

Treatment of Chronic Lymphocytic Leukemia

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Introduction

The last decade has been one of great advances in the therapy of chronic lymphocytic leukemia (CLL). Therapeutic advances have been documented in almost every category of therapy. There has been renewed interest in the role of splenectomy for treatment of cytopenias associated with CLL. Immunoglobulin administration has been shown to confer a reduction in risk of certain infections in patients with CLL. The introduction of a new class of molecules, the newer purine analogs, has resulted in significant improvement in response rates with a greater tendency toward achievement of complete remission. Several new anti-CD20 monoclonal antibodies provide significant promise for immunotherapy of CLL, along with evidence that interferon may be more active in CLL in minimal disease states than it was during initial testing in advanced states. Finally, allogeneic transplant has been demonstrated to be a feasible and possible therapy for those CLL patients who are young enough to tolerate the treatment and who have an HLA-identical sibling. Autologous transplant following intensive *in vivo* purging with purine analogs has been shown to also be a feasible therapy but the long-term outcome of this approach remains unclear. The advancing technology in the area of stem cell selection suggests that an autologous stem cell transplant may be a viable curative approach in the future. Here we will review these various advances and evaluate what position they might occupy in the therapeutic armamentarium of CLL.

Treatment Indications

Indications for treatment have been largely discussed in the session on biology and staging of CLL. All newly diagnosed patients who present with marrow failure in the form of anemia or thrombocytopenia, constitutional symptoms including fever, night sweats or 10% or greater loss of body weight, bulky disease as manifested by a blood lymphocyte count of $250,000 \times 10^9$ per liter or greater, large lymph node masses or splenomegaly are eligible for initial treatment. Patients who present with the disease but do not meet these criteria may become eligible when previously untreated indolent disease progresses to meet these treatment indications.

Other indications such as autoimmune hemolytic anemia or thrombocytopenia unresponsive to steroids may indicate a need for therapy. Similarly, as discussed in the previous session, degree and pattern of marrow lymphocytic infiltration, cytogenetic findings and lymphocyte doubling time are factors which may impact upon timing of treatment. As marrow transplantation becomes a more viable treatment option, age becomes another factor for consideration as one plans the treatment strategy for individual patients.

Patients with early, stable CLL should not be treated unless the disease progresses to the point of large tumor burden, bone marrow failure or the development of other symptoms. This approach is based on the knowledge that patients with early, stable

disease may survive as long as age-matched normal subjects⁽¹⁾ and on the fact that treatment of patients in early stage disease with chlorambucil in any of the regimens delays the rate of disease progression but does not increase survival.^(2,3,4) Continuous administration of alkylating agents to early stage patients may in fact be associated with a shortened survival due to the development of epithelial cancers as a consequence of alkylating agent exposure.⁽²⁾

Alkylating Agents

Chlorambucil 0.4 to 0.8 mg/kg of body weight per day orally every two weeks is still considered standard treatment for advanced stage CLL. Treatment is continued as long as the patient responds and patients usually receive a minimum of six courses. Such therapy is associated with responses in 50-70% of cases but complete responses are extremely rare. Other regimens of intermittent and continuous chlorambucil administration show similar results to this regimen. Because of the lymphocytotoxic effects of prednisone, the idea of the combination of chlorambucil and prednisone was explored and shown to yield no better results than treatment with chlorambucil alone.^(3,4) Although patients with such combination chemotherapy have higher response rates, survival is not prolonged.⁽⁵⁾

Table 1. Therapeutic options for CLL.

Alkylating Agents (Chlorambucil)
Purine Analogs (deoxycoformycin, fludarabine, 2-CdA)
Immunotherapy (anti-CD20, MoAb, interferon)
Growth Factors (erythropoietin, G-CSF)
Immune Globulin
Splenectomy
Bone Marrow/Stem Cell Transplant (allogeneic, autologous)

Maintenance therapy has not been employed in CLL due in part to the fact that chronic exposure to alkylators, as discussed above, has significant known complications and is generally not advised. Treatment is generally discontinued once a stable maximal response has been achieved and is reinitiated when there is evidence of disease progression. In most cases, reinitiation of therapy is associated with a less favorable response than the initial treatment. Failure to achieve as good a remission is likely to be due to the development of alkylator resistance, thought to be due in part to induction of mdr and p53 gene mutations.

Newer Purine Analogs

For patients who have no initial response to chlorambucil or who relapse after chlorambucil therapy, purine analogs have been extensively studied and have now been established to be standard second line therapy. The newer purine analogs - deoxycoformycin (DCF), fludarabine and 2-chlorodeoxyadenosine (2-CdA) - demonstrate

potent activity against CLL. These drugs are unique among anti-metabolites in their ability to kill nondividing and dividing lymphocytes with equal potency, making them ideal agents for treating lymphoid malignancies of low growth fraction such as CLL.⁽⁶⁾ This may be in part why they have been associated with such a high rate of complete response in comparison to prior clinical experience with alkylator therapy. Activity of these molecules in previously treated CLL can be seen in Table 2.

Table 2. Purine analogs in previously treated CLL.

| Agent | # Reference | Patients | # response (%) | Complete response (%) |
|-------------|--------------------------|----------|----------------|-----------------------|
| DCF | Grever et al (6) | 27 | 5 (18) | 1 (4) |
| | Dillman et al (7) | 26 | 4 (16) | 1 (4) |
| | Ho et al (8) | 26 | 7 (27) | 0 |
| | Deardon and Catovsky (9) | 17 | 6 (35) | 0 |
| | | | | |
| Fludarabine | Grever et al (10) | 21 | 4 (19) | 1 (5) |
| | Keating et al (11) | 78 | 45 (57) | 30 (38) |
| | Hiddeman et al (12) | 20 | 11 (55) | 4 (20) |
| | Puccio et al (13) | 42 | 22 (52) | 0 |
| | Bergmann et al (14) | 18 | 12 (67) | 0 |
| | Spriano et al (15) | 23 | 10 (43) | 1 (4) |
| 2-CdA | Saven et al (16) | 90 | 44 (48) | 4 (4) |
| | Juliusson et al (17) | 18 | 12 (67) | 7 (39) |
| | Betticher et al (18) | 11 | 8 (72) | 3 (27) |
| | Tallman et al (19) | 26 | 8 (31) | 0 |

Deoxycoformycin is administered at 4 mg/m² IV every two weeks and is associated with the lowest response rate of this class of molecules, with overall response rates ranging from 16-35%.^(6,7,8,9) Fludarabine is administered at 25 mg/m² intravenously for 5 days every 4 weeks, with response rates ranging from 19- 67% and a complete remission rate ranging from 0-38%.^(10,11,12,13,14,15) 2-chlorodeoxyadenosine is administered at 0.09-0.1 mg/kg/day by continuous intravenous infusion for 7 days or 0.12 to 0.14 mg/kg/day as a 2 hours bolus infusion for 5 consecutive days. This treatment has been associated with a 31-72% response rate in previously treated CLL, with 4-39% complete remissions.^(16,17,18,19) Attempts to combine 2-CdA and fludarabine with mitoxantrone, cyclophosphamide, and chlorambucil are underway with varying results. These data have established purine analogs as standard second line therapy for alkylator failed CLL.

Given the high response rate of purine analogs in failed CLL, the role of purine analogs as first line therapy has been questioned. All three of these drugs have been administered to previously untreated patients, with response rates that are significantly

increased over those in failed patients.^(7,11,15,20,21,22) Results from such studies are shown in Table 3. Randomized trials comparing fludarabine, with chlorambucil or with various combinations of cyclophosphamide, vincristine, prednisone and doxorubicin, show higher response rates and complete response rates with fludarabine, but there is no data yet to indicate whether or not this is associated with a prolonged survival.^(23,24) Obviously survival is the most meaningful end point in a chronic low grade disorder like CLL for many reasons, but survival takes on an especially great importance as an end point in these comparative trials because of the apparently increased side effects of the newer purine analogs over alkylating agents.

Table 3. Purine analogs in previously untreated CLL.

| Agent | Reference | # Patients | # responses (%) | complete responses (%) |
|-------------|----------------------|------------|-----------------|------------------------|
| DCF | Dillman et al (7) | 13 | 6 (46) | 0 |
| Fludarabine | Keating et al (11) | 35 | 28 (80) | 26 (74) |
| | Spriano et.al (15) | 4 | 4 (100) | 1 (25) |
| 2-CdA | Saven et al (20) | 20 | 17 (85) | 5 (25) |
| | Juliusson et al (21) | 17 | 9 (70) | 4 (41) |
| | Delannoy et al (22) | 19 | 14 (73) | 9 (47) |

Bone marrow suppression is the principal toxic effect of purine analogs. They are associated with a cumulative myelosuppression and immunosuppression, which can cause prolonged pancytopenia, especially thrombocytopenia, and prolonged lowering of the CD4 counts. This myelosuppression and immunosuppression has been associated in some cases with opportunistic infections including cytomegalovirus, toxoplasmosis, pneumocystis, legionella and listeria. The incidence of these opportunistic infections is much greater if a patient is receiving concurrent steroids or steroids anytime in the fairly short follow up period after purine analog therapy. Acute tumor lysis syndrome and autoimmune hemolytic anemia have also been reported as possible side effects in association with administration of purine analogs.⁽⁵⁾ Because of this fairly significant toxicity profile, it will be very important to establish a survival advantage before establishing purine analogs as appropriate and standard first line therapy for CLL.

Management of Cytopenias from Causes Other Than Marrow Failure

One should be alert to the fact that the development of anemia and thrombocytopenia may be directly due to development of autoimmune manifestations and/or hypersplenism instead of or in addition to marrow failure. Autoimmune hemolytic anemia and autoimmune thrombocytopenia may be treated with corticosteroids. Patients

who do not respond to corticosteroids after 4 to 8 weeks may be treated with cytotoxic agents, high-dose gammaglobulin, splenectomy, or cyclosporin. The evaluation of the etiology of cytopenias can be quite difficult as in many cases of CLL they are due to multiple causes including marrow failure, hypersplenism due to an enlarged CLL-infiltrated spleen and autoimmune phenomenon. One should be especially careful in treating autoimmune manifestations with steroids when a patient has recently been treated with a purine analog. The addition of steroids during the time period of low CD4 following purine analogs may be associated with serious and sometimes fatal opportunistic infections as described above and usually should be accompanied by prophylactic antibiotics. More recently, cyclosporin has been associated with improvement in pure red cell aplasia associated with CLL and may represent a new treatment option for this complication.⁽²⁵⁾

Treatment of Infection

Hypogammaglobulinemia is a frequent occurrence in association with CLL and is thought to be the main cause of infections associated with this disease. A randomized study of intravenous immunoglobulin 400 mg/kg every 3 weeks reduced bacterial infections but did not prevent viral or fungal infections and had no effect on survival.⁽²⁶⁾ Cost benefit considerations have made the use of immunoglobulin in all patients with hypogammaglobulinemia difficult to justify, especially since it does not impact on survival. Lower doses of immunoglobulin such as 250 mg/kg every 4 to 6 weeks may be as effective as high doses and less costly, but they have not been adequately studied to permit us to draw such conclusions.^(27,28) Patients with CLL who are neutropenic and febrile are generally treated with broad spectrum antibiotics, but every effort should be made to identify the etiology of the infection. It is extremely important to look carefully for opportunistic infections, especially in the setting of prednisone administration or prior use of purine analogs, or both. Recombinant hematopoietic growth factors such as G-CSF and GM-CSF may be useful in overcoming neutropenia related to treatment, but the exact role of such neutrophil growth factors remains obscure in CLL.⁽²⁹⁾ Erythropoietin has recently been shown to be effective in the treatment of anemia associated with CLL and may represent a reasonable adjunctive measure.^(30,31)

Splenectomy

In recent years, retrospective analysis of the role of splenectomy in CLL has been performed. Splenectomy can be a highly effective therapeutic measure in patients with large spleens to reduce cytopenias, reduce transfusion requirement of red cells and platelets, and improve abdominal systems associated with hypersplenism.⁽³²⁾ The procedure is associated with a low perioperative mortality. Administration of the purine analogs may be limited by thrombocytopenia. The inability of transfused platelets to survive an adequate time period due to hypersplenism may significantly limit the amount of purine analog that one can deliver. Therefore, in certain select situations, splenectomy prior to administration of purine analogs may allow intensification of the purine analog regimen leading to a better ultimate outcome.

Immunological Therapies

Initial enthusiasm for interferon alpha was not validated by favorable responses, leading to waning interest in this agent for CLL. Subsequent trials, however, showed that administering interferon at a time of minimal disease, especially in early stage patients, is associated with a higher response rate, especially in these patients who have not received prior therapy.⁽³³⁾ Therefore, some interest has been generated in its potential role along with chemotherapy in early stage disease. The CAMPATH 1H monoclonal antibody has been investigated and was shown to be highly effective in the treatment of CLL, generating quite dramatic responses. However, it was associated with some opportunistic infections and its clinical development was discontinued by its sponsoring company.⁽³⁴⁾ Recently two monoclonal anti CD20 antibodies, the C2B8 antibody from IDEC Pharmaceuticals and the Coulter B1 antibody from Coulter Pharmaceuticals, have demonstrated promising results in CD20 positive small lymphocytic diseases such as CLL.^(35,36,37) The fact that responses are seen even in patients with bulky disease suggests that these antibodies, either cold or radiolabelled, may play a significant role in the future armamentarium of CLL. Whether their role will be as manipulators of minimal residual disease, in conjunction with chemotherapy or as single agents, remains to be determined. However, after several decades of disappointing and lackluster work with monoclonal antibodies, it looks as though we finally have identified several which may be promising therapeutic agents for CLL and related diseases.

Bone Marrow or Stem Cell Transplantation

The ability to regularly induce complete remissions in CLL indicates that strategies for cure may be possible. With this in mind, several series of allogeneic and autologous transplantation for CLL have been undertaken. Fifty-four patients were reported from the European and International Bone Marrow Transplant Registries. Of the 54 patients, 38 (70%) entered remission and 24 (44%) are alive at over two years median follow-up after transplant. Five patients (9%) died of progressive leukemia and 25 (46%) of treatment related complications.⁽³⁷⁾ Two single-institution studies from M.D. Anderson and Dana-Farber have shown a much lower treatment-related mortality, with clinical and molecular responses in many participants.^(39,40)

There are three reports of autologous transplantation for CLL.^(39,40,41) In total, about 40 patients have been described in the literature; in about half of the patients the bone marrow was purged with monoclonal antibodies against a variety of B-cell markers, CD19, CD20, CD10 and CD5, while the other half were transplanted without purging. While this is a feasible approach and the majority of patients survive the transplant, the follow-up period is too short to draw conclusions about the success of this treatment. Bone marrow/stem cell transplantation remains a highly experimental approach, but when combined with the ability of purine analogs to induce high rates of complete remission and the possibility of immunomodulation through the use of anti-CD20 monoclonal antibodies, transplantation may ultimately represent a curative strategy for CLL in the future.

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