zone B cell irrespective of whether it has undergone SHM (mutated CLL) or no SHM (unmutated CLL). These antigen experienced cells may then be

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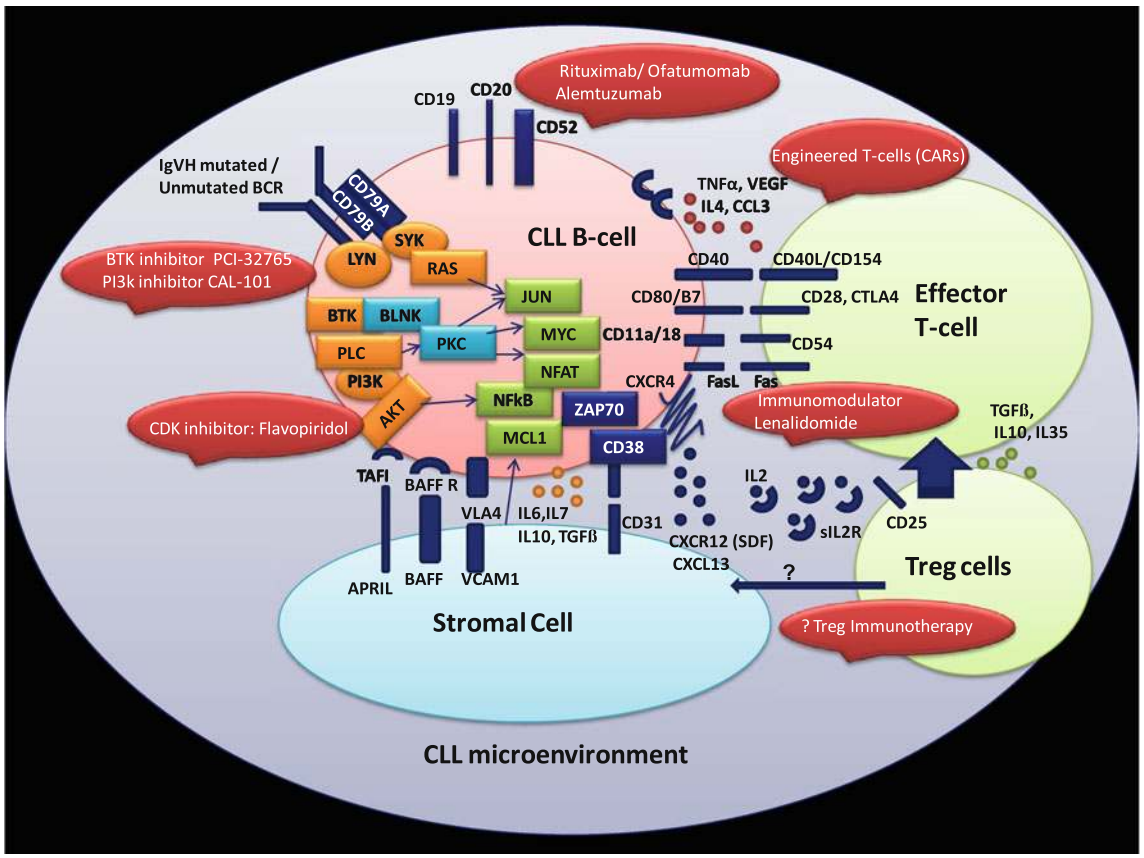

Fig. 1 Microenvironmental interactions of the malignant B cell with the stromal cells, effector T-cells and T-regulatory cells in the peripheral blood, lymph-node and bone marrow. Key events occurring in the microenvironment include 1. stimulation of the BCR 2. BCR signaling 3. Interactions with stromal cells 4. Interactions with T-effector and T-regulatory cells. Potential sites of therapeutic targets are also shown

continuously activated through persisting antigen [2]. They acquire genetic alterations that lead to outgrow of clones with a monoclonal B lymphocytosis (MBL) phenotype. Some ultimately undergo oncogenic transformation to CLL. Six percent of the normal elderly population develops MBL. MBL is precursor to CLL in 1–2 % cases [3]. Recent studies have questioned the existence of MBL as a distinct entity. It may be appropriate to consider MBL as early stage CLL as both are similar in terms of biologic, genetic and clinical behavior [4].

In unmutated CLL because V-gene mutations do not occur, repetitive interactions between antigens and polyreactive B cell receptors (BCR) of the initially selected clone promote clonal growth. In mutated CLL, V-gene mutations develop that can abrogate the polyreactivity of the BCR and thereby alter their ability to bind the original antigen or autoantigen ("clonal ignorance"). Alternatively, these mutated cells become anergic owing to excessive B cell-receptor stimulation because of the acquisition of more avid receptors [5]. Differences in the signals received through the BCR and other receptors determine the extent of clonal expansion.

Microenvironment in CLL (Fig. 1)

The CLL microenvironment is a complex system of many cell types which are involved in active molecular cross talk providing a functional support to the CLL cells. These accessory cells include endothelial cells and their precursors, pericytes, smooth muscle cells, fibroblasts, neutrophils, mast cells, T, B and Natural killer lymphocytes, and antigen presenting cells like dendritic cells and macrophages. The microenvironment is an essential, integral part of any cancer [6].

B cell receptor signaling is the principal event that occurs in the CLL microenvironment. The BCR is a key survival molecule for normal B cells and most B cell malignancies. BCR is composed of a membrane associated immunoglobulin, noncovalently associated with a disulfide linked CD79a and CD79b heterodimer. CD79a and CD79b serve as the receptors of primary signal transduction. Initial antigen binding leads to the formation of a signalosome, a complex of kinases and scaffold proteins. The triggering event is phosphorylation of the immunoreceptor tyrosine based activation motifs (ITAMs) of CD79a and CD79b by

SRC family kinase LYN. The BCR signal is further propagated by SYK via B cell linker protein and downstream signals of Brutons tyrosine kinase (BTK) and phospholipase C (PLC). PLC generates secondary messengers, inositol triphosphate and diacylglycerol (DAG), which leads to activation of protein kinase C (PKC). PKC further activates nuclear factor kB (NF-kB), mitogen activated protein kinases (MAPK). Finally these all signals are modulated to determine proliferation, survival, and migration via transcriptional modulation and phosphorylation (Mcl-1, Cyclins, MYC) [7].

Bone marrow stromal cells viz nurse like cells (NLC) and follicular dendritic cells (FDC) are key regulators of normal B lymphopoiesis. These synthesize several cytokines including colony stimulating factors, IL6, IL7, IL10 and TGFß and stem cell factor thereby regulating CLL B cells. Various adhesion integrins like VLA-4 and its ligand VCAM-1 are involved in adhesion of stromal cells to CLL B cells. NLCs protect CLL cells from apoptosis through CXCL12 (stromal cell derived factor SDF-1), B-cell activating factor (BAFF), CD31 and plexinB1. FDC also rescue CLL B-cells from apoptosis in vitro by up-regulating anti-apoptotic Bcl-2 family protein Mcl1 [8].

Within the LN the largest contributor to CLL survival known to date is the T helper cell, via cell–cell contact with B-CLL cell. In normal B cell development antigen engaged B cells migrate toward Th cells by chemotaxis forming B-T conjugates in pseudofollicles or proliferation centers. There occurs crosslinking and signaling via CD40 (expressed on B cell) and CD40L (CD154 expressed on Th cell). This interaction is critical to induce and sustain B cell response. Various cytokines are released during this T–B interaction to further enhance the co-operation. CLL B-cells produce and express ligands and receptors for many survival cytokines viz. IL-2, IL-4, IL-8, TNFα, IFNα, and VEGF. They promote their own survival via autocrine and paracrine pathways [9].

Despite all the advancements in the knowledge of the biology of CLL, few unanswered questions remain. The nature of the antigen triggering the entire process, the reasons for low expression of BCR, the reasons for somatic mutation only in some CLL cells and the mechanisms of immune surveillance escape, all remain an enigma.

Prognostic Markers in CLL

The heterogeneous clinical profile of CLL patients has lead many researchers to propose several prognostic markers over the past few decades. Currently there is problem of plenty when it comes to choosing the right prognostic marker at the right time [10]. Rai [11] and Binet [12] staging have been the cornerstone of prognosticating patients for decades (Table 1). However there are inherent inadequacies in these traditional markers. Binet/Rai staging does not distinguish between autoimmune cytopenias or marrow infiltration as a cause of anemia or thrombocytopenia and that results in classifying a patient as having stage C or high risk disease. Recently it has been identified that autoimmune cytopenias do not confer a poor prognosis in CLL [13]. Also it cannot predict indolent or aggressive nature of CLL. Lymphocyte doubling time has also been used for years; however it requires at least three patient visits over a period for its estimation [14]. This can be uncomfortable for patients wishing to know their prognosis at first visit. ß-2 microglobulin is a nonspecific but reliable marker and is used for most lymphomas and leukemias [15]. Recently cytogenetics by FISH has helped to identify certain subsets in CLL with 17p deletion and 11q deletion which perform poorly and may be indications for early intervention [16, 17]. Whether these would be of any use even in asymptomatic patients still remains controversial. IgVH gene mutation status [18], though a good marker, has been restricted to research labs due to non availability. CD38 [19] and ZAP70 [20] are used currently as surrogate markers for IgVH mutation status. Both have not lived up to the expectations. CD38 expression changes during course of the disease, while ZAP70 has suffered from lack of reproducibility between labs. There is some data to suggest that Absolute Treg cell count may serve as a reliable prognostic marker in the near future [21]. It is important to counsel

Table 1 Modified Rai and Binet staging for CLL

	Modified Rai	Binet	Survival
Lymphocytosis	Low risk	A	>10 years
		<3 involved groups	
Lymphocytosis + nodal involvement ± organomegaly	Intermediate risk	B	5–9 years
		≥3 involved groups	
Lymphocytosis + anemia/thrombocytopenia	High risk	C	2–5 years
	Hb < 11g/dl	Hb < 10gm/dl	
	Platelet < 100,000/μl	Platelet < 100,000/μl	

patients regarding the availability of prognostic markers and its application. They should be informed that currently there are no indications for early treatment in an asymptomatic patient outside of a clinical trial. It should be stressed that statistics are for a population and not an individual. Many patients desire such information; others decline such testing to avoid stress of knowing unfavorable markers without ability to effective intervene.

When to Treat?

This is the most important question in CLL management. International working group guidelines have become the standard for decision regarding starting therapy [22] (Table 2) and also for response assessment. It is important that only patients with active or progressive disease be put on treatment. Treatment of all other patients is generally not indicated outside a clinical trial.

Treatment Options

The treatment goals have changed over the decades from palliation in the 1970s, to complete remission in 2000, to progression free survival and minimal residual disease negative CR in the last decade. The treatment armamentarium has also expanded over the years from alkylating agents in 1960s, to purine analogues in 1980s and chemoimmunotherapy in 2000.

First Weapon: Alkylating agents

Chlorambucil, the first of the alkylating agents was synthesized in 1953. The electrophilic alkyl group of chlorambucil covalently binds to cellular nucleophilic sites resulting in DNA cross linkages and cytotoxicity. It was first shown to be effective in CLL in 1956 [23]. A meta-analysis showed no survival benefit for combination chemotherapy (CHOP/CVP) over chlorambucil [24]. Chlorambucil and prednisolone was the frontline therapy for decades. It is still the combination of choice in frail or patients with comorbidities. It has low toxicity profile, is cheap and has convenient dosing. However it has very low CR rates. There is a theoretical risk of secondary leukemia and of myelodysplasia. Bendamustine, another alkylating agent with additional benzimidazole group was synthesized in 1960. However it received FDA approval for CLL only in 2008, after it was demonstrated to have higher response rates, longer remissions and progression free survival in comparison to chlorambucil [25]. It has a different mechanism of action than chlorambucil, apoptosis is one, however the exact mechanism remains unknown.

Table 2 Indications of treatment in CLL (from most common to least common)

1 Progressive marrow failure, anemia ± thrombocytopenia
2 Autoimmune cytopenias poorly responsive to treatment
3 Significant constitutional symptoms
4 Massive nodes (10 cm)/progressive/symptomatic lymphadenopathy
5 Massive/progressive/symptomatic splenomegaly
6 Lymphocyte doubling time ≤6 months

Second Weapon: Purine Analogues

Fludarabine (F) was synthesized as a rational process to develop more active analogues of cytarabine. It has multiple mechanisms of action. It is converted to F-Ara-ATP inside the cell where it competes with dATP for incorporation in DNA leading to chain termination. It also Inhibits DNA replication by inhibiting DNA polymerase, ribonucleotide reductase and DNA primase. It has also been found to reduce number of Treg cells. F has higher ORR and CR-rate in comparison to chlorambucil. However no difference for PFS, OS could be demonstrated in the initial study [26]. A long term follow-up of the same study showed that survival curves begin to separate in favor of F at 6 years [27]. These benefits may not be valid in elderly populations, where the superiority of purine analogues over chlorambucil could not be demonstrated [28]. When F was compared with F–cyclophosphamide (FC) combination, there was significantly higher OR (95.3 vs. 84.1 %), CR (20.3 vs. 8.6 %) and longer PFS in the FC arm. But no difference in the overall survival could be demonstrated. It become the first line standard from 2006 [29]. The optimum dosing and duration of all treatments including chlorambucil for survival benefit needs to be determined [30].

Third Weapon: Monoclonal Antibodies

The prognosis had not substantially improved over time and there was a need for therapies with impact on overall survival. The time was right for use of monoclonal antibodies in CLL. They had already proved to be effective in other lymphomas. Their mode of action through complement mediated cytotoxicity and antibody dependent cellular toxicity (ADCC) is different. It was the reason for their entry in clinical trials in CLL. Results of initial trials with single agent rituximab in relapsed/refractory CLL were disappointing with no CRs but only partial responses [31, 32]. Subsequent studies of single agent rituximab as first line therapy showed that therapy-naive patients fared better with rituximab than previously treated patients. Though complete responses were rare in this trial, maintenance therapy improved the outcome relative to a single course of treatment [33]. The exact mechanism and reason why rituximab

(antiCD20) is effective in CLL which has low CD20 expression still remains unknown. CD52 expression in CLL is 45 times that of CD20. It was only matter of time that alemtuzumab (antiCD52) was explored in phase II studies in previously treated CLL. Significant objective response rates ranging from 33 to 70 % were documented with median duration of response exceeding 12 months [34, 35]. In another study median overall survival was 16 months for all patients, extending up to 24 months for responders. Median survival among responders was not reached till the end of the study [36]. This led to study of single agent alemtuzumab as first line. Result were an impressive 87 % OR, 19 % CR and 68 % PR [37]. The currently available evidence suggests an OS, CR and PFS benefit for alemtuzumab compared with no further therapy [38]. Alemtuzumab has limited effectiveness in bulky lymph nodal disease. Because of its toxicity profile, an increased risk for CMV infections, alemtuzumab is reserved for high risk and relapsed/refractory CLL. The role of alemtuzumab versus rituximab still remains unclear [38].

Multipronged Approach: Chemoimmunotherapy

The above three weapons were used in different combinations in the years to come. Each combination was compared to the gold standard that was set prior to that in superiority demonstrating randomized controlled studies (RCT). First F + rituximab (FR) was compared to F alone in a superiority trial. There were two arms in this study; patients were randomized to receive F for six cycles followed by R maintenance for four cycles sequentially or FR concurrently followed by R maintenance. Patients in the concurrent treatment arm had a higher ORR and CR rate (90 and 47 %, respectively) than those in the sequential treatment arm (77 and 28 %, respectively). Of note, patients in the sequential arm had not yet received rituximab upon evaluation of induction response, suggesting that the combination of rituximab and F was more effective than F alone [39]. Next F + C (FC) was compared to F + C + rituximab (FCR) in patients with good physical fitness and low cumulative illness rating scale. There was significantly higher CR (44.5 vs 22.9 %) and lower progressive disease (3.3 vs 8.1 %) in the FCR arm. This study established FCR as the standard first line from 2010 onwards [40]. The above two studies for the first time demonstrated survival advantage in CLL. The problem with FCR is that it has a significant toxicity profile and cannot be used in patients with significant comorbidities. In the search for less toxic combinations, bendamustine + rituximab (BR) was studied as first line. The overall response rates and CR rates were to the tune of 91 and 33 % respectively [41]. This was respectable in comparison to FCR which is the gold standard, where ORR was 95 % and CR was variable from 44 to 72 % [36, 42]. Ongoing RCTs are comparing BR and FCR as first line.

Hematopoietic Stem Cell Transplantation

Allogeneic SCT remains the only possible curative modality for CLL patients. Studies have demonstrated the existence of graft versus leukemia (GVL) effect in CLL [43]. Long term follow-up studies have shown durable CRs, nevertheless late relapses are known to occur [44]. Allogeneic SCT achieves long term DFS and possibly cure in one-third to two-third of the recipients. PFS and OS with allogeneic SCT is 36 % and 51 % at 5 years [45]. The choice between myeloablative and reduced intensity conditioning (RIC) needs to be balanced for transplant related mortality and relapse rates. Recent studies have shown that PFS and OS may be better in the RIC than myeloablative group due to the high nonrelapse related mortality in the myeloablative group [46]. The major indications for allogeneic SCT in CLL are summarized in Table 3.

Autologous HSCT

Autologous HSCT was compared to FCR in a RCT [48]. The event free and progression free survival were longer in patients receiving autologous SCT; however this did not translate into improved overall survival. It was concluded that the negative impact biomarkers like p53 aberrations that confer resistance to conventional therapy are not overcome by autografts. Currently autologous SCT for CLL cannot be justified outside of a clinical trial.

Tailored Approach

The treatment needs to be tailored according to the disease and patient factors. Asymptomatic patients in Binet A and B must not be treated outside of a clinical trial. Disease related factors include risk assessment according to various prognostic markers. Particularly 17p deletion necessitates more aggressive management. Patient related factors include tolerability depending on age, comorbidities and performance status. Depending on this patients can be categorized into three groups (Table 4). The "green group" includes patients who have good clinical status defined by good performance status (PS < 2) and have no

Table 3 EBMT CLL transplantation consensus criteria [47]

1 Patients with de novo deletion 17p13 or p53 mutation requiring treatment

2 Relapse within 24 months of chemoimmunotherapy

3 Non response or relapse within 12 months of purine based chemotherapy

Table 4 Current management approach for treatment naive CLL

Group status	Treatment options	Treatment regimen	OR %	CR %	PFS months
Non high risk Good clinical status	FCR (51)	F 25 mg/m² x 3 days C 250 mg/m² x 3 days R 375 mg/m² day 0 cycle 1 & 500 mg/m² day 1 cycle 2–6	95	44	52
	BR (52)	B 90 mg/m² days 1and 2 R 375 mg/m² day 0 cycle 1 & 500 mg/m² day 1 cycle 2-6	91	33	NR
	FR (53)	F 25 mg/m² x 5 days R 375 mg/m² day 1 & 4 cycle 1 375 mg/m² day 1 cycle 2-6	90	47	42
Non High risk Poor clinical status	Chlorambucil (54)	Cl 0.8 mg/kg day 1 and day 15	48	3	8.3
	Bendamustine (52)	B 100 mg/m² day 1 and 2	68	31	21.6
	FCR lite (55)	R 375 mg/m² day 1, 500 mg/m² day 14 cycle 1 500 mg/m² day 1 & 14 cycles 2-6 F 20 mg/m² x 3 days C 150 mg/m² x 3 days	100	77	NA
	Rituximab+ Chlorambucil (56)	R 375 mg/m² day 1, cycle 1 500 mg/m² day 1 cycles 2–6 Cl 10 mg/m²/day x 7 days	82	9	NA
High risk	Alemtuzumab (57) + SCT	10 mg sc thrice a week x 12 weeks followed by Allogeneic SCT	40	7	10.7

OR overall response, *CR* complete response, *PFS* progression free survival, *NR* not reached, *NA* not available

comorbidities. The goal in such group of patients is cure with longer remissions using more intensive therapies. The other "yellow group" includes patients with poor performance status and have comorbidities. Here the goal is disease control with less intensive therapies. The first line standard for patients in "green group" is FCR. However BR and FR are acceptable alternatives. For patients in "yellow group" chlorambucil is still an option. Other options in this group include bendamustine alone, chlorambucil + rituximab or dose reduced FCR (FCR lite) [49]. The "red group" includes patients with high risk CLL (del17p). Young patients with good clinical status in this group are candidates for allogeneic SCT following induction therapy, if a suitable donor is available. Patients with poor clinical status in this group are candidates for experimental therapy [50].

Drugs for Relapsed/Refractory CLL

Disease refractoriness was traditionally described in terms of F refractory CLL. CLL, non responding or relapsing within 6 months of F was included in this group. However it was seen that even relapses up to 36 months fared poorly and this accounted for one-third of all treated patients. So the definition of treatment resistant CLL has been expanded to include late relapses also. It was the need of the hour to develop drugs with different mechanisms of action for relapsed/refractory CLL.

Lenalidomide, an immunomodulator, after its success in multiple myeloma was tried in CLL. Lenalidomide has multiple effects on modulation of T cell function in CLL [58]. It causes upregulation of CD40L resulting in increased T cell proliferation and production of Th1 cytokines. Increased expression of CD40, CD80 and CD86 leads to improved CLL B-cell antigen presentation. Repair of actin cytoskeletal signaling is associated with improved immunological synapse formation and effector CD8 T cell activity. Although lenalidomide has shown some activity in CLL, it has significant dose limiting toxicity and poor patient tolerability [59].

Ofatumomab targets a different epitope on CD20 than rituximab. It is generated by hybridoma technique. It has a slower off-rate, which might result in increased effectiveness in initiating complement-dependent cytotoxicity. Ofatumumab shows greater in vitro activity against CLL cells than rituximab, and is able to lyse rituximab-resistant cells that express low levels of CD20. It received FDA approval in 2009. Two doses of ofatumomab 500 and 1,000 mg were compared in combination with FC. It was seen that the CR rates were (50 vs. 35 %) in favor of higher dose, but at the cost of significant higher grade 3/4 neutropenia and infections [60].

Table 5 Current management approach for early relapsed/refractory CLL

Group status	Treatment options	Treatment regimen	OR %	OS months	PFS months
Non high risk Good clinical status	FCR (65)	F 25 mg/m^2 C 250 mg/m^2 x 3 days R 375 mg/m^2 day 0 cycle 1 & 500 mg/m^2 day 1 cycle 2–6	56	38	8
	Alemtuzumab (66)	30 mg sc 3 times a week x 12 weeks	34	19.1	7.7
	Lenalidomide (67)	10 mg/day	25	NR	12
Non High risk Poor clinical status	BR (68)	B 70 mg/m^2 days 1and 2 R 375 mg/m^2 day 0 cycle1 & 500 mg/m^2 day 1 cycle 2-6	59	9	14.7
High risk	Alemtuzumab+ HDD (69)	Dex 40 mg x 4 days every 14 days 30 mg sc 3 times a week x 12 weeks	51	-	-
	R + HDMP (70)	HDMP 1gm/m^2 x 5 days every 28 days R 375 mg/m^2 weekly x 4 weeks	91	-	-

HDD high dose dexamethasone, *HDMP* high dose methylprednisolone, *OR* overall response, *OS* overall survival, *PFS* progression free survival, *NR* not reached

GA101

This is the first humanized and glycol-engineered type2 monoclonal anti CD20 antibody. It shows increased ADCC and apoptosis compared to rituximab. In a phase 1 study of 13 patients with poor risk cytogenetics and relapsed/refractory CLL, the overall response rates were 62 % [61].

B Cell Receptor Inhibitors

CAL-101 is an oral inhibitor of phosphatidylinositol 3-kinase (P13K) signaling. In phase 1 studies it had nodal response rates of 80 %. However, it paradoxically caused peripheral blood lymphocytosis by causing compartmental shift from the tissue microenvironment [62]. Brutons tyrosine kinase inhibitor PCI32765 has nodal response rates of 87 % and has demonstrated promising clinical activity in CLL [63].

Flavopiridol is a synthetic flavone that inhibits cyclin dependent kinase CDK1, 2 and 9. It has shown some promise in poor prognostic population but has considerable toxicity [64].

Treatment Aapproach for Relapsed/Refractory CLL (Table 5)

Repeat testing for del17p should be done in all such relapsed patients. Patients relapsing early i.e. within 1 year of purine based chemotherapy or within 2 years of chemo-immunotherapy within the "green group" should be started on non cross resistant regimens like FCR or novel drugs like alemtuzumab, lenalidomide, ofatumomab or included in clinical trials. BR is an option for patients in the "yellow group". Alemtuzumab is avoided if the disease is bulky F refractory (BFR). The mechanism of glucocorticoids is p53 independent. Hence combinations of high dose steroids and alemtuzumab/rituximab have been found to be effective in the "red group". Young patients with matched sibling donor should be considered for allogeneic SCT following remission induction. For late relapses, patients can be treated with the same or a different first line chemoimmunotherapy.

Minimal Residual Disease

Analogous to other leukemias, achievement of MRD negative remissions has been studied in CLL. It has been seen that patients with MRD negativity at the end of chemotherapy have higher PFS and OS in comparison to patients not achieving MRD. The method of assessing MRD is critical. The methods with better sensitivity include Flow MRD and Allele specific PCR. Alemtuzumab consolidation for 6–16 weeks has achieved MRD negativity varying from 20 to 56 % [70, 71]. Other drugs that are being tried as consolidation strategies to eradicate MRD include rituximab, lenalidomide. Currently consolidation is not recommended outside of a clinical trial.

CARS for Cure

Chimeric antigen receptor modified autologous T cells (CARs) are designer T-cells with specificity for CD19 coupled with CD137 (Costimulatory receptor) and

CD3-zeta signaling domain transduced with lentiviral vectors. When these were infused in 3 CLL patients as a part of phase1 study, the results were astonishing with no evidence of adenopathy or disease in the bone marrow at 28 days. There was ongoing remission at 10 months of the study [72]. The advantage of CARs lies in the HLA independent antigen recognition making them broadly applicable [73]. There have been studies showing the application of such engineered T-cells for adoptive T-cell transfer therapy in other diseases [74]. Until similar studies with long term follow-up are available, such therapies will be restricted to the realm of clinical trials.

The final word is that both the origins and cure of CLL has eluded the human race. CLL remains an incurable disease outside allogeneic stem cell transplantation, which has its own complications. Biology and therapeutics go hand in hand. As our understanding of the disease biology progresses, we might find clues to conquer this disease ultimately. Similar to the targeted therapies that have worked wonders in chronic myeloid leukemia and acute promyelocytic leukemia the future of CLL lies in immunotherapy [75] and molecular targeted therapies. A combined multimodality approach might see us achieving our ultimate goal in CLL.

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