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 GCCLLSG 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, ofatumumab, 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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REFERENCES


2. Hallek M, Fingerle-Rowson G, Fink AM, et al: Immunopharmacotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL) [abstract]. Blood. 2008;112(11): Abstract 325.


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 Goronzky 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 Goronzky’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.
cells. The big question here concerns the functional consequences of these events. The authors suggest that age-associated increased expression of negative receptors implies a contribution to immune defects in the elderly. However, there is an alternative explanation that does not view these events as pathological.

First, we need to ask whether these results are generally applicable. KIR2DL3 may not be typical of the range of negative receptors expressed by CD8 cells. However, Li et al specifically selected this gene because its promoter shares much of its sequence with other KIR promoters, so this seems unlikely. Second, their study design was cross-sectional, so by definition the young and elderly population may have been different from the beginning, and the observed effects not necessarily ascribed to aging but to variables such as medication, nutrition, and so forth. However, data from several other studies are consistent with greater expression of KIR and other negative receptors on CD8 cells from older persons, so this is also unlikely. Third, the proportions of later-stage differentiated cells are higher in older than in younger people, presumably due to greater pathogen exposure in the former. Therefore, Li et al sorted CD8 subpopulations and found that late-stage differentiated cells from young persons showed less demethylation than the same subsets from the elderly. This is a strong argument in favor of some age-associated component in addition to the large effect seen as a result of altered cell subset distribution due to the immunological history of the person. Although an accumulation of such cells may indeed contribute to immune defects in the elderly, as suggested by the authors, it may also be the case that they are actually crucial to survival. This argument is based on the fact that the one pathogen that most effectively drives the accumulation of these late-stage differentiated cells in humans is the persistent herpesvirus, cytomegalovirus. Because most elderly people are infected with this virus, it is difficult to separate its effects from those of aging. Where this has been done, it was concluded that it is primarily CMV that is responsible for driving these “age-associated” changes. Therefore, it may be proposed that the increased levels of expression of negative receptors by CD8 cells is in response to the necessity of maintaining these cells in an activated state as effectors responsible for CMV immunosurveillance. An antiproliferative, apoptosis-resistant, CD28−, KIR+ phenotype (commonly but perhaps erroneously assumed to reflect “senescence”) might, in fact, be protective and help to retain essential effector cells because CMV-specific cells constantly exposed to viral antigens might otherwise be stimulated to proliferate until they reached exhaustion and were clonally deleted. There is some published evidence from longitudinal studies that these CD8 clonal expansions occurring late in life are indeed predominantly CMV-specific, and that at the end stage of life, the loss of these clones is the immunological factor directly associated with mortality. Because younger persons may not yet have acquired CMV infection, or may not have cohabited with the virus for such an extended period, the majority of their memory cells will not be CMV-specific and might behave differently vis-à-vis KIR promoter demethylation. It would be fascinating to know whether and what fraction of the subjects studied by Li et al were CMV-positive and whether this alternative explanation is the more likely one.

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REFERENCES

Comment on Houot et al, page 3431

The doctor’s dilemma: stimulating T cells

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In this issue of Blood, Houot and colleagues report that T cells infiltrating human lymphomas express CD137, and that an agonistic CD137 antibody stimulates immune responses that exhibit potent activity against lymphomas transplanted into mice. The goal of recruiting the armory of the adaptive immune system, particularly T cells, against cancer has long attracted investigators. Since initial case reports that concurrent infections could result in responses or even cures of cancer, and exhortations to “stimulate the phagocytes” more than 100 years ago, researchers have sought methods to redirect cytotoxic responses against cells infected with pathogens instead of against cells transformed by somatic mutations. Unfortunately, thus far these hopes have not materialized into major impacts on cancer outcome. Nevertheless, immune–mediated treatments are firmly established within mainstream clinical practice, such as graft–versus-leukemia/lymphoma effects, and monoclonal antibodies directed against tumor antigens—for example, rituximab—work, in part, through effects on T cells.

Although far from complete, our understanding of T-cell subsets continues to advance rapidly. Not only have various effector subsets, such as Th17, come to the fore, but several suppressive T cells, known as regulatory T (Treg) cells, are now characterized. Such cells act as negative feedback regulators...
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