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How I treat chronic lymphocytic leukemia in older patients

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is a disease predominantly of the elderly, with a median age at diagnosis of 72 years. Although many advances have been made in the care of these patients with the addition of a variety of active drugs to the therapeutic armamentarium, treatment in the elderly remains complicated by factors as comorbidities, functional status, and fitness, as well as underrepresentation in many clinical trials. We will review the data on initial CLL treatment approaches, as well as therapy in the relapsed/refractory disease setting, with a focus on the elderly. We will also address the impact of comorbidities on treatment choices, and the importance of assessing the functional status and fitness of elderly patients when choosing appropriate therapies. Treatment recommendations for the older treatment naïve patient, both fit and less fit, as well as those receiving later therapies, will be summarized, with an emphasis not only on chronologic age, but also fitness for treatment.

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1. Introduction

Significant progress has been made in the past two decades in the management of chronic lymphocytic leukemia (CLL), which is a disorder predominantly of the elderly, with median age at diagnosis of 72 years (yrs) [1–3]. At diagnosis, 30% of patients are aged 70–79 yrs, and 23% are ≥80 yrs of age [1]. A new diagnosis of CLL results in a shortened life expectancy in most patients [4–6]. Elderly patients have been underrepresented in prior treatment trials, with median ages of enrolled patients being ≥10 yrs younger than the average age at diagnosis [7]. Many of these trials also excluded patients of poorer performance status (PS ≥ 2) or significant comorbidities. Although select elderly individuals may be offered aggressive treatment approaches, fludarabine, cyclophosphamide, rituximab (FCR) cannot be tolerated by the majority of CLL patients with comorbidities who start therapy at age ≥70 yrs [8]. Effective treatments are needed for these patients, as the majority will die of CLL or its complications [9]. In this review, we will address the evaluation of fitness in this elderly cohort, as well as recommendations for initial and later therapies based upon such assessments.

2. Assessment of Fitness and Comorbidity Burden for Treatment Consideration

Indications for treatment initiation in elderly CLL patients are similar to those for younger patients [10] (Table 1). Factors that do not necessitate therapy initiation include the level of the absolute lymphocyte count, asymptomatic or slowly progressive lymphadenopathy, or frequent/recurrent infections.

Chronologic age is not a surrogate for physiologic age or fitness. Comorbidities may be assessed by measures such as the Cumulative Index Rating Scale (CIRS) and the Charlson Comorbidity Index [11,12]. In one series, 89% of the newly diagnosed CLL patients had at least one comorbidity, including 46% with ≥1 major comorbidity, such as vascular or pulmonary disease or diabetes [13]. Assessment of functional status is best done by measures such as the Comprehensive Geriatric Assessment (CGA), which includes consideration of functionality, coexisting health problems, social support, cognitive ability, nutritional status, and geriatric syndromes (dementia, delirium, falls, failure to thrive, depression, polypharmacy) [14–17]. Such assessments help to predict chemotherapy tolerance in the elderly [18,19]. Unfortunately, studies examining the interaction between comorbidities and CLL therapy are limited. In one large series, it was suggested that durable disease control was the most important factor in the outcome of CLL patients with comorbidities [20].

Table 1 – Indications for initiation of therapy in CLL patients.

Evidence of progressive marrow failure (worsening anemia and/or thrombocytopenia)
Massive and/or symptomatic splenomegaly
Massive and/or symptomatic lymphadenopathy
Progressive lymphocytosis, with >50% increase over two months, or lymphocyte doubling time <6 months
Autoimmune anemia and/or thrombocytopenia with poor response to treatment
Constitutional symptoms/signs, including:
Unintentional weight loss 10% over 6 months
Significant fatigue
Fevers without infection
Night sweats >1 month

(Adapted from reference [10]).

3. Initial Therapy

3.1. *First Line Therapy in Healthy, Fit Patients Without del(17p)*

The approach to initial CLL therapy has evolved, with the introduction of the purine analogs, alemtuzumab, bendamustine, and more recently newer agents as ibrutinib, idelalisib, and obinutuzumab. Unfortunately, many of these trials are not of phase III design, and older patients have been underrepresented in the majority. Single agent chlorambucil is the comparator agent in many phase III trials based upon FDA guidance.

Patients with a CIRS score <6 and preserved renal function can tolerate initial aggressive chemoimmunotherapy such as FCR, which is a standard of care in young/healthy individuals [21,22]. In the phase III trial comparing initial therapy with fludarabine plus cyclophosphamide (FC) to FCR in fit patients, FCR resulted in improved overall response rate (ORR) and progression-free survival (PFS), regardless of age [22]. The ORR (complete response (CR)) rates with FC and FCR were 79%(19%) versus 89%(45%), respectively ($p < 0.001$, $p < 0.0001$) in patients <65 yrs of age, and 83%(24%) versus 93%(43%) ($p = 0.028$ for ORR, $p = 0.003$ for CR) for those ≥65 yrs of age. Three-yr PFS was significantly prolonged with FCR in patients <65 yrs of age (46% versus 64% respectively, $p < 0.0001$), as well as those ≥65 yrs of age (43% versus 68% respectively, $p = 0.001$). A prolongation in overall survival (OS) was seen with FCR therapy as compared with FC ($p = 0.017$). However, this benefit was confined to those patients <65 yrs of age, and not those ≥65 yrs ($p = 0.059$ and 0.103, respectively). Although FCR was associated with more grade 3/4 neutropenia than FC (34% versus 21%, respectively, $p < 0.0001$), the incidence of severe infection was comparable with both regimens. Another option is FCR-lite, with low dose fludarabine and cyclophosphamide and high dose rituximab, including rituximab maintenance therapy [23,24]. In a phase II trial in patients (median age 58 yrs (range, 36–85 yrs)), ORR(CR) rates were 93%(73%), with median PFS of 5.8 yrs.