Comment on Eichhorst et al, page 3382

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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.3 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.3 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.4 The authors concluded that there is a lack of evidence-based data with regard to
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 colleagues 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. 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. 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. 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 group 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 exhibit 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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