

ACUTE MYELOGENOUS LEUKEMIA (AML) WORKING GROUP
ROCKVILLE, MD
OCTOBER 4, 2010
SUMMARY

The AML Working Group of NCI's Leukemia Steering Committee held a series of conference calls followed by a one day meeting to strategize about future clinical trials in AML. Participants included academic clinical oncologists, community clinical oncologists, translational scientists, biostatisticians, and patient advocates. Participants were divided into three subgroups, which discussed specific topics in breakout sessions during the meeting, and provided a summary to the full group at the end of the day.

GROUP 1 – IMPROVING THE SPEED AND EFFICIENCY OF THE DESIGN, LAUNCH, AND CONDUCT OF CLINICAL TRIALS

Participants: Elihu Estey, Boris Freidlin, Vincent Ho, Mary Horowitz, Ken Kopecky, Richard Larson, Richard Little, Brent Logan, David Rizzieri, Peter Thall, Daniel Weisdorf

Goals and overview: The goal of Sub Group 1 (SG1) was to generate ideas that will improve the speed and efficiency of the design, launch, and conduct of clinical trials. Participants were tasked to consider whether new approaches can be developed or existing methodologies improved, which can be easily and quickly implemented and lead to trials yielding sufficiently reliable results in a shorter amount of time than what is currently standard.

Discussion: To improve the design of clinical trials in a way that will ensure the rapid accrual of patients and/or trial completion, the current standard of how trials are run may need to be overhauled. The standard ideas of failure and success need to be re-imagined. Multi-arm phase II/III trials can be designed where a higher degree of error is accepted (in the phase II stage), such as stopping the trial early for futility/toxicity issues. If the natural history of the disease with the current therapy is well characterized, a control arm may not be needed for a phase II trial. Potential clinical outcomes can be modeled (using early or intermediate outcomes) to determine the appropriate stopping rules for dropping ineffective arms, presenting a toxicity/efficacy trade-off. The criteria for when it is appropriate to proceed to a phase III trial needs to be re-examined. Also, there is a need for upfront contingency plans for biomarker results.

No single design can be expected to fit the requirements and context of every study, or even a large subset of studies that are likely to be conducted. The requirements for each study must be carefully considered, and optimal designs must be developed on a case-by-case basis. With this in mind, the following general considerations should be applied.

- New agents can be moved from phase I to phase II in the upfront or maintenance setting rather than only in relapsed patients in appropriately selected disease groups.
- The presence or absence of MRD (minimal residual disease) should be considered as an endpoint for maintenance or an entry point for a trial.
- In the upfront setting, multi-drug combinations should be considered when it is biologically reasonable since single agents are unlikely to make a large impact.
- Eligibility criteria should be broadened and not necessarily limited to the disease population thought to benefit most from the proposed treatment; a possible consideration is nested

subgroups or other appropriate designs, such as biomarker (+) or (-) patients. Special attention will need to be paid to accepted criteria so as not to dilute the patient population. (This will require existence of a biomarker that can be uniformly assessed in timely manner).

- The assessment of genomic biomarkers will require larger studies for power.

Trials should be planned strategically so that important questions are addressed quickly and build on results from previous trials. Researchers should not wait until all of the results from trials are available before beginning the next trial. Trials should be constantly ongoing (provided there is an interesting question to be asked). Gaps should be avoided and approaches to facilitate participation in international trials to address any gaps need to be considered.

Data and Safety Monitoring Committees (DSSCs) should be asked for access to preliminary results of ongoing trials for purposes of planning subsequent trials. However, care must be taken to ensure that the results remain confidential, in order to prevent unauthorized early disclosure of results, or imputation of those early results, from affecting the ongoing trial.

CTEP may need to play a more pro-active roll in helping to facilitate interaction with the pharmaceutical industry and speed activation of studies. Standard CRFs (case report form) and core sets of data, with uniform outcome endpoints, used across trials can allow data from multiple trials for secondary analyses to be better collected.

Accelerating the rate of accrual would solve most of the statistical issues regarding the speed and efficiency of clinical trials. To achieve this end will require marked improvement in the incentives to participate in clinical trials, both for patients and for physicians as well as the entire health care enterprise. This problem is particularly exacerbated in the case of rare diseases and/or biological subsets of uncommon diseases where small numbers of subjects make even single-arm phase II studies quite difficult to complete in a timely way. A specific issue to be considered is the problems presented due to public or private insurance. Accrual issues must also be addressed at the local level.

Probable solutions could include providing better incentives, assistance with patient consent, and electronic data capture capabilities. Active and joint participation by CTEP, FDA, and OHRP to facilitate the clinical trials process would likely speed the evaluation of new therapies.

An omnibus protocol, which includes multiple interventions in specific subgroups (defined, e.g., by risk level or genetic abnormality), may reduce reluctance of institutions to expend the time and effort to open trials on which they will enroll very few patients yearly. However, an omnibus protocol is likely to be unwieldy as different regimens targeting various subsets are unlikely to be activated simultaneously. In addition, IRBs are likely to see such an omnibus protocol as multiple individual studies, each of which requires independent review and approval.

GROUP 2 – OPTIMIZE USE OF SCIENTIFIC INNOVATIONS AND RESOURCES

Participants: Jerry Radich, Clara Bloomfield, Guido Marcucci, Ari Melnick, Jean-Pierre Issa, Elisabeth Paietta, Deborah Jaffe

Goals and overview: The topic for Sub Group 2 (SG2) was how to optimize use of scientific innovations and resources. SG2 started by discussing these questions:

1. For a new phase III trial where all cooperative groups are participating, which group(s) should perform the correlative studies? Do we pick the best experts from each group? Should each group do their own studies?
2. How do we write protocols/consents to ensure that all samples go directly to the correct labs?
3. How can investigators get more latitude in using repository samples to propel the work on the next generation of studies?

General Discussion:

The AML field has an outstanding track record for personalized/molecular medicine. Molecular tests need to be built into the design of prospective trials. There was a discussion of cross-validation of laboratories, how to assign laboratory responsibility, whether or not to have a centralized laboratory for all or specific tests.

Issues to Consider:

1. Should each cooperative group perform their own laboratory tests and manage their data or should one group be selected to perform certain tests? If so, how should selections be made--by the LKSC, a subgroup/working group of the LKSC, or collaboratively among the laboratories?
2. How will technology be applied to the treatment of AML: will it vary depending on complexity of the technology, i.e., complex versus moderate versus easy? For complex questions and assays, most laboratories prefer their own validated tests. Higher complexity assays such as FLT-3 are harder to standardize across cooperative groups. The type of trial is central to the determination of which labs perform which assays.
3. For high complexity assays only performed in a few labs, how will the decision be made in regards to whom will do which assay?
4. How will we pay for assays performed on cooperative trials?
5. What about intellectual property: who will own the data--the cooperative group or the individual lab?

For the collaborative trial, stratification of AML patients needs to be standardized across cooperative groups. The essential stratification markers and standard assays need to be defined. Common assays such as cytogenetics, as well as the molecular tests associated with prognosis, need to be standardized across cooperative groups. This will facilitate enrollment and comparison of data.

Standard assays for each group:

Cytogenetics
FLT-3 ITD and ALM
NPM1
CEBPA
CBF translocations
cKit

Specialized assays:

Genome sequencing
SNPs
mRNA assays
miRNA assays
methylation
proteomics

Summary/plan:

- SG2 will form an ad hoc correlative science AML group. This group will decide on the distribution of lab studies; work on standardization of assays; and interact with the PIs of new trials to integrate assays into the trials. SG2 encourages the design of trials based on molecular subsets, and notes the importance of early input during trial development.
- In addition, the ad hoc group will work with the cooperative group statisticians to develop a core database where the results from the different labs can be deposited.

- The group will work to develop a common consent that can be used for correlative sciences, with an eye towards eventual public domain release. This will be essential in the next generation of correlative studies, which will include genome sequencing. ECOG has a consent that will be distributed for consideration.
- Any work by this group will be summarized and distributed both to the group and to the large domain of clinical investigators included at this meeting. Monthly updates on ongoing projects will be the goal. In addition, efforts will be made to involve CMS and the FDA early concerning new initiatives that involve trial design.

Group 3 - Improving selection, prioritization, support and completion of clinical trials

Participants: Fred Appelbaum, Deborah Banker, Harry Erba, Steven Gore, LeeAnn Jensen, Marcos de Lima, Wendy Stock, Richard Stone, Martin Tallman, Geoffrey Uy

Goals and overview: The goal of Sub Group 3 (SG3) was to survey the existing clinical trials in AML, identify gaps, and recommend a plan for the next national trial(s) that should be undertaken. The plan for a national study should include incentives for participation by community oncologists and provide opportunities for junior investigators to lead the trial(s).

A uniform entry point for diagnostic testing to assign patients to treatment groups was agreed to be an essential component of a national treatment strategy for AML (and for future trials of ALL). Tests should distinguish groups with known mutations and complex karyotypes from patients without. HLA typing should be included. The number of consent forms should be limited to two: one for sample collection and diagnostic assessment and one for the treatment protocol. Cells should be collected in **one** bone marrow biopsy and allocated for all other uses. In order for the diagnostic component to be maximally valuable, it should quickly (within 48 hours) identify patients with high risk disease. It was recognized that subsetting the patient population based on karyotype and mutation(s) precludes comparison to historical controls as in a single arm trial.

A brief review of ongoing national cooperative group trials is listed below:

Pending but approved/ Ongoing / recently completed AML studies

AML ≤ 60

ECOG 1900 (Fernandez): Phase III daunorubicin 45mg /m² vs 90 mg /m² (completed)

CALGB 10503 (Blum): Phase II of decitabine maintenance (completed)

CALGB 10603 (Stone): Phase III chemo +/- midostaurin (will complete accrual in approximately 1 yr)

CALGB 10801 (Marcucci): Phase II of chemo + dasatinib in CBF leukemias (pending)

SWOG 0106 (Petersdorf): Phase III chemo +/- Mylotarg (terminated for lack of efficacy)

MD Anderson (Faderl): Phase II clofarabine 22.5 mg /m² d1-5 + idarubicin 6 mg /m² d1-3 + ara-C 750 mg /m² d1-5

AML > 60

ECOG 1905 (Gore): Randomized phase II azacytidine + MS 275 in MDS / Tx related AML (tx related arm open only)

ECOG 2906 (Foran): dauno/ara-C + intDAC consolidation vs. clofarabine induction 30 mg /m² and consolidation 20 mg /m² for fit patients with second randomization to decitabine maintenance

CALGB 11001 (Uy): Phase II chemo +/- sorafenib in FLT3 followed by sorafenib maintenance
CALGB 11002 (Roboz): randomized phase II of 10 day decitabine vs. decitabine + bortezomib vs
decitabine + lenalidomide (pending)
SWOG 0703 (Nand): azacytidine/Mylotarg (accrued ~ 90 of 150)

APL

SWOG 0521 (Coutre): Phase III of maintenance vs observation in low risk APL: (closed because of low accrual)
SWOG 0535 (Lancet): Phase II of ATRA, arsenic + mylotarg in high risk APL: (suspended pending drug supply; will reopen)

Relapsed / refractory

SWOG 0919 (Advani): Phase II idarubicin + ara-C + pravastatin

Discussion

There was general consensus **that future studies of AML should be tailored to cytogenetic and molecularly defined subsets of patients**. Acknowledging that this area is in constant evolution, the current therapeutically relevant subsets of patients include:

1. CBF (core binding factor) leukemias
2. Acute promyelocytic leukemia
3. FLT3+ mutant
4. High risk cytogenetics / secondary AML
5. Others: includes most of cytogenetically normal AML; for purposes of discussion, this cohort will be referred to as AML not otherwise specified (NOS)

Recognizing that none of the three major cooperative groups currently have an open upfront study for younger AML patients (with the exception of APL and FLT3 subsets; and planned study for CBF AML), this was felt to be the greatest need for rapid protocol development. The group was charged with rapidly developing the framework for an upfront AML study for younger patients (to be redefined as age ≤ 65 years old). The participants agreed that "older" AML patients are currently being addressed by existing trials and new strategies could be addressed later.

The national strategy for AML should separate NOS from high risk AML patients quickly (initial 80% chance of correct categorization within 2 day window) and assign high risk patients to a transplant algorithm. If an NOS patient is later determined to be high risk, they should enter the transplant treatment algorithm at that point.

Another area of general agreement was the need to consider phase II questions in light of an eventual phase III trial. A randomized intergroup phase II/III design was suggested, with stringent early stopping guidelines for futility of a given arm. Sub Group 1 (clinical trial design issues) should recommend an appropriate design to seamlessly flow from the initial randomized phase II study to a phase III study. (It was suggested that the study concept be written such that as much phase II interim data as possible is available to the investigators and AML WG to facilitate the design of subsequent treatment and correlative studies.)

The need for a national allogeneic transplant trial (especially for high risk patients and also for patients ages 55 - 70) was discussed. It would be interesting to test an alternate-induction question, for example

the efficacy of hypomethylating agents in this group characterized by resistance to standard AML chemotherapy. It is important that every potential patient is registered so that selection bias is minimized and the study outcome is representative of the true patient population. The site-determined transplant regimen would be specified at the time of registration. NMDP is willing to facilitate rapid HLA typing and donor searches. Donor sources could include MUD, siblings, related haplo-matches, and cord blood, based on institutional preference.

Recommendations:

1. **A single, shared, diagnostic study** across all three cooperative groups should be implemented to allow for cytogenetic and molecular diagnostics, risk stratification and collection of diagnostic samples required in the treatment study. Clara Bloomfield will poll the other cooperative groups to determine whether rapid cytogenetic testing by central review is feasible.
2. **APL**
Currently there is a strong disincentive for institutions to open low accruing studies in rare diseases given the limited financial reimbursement, high infrastructure costs. This is compounded by the successful therapies that are now available for APL which has become a highly curable disease. Because this is a rare subgroup of patients, efforts should be made to join currently ongoing international studies.
3. **CBF leukemias**
CALGB 10801 (PI: Marcucci) is a single arm study of 7+3+dasatinib using daunorubicin 60 mg/m². Based on the results of this initial study, the AML WG might consider a follow-up intergroup study. Alternatively, the feasibility of opening this as an intergroup study and amending the study to increase accrual should be explored. CALGB will lead this effort.
4. **FLT3+**
Two current CALGB studies, 10603 for pts < 60 and 11001 for over 60, are testing the addition of FLT3 inhibitors (midostaurin and sorafenib) to standard chemotherapy. SG3 agreed that newer TKIs in particular AC220 should be tested. However, there currently are no pilot data combining AC220 with chemotherapy. Pending a feasibility study of AC220 + chemotherapy, ECOG will lead the next FLT3+ study.
5. **AML (NOS); mostly cytogenetically normal**
SG3 recommended that SWOG lead a 3-4 arm Phase II/III study in patients with upfront AML with early stopping rules to eliminate the less favorable arms. Harry Erba will lead a breakout group to review phase II studies in AML and prioritize the most promising ones for the next upfront AML study. Over the next two weeks, he will contact investigators and ask them to share their data with the working group. With the assistance of Eli Estey, the group will review the data and make recommendations on the best two or three agents to compare with the control arm of daunorubicin 90 mg /m² /day x 3 and cytarabine 100 mg /m² /day x 7 (3+7). Regimens being considered are:
 - 7+3+cladribine
 - 7+3+vorinostat
 - 7+3+pravastatin
 - 7+3+bortezomib
 - FLAM (flavoperidol, ara-c, mitoxantrone)

- G-CLAC (G-CSF, clofarabine, ara-c)
- Clofarabine, idatubicin, cytarabine
- MEC+ plerixafor
- MEC+ sirolimus

The goal is to have these data reviewed in time to make an informed decision by ASH.

For younger AML patients, SG3 suggested an upper age limit of 65 years based on the recently published HOVON study supporting the use of higher doses of anthracyclines in this patient population.

6. High risk AML

As discussed above, SWOG is planning a study for cytogenetically high risk patients. The objective of the study is to determine the feasibility of allo-HSCT for high risk patients. The NMDP will provide funding for the HLA typing of all patients at diagnosis. The goal would be to perform either a matched sibling, matched unrelated donor or unrelated cord blood donor for these patients within 4 months of diagnosis. The second objective would be to investigate an induction question – perhaps testing the use of front-line hypomethylating agents. If it is deemed unfeasible to identify this group of patients prior to the initiation of treatment, this group will be combined with the intermediate group patients.

Participants

Fred Appelbaum, M.D.
Fred Hutchinson Cancer Research Center

Steven Gore, M.D.
Sidney Kimmel Cancer Center

Deborah Banker, Ph.D.
The Leukemia & Lymphoma Society

Vincent Ho, M.D.
Dana-Farber Cancer Institute

Clara Bloomfield, M.D.
OSU Comprehensive Cancer Center

Mary Horowitz, M.D., M.S.
Medical College of Wisconsin

Marcos de Lima, M.D.
MD Anderson Cancer Center

Jean-Pierre Issa, M.D.
MD Anderson Cancer Center

Harry Erba, M.D., Ph.D.
University of Michigan

Deborah Jaffe, Ph.D.
NCI Coordinating Center for Clinical Trials

Elihu Estey, M.D.
Fred Hutchinson Cancer Research Center

LeeAnn Jensen, Ph.D.
NCI Coordinating Center for Clinical Trials

Boris Freidlin, Ph.D.
NCI Biometric Research

Heather Johnson
The EMMES Corporation

Sergio Giralto, M.D.
Memorial Sloan-Kettering Cancer Center

Ken Kopecky, Ph.D.
Fred Hutchinson Cancer Research Center

Richard Larson, M.D.
University of Chicago Medical Center

Richard Little, M.D.
NCI Cancer Therapy Evaluation Program

Brent Logan, Ph.D.
Medical College of Wisconsin

Guido Marcucci, M.D.
OSU Comprehensive Cancer Center

Ari Melnick, M.D.
Weill Cornell Medical College

Elisabeth Paietta, Ph.D.
Montefiore Medical Center

Jerry Radich, M.D. (Chair)
Fred Hutchinson Cancer Research Center

David Rizzieri, M.D.
Duke Comprehensive Cancer Center

Wendy Stock, M.D.
University of Chicago Medical Center

Richard Stone, M.D.
Dana-Farber Cancer Institute

Martin Tallman, M.D.
Memorial Sloan-Kettering Cancer Center

Peter Thall, Ph.D.
MD Anderson Cancer Center

Geoffrey Uy, M.D.
Washington University School of Medicine

Daniel Weisdorf, M.D.
Masonic Cancer Center

Roy Wu, Ph.D.
NCI Cancer Therapy Evaluation Program