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Toward chemotherapy-free treatment of CLL

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Badoux and colleagues in this issue of Blood report on the use of lenalidomide as first-line treatment of CLL.1 This study appears simple at first glance, but it is remarkable in several respects.

First, the most important and biggest subgroup of CLL patients—the elderly, who are usually neglected in clinical trials—is studied. Second, the authors were ambitious enough to design a nonchemotherapeutic first-line treatment approach for these patients. Third, they included carefully preplanned correlative analysis not only focusing on the usual biologic disease characteristics but also on topics of specific relevance for the treatment modality chosen. Fourth, they chose a wise dosing schedule that anticipated a schedule that was later established by clinical phase-I testing. Fifth, although recently accrued, the population has a complete and almost maximal follow-up time documenting the overall excellent data quality.

Major breakthroughs have been made in CLL in recent years.2,3 Among the biggest steps forward are: (1) the introduction of chemoinmunotherapy with FCR (fludarabine, cyclophosphamide, and rituximab, or similar regimens), which appears to improve overall survival4,5; and (2) the identification of subgroups of patients (deletion 17p, TP53 mutation) that do not benefit as much as others from this approach and are prime candidates for novel treatment options.3,6 However, these advances are largely limited to young and physically fit CLL patients, which constitute a minority of all patients. Progress has been much more difficult in the elderly with a considerable degree of comorbidity. Only very little data are available regarding treatment approaches for CLL patients of advanced age and with comorbidities.6,7 In fact, chlorambucil can still be considered the standard treatment for these patients. However, chlorambucil leads to an unsatisfactory overall response rate of 50%-60% with virtually no complete responses and short progression-free survival as well as overall survival.6,7 It is of note that the data reported by Badoux and colleagues here point to very similar efficacy of lenalidomide as a single agent in CLL with a slow but steady improvement over time.1 Not unexpectedly, the major side effect of treatment was hematotoxicity, but this was accompanied by a lower-than-expected rate of severe infection. Most likely, both aspects result from the particular mechanisms of action of lenalidomide in CLL, which appear to be much more related to its immunomodulatory properties than in other diseases.

Lenalidomide has pleiotropic effects and multiple molecular targets, depending on the cellular context.8 In multiple myeloma, it has direct cellular toxicity, which does not seem to be the case for CLL cells. Lenalidomide impacts on several signaling pathways, on the intercellular cross-talk and hematopoietic tissue composition. In CLL, the therapeutic effects are possibly caused by targeting the interaction of the leukemic cells with their microenvironment and even by the induction of a cellular and humoral antitumor response. One of the intracellular
targets of lenalidomide is PI3K signaling, which activates the central transcription factors NFkB and NFAT, one of whose targets in CLL cells is the receptor CD154 (CD40L; see figure). The induction of CD154 in CLL cells is vital for the reversal of several aspects of the pathophenotype of the disease; presentation of the CD154 ligand on the CLL cell surface reactivates T and B cells and thereby increases the production of immunoglobulin by the residual normal B-cell population. On the same note, levels of the cytokines CCL3 and CCL4 are increased in CLL, and both are chemoattractants for T cells and thought to be mostly produced by the CLL cells in the microenvironment of the lymph node on stimulation of BCR signaling (see figure). Most importantly, it was shown that lenalidomide leads to functional T-cell activity in CLL with reinstitution of immune synapse formation. Badoux and colleagues now could indeed show within a clinical trial that in CLL cells of patients that respond to therapy, levels of CCL3 and CCL4 decrease upon treatment with lenalidomide, while in patients not responding to therapy, CCL3 and CCL4 levels increase. As this increase is not correlated with CLL cell numbers, the authors suggest continued BCR stimulation as a possible cause. Similarly and in line with effects observed in vitro, levels of CD154 increase in CLL cells of patients treated with lenalidomide. Underlining the role of BCR signaling in the molecular mode of action of lenalidomide, more patients with unmutated IGHV achieved a response in the current trial, even though these patients usually show more aggressive disease. Therefore, when entering the era of targeted molecular therapy, it becomes more and more obvious that understanding the mechanisms of action of novel compounds is the key for finding the optimal therapeutic strategy.

In summary, with this trial Badoux et al have targeted a particularly important and difficult-to-treat population in CLL, the elderly, with a very interesting agent that has properties distinct from the usual chemotherapeutic treatment approaches. The current study provides the basis for biologically and clinically interesting future perspectives combining lenalidomide with other agents, and trials investigating this are already under way based on the present study. Numerous other agents targeting the biology of CLL are currently under investigation. Overall, we can hope that with the advent of these agents, chemotherapy may be overcome as the mainstay of our CLL treatment one day.

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REFERENCES

GENE THERAPY

Comment on Ahmadi et al, page 3528

TCR expression; quantitative easing by CD3

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In this issue of Blood, Ahmadi et al show that the expression of a transgenic TCR can be increased 10-fold or more by cotransfer of CD3 cDNA, thereby augmenting antitumor activity.

Genetically modifying T cells to express transgenic TCR α and β chains of high affinity or a synthetic chimeric antigen receptor is an attractive strategy to generate tumor-directed antigen-specific T cells. Recent studies have shown encouraging clinical responses in melanoma patients treated with T cells genetically modified with melanoma-associated antigen recognized by T cells (MART-1)-specific TCRs, colon cancer patients treated with CEA-specific TCRs, and patients with NY-ESO-1-positive tumors treated with autologous T cells transduced with a NY-ESO-1 TCR.

One major limitation of TCR gene transfer is the development of hybrid TCRs that contain a mixture of native and transgenic receptors that may result in inefficient expression of the transferred TCRs and consequent loss (and occasionally unwanted gain) of function. Several different strategies have been developed to increase the expression of introduced α and β chains by reducing the mispairing with endogenous TCR chains. Ahmadi et al take a new approach. They hypothesize that it is endogenous CD3 components of the TCRs that are rate-limiting for αβ TCR expression and, hence, for tumor-directed T-cell function after the introduction of transgenic TCRs. In preclinical models, they evaluated transgenic TCRs, with specificity for Wilms Tumor antigen 1 and influenza nucleoprotein, and found that cotransduction of CD3 and αβ TCR cDNA produced a 1-log increase in TCR surface expression and increased in vitro cytokine production on exposure to tumor antigen compared with T cells modified with the αβ TCR only (see figure). They then evaluated this strategy in murine models and found that when T cells were genetically modified with both the TCRs and CD3, they infiltrated tumors more rapidly and in larger numbers than cells transduced with the TCRs alone. After tumor clearance, the TCR +CD3–modified T cells persisted at higher levels than T cells containing only the TCRs, and mounted a more effective memory response when rechallenged with antigen. Taken together, these results suggest that transfer of additional exogenous CD3 molecules may effectively enhance the activity and persistence of TCR gene–modified T cells.
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