

Treatment of chronic lymphocytic leukemia in the elderly

HOT SPOT

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The median age of diagnosis of chronic lymphocytic leukemia (CLL) is 72, with an incidence of 22 to 30 per 100,000 individuals. Although the elderly population (age > 70) represents the majority of patients living with this disease, this group is surprisingly under-represented in the clinical trials that dictate therapy. Moreover, elderly patients are heterogeneous, and prognosis is likely determined by various comorbidities and functional fitness more so than chronologic age. Despite research advances that have identified immune-chemotherapy options for first-line treatment, many current regimens may be associated with toxicity rates that preclude their routine use in more frail older individuals.

Treatment of CLL

- The traditional goal of therapy remains the palliation of symptoms including constitutional symptoms, bulky progressive adenopathy or cytopenias from marrow failure. Asymptomatic individuals can still be observed (“watch and wait”) until symptoms necessitate therapy.
- When treatment is needed, an expanding array of immuno and chemotherapy combinations are considerations:
 - The historical mainstay of therapy was chlorambucil; responses were moderate (~30% to 40%) and slow in onset, but the therapy was well tolerated, convenient (oral), low-cost, and widely adopted.
 - Over the last decade, clinical trials have shown improvements in response and progression-free survival (PFS) when (1) the purine analog fludarabine was compared to chlorambucil (CALGB 9011 study); and, subsequently, (2) when fludarabine combined with cyclophosphamide (FC) was compared to fludarabine alone (German CLL4 and ECOG E2997).
 - These studies have typically enrolled younger individuals (median age 57 to 63) with CLL, limiting the generalizability of their conclusions.
 - Most recently, a phase III German (CLL8) study identified a survival advantage with the addition of rituximab to the FC backbone (FCR) when compared to FC alone (six cycles) (Hallek, 2008).
- Therefore, in Ontario, a fludarabine-based regimen in combination with rituximab is an evolving standard of care for patients with symptomatic CLL.
- Although fludarabine again demonstrated a higher response rate (72% versus 51%; $p=0.003$) than chlorambucil, this did not translate into an improvement in PFS or overall survival.
- Thus, monotherapy with chlorambucil remains a reasonable first-line therapy for older/frail patients.

Treatment in the elderly

What remains unclear is whether these same benefits apply to older individuals or those with more extensive comorbidities. Of note, enrolment in the CLL8 study of FC-rituximab was restricted to fit individuals (as measured by a cumulative illness rating scale) with preserved renal function (creatinine clearance ≥ 70 mL/min) and the median age in the study was only 61. Few studies specific to the elderly population have been completed.

- One exception is the German CLL5 phase III study of patients 65 and older that returned to a comparison of front-line fludarabine versus chlorambucil.

If the increased intensity associated with combination chemotherapy is not improving outcomes in the elderly/frail, what other strategies are available?

- The addition of rituximab to chlorambucil could potentially increase the efficacy without excessive additional toxicity; phase II studies investigating this approach are currently pending (ClinicalTrials.gov identifier NCT00738374).
- Other potential antibody partners for chlorambucil include ofatumomab (with enhanced complement-mediated cytotoxicity compared to rituximab), GA101 (enhanced antibody-dependent cell-mediated cytotoxicity) and superior caspase-

independent apoptosis), and lumiliximab (primatized antibody to CD23).

- At Sunnybrook Health Sciences Centre, an upcoming industry-sponsored randomized controlled trial will compare chlorambucil with ofatumumab to chlorambucil alone, specifically targeting patients who are not candidates for fludarabine-based induction.
- Finally, alemtuzumab is a fully humanized monoclonal antibody against CD52 and is associated with response rates of 33% to 53% in patients with advanced/refractory CLL. It has particular activity against genetically identified high-risk

patients (with del(17p) and p53 mutations) in which standard therapies are often ineffective.

However, infectious complications are not trivial and the tolerability of this option in the elderly remains to be determined.

- An alternative chemotherapy backbone to chlorambucil is an option. Bendamustine is a bi-functional alkylator with antimetabolite properties. In a comparison with chlorambucil, bendamustine improved PFS with somewhat greater myelosuppression, but without an increase in infectious complications (albeit again in a younger population of randomized patients).
- Finally, current drug classes of promise include immunomodulatory agents (lenalidomide), cyclin-dependent kinase inhibitors (flavopirodol), and bcl-2 family member inhibitors (oblimersen). Studies for these options are ongoing.

Approach to CLL in the elderly

Overall, the approach to treatment of CLL needs to be tailored to the individual. The functional status and comorbidity burden likely over-ride the

prognostic value of age alone, though all must be considered in choosing treatment:

- Patients without symptoms can still be followed on a “watch and wait” strategy alone. Once symptomatic, treatments should be initiated.
- Clinical trials are still essential to define the optimal approach. If available, these should be prioritized for all eligible and interested individuals.
- Those in excellent physical condition (measured according to a cumulative illness rating scale) should be offered a fludarabine-based backbone (FC or F) in combination with rituximab.
- Those with moderate physical limitations may also be offered this therapy, but might opt for single agent fludarabine in combination with rituximab.
- Individuals with poor functional status or dramatic comorbidities should be offered chlorambucil.

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