Acute myeloid leukemia - Section 3

Epigenetic treatment and beyond in acute myeloid leukemia

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Take Home Messages
- Although hypomethylating agents (HMA) have been widely adopted in the treatment of elderly AML “unfit” for intensive chemotherapy, consensus criteria defining which patients are deemed “unfit” or not suited to receive HMA are lacking.
- New HMA formulations to target DNA methylation, as well as therapeutic approaches to target methylation and acetylation status of histone activating and repressive marks are in active clinical development
- Emerging novel combination therapies delivering enhanced outcomes in AML are rapidly evolving with potential to change the therapeutic landscape.

Why target the epigenome?
Recurring mutations in AML frequently affect epigenetic regulators, leading to altered gene expression programs orchestrating leukemogenesis. These epigenetic alterations perturb DNA promoter methylation or histone methylation/acetylation, resulting in pathogenic gene expression changes critical for several phases of AML pathophysiology, including enhanced stem cell renewal, impaired normal cell differentiation, primary and potentially adaptive chemoresistance. As epigenomic changes often feature in pre-leukemic syndromes and age-related clonal hematopoiesis, a higher frequency of mutations affecting epigenetic regulators (e.g. DNMT3A, TET2, ASXL1, IDH1/2 and RUNX1) are found in older patients with AML.1,2 Epigenetic regulation is conducted by an array of writers, readers and erasers, which reversibly modify DNA methylation and remodel chromatin through histone acetylation or methylation. Epigenetic enzymes therefore represent attractive targets for cancer therapy, with the goal of re-establishing physiological cell processes (Figure 1).

Current state-of-the-art

Patient selection for hypomethylating agents
Pivotal studies with DNA methyltransferase inhibitors performed in elderly patients with AML (≥65 years) showed a trend for improved overall survival (OS) for both 5-azacitidine (Vidaza®)(10.4 vs 6.5 months; p=0.10)3 and decitabine (Dacogen®)(7.7 vs 5.0 months; p=0.11),4 compared to conventional care, prompting wide adoption of hypomethylating agents (HMAs) as preferred treatment for patients unfit for intensive chemotherapy. Composite response rates (CR/Cri or CRp) were 18-28% among recipients of HMA therapy. An extended 10-day schedule of decitabine (20 mg/m² x D1-10) in elderly patients (≥60 years), reported a higher complete response rate of 47%.4 The 10-day schedule may have utility in temporary clonal suppression of mutant TP53.5 This has prompted a randomised comparison of 5 vs 10-day decitabine to determine the clinical validity of extended dosing schedules [NCT01786343].

Biomarkers of DNMTi activity
Clinically reproducible and validated molecular biomarkers of response to HMA for patients with AML continues to be an elusive goal.7 A retrospective analysis of 159 patients has recently suggested that the dual presence of both DNMT3A and NPM1 mutations correlated with responses to HMAs collectively in the frontline (73% vs 21%; p=0.007) and combined frontline/relapsed/refractory settings (62% vs 28%; p=0.017), whereas DNMT3A mutation alone was only associated with a higher response in the frontline setting (57% vs 29%; p=0.001). Unlike prior studies, HMA therapy responses did not appear enhanced by the presence of TET2 or IDH mutations.8-10 In the near future, more efficacious epigenetic drug combinations for patients with AML producing response rates >60% may require biomarker-oriented research to shift focus toward identifying markers of resistance, rather than response.

Alternative hypomethylating agents in late clinical development
SGI-110 (guadecitabine) is a second generation HMA that has been examined at various dosing schedules among 107 patients.
Composite CRs ranged between 54-59% and the recommended phase 2 schedule was 60 mg/m² for 5 days. A pivotal phase III trial comparing guadecitabine to standard of care is ongoing to determine if this new HMA will be sufficiently active to replace current options (NCT02348489).

An oral formulation of azacitidine (CC-486) permitting more convenient administration has completed accrual in a pivotal maintenance study among 460 patients with AML ≥55 years in CR1 after intensive chemotherapy (QUAZAR AML-001 trial; NCT01757535). This study has the potential to demonstrate whether epigenetic therapy can reprogram AML progenitors in the maintenance phase and modulate the natural history of the disease after intensive chemotherapy.

**Emerging epigenetic therapies**

A plethora of emerging epigenetic modifying therapies targeting histone activating and repressive marks are being tested pre-clinically and in the clinic (illustrated in Figure 1). These agents expand the repertoire of drugs aiming to modulate gene expression signatures in AML for therapeutic benefit. Many novel epigenetic therapies are in early clinical development; predominantly in patients with relapsed and refractory AML. However, the gradual time-course for clinical effect (e.g., differentiation), inherent to many epigenetic-targeted therapies, makes clinical development highly challenging among patient populations with advanced and frequently aggressive stages of AML. Innovate clinical trial designs to better characterise the effects of epigenetic targeted therapies would be advantageous. A maintenance strategy designed to demonstrate changes in measurable residual disease could be one such approach.

**Selected epigenetic combination strategies**

In an attempt to enhance efficacy, novel therapies are frequently combined with HMA s, either empirically or rationally, in an attempt to augment anti-leukemic activity. Some examples in clinical development are outlined below:

**HDAC inhibitors (HDACi)**. The observation, almost two decades ago, that HDAC and DNMT inhibitors could synergistically enhance the expression of silenced cancer genes continues to be explored clinically, despite many HDACi/DNMT3i combinations suffering from poor drug tolerance. A randomised phase 2b study showed that the addition of panobinostat to azacitidine among patients with AML, MDS and CMML improved response rate, but not survival. Another phase 2 study with an alternative HDACi pracinostat in combination with azacitidine produced a more promising CR rate of 42%. This has led to evaluation of the combination in a 500-patient pivotal study (NCT03151408).

**FLT3 inhibitors**. Several exploratory studies combining HMAs with FLT3 inhibitors (midostaurin, sorafenib, quizartinib) have been conducted. This approach is supported by recent studies suggesting that synergistic hypermethylation may occur from the dual effect of an epigenetic mutation (e.g., TET2 loss of function) linked to gain of tyrosine kinase activity, such as from...
**FLT3-ITD**, leading to silencing of a critical target gene, such as GATA2, not observed in the context of either mutation alone. Validation of this and other synergistic AML mutation combinations will allow responder sub-populations to be rationally identified from DNMTi/FLT3i-based combination trials.

**BH3-mimetics.** The BH3-mimetic venetoclax targets pro-survival BCL-2 in AML cells and has been shown in a phase 1b/2 study in combination with HMAs to have promising efficacy in elderly unfit patients with AML, with composite CR/CRi rates ~65% appearing to surpass historical expectations with HMAs alone. Similar results have been observed with venetoclax in combination with low-dose cytarabine (LDAC). These results have led to parallel pivotal phase 3 studies to determine if these combinations have the potential to become the new standard of care for the treatment of elderly patients with AML (NCT02993523 and NCT03069352). Future studies will likely determine if venetoclax in combination with HMAs has greater efficacy than LDAC in certain subsets of AML, such as adverse cytogenetic risk or other molecular sub-groups.

**All trans retinoic acid (ATRA).** Among other mechanisms, ATRA has been proposed to downregulate BCL-2 in AML blasts/progenitors. The randomised addition of ATRA to a 5-day decitabine schedule in unfit patients with AML ≥60 years (DECIDER study) led to improved survival (8.2 vs 5.1 months; p=0.003), despite a non-significant improvement in response (21.9% vs 13.5%; p=0.12). The mechanistic basis underlying this improved survival remains to be determined.

**Checkpoint inhibitors.** HMAs are described to have positive effects on immunoregulatory cells in AML, but to also upregulate PD1 and other immune checkpoints, promoting T-cell exhaustion and thereby limiting clinical benefit (summarised in). This has prompted exploratory clinical trials combining HMAs with checkpoint inhibitors, with encouraging early results suggesting the potential for prolonged response duration.

**Future perspectives**

The epigenetic machinery is multi-faceted and complex. Hypomethylating agents catapulted epigenetic therapy into the clinical domain and continue to form the backbone of elderly AML therapy. Despite the recent emergence of numerous novel epigenetic modifying drugs, major challenges for the field remain. Firstly, can we identify rational biomarkers that can adequately identify “responder” sub-populations from the broad landscape that typifies AML. Second, will epigenetic therapies have sufficient anti-leukemic specificity to enable clinical benefit to exceed acceptable levels of toxicity. Third, are current clinical trial designs focussed on the relapsed/refractory setting failing to reveal the full benefits of this drug class. Finally, with the emergence of so many novel anti-leukemic drug options; most in early phase clinical development, how can academic and industry stakeholders most efficiently and successfully identify which epigenetic drugs, combinations and disease pathways should be prioritised for registration-phase clinical development.

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