In this issue of Blood, Eichhorst and colleagues report on the results of the German CLL Study Group (GCLLSG) CLL5 study.1 The importance of this randomized trial is that it restricted enrollment to more elderly patients who are the most representative of the population who have this disease.

There have been major advances reported over the past decade in previously untreated chronic lymphocytic leukemia (CLL) with chemo-immunotherapy approaches now the treatment of choice.2 A decade ago, chlorambucil was the treatment of choice. However, CLL is a disease of the elderly with a median age at diagnosis of 72 years, and almost 70% of CLL patients are older than 65 years at the time of diagnosis. These more elderly patients have been vastly underrepresented in clinical trials. Moreover, elderly patients may not have sufficiently good performance status to tolerate the aggressive chemo-immunotherapy approaches. There were elderly patients included in a randomized clinical trial in the United Kingdom comparing treatment with chlorambucil, fludarabine, or fludarabine and chlorambucil. These patients appeared to tolerate combination chemotherapy. However, there was considerable patient selection bias here, considering that physicians must have been prepared to treat these patients with combination chemotherapy so only patients with sufficiently good performance status to tolerate the more aggressive regimens were enrolled. Of note, among the patients in the United Kingdom who were older than 70 years, there was also no improved outcome for those patients receiving fludarabine alone. The advance in the CLL5 study is that both study arms were deemed tolerable for the intended patient population and therefore the results are likely to be more applicable to the more elderly patients seen in practice. This multicenter phase 3 trial enrolled patients older than 65 years and compared first-line therapy with fludarabine to chlorambucil. Chlorambucil was the first effective agent used in the treatment of CLL. The drug has largely fallen out of fashion in the United States but continues to be widely used in Europe. A total of 193 patients with a median age of 70 years were randomized to receive intravenous fludarabine or oral chlorambucil. The results demonstrated that, although patients receiving fludarabine had a higher response rate than those receiving chlorambucil, there was no difference in progression-free survival or overall survival. In fact, as shown in Figure 2 of the article, median survival was 18 months longer for those receiving chlorambucil, although the differences did not achieve statistical significance.1 The results demonstrate no clinical benefit for fludarabine over chlorambucil as first-line therapy of elderly CLL patients.

It is clear that the performance status is more important than the chronological age of the patient. It is extremely important to assess the patient’s comorbidities and fitness before recommending treatment. Several different methods are used to assess the fitness of patients. The International Society of Geriatric Oncology Chemotherapy Taskforce published consensus recommendations on chemotherapy in the elderly. The authors concluded that there is a lack of evidence-based data with regard to the cumulative illness rating score can be used to determine the appropriate chemotherapy treatment in CLL. Professional illustration by Debra T. Dartez.

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Cumulative Illness Rating Scale

- GO: Suitable for standard treatment
- SLOW: Suitable for reduced treatment
- NO: Suitable for supportive care

The cumulative illness rating score can be used to determine the appropriate chemotherapy treatment in CLL. Professional illustration by Debra T. Dartez.
chemotherapy and that consensus recommendations had to be made on the basis of inadequate data. One of the systems that has been widely used by geriatricians but not by oncologists is the Cumulative Illness Rating Scale (CIRS), which assesses whether comorbidities exist in different organ systems. The German CLL study group has taken a lead in this respect and has incorporated physiologic assessment to guide the choice of chemotherapy in any given patient. The group defines fit patients with no comorbidities who can tolerate combination chemo-immunotherapies at full dose as “go-go” patients. Patients who have reduced performance scores, and who may tolerate dose-reduced monotherapy, are termed “slow-go” patients. The relationship of comorbidity and drug pharmacokinetics is unknown and requires further study. The basis for enrollment in ongoing GCLLSG studies is not the age of the patient, but whether they fit into the “go-go” or “slow-go” categories as outlined in the figure.

Currently, the disease remains incurable using standard treatment approaches. There is no justification in offering therapy earlier in their clinical course; a meta-analysis of more than 2000 patients enrolled in previous trials demonstrated no survival advantage for early treatment versus a “watch and wait” approach. It should be noted that these studies were all performed using alkylating agents. The aim of treatment is to improve the quality of life of patients. Measures of quality of life are critical in interpreting clinical trials, particularly in the elderly. A quality-of-life assessment was incorporated into the CLL5 study, although it is disappointing that a minority of patients completed it. If more elderly patients are to have improved outcome, then alternative approaches have to be taken.

At first glance, it would appear that the results of this study put us back a decade by suggesting that chlorambucil is the optimal treatment for elderly frail patients with CLL. It is extremely important that appropriate clinical studies that address the needs of this previously neglected patient population are finally being designed. Ongoing clinical trials focusing on the more elderly frail patients are assessing whether the addition of monoclonal antibodies including rituximab, ofatumomab, and newer chemotherapeutic agents result in improvement compared with chlorambucil alone. Additional agents being assessed in clinical trials in this patient population include bendamustine alone and in combination with rituximab, lenalidomide, and ABT263.

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Comment on Li et al, page 3422

**Accumulations of KIR+ T cells in the elderly**

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Mechanisms controlling the age-associated gradual acquisition by CD8 T cells of natural killer cell receptors negatively regulating lymphocyte stimulation have remained obscure. Now, data from Li and colleagues1 imply that a state of transcriptional activation and histone stoichiometry in CD8 but not CD4 T cells from elderly people results in epigenetic control of KIR genes by a mechanism involving displacement of DNA methyltransferase 1.

Late-stage differentiated CD8 T cells accumulate in the elderly with a corresponding reduction of naive T cells. Pathogen exposure throughout life drives the differentiation of naive cells toward differentiated cells, which are required for maintaining specific immunologic memory at the expense of responses to new infectious agents.2 T-cell homeostasis ensures that the number of peripheral T cells remains constant; hence, accumulations of late-differentiated cells leave less “space” for other cells.3 Late-stage CD8 cells no longer express the costimulatory molecule CD28, but, as shown in earlier work by Goronzy et al, this may not represent a permanent differentiation marker.4 Later in the differentiation pathway, CD8 T cells begin to express molecules that mediate signals blocking T-cell proliferation; many of these belong to families of receptors expressed on natural killer cells but not on naive T cells. The regulation of the expression of these molecules, the signals responsible for their acquisition, and the functional consequences of their expression have remained obscure until now.

In this issue of Blood, work from Goronzy’s group1 goes some way toward dissecting the responsible mechanisms. They study the representative KIR2DL3 gene encoding surface receptor CD158b. They elegantly demonstrate that in CD8, but not CD4 cells, the KIR2DL3 promoter exhibits what they term age-associated patchy and stochastic demethylation, and hence activation. Moreover, they show that this is likely caused by decreased recruitment of DNA-methyltransferase 1 (DNMT1) to the promoter, and suggest that this may, in turn, be caused by displacement of DNMT1 due to the state of transcriptional activation and histone stoichiometry of CD8.
One step back but 2 steps forward

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