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"Epigenetic" Modification as Therapy for Acute Myeloid Leukemia

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Decitabine, and its kissing cousin 5-azacytidine are decades-old drugs that are used frequently for the treatment of all myelodysplasia (MDS) risk groups as well as patients with acute myeloid leukemia (AML), most often for older individuals and those felt to be too frail to tolerate conventional, intensive chemotherapy. In this issue of *Cancer,* Roboz et al[1] report on the use of guadecitabine, a new formulation of decitabine, in patients with AML that has relapsed or is refractory to standard treatment.

Guadecitabine is a dinucleotide of decitabine and deoxyguanosine linked by an enzymatically digestible phosphodiester bond, which results in a slower release of decitabine with the expectation that the longer exposure will result in greater cytotoxicity and improved response rates. The mechanisms of cell death produced by decitabine and 5-azacytidine are not completely understood, with evidence showing that these drugs, particularly at higher doses, have a conventional direct cytotoxic effect. At lower doses, an epigenetic effect mediated by DNA hypomethylation and consequent reexpression of genes silenced by hypermethylation is posited. There is no definitive consensus on what constitutes "higher" and "lower," and one could surmise that this could vary with the biology of the leukemia cells in individual patients. Indeed, this ambiguity is apparent in the description of guadecitabine, originally known as SGI-110, on the Web site of the company developing the drug, Astex Pharmaceuticals[2]:

> Guadecitabine was rationally designed to prolong the exposure of tumor cells to the active metabolite, decitabine, ensuring greater uptake of decitabine into the DNA of rapidly dividing cancer cells.
>
> As a next-generation DNA hypomethylating agent, guadecitabine inhibits DNMT to reverse aberrant DNA methylation, an epigenetic change characteristic of many cancer cells, restoring the expression of silenced tumor suppressor genes and tumor-associated antigens.

Because there is no dearth of cytotoxic agents, such as cytarabine, which preferentially kill "rapidly dividing cancer cells," it is the hypomethylating hypothesis that has generated the

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CONFLICT OF INTEREST DISCLOSURES

Charles A. Schiffer reports participation in an advisory board for Celgene and participation in data safety and monitoring boards for Pfizer, Ambit, Astellas, Pharmacyclics, Takeda, and Juno outside the submitted work.

most attention in the laboratory and in commercial promotional materials. Distinctive changes in the epigenome have been described in AML and indeed correlate closely with AML subgroups defined by cytogenetics,[3] and mutations in epigenetic modifiers such as *DMNT3A, TET2,* and *IDH1/2* are common in MDS and AML in older patients, frequently in association with other functional classes of mutations.[4]

Moreover, decitabine and 5-azacytidine clearly produce hypomethylation of genes in AML patients. Using the long interspersed nuclear element 1 (LINE-1) assay as a surrogate for global DNA methylation,[5] Roboz et al[1] noted a maximum of 25% to 30% hypomethylation; it was highest with the 10-day schedule and decreased after the guadecitabine was stopped. This was felt to be a greater hypomethylation effect than that seen with decitabine or 5-azacytidine. However, there remains continued scientific frustration, in that there is little information about which specific genes regain how much expression after demethylation of their promoters. Although it is intuitively attractive to assume that “good” genes antagonistic to leukemia cell survival are the ones suppressed by hypermethylation and that their “release” might encourage cell death or terminal differentiation, this is an unproved hypothesis at best. Hence, epigenetic modification, by either hypomethylation or changes in histone deacetylation, remains an empiric, “untargeted” approach until further laboratory dissection of this genetic landscape is available. In this regard, studies have failed to clearly show a preferential benefit from hypomethylating agent (HMA) treatment in patients whose leukemia cells harbor mutations in *DMNT3A* and/or *TET2.*

The current study compared 2 doses and 5- and 10-day schedules of guadecitabine administration, and complete response rates of 8% and 19%, respectively, were noted, with multiple courses of therapy required for most patients.[1] When patients who achieved a complete response with an incomplete count recovery were added, the response rate increased, but the median duration of the complete response was short, and this is consistent with the historically refractory nature of AML in this patient population. Earlier studies with guadecitabine produced generally similar results,[6,7] with higher response rates in previously untreated patients. No direct clinical comparisons of decitabine and guadecitabine have been performed; thus, whether the manipulation of the chemical structure produces superior outcomes in comparison with the “native” compound is not known.

Large international, multicenter, randomized trials, presumably aimed at regulatory approval, are in progress. The first (NCT02907359) compares guadecitabine with physician choice in subjects with MDS or chronic myelomonocytic leukemia who have experienced failure or relapse after treatment with azacitidine, decitabine, or both, whereas another (NCT02920008) compares guadecitabine with “treatment choice,” which is sometimes termed “conventional care,” in patients with previously treated AML. As in other trials,[8] treatment choice can consist of a potpourri of high-dose chemotherapy regimens, low-dose cytarabine, decitabine, azacytidine, or best supportive care. The primary endpoint for both trials is overall survival.

What can be learned from these trials? The results reported by Roboz et al[1] are of interest but are not decidedly better than what might have been achieved with other chemotherapy approaches. In phase 2 studies and even randomized studies in this group of higher risk

MDS/AML patients, selection factors are a major impediment when one is trying to compare results from different trials. For example, patients with more proliferative AML with higher white blood cell and blast counts are infrequently included in trials of HMAs, which tend to include patients with more "MDS-like" AML or those "too frail for induction chemotherapy."[9] Beating the paper tiger of low-dose cytarabine or showing longer survival in comparison with best supportive care may represent a small benefit for this hard-to-characterize subgroup of patients and may make a drug approvable, but it will not substantively advance AML treatment. Moreover, a randomized trial comparing decitabine with best supportive care or low-dose cytarabine as initial therapy for older patients with de novo or secondary AML with intermediate-or poor-risk cytogenetics[10] failed to produce sufficient benefit to merit approval by the US Food and Drug Administration for this indication.

AML in older patients and in those with prior MDS is highly resistant to cytotoxic therapy, likely in part because the pharmacologic mechanisms of resistance of nonmalignant stem cells of the hematopoietic system and other organs, in place to permit these cells to survive the potentially hostile chemical/bacteria/fungal products to which they are continually exposed, have been exaggerated. Although some older AML patients harbor targetable mutations such as *IDH1* and *IDH2*,[4] these are a minority, and most such mutations have likely already been discovered. The limits of HMA-based epigenetic treatment have also been defined. A variety of combination regimens, perhaps most notably attempts to combine HMAs with histone deacetylase inhibitors, have been explored. However, the combinations were not better than single-agent therapy in 2 randomized trials in which vorinostat or entinostat was added to 5-azacytidine.[11,12] Although questions about the choice, dose, and schedule of histone deacetylase inhibitor can be raised, these results dampen enthusiasm for other such double "whack a gene expression" clinical experiments.

Hence, decidedly different approaches will be needed to increase the cure rate, with immunologic manipulation perhaps being the most intriguing new candidate. In this regard, there are very preliminary data suggesting that treatment with HMAs might enhance the response rate with programmed death ligand 1 inhibitors, which have shown disappointing results in MDS when they have been used alone.[13] It is hypothesized that upregulation of programmed death 1 and programmed death ligand 1 by HMAs might increase the sensitivity to available inhibitors or that HMAs might induce the release of more or different antigens recognizable by autologous cytotoxic T cells with increased killing of target AML cells. If verified, this would be an exciting twist in the epigenetic journey of HMAs, which, despite their biologically intriguing mechanism of action, have produced modest overall clinical benefits to date.

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REFERENCES

1. Roboz GJ, Kantarjian H, Lee KWL, et al. Dose, schedule, safety, and efficacy of guadecitabine in relapsed or refractory acute myeloid leukemia. Cancer. 2018;124:325–334. [PubMed: 29211308]
2. Astex Pharmaceuticals. Guadecitabine (SGI-110). http://astx.com/research-development/clinical-pipeline/guadecitabine-sgi-110-dnmt-inhibitor-treatment-naive-aml/. Accessed October 2017.
3. Figueroa ME, Lugthart S, Li Y, et al. DNA methylation signatures identify biologically distinct subtypes in acute myeloid leukemia. Cancer Cell. 2010;17:13–27. [PubMed: 20060365]
4. Papaemmanuil E, Dohner H, Campbell PJ. Genomic classification in acute myeloid leukemia. N Engl J Med 2016;375:900–901.
5. Yang AS, Estecio MR, Doshi K, Kondo Y, Tajara EH, Issa JP. A simple method for estimating global DNA methylation using bisulfite PCR of repetitive DNA elements. Nucleic Acids Res 2004;32:e38.
6. Issa JJ, Roboz G, Rizzieri D, et al. Safety and tolerability of guadecitabine (SGI-110) in patients with myelodysplastic syndrome and acute myeloid leukaemia: a multicentre, randomised, dose-escalation phase 1 study. Lancet Oncol 2015;16:1099–1110. [PubMed: 26296954]
7. Kantarjian HM, Roboz GJ, Kropf PL, et al. Guadecitabine (SGI-110) in treatment-naive patients with acute myeloid leukaemia: phase 2 results from a multicentre, randomised, phase 1/2 trial. Lancet Oncol 2017;18:1317–1326. [PubMed: 28844816]
8. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009;10:223–232. [PubMed: 19230772]
9. Schiffer CA. "I am older, not elderly," said the patient with acute myeloid leukemia. J Clin Oncol 2010;28:521–523. [PubMed: 20026796]
10. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol 2012;30:2670–2677. [PubMed: 22689805]
11. Prebet T, Sun Z, Ketterling RP, et al. Azacitidine with or without entinostat for the treatment of therapy-related myeloid neoplasm: further results of the E1905 North American Leukemia Intergroup study. Br J Haematol 2016;172:384–391. [PubMed: 26577691]
12. Sekeres MA, Othus M, List AF, et al. Randomized phase II study of azacitidine alone or in combination with lenalidomide or with vorinostat in higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia: North American Intergroup Study SWOG S1117. J Clin Oncol 2017;35:2745–2753. [PubMed: 28486043]
13. Daver N, Basu S, Garcia-Manero G, et al. Phase IB/II study of nivolumab in combination with azacytidine (AZA) in patients (pts) with relapsed acute myeloid leukemia (AML). Blood. 2016;128:763. [PubMed: 27354720]