

34 Current and Future Therapies of Chronic Lymphocytic Leukemia (CLL)

Abstract: Despite advances in anticancer therapeutics, chronic lymphocytic leukemia (CLL) remains incurable. Alkylator-based therapies were the mainstay of treatment of CLL for several decades. A higher response rate with prolongation of progression free survival (PFS) was noticed with the purine analogue fludarabine compared to chlorambucil or CAP. Combining fludarabine and cyclophosphamide (FC) suggests increased efficacy compared to fludarabine alone. Rituximab combined with fludarabine and cyclophosphamide was found to induce overall response rate of 95% and complete response rate of 70% when used as front line therapy in CLL. Preliminary studies with alemtuzumab suggest that alemtuzumab alone or after fludarabine treatment is likely to be effective. Young patients with poor risk CLL, are being offered therapies such as stem cell transplantation (SCT). The major problem after autologous SCT remains relapse of disease. Allogeneic SCT for CLL is associated with significant morbidity and mortality. Various novel agents are undergoing trial in CLL. Lenalidamide as a single agent and thalidomide in combination with fludarabine has shown good results. Most promising of the newer agents include the cyclin-dependent kinase inhibitor, flavopiridol. Other novel agents include the histone deacetylase inhibitor depsipeptide, the cyclin-dependent kinase inhibitor UCN-01, the protein kinase C modulator bryostatin 1, and the antisense oligonucleotide oblimersen and the small molecule gossypol. A number of novel monoclonal antibody agents including engineered anti-CD20, anti-HLA-DR, anti-CD40 and anti-CD23 are being investigated. We expect to learn more on further progress in this field.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is one of the most common types of adult leukemia in the western countries. Progressive accumulation of well differentiated malignant cells that have arrested in G₀/G₁ phase of the cell cycle is characteristic of CLL.¹ Despite advances in anticancer therapeutics, CLL remains incurable. Patients with CLL generally are asymptomatic at diagnosis. In the 1970s, Rai and Binet independently developed simple and reproducible prognostic systems allowing patients with CLL to be classified into different risk groups, making it clear that in some instances the prognosis of patients with CLL is extremely poor.^{2,3} Due to the absence of a defined survival advantage to early treatment intervention, therapy is generally not initiated until patients develop symptoms. It may be the best operational decision in most patients to continue the policy of no treatment with reassessment at intervals of 3 to 6 months. A decision to start anti-leukemic therapy is made in the presence of any of the following – Disease related progressive symptoms (e.g. weight loss, fever, night sweats, weakness), progressively worsening anemia or thrombocytopenia, autoimmune hemolytic anemia or thrombocytopenia poorly responsive to corticosteroid therapy, massive splenomegaly (> 6 cm) or lymphadenopathy (> 10 cm), lymphocyte doubling time < 6 months, recurrent infections response to treatment has been

assessed in clinical trials by NCI-WG criteria.⁴ Complete response (CR) requires no evidence of disease on physical examination and microscopic examination of blood (Absolute Lymphocyte Count < 4000/ul) and bone marrow (< 30% lymphocytes, no nodules) and recovery of hemoglobin, neutrophil and platelet counts. Recently, more sensitive tests to evaluate residual disease have become available, specifically multicolor flowcytometry and allele-specific PCR for the immunoglobulin heavy chain variable gene (IgV_H) . Presence of one or both of these suggests minimal residual disease (MRD). Patients free of MRD following treatment have a longer remission duration and longer survival.^{5,6} Therefore, in addition to improving CR rates, investigators are focusing on eliminating MRD.

CHEMOTHERAPY

Alkylator-based Therapies

This group of drugs were the mainstay of treatment of CLL for several decades, chlorambucil and cyclophosphamide are both equally effective. It often provides a period of relief from any symptoms. The CR rate is less than 10% and the overall response rate (OR) 50-60%. However several randomized trials have failed to demonstrate its ability to improve survival.⁷⁻⁹

Glucocorticoids are often used as a single agents or in combination with other drugs. A large trial by CALGB revealed that in high risk patients chlorambucil and prednisolone improves disease free survival.¹⁰ The French co-operative group demonstrated a significant better survival of advanced stage patients after treatment with CHOP (cyclophosphamide, vincristine, prednisolone and doxorubicin) compared with patients who received COP.¹¹ A meta-analysis of 10 randomized trials involving 2035 patients with advanced CLL in which chlorambucil was compared with several combination chemotherapies, an improvement in response rates was observed for combination chemotherapies but in none of these trials, this improvement translated into improved survival.⁹

Purine Analogue Based Therapy

The introduction of the purine analogues during the mid-1980s invigorated research in CLL. Fludarabine is the most extensively studied purine analogue. Front line single arm phase II clinical trials demonstrated that single agent fludarabine induced CR in 20-30% and the OR rate approximately 80%.^{12,13} Three large phase III trials¹⁴⁻¹⁶ in symptomatic, untreated CLL patients have been published comparing fludarabine with alkylator-based regimens. Results from these studies have noted a higher response rate with prolongation of progression free survival (PFS) with fludarabine compared with chlorambucil or CAP. However, there was no survival benefit. 2-chlorodeoxyadenosine and pentostatic (2-deoxycoformycin) also have single agent activity in treating patients with CLL.¹⁷

Purine Analogue with Alkylating Agents

Cyclophosphamide potentiates the activity of fludarabine. Phase II trials combining fludarabine and cyclophosphamide (FC) suggests increased efficacy compared to fludarabine alone.¹⁸ Although the purine analogues induce higher overall response rates and longer duration of remission than alkylator-based therapies, these agents are not curative and patients will relapse and eventually become refractory to therapy. It thus emphasizes the need for exploration of newer modalities.

Monoclonal Antibodies—A Promising New Modality in CLL

Rituximab (anti CD 20 antibody) is the best studied and most widely used monoclonal antibody for the treatment of lymphoid malignancies. A British study with rituximab achieved only partial

response in 10% of relapsed, refractory CLL.¹⁹ A Nordic multi-center study observed an OR rate of 35% in 24 heavily pretreated CLL patients. Seventeen of 20 patients (85%) with adenopathy experienced > 50% reduction in nodal disease, whereas only 2 of 18 patients (11%) had reduction of marrow infiltration.²⁰ The combined results of these studies suggest that rituximab as a single agent has limited activity in CLL.

Combination Therapy

Several published studies have combined rituximab with fludarabine based therapies in previously untreated CLL. A multicenter European phase II study of concurrent fludarabine and rituximab achieved an OR rate of 87% (CR 32%) with a median duration of response of 75 weeks.²¹ Another large randomized phase II study,²² undertaken by the Cancer and Leukemia Group B (CALGB), assigned previously untreated patients to receive six monthly courses of standard-dose fludarabine with concurrent or sequential rituximab. The OR rate with the concurrent regimen was 90% compared with 77% with the sequential regimen. The combination of fludarabine, cyclophosphamide and rituximab (FCR) has been evaluated in both chemotherapy naïve and previously treated patients with CLL. In untreated patients with CLL, CR rate with FCR was found to be 70% and OR rate 95%.²³ Over 40% of complete responders were free of MRD.

Alemtuzumab

Alemtuzumab (Campath-1H) is a humanized anti-CD52 monoclonal antibody expressed on the surface of nearly all human lymphocytes, monocytes, and macrophages. In phase II clinical trials alemtuzumab was found to be most effective at clearing disease from peripheral blood (CR 95%), but bone marrow (CR + nodular PR 66%) and nodal disease (OR rate 87%, CR 29%) also responded to therapy.^{24,25} Some patients who achieved CR in the bone marrow required the full 18 weeks of therapy to do so, suggesting that prolonged administration of alemtuzumab may be necessary to clear CLL from bone marrow. Preliminary data from two studies^{26,27} suggest that administering alemtuzumab after fludarabine treatment is also feasible and likely to be effective.

Stem Cell Transplantation

Young patients with poor risk CLL, who almost invariably die of their disease, are being offered therapies such as stem cell transplantation (SCT) to prolong survival and potentially cure their disease. A retrospective matched-pair analysis suggested a survival advantage for autologous SCT over conventional therapy.²⁸ A pilot study from the Medical Research Council enrolled previously untreated patients and followed them prospectively to assess the feasibility of performing autologous SCT.²⁹ The CR rate after transplantation was 74%. The predicted 5-year overall survival was 77.5% and 5-year disease-free survival was 51.5%. Of concern 8% patients developed post-transplant acute myeloid leukemia/myelodysplastic syndrome. The major problem after autologous SCT remains relapse of disease.

Allogeneic Stem Cell Transplantation

Allogeneic SCT for CLL is associated with significant morbidity and mortality. Despite this, there is evidence that patients who survive can have long term disease control.^{30,31} Studies from the MD Anderson suggest improved outcome after myeloablative allogeneic compared to autologous transplant.³² In a phase II study at Dana-Farber Cancer Institute.³³ The 100-day mortality was 4% in both autologous and allogeneic SCT groups, the 6-year overall survival was 58% after autologous and 55% after allogeneic SCT.

Non-myeloablative SCT for CLL

Reduced-intensity conditioning regimens appear to be associated with a decreased mortality after allogeneic transplantation, and allow transplantation in older patients, making this approach applicable to increased numbers of CLL patients. The outcome after allogeneic transplantation of 73 patients with reduced-intensity conditioning was compared with that of 82 matched patients from the European Bone Marrow Transplant Registry database who had undergone standard myeloablative conditioning for CLL during the same time period. Patients undergoing reduced-intensity conditioning had a significant reduction of treatment related mortality, but a higher incidence of relapse. There was no significant difference in event-free or overall survival between the two groups.³⁴

NOVEL AGENTS FOR TREATMENT OF CLL

Immunomodulators

The tumor microenvironment has a role in the increased survival, the ability to evade programmed cell death, and the T-cell dysregulation that results in progressive unchecked accumulation of malignant B cells. Thus, targeting of the microenvironment, by changing the concentration of various cytokines or modulating immune effector cells, or both, is a potential approach for treatment of CLL.

Thalidomide

Single agent thalidomide was found to be ineffective in refractory CLL patients,³⁵ but it was hypothesized that disrupting the microenvironment with thalidomide would render CLL cells more susceptible to the proapoptotic effects of the antimetabolite fludarabine. A phase II trial³⁶ at Cornell University, NY, USA, is currently investigating single agent thalidomide versus thalidomide and fludarabine in patients who have relapsed or refractory disease. Overall response was 50% for the combination treatment versus 12.5% for single-agent thalidomide. Trompeter and co-workers³⁷ are doing a pilot study of the role of thalidomide in combination with cyclophosphamide and dexamethasone in patients with relapsed or refractory CLL.

Lenalidomide

Lenalidomide is a less toxic analogue of thalidomide. In a phase II trial³⁸ for 29 relapsed/refractory CLL patients, 25 mg of lenalidomide was given orally everyday for 21 days of a 28-days cycle, and there were 3 complete and 10 partial responders in 19 assessable patients. Two patients had molecular complete remission.

Flavopiridol

The cyclin-dependent kinase inhibitor, flavopiridol, which has shown responses rate upto 50% in heavily pretreated patients.³⁹ A phase II trial is ongoing, and flavopiridol based combinations are also being developed.⁴⁰

UCN-01

Kitada and colleagues reported that UCN-01 consistently induced apoptosis of B-CLL cells in culture and down regulated anti-apoptosis protein.⁴¹

Compound 506U78

Compound 506U78 is methoxypurine ara-G and is soluble in water. Gandhi and coworkers presented their initial clinical and pharmacokinetic data on patients with CLL and prolymphocytic leukemias either singly or in combination with fludarabine.⁴²

Oblimersen

The antisense oligonucleotide oblimersen was compared with FC in a randomized phase II trials in previously treated CLL patients. Those who received oblimersen had a higher combined CR + nPR rate than those who received FC alone.⁴³

Anti-CD40 and Anti-CD23 mAb (CHIR-12.12, Lumiliximab)

A number of novel monoclonal antibody agents including engineered anti-HLA-DR, anti-CD40 and anti-CD23 are being investigated. Phase I clinical trial of anti CD40 and anti CD23 antibody for previously treated patients with CLL is ongoing.^{44,45}

Vaccine Strategies for CLL

The rationale for vaccine strategies is to induce host cell mediated immune response against autologous malignant cells as a modality to eliminate tumor and provide lasting protection from recurrence. A replication -defective adenovirus vector was used to transducer autologous CLL B cells to express CD 40 ligand - CD154. Cross-linking with CD40 induces expression of co-stimulatory antigens such as CD80 and CD86 which stimulates autologous T cells to induce a productive immune response.⁴⁶

Gold Nanoparticles in B-chronic Lymphocytic Leukemia

Vascular Endothelial Growth Factor (VEGF) signaling pathway generates apoptosis resistance in CLL B cells. VEGF antibody (AbVF) were attached to the gold nanoparticles (GNP) and determined their ability to kill CLL B cells. The induction of apoptosis with gold-AbVF was significantly higher than the CLL cells exposed to only AbVF or GNP.⁴⁷ This opens up new opportunities in the treatment of CLL-B using gold nanoparticles and integrates nanoscience with therapy in CLL.

After too many years of stagnation, advances in CLL therapy are finally being made. More trials are still needed. These biologic agents and new drugs offer more than a glimmer of hope for improved therapy of CLL in the foreseeable future. We expect to learn more on further progress in this field.

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MULTIPLE CHOICE QUESTIONS

1. **Which one of the following statement is correct?**
 - A. Fludarabine alone is as effective as Fludarabine, cyclophosphamide
 - B. OR, CR and survival rate was better with fludarabine compared to chlorumbucil
 - C. 2-CDA and Pentostatin are as effective as CLL
2. **Indication of treatment in CLL:**
 - A. Absolute lymphocyte count > 100,000/ cu mm
 - B. Lymphocyte doubling time < 6 months
 - C. Hb% < 11 g%
 - D. All of the above
 - E. None of the above
3. **Regarding monoclonal antibodies in CLL:**
 - A. Rituximab and alemtuzumab both are equally effective.
 - B. Combining chemotherapy increases efficacy
 - C. Alemtuzumab is less toxic than rituximab.
 - D. Novel mAb in CLL are anti-CD22 and CD 19
4. **Which of the following statement is correct?**
 - A. Thalidomide and its analogue lenalidamide acts by DNA damage
 - B. Thalidomide is more effective than lenalidamide
 - C. Lenalidamide is less toxic
 - D. These agents should be used as a single agents.
5. **Minimal residual disease in CLL is assessed by:**
 - A. Flowcytometry
 - B. PCR
 - C. Both
 - D. None
6. **Mark the wrong statement:**
 - A. Autologous stem cell transplant cures CLL
 - B. Survival is better non-myeloablative SCT than conventional SCT
 - C. Chances of second malignancy was high with SCT
 - D. All of the above
 - E. None of the above

1. C 2. E 3. B 4. C 5. C 6. C