infection and inflammatory conditions including immune-mediated bone marrow failure and the often-profound pancytopenia seen in those patients treated with interferons. Apparently, IFN-α and IFN-γ have similar effects in this Irml pathway (Margaret Goodell, personal communication, June 2011).

These observations have immediate clinical consequences as an easier-to-tolerate pegylated form of IFN-α has been shown to induce complete clinical remission in a majority of patients with polycythemia vera1 and essential thrombocythemia11 and to decrease JAK2 allelic burden and, in some cases, decrease the proportion of cytogenetic abnormality. Previously, Liu and coworkers2 have also shown that IFN-α is the only shown agent that can convert clonal polycythemia vera myeloid hematopoiesis to polyclonal hematopoiesis. As presented at the 2010 American Society of Hematology Meeting, pegylated IFN-α in some patients selectively decreased the JAK2V617F allelic burden without rescuing nonclonal hematopoiesis in some patients, yet in other patients, it resuscitates normal hematopoietic cells with a conversion of polyclonal cells without much change of JAK2V617F allelic burden.

Whether these observations could be explained solely by the effect on stem cells is not clear, as alternate mechanisms, or a combination of other mechanisms (such as stimulation of so-called testicular cancer antigens and the immune response against them) as has been shown in chronic myelocytic leukemia and more recently in polycythemia vera,12 or direct suppression of JAK2V617F–bearing hematopoietic progenitors13 remains to be determined. It also remains to be shown if the interferon effect on the stem cells selectively stimulates clonal JAK2V617F–, stem cell of JAK2V617F– subclone, or normal dormant hematopoietic cells (figure panel B).

Finally, the salutary effect of interferon therapy, which has been used in clinical practice without a full understanding of its mechanisms, is becoming clearer. One can hope that the direct targeting of the control mechanisms that protect stem cells from their depletion without other systemic detrimental effects of interferon, such as depression or promotion of autoimmune complications, could be transferred to a more targeted clinical benefit.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES


●●● CLINICAL TRIALS

Comment on Scandura et al, page 1472

Epigenetic priming: the target?

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Despite major advances made over the past 2 decades in our understanding of underlying disease mechanisms, prognostication, risk-adapted treatment stratification, and patient care, clinical outcomes in AML (acute myeloid leukemia) remain overall poor.1

This lack of improvement stresses the need for novel therapeutic strategies, including targeted treatment approaches tailored toward specific biologic and genetic subsets. In this issue of Blood, Scandura and colleagues report the findings of their innovative approach of epigenetic priming in younger, de novo AML patients with the hypomethylating agent, decitabine, followed by intensive induction chemotherapy.2

This work stems from the notion that in addition to recurrent structural chromosome and gene aberrations, epigenetic changes (those that alter gene transcription without changing DNA sequences) also occur in AML blasts.3 DNA hypermethylation is one form of reversible epigenetic alteration that occurs through DNA methyltransferases (DNMTs) enzymatically adding a methyl (CH3) group to cytosine in the context of cytosine-guanine (CpG) dinucleotide sequences. In AML, hypermethylation of CpG islands, CpG-rich regions often associated with gene promoters, results in the silencing of tumor suppressor genes and other genes important for hematopoietic differentiation. Different DNMT isoforms have distinct roles in genomic methylation in normal and malignant cells. DNMT1 is the most abundant, and preferentially methylates newly synthesized hemimethylated DNA strands during DNA replication in proliferating cells. In contrast, DNMT3a and DNMT3B are responsible for establishing de novo methylation.4 In AML, all 3 DNMT isoenzymes are overexpressed in malignant blasts compared with normal bone marrow cells.3 DNA hypermethylation has been found to be a suitable therapeutic target for nucleoside analogs called azacitidine (ie, azacitidine and decitabine), approved for treatment of myelodysplastic syndrome.6 In AML, we and others have demonstrated that decitabine incorporates into newly synthesized DNA, covalently binds DNMTs and blocks their activity thereby inducing DNA hypomethylation, gene re-expression, and clinical response.

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In a recent phase 2 trial of decitabine given at an optimal biologic dose of 20 mg/m² per day for 10 days, we showed a complete remission (CR) rate of 47% and a median survival of >12 months in a cohort of untreated AML patients aged ≥60 years (n = 53). This clinical response was achieved without the toxicity and prolonged hospitalization usually observed in older patients treated with cytarabine/anthracycline (7 + 3)-based cytotoxic chemotherapy. Despite these encouraging results, long-term remission was a rare event in this older patient population, suggesting that novel strategies to capitalize on initial results with low-dose, single-agent decitabine are necessary. In recent years, several groups have combined decitabine or azacitidine with histone deacetylase inhibitors with the intent to reverse chromatin histone hypoacetylation (another epigenetic change associated with transcriptional repression) along with reducing DNA hypermethylation, to induce synergistic re-expression of epigenetically repressed genes. Although results are encouraging, this approach has not yet been demonstrated as superior to single-agent azanucleoside in randomized trials, and novel epigenetic-targeting strategies are being pursued.

Based on preclinical data showing that DNA hypomethylating agents can sensitize chemoresistant cancer cells to cytotoxic therapy, Scandura et al have conducted a phase 1 clinical trial testing the feasibility, safety, and biologic activity of epigenetic priming with decitabine before 7 + 3 induction chemotherapy in patients ≥60 years of age with untreated AML and unfavorable karyotype (n = 30). The study design allowed for dose escalation of 2 different schedules of decitabine (bolus vs infusion). The toxicity of epigenetic primed induction was similar to that of standard induction chemotherapy alone. No delay in count recovery was observed and, in fact, patients had rather prompt platelet recoveries compared with those typically seen with standard induction therapy. The CR rate was 57%, which rose to 83% after salvage treatment for refractory patients. Pharmacodynamic studies identified different levels of hypomethylation of the HIST1H2AA and LINE1 repetitive elements in distinct cell subpopulations, with a trend for more hypomethylation observed in patients achieving CR compared with nonresponders. However, no threshold of posttreatment DNA hypomethylation levels was found to predict disease response.

This study provides intriguing data with clinical results encouraging for the planning of a phase 2 study. The authors should be commended for the trial design and elegant correlative studies. Nevertheless, it should also be recognized that the presented pharmacodynamic studies do not provide sufficient information to support decitabine’s activity as that of an epigenetic priming agent. Changes in methylation status and expression levels of genes likely to participate in myeloid leukemogenesis or pretreatment DNA methylation levels predictive of disease response were not reported. This raises the question of whether decitabine is able to sensitize patients to cytotoxic therapy by relieving epigenetic gene silencing or rather that its clinical activity may simply be because of increased, untargeted cytotoxicity with the combination of 2 nucleoside analogs (ie, decitabine plus cytarabine). Of course, the potential shortcomings of the correlative studies should be considered in light of the relatively small number of patients analyzed, biologic variability, limited sampling time points, and lack of standardized quantitative DNA methylation assays. Increasing the sample size for the correlative studies and/or using other assays, such as genome-wide methylation profiling arrays, could expand the search of novel markers and help successfully identify distinct genomic loci whose methylation status and expression levels are associated or even predictive of response to decitabine. Finally, it is possible that markers other than DNA methylation status may be useful predictors for clinical response to decitabine. For example, our group has shown that high levels of microRNA miR-29b, which targets DNMT3s, and lower levels of DNMT3A are associated with higher CR rate in decitabine-treated patients. Thus, one could postulate that lower DNMT expression and/or enzymatic activity may be better predictors for clinical response to hypomethylating agents. With the jury still out on the optimal usage of decitabine in the management of AML, identification of predictive markers that reliably support the epigenetic targeting activity of decitabine is essential for optimal patient selection and building on the initial success of this agent in the clinic.

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REFERENCES

LYMPHOID NEOPLASIA

Comment on Chang et al, page 1591

Sun, mother of life, prevents cancer

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In this issue of Blood, based on a large, prospective cohort study of 121,216 California women, Chang et al report on an inverse association between ultraviolet radiation exposure and a 40% to 50% reduced risk of developing non-Hodgkin lymphoma (NHL)—particularly diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)—and multiple myeloma.1
Epigenetic priming: the target?

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