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 genetically 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 leukogenesis 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, untreated 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.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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
Using the large, prospective California Teachers Study cohort, the authors identified 629 and 119 women who developed NHL (including CLL/SLL) and multiple myeloma after joining the cohort. The authors examined the association of prospectively ascertained residential ambient ultraviolet radiation exposure among these patients (cases) in relation to the entire cohort (controls). In their statistical models, they evaluated the observed 40% to 50% reduced risk of developing NHL and multiple myeloma in relation to skin sensitivity to sunlight, race/ethnicity, body mass index, and socioeconomic status. None of these factors modified the observed association between ultraviolet radiation exposure and a decreased risk for lymphoid malignancies.

Interestingly, in their analyses, Chang et al did not find dietary vitamin D to be associated with the risk of developing lymphoma or multiple myeloma. Thus, the results from this large prospective study suggest that regular routine residential ultraviolet exposure may have a protective effect against lymphoma and multiple myeloma; and this may be because of mechanisms that are independent of vitamin D.

As pointed out by Chang et al, a protective effect of exposure to ultraviolet radiation on the risk of NHL has been reported for more than a decade. Because most prior studies have been retrospective in nature, one may raise concerns about potential types of bias (eg, recall, selection, and survival bias). However, the current prospective study shows results that are similar to these prior investigations.

The new observation in the present study is the lack of an association between vitamin D from diet and the risk of lymphoid malignancies. Chang et al had access to dietary intake data from a food questionnaire, including information from data (food and multivitamins) and dietary (food only) vitamin D, as well as total and dietary calcium and dietary retinol (because the latter 2 micronutrients are negative regulators of biologically available vitamin D). Total and dietary intake of vitamin D, retinol, and calcium were not associated with risk of NHL or multiple myeloma; the same was true when the analysis was restricted to participants who did not use multivitamins, vitamin A supplements, calcium supplements, dietary vitamin D, retinol, or calcium. In their report, Chang et al discuss strengths and limitations of their study.

REFERENCES

Mutants strike again in APL

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In 2 patients with As$_2$O$_3$-refractory acute promyelocytic leukemia (APL), Goto et al identified missense mutations in the PML-region B2-box domain that neighbor the dicysteine motif recently found to be critical for PML-RAR$\alpha$ degradation, a requirement for curative anti-APL effect. As$_2$O$_3$ has emerged as the most clinically effective agent in APL (reviewed in Chen et al$^2$). Like the antecedent agent all-trans retinoic acid (ATRA) that targets PML-RAR$\alpha$, the underlying pathogenic driver in APL, primary resistance to remission induction is extremely rare. Its superiority to ATRA is demonstrated by the capacity of As$_2$O$_3$ to produce sustained remissions and apparent disease cure even when administered as a single agent in the majority of cases. When relapse occurs after As$_2$O$_3$ treatment, second and additional remissions can usually be achieved, however, these secondary remissions become progressively less durable. This pattern of resistance development suggests a pharmacometabolic basis for the development of clinical resistance to As$_2$O$_3$. Similarly, clinical ATRA resistance was demonstrated to have a pharmacometabolic component, but when the dose-schedule was adjusted to avoid tachyphylaxis, the only established mechanism of clinical ATRA resistance is the acquisition of mutations in the RAR$\alpha$–region ligand binding domain (LBD) of PML-RAR$\alpha$. Now, Goto et al report the first molecular basis for clinical resistance to As$_2$O$_3$ in APL, missense mutations in the PML-region B2-box domain of PML-RAR$\alpha$.

The findings of Goto et al indicate that clinically administered As$_2$O$_3$ was able to select APL cells with mutations in critical PML-RAR$\alpha$ target sites, despite pharmacokinetic studies indicating that in Japanese patients the reactive trivalent form of arsenic only reaches low nanomolar concentrations in plasma. Thus, these findings provide critical support for the clinical relevance of a molecular model of As$_2$O$_3$ action developed in preclinical investigations conducted at much higher (≥1 µM) As$_2$O$_3$ concentrations (reviewed in Chen et al$^2$). As shown in the figure, PML-RAR$\alpha$ exists as predominant homodimers in APL cells because of intermolecular noncovalent bonding of coiled-coil domains, the third component of the tripartite RBCC (Ring/Box/Coiled Coil) domain at the PML-region amino-terminus. Exposure to As$_2$O$_3$ produces
Sun, mother of life, prevents cancer

Ola Landgren