Project 2025: Proposals for the Continued Success of Drug Development in Acute Myeloid Leukemia

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ABSTRACT

The Food and Drug Administration Oncology Center of Excellence initiated Project 2025 to develop 5-year goals in specific areas of oncology drug development. This meeting, in October 2020, brought together a panel of regulators and academic experts in acute myeloid leukemia (AML) to discuss opportunities to maximize the success that has recently occurred in AML drug development. The panel discussed challenges and opportunities in clinical trial design and novel endpoints, and outlined key considerations for drug development to facilitate continued growth in the field.

Introduction

Therapeutic options for acute myeloid leukemia (AML) are rapidly evolving and the treatment landscape is in the midst of a dramatic shift, reflecting a more sophisticated understanding of the molecular composition of malignant clones: from years of incremental improvement in treatment to a spate of approved therapies; from therapeutic nihilism to realistic optimism for durable disease control and even cure. To capitalize on the positive momentum in the field and further advance the development of effective therapies in AML, a panel of academic AML experts was convened in October 2020 and charged with constructing a vision for future directions in the development of new therapies and clinical trial design. The meeting was conducted by the FDA Oncology Center of Excellence (OCE) Project 2025, which promotes interdisciplinary collaborations in oncology drug development, with a focus on setting and attaining 5-year goals. In this article, we summarize our discussions, review recent progress, and highlight opportunities to help guide the field forward.

Victories and Challenges

Advances in AML are evident from the number and pace of new drug approvals. Targeted and nontargeted drugs for newly diagnosed as well as relapsed or refractory patients that result in durable responses, transfusion reductions or independence, and/or improvement in overall survival (OS), have been developed and approved in a relatively short period of time (**Fig. 1**). Many of these new therapies target fundamental properties of AML and are the result of years of research into the biology of the disease. On the regulatory side, the development of expedited programs and innovative and flexible approval pathways (1) have accelerated the process of bringing safe and effective drugs to our patients. Specifically, the accelerated approval pathway, which allows for approval on the basis of an intermediate clinical endpoint reasonably likely to predict clinical benefit [e.g., complete remission (CR) rate; ref. 2], resulted in the approval of venetoclax for AML almost 2 years before the completion of randomized phase III trials led to its regular approval. FDA has also demonstrated flexibility in the use of novel endpoints, such as durable CR + CR with partial hematologic recovery (CRh) rate, supported by data on achievement of transfusion independence, to support regular approval for isocitrate dehydrogenase and FMS-like tyrosine kinase 3 inhibitors (3, 4).

Improved outcomes in younger patients were noted prior to 2017, the era of abundance in AML drug approvals (**Fig. 1**), largely due to improvements in anti-microbials and supportive care measures that facilitated the administration of conventional intensive cytotoxic chemotherapy. For older patients with AML, particularly those with comorbidities or poor-risk disease features, advances have been less apparent, and cure is still extremely rare (5). Although classical clinical trial designs did contribute to recent drug approvals, there is valid and growing concern that continued success using current development strategies will be difficult. Patients with AML are increasingly segmented into biologically-defined subsets, and accruing patients to multiple adequately-powered phase III studies will be arduous, if not impossible. Also, although some novel therapies are ultimately shown to work well in select patients, often these responders cannot be reliably predicted at the outset of the clinical trial. Additional major challenges include developing therapies for the many patients who lack an identifiable molecular target, overcoming resistance to novel therapies, determining optimal combinations, and schedules of novel drug regimens, ascertaining the potential role of immunotherapies, and eliminating measurable residual disease (MRD).

Rethinking Assumptions about AML

Across many disciplines, including AML, years of tradition and habit can lead to stagnation, impairing progress. Challenging assumptions is therefore important. The gold standard for success in AML therapy has been measured by improved OS. This was feasible and appropriate when there were few effective therapies and patients' treatment courses were relatively homogenous. However, this metric is increasingly unreliable when a novel agent is given at a particular timepoint and evaluated as part of an individual patient's unique

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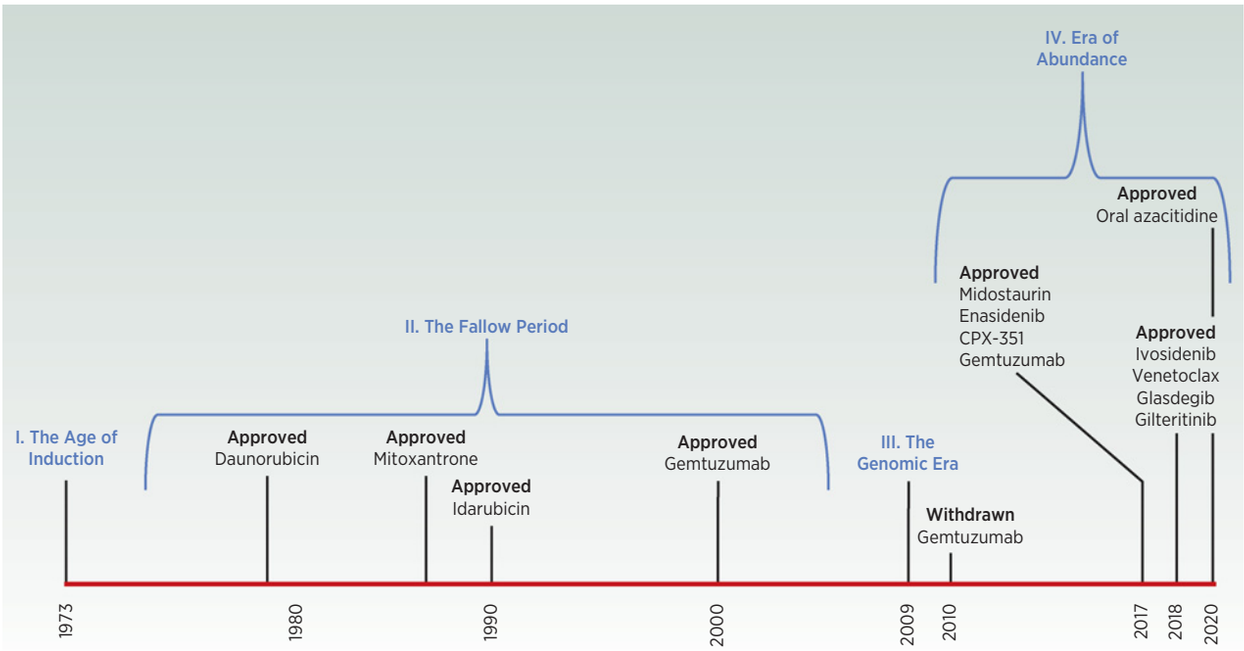

Figure 1.
FDA approvals for AML over time.

trajectory through remission induction, consolidation with or without stem cell transplantation, maintenance, and relapse. Certain statistical approaches may mitigate this problem to some degree (6). Also, alternative endpoints have been increasingly considered. For example, event-free survival was used to obtain approval for gemtuzumab ozogamicin in 2017 (7) and response duration, which is not influenced by subsequent interventions (other than maintenance), was considered as an endpoint in the clinical trials of enasidenib, ivosidenib, and gilteritinib for patients with AML treated without curative intent (3, 4, 8). Other new metrics could include rigorously-determined quality of life measures, sustained transfusion independence, or MRD-based endpoints (9).

The next 5 years should also bring a re-assessment of how to prognosticate outcomes as well as evaluate responses and endpoints in older patients with AML. Current prognostication and classification schemas are biased to the outcomes of younger patients treated with intensive chemotherapy (10), and cannot be applied to the predominant population of older patients with AML, who are increasingly receiving novel therapies with noncytotoxic mechanisms of action. Although CR occurring after standard intensive chemotherapy is clearly associated with improved survival in younger patients treated with intensive chemotherapy, CR does not always improve OS for older patients (11). For treatments administered with palliative intent, other responses, such as CRh accompanied by durable transfusion independence, have been considered beneficial when evaluated in the context of continuously administered, relatively nontoxic and non-myelosuppressive regimens.

Another assumption that should be challenged is whether a patient fit for intensive induction chemotherapy should necessarily receive this therapy. This is an increasingly important consideration now that lower-intensity treatment options can produce high rates of remission that, in certain patient subgroups, rival the response rates obtained with intensive regimens. Challenges related to attempts to measure fitness, and a lack of consensus in how to do so (12, 13), may now be circumvented by instead determining whether a patient is more likely to benefit from induction chemotherapy or another therapeutic approach; such is the advantage of having more than one treatment to offer. Ultimately, randomized trials in which "fit" patients are assigned to receive intensive chemotherapy or a less intensive approach with new agents may be required. An example of one such trial design in development is the MyeloMATCH initiative, a collaborative, federally funded set of trials to be sponsored by the NCI and its National Clinical Trials Network.

Rethinking Clinical Trials for AML

The panel felt it was unlikely that further significant improvements in AML outcomes will be identified without changes in the way clinical trials are structured, given the relative rarity of AML and concerns that requiring a phase III study for each new question will outstrip the "supply" of patients (14). One solution to this problem is to allow for historical controls in "randomized" studies. The NCI-funded cancer cooperative groups have conducted many large AML clinical trials, and a multitude of other trials have been conducted by industry sponsors. Using these databases, the development of a "control cohort" of patients, annotated with baseline clinical factors, could be used to compare with outcomes from patients who receive novel therapies in single-arm clinical trials. Similar efforts to collect data from clinical trials serve as an encouraging example and are ongoing (15). The panel encouraged consideration of the use of a hybrid model, in which a randomized study would enroll an initial cohort of control and experimental patients. A database of historical patient-level data could then be consulted, and an exchangeability analysis could identify additional

Table 1. Published randomized clinical trials in the last 10 years that have added an investigational therapy onto an intensive induction chemotherapy backbone.

Investigational drug	Year published	Number of patients	Study phase	Primary outcome
Bevacizumab (22)	2012	171	Phase II	Toxicity, complete remission rate
Cladribine, fludarabine (23)	2012	652	Phase III	Complete remission rate
Gemtuzumab[a] (20)	2012	280	Phase III	Event-free survival
Homoharringtonine (24)	2013	620	Phase III	Complete remission rate
Sorafenib (25)	2013	201	Phase III	Event-free survival
Sorafenib (26)	2015	276	Phase II	Event-free survival
All-trans-retinoic acid (27)	2016	1,100	Phase III	Event-free survival
Midostaurin[a] (28)	2017	717	Phase III	Overall survival
Avocidib/flavopuridol (29)	2018	165	Phase II	Complete remission rate
Lomustine (30)	2018	459	Phase III	Overall survival
Eltrombopag (31)	2019	148	Phase II	Toxicity
Pioglitazone (32)	2019	40	Phase II	Complete remission rate
Lenalidomide (33)	2020	222	Phase II	Event-free survival
Oblimersen (34)	2021	506	Phase III	Overall survival

[a]FDA approved.

cohorts of patients from the database who are sufficiently "exchangeable." These patients would be "virtually" enrolled and compared with subsequent patients who were actually enrolled to the experimental arm (16, 17). This design could expedite clinical trials and decrease the numbers of patients needed. However, the panel acknowledged limitations to this approach, given changes in treatment landscapes and supportive care over time, as well as differences in unmeasured covariates that could not be controlled for in the absence of randomized clinical trials. Other approaches, including Bayesian trial designs, and employing novel endpoints (event-free survival or MRD negativity, as described above), should also be considered.

The sanctity of intensive induction chemotherapy ("7+3") as the standard of care for newly diagnosed, "fit" patients with AML, and as the backbone for regimens to which we add novel agents, should also be examined (18). Over the years, despite multiple attempts, only midostaurin and gemtuzumab have received regulatory approval as an add-on therapy to 7+3 (**Table 1**; refs. 19, 20). This precedent has many challenges. Patients who receive 7+3 have high response rates; new therapies are often tested in phase II trials with response rates that are compared with historical expectations for 7+3. ****A "negative" trial structured this way will likely not result in a drug moving on to a phase III study that could show superior OS, despite the fact that response rates and OS are different endpoints and not necessarily coupled. Alternatively, if OS is the only endpoint of interest, the experience of midostaurin, requiring 9 years and the screening of 3,277 patients (19), will be nearly impossible to replicate for every promising therapy in less common molecular disease subsets. In addition, 7+3 without consolidation is rarely curative, and is toxic with a considerable rate of morbidity and mortality in "real-world" settings (21), making it a challenging backbone therapy. Furthermore, the default use of cytotoxic agents as backbones may mitigate the benefits of molecularly targeted agents—which can require more time to work, and are often designed and tested in a bone marrow milieu that is not undergoing rapid necrosis and apoptotic damage. Finally, continuing to require compatibility with 7+3 raises concerns that this will apply selective pressure to drug development pipelines that reward not necessarily the best treatments, but rather the ones that synergize best with 7+3. As a result, the panel questioned the requirement that every new agent, after it shows some activity in the relapsed and refractory setting, be paired with 7+3 and studied in newly-diagnosed patients, and argued for more flexibility in trial designs that are based on rational mechanisms rather than historic precedent. Furthermore, pairing novel treatments with less intensive regimens, or using them in the MRD-positive or post-remission maintenance setting, may prove more beneficial. **Table 2** contains key considerations for drug development in AML from the panel.

Conclusions

Patients with AML are finally benefitting from of decades of work spent in the laboratory, investigating the subcellular processes and molecular characteristics that enable the development, proliferation, and persistence of this disease. These translational achievements, to date, have mostly been initially tested in older patients with AML with significant comorbidities. Now is the time for innovative clinical trial designs, bold randomizations that are "fitness" agnostic, flexible control arms, and maximal collaboration

Table 2. Key considerations for drug development in AML.

- Randomized trials are preferred for the evaluation of novel drugs and drug combinations. However, the feasibility of these studies can be limiting, and as a result, modifications and other trial designs must be strongly considered, including:
  - "Physician's Choice" control arms, particularly in situations for which there is no clearly defined standard of care.
  - The utilization of historical controls and/or the use of exchangeability to augment or accelerate randomized trials.
  - Single arm studies in some scenarios (e.g., in biologically defined patient subgroups without existing standard-of-care targeted therapies or for relatively nontoxic and/or nonmyelosuppressive therapies).
- MRD assessments performed using a variety of platforms (e.g., multiparameter flow cytometry, polymerase chain reaction, next-generation sequencing) are strongly encouraged for all AML clinical trials, irrespective of the trial endpoint.
- Clinical trials should consider using MRD-negative complete remission as an endpoint supporting evidence of efficacy.
- Therapies with novel mechanisms of action may require novel endpoints.

between academia, industry, and regulatory agencies, so that we can continue to test multiple new agents in the AML pipeline that have promise to help our patients.

Disclaimer

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

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