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Fred Hutchinson Cancer Research Center
University of Washington
Seattle Cancer Care Alliance

Decitabine plus cytarabine for Induction of Remission in Newly Diagnosed Elderly Acute Myeloid Leukemia (AML) and Advanced Myelodysplastic Syndrome (MDS)

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1. Objectives

a.) Examine whether a combination of decitabine given for 10 days (days 1-10), rather than the usual 5 days, plus "standard dose ara-C (100 mg/m2 daily days 1-7) might improve 6-month survival probability from the historical 65% to 80% in patients age ≥ 60 with newly diagnosed AML

b.) Test whether this combination might maintain CR rate at our historic 45% in these patients

c.) Study factors that lead physicians to escalate or maintain ara-C doses in those patients who have had an "intermediate response" short of CR to the first 2 cycles of the combination

d.) While maintaining awareness of confounding covariates, examine the effect of such dose escalation on CR rate

2. Rationale

It is generally recognized that most patients age ≥ 60 with newly-diagnosed AML live less than 9-12 months with therapies such as 3 days of daunorubicin (or idarubicin) and 7 of ara-C ("3+7"), low-dose ara-C (LDAC) and, more recently, azacitdine or decitabine (1,2). The principal cause of death is not treatment-related mortality, rates of which appear to be declining sharply even after 3+7 (3). Rather failure is generally due to "resistance", i.e. failure to enter CR despite living long enough to do so or relapse from CR (4, 5). Principal covariates associated with resistance are cytogenetics (1) (for failure to enter CR), and, for relapse, cytogenetics, slow count recovery(6), molecular markers (aberrations in NPM, CEBPA, ASXL, DNMT3a) (7),type of response (CR vs. CRp or CRi) (8), and minimal residual disease at CR (9).

Given their poor predicted outcome with standard therapy, older patients are typically candidates for "clinical trials" (1). However a search of the NCI website clinicaltrials.gov indicates > 50 trials for older patients with newly-diagnosed AML. This can only indicate that pre-clinical rationales are insufficient to indicate which trial is best. The failure of most new agents to substantially improve outcome despite their seemingly compelling rationales lends further support to this supposition. Thus empiricism still rules development of therapy for AML. As a corollary, there is currently an emphasis on trials that enroll a relatively small number of patients, allowing more drugs to be tested (10, 11).

Our most recent effort in these patients involved tosedostat (an aminopeptidase inhibitor) combined with either ara-C or decitabine, as decided by randomization (protocol 2566). However a case of myocarditis in a patient given single agent tosedostat at another hospital prompted the FDA to interdict use of tosedostat in all studies. Nonetheless, although formal stopping criteria had not been met, it appeared unlikely that either arm of

our study would lead to a major improvement in survival (OS) or CR, although both arms had relatively little toxicity, allowing patients to spend the majority of their time as outpatients. Given that we have placed 3 patients on the tosedostat + decitabine or ara-C monthly for 12 months, that the length of the FDA hold is uncertain, and that the likelihood of major success with these combinations seemed small we have decided we need a replacement study.

While recognizing that there are many candidates for such a study, we have chosen a combination of decitabine and cytarabine. Reasons are as follows:

a.) Data suggesting 10 days of decitabine produces higher response rates than the usual 5 days (12,13).

b.) Decitabine followed by standard chemotherapy 7+3 appeared to be promising in a published phase I study (14). The rationale for decitabine in older patients is that there is abnormal DNA methylation in AML and hypomethylation agents have had efficacy in myelodysplastic syndrome, and to a lesser extent, AML. The theory is that hypomethylating agents may act by "priming" cells to susceptibility to subsequent chemotherapy. Toward the goal of studying this principle, our center currently has an ongoing trial of decitabine followed by MEC (mitoxantrone/etoposide/cytarabine) chemotherapy for relapsed patients (protocol 2652) (NCT01729845).

c.) Although ara-C has yet to be combined with 10 days of decitabine, the absence of toxicity with tosedostat + much higher doses of ara-C than proposed here (1 g/m2 vs. 0.1 g/m2) suggests excess toxicity will not be an issue given that the patients to be treated are very similar to those treated in the tosedostat trial; in any event stopping rules are in place for short survival.

d.) Two studies were presented in abstract form describing combinations of concurrent decitabine and cytarabine administration in patients. One pilot study combined decitabine 20 mg/m^2/day X 5 days and cytarabine 20 mg/m^2/day X 5 days with G-CSF priming in patients with MDS or AML (NCT00740181) (15). Grade 3 and 4 toxicities included mucositis and pulmonary infiltrates/infection. One of 5 patients achieved CR, two had progressive disease, and 2 were not evaluable. The other study combined ara-C and decitabine at higher doses than proposed here (150 mg/m^2/dose for ara-C and 25-30 mg/m^2/dose for decitabine) for 7 + 4 days (followed by SCT) with a higher CR rate and without increase in either severe infection rate or earlymortality over decitabine alone in MDS (NCT01674985) (16). There is a 3rd study listed on clinicaltrials.gov entitled "Phase II Study of Decitabine and Cytarabine for Older Patients with Newly Diagnosed Acute Myelogenous Leukemia (AML) (NCT01829503) that is open for enrollment.

e.) There was a preclinical study in xenograft mice, where different schedules of decitabine and cytarabine were administered either concurrent or sequential, with no difference observed in the reduction of leukemia burden, although there were differences in methylation (17).

f.) The absence of pharmaceutical company sponsorship will permit flexibility, thus allowing us to examine how physicians use data to decide on dose escalation. In particular, after receipt of 2 courses of therapy patients will be classified as being

in CR (<5% marrow blasts by morphology, neutrophil count > 1,000, platelet count > 100,000) or not. Patients not in CR will be further classified as having (a) <5% marrow blasts by morphology (but with counts not meeting the above criteria for CR), (b) ≥ 20% marrow blasts by morphology, or (c) 5-19% marrow blasts by morphology. Patients in (a) will receive a 3rd cycle at the same doses and patients in (b) will receive an escalated dose of ara-C (1g/m2 daily days 1-5, as in the ara-C arm of the tosedostat study). For patients in group (c) physicians will decide whether to keep the ara-C dose at 0.1g/m2 daily days 1-7 or to escalate it to the 1g/m2 daily X 5 dose noted in (b) above. We will formally elicit the criteria used to arrive at this decision. These might include marrow cellularity, decrease in blasts or cellularity (or their product) compared to pre-treatment, toxicity (although dose escalation will not be allowed if grade ≥ 3 non-hematopoietic toxicity occurred on the first 2 courses), patient age or wishes etc. It is not apparent that the decision-making process for dose escalation has been investigated before. That this is a topic of interest however seems clear from our observations that while generally the higher the blast count the more likely that physicians are to begin a 2nd course within 1 week of a day 14 marrow there is considerable overlap with some patients with high marrow blast counts not receiving a 2nd course and vice versa and with the reasons for these decisions quite opaque (18).

g.) In turn the schema outlined in 3 will permit us to compare outcomes in patients in the intermediate (5-19% blast) group according to whether they received the same or an escalated dose on course 3. Of course the effect of a dose increase would likely be confounded by the effect of reasons the patient did or did not receive an escalated dose. However we will able to examine outcome on course 3 according to the reasons for giving/not giving an escalated dose.

3. Patient Eligibility

a.) Newly-diagnosed AML by WHO criteria (≥ 20% myeloid blasts by morphology in either blood or marrow)

b.) High-risk MDS or MPN including CMML2 as defined by 10-19 % myeloid blasts in either blood or marrow

c.) Age ≥ 60

d.) Patients may have received azacitidine, decitabine, or lenalidomide but no "cytotoxic therapy" such as ara-C or anthracyclines. Data suggest that failure to respond to azacitidine reduces probability of response to 3+7(19). Hence in the interest of having a relatively homogeneous population, while patients who have received and failed azacitidine or decitabine will be eligible for this study, they will be analyzed separately from patients who have not received these drugs.

e.) Treatment related mortality (TRM) score < 22.9 (18). Patients with TRM scores > 13.1, in whom the risk of death within 28 days of beginning induction therapy has averaged 41%, will preferentially be placed on protocol 2642.

f.) Provision of written informed consent

g.) Note, unlike pharmaceutical company sponsored protocols eligibility is not conditioned on bilirubin, creatinine, or absence of other malignancy within the past 2-3 years. The TRM score incorporates creatinine and thus a high creatinine

can in principle be offset by favorable values for the other covariates in the TRM score (20). Bilirubin was not a covariate in the TRM. Furthermore, in the doses we are using, dose adjustment of decitabine or ara-C is not indicated in the presence of renal or hepatic abnormalities. Our broad eligibility criteria may increase the likelihood that our results will be generalizable. The inability to reproduce results of early phase AML studies has been a problem in the past (21).

4. Pre-treatment Evaluation

The following is a recommendation and will be collected from standard of care evaluations; missing items will not be considered a protocol deviation.

a.) CBC, differential, platelet count
b.) Chemistry to include bilirubin, ALT, AST, albumin, BUN, creatinine, electrolytes including calcium and magnesium
c.) If not done within the previous 30 days bone marrow for morphology, flow, cytogenetics, FISH, and, with insurance approval, ONCOPLEX

5. Treatment Plan

The following is a recommendation and will be collected from standard of care evaluations; variations to the schedule will be done with physician discretion and will not be considered a protocol deviation.

a.) Decitabine 20 mg/m2 daily IV days 1 through 10
b.) Ara-C 100 mg/m2 once daily by IV bolus days 1 through 7
c.) Patients will receive 2 such courses given 28-35 days apart regardless of blood counts.
d.) On course 1 hydroxyurea will be given if the blast count (WBC X % blasts) either remains > 50,000 for 3 days after beginning decitabine+ ara-C or reaches this level after therapy is begun. Patients will be removed from study if hydroxyurea is still required more than 3 weeks after therapy is begun
e.) Bone marrow will be examined 4-5 weeks after initiation of course 2, with decisions based on the result of this marrow and on assessment of non-hematologic toxicity on courses 1 and 2.
f.) Patients will be re-evaluated after any 3rd course

Marrow response after course 2	Non hematologic toxicity	Plan
< 5% blasts (flow)	< grade 3	Course3 at same doses (dec 20 mg/m2 days 1-10, ara-C 100 mg/m2 days 1-7)
>19% blasts (flow)	< grade 3	Course 3 at same dose decitabine, but ara-C at 1 g/m2 daily X5 (days 1-5)

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5-19% blasts (flow)	<grade3	Doctor decides between the 2 ara-C doses; reasons for decision elicited

<5% blasts (flow)	>grade 2	Course 3 at same doses as courses 1 and 2, but duration shortened to decitabine days 1-8 and ara-C days 1-5.
> 4% blasts (flow)	>grade2	Off study

Response after course 3	Non hematologic toxicity	Plan
CR, CRp, CRi	< grade 3 >grade 2	1-2 more courses at same dose as course 3 1-2 more courses at 20-50 % dose decreases
None of above	N/A	Off study

CR = < 5% marrow blasts (by morphology), ANC > 1000, platelet count > 100,000
CRp = as for CR but with platelet count < 100,000
CRi = <5% marrow blasts by morphology and either (a) marrow cellularity ≥15 %, (b) at least 200 cells counted , or (c) ANC 500-1,000

6.) Post-treatment Testing

The following is a recommendation and will be collected form standard of care evaluations; missing items will not be considered a protocol deviation.

a.) CBC, differential, platelets at least twice weekly
b.) Electrolytes, BUN, creatinine at least weekly
c.) Bone marrow exam after 2 cycles of therapy, as described above
d.) If patient has 5-19% blasts by flow note reasons for decision to keep ara-C dose as on courses 1-2 or to increase it (see from below)

7.) Criteria For Removal From Study

a.) Requirement for hydroxyurea to keep WBC < 50,000 more than 3 weeks after beginning treatment (see E4. above)
b.) > grade 2 non-hematologic toxicity and > 4% blasts (by flow) after course 2
c.) No CR, CRp, CRi after course 3
d.) Physician's or patient's decision

If a subject prefers to be treated by a local provider after enrolling in this study, that will be considered end-of-treatment per this protocol and long-term, post-treatment follow-up will begin. This follow-up will be obtained for all subjects up to 6 months after the last dose of study medication. Long-term follow-up information will be gathered via telephone or e-mail with the subject's referring physician offices. This data will be collected in the source documents (e.g., subject medical record) and transcribed into the appropriate CRF.

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8). Statistical Considerations

a.) **Primary objectives**

The protocol's primary objective is to evaluate whether it is plausible (as defined by posterior probabilities, described below in section c) that the combination of decitabine + ara-C administered as in section 5 will increase the proportion of patients alive at 6 months after enrollment on the protocol (OS6) while not decreasing the proportion that achieve CR compared to historical rates.

b.) **Historical data for OS6 and CR**

Historical data for OS 6 are derived from a completed SWOG trial of azacitidine + gemtuzumab ozogamicin in patients whose eligibility requirements were similar to those here. In that study of 79 patients, 6 month overall survival (OS6) was 65% (M. Othus, personal communication). Historical data for CR rate are derived from our recent closed tosedostat study (FHCRC protocol 2566) in which 43% of 33 patients achieved CR. OS6 data are not yet mature enough from this study; hence our use of data from the SWOG study.

c.) **Study design**

The study is powered for a 15% improvement in OS6, from 65% (null hypothesis, based on historical data) to 80% (alternative hypothesis). In addition, we want to maintain a high probability that the CR rate is not decreased below the historical rate of 45%.

Making the design adaptive is difficult given the accrual rate and the 6 months needed to observe survival. A relatively small cohort size (for example 3) would make the study logistically impossible while a relatively large cohort size (for example 20) might make the trial unsafe. As a balance, we will evaluate stopping rules based on the first 10 and first 20 patients. Accrual will be held while the first 10 and 20 patients are being collected. The maximum sample size is 30.

Stopping Rules- accrual would stop should either of the rules below be met

i) OS6 The trial will stop if the number of patients alive at 6 months is $\leq 5/10$ or $\leq 12/20$.

ii) CR – The trial will stop accrual if the number of patients who achieve CR is $\leq 1/10$ or 4/20.

If the study completes full accrual, we will declare this regimen not of further interest if either the OS6 rate is $\leq 19/30$ or if $\leq 7/30$ achieve CR.

The maximum sample size will be 30. We see approximately 90 patients older than 60 with newly-diagnosed AML annually. This trial will replace protocol 2566. While there will be competing trials, 2566 accrued 30 patients in 1 year and we anticipate that this study will have similar accrual. Enrollment would begin once IRB approval is secured. We believe it important to monitor both survival and CR. Although historically it has been thought that there was a tight link between survival and CR, more recent evidence does not support this assumption. In particular, studies by the MRC/NCRI group in the UK indicate that CR rates can increase without effect on overall survival (OS), with OS the most important outcome for the patient. Hence we do not require an **improvement** in CR rate. However, data from SWOG and MD Anderson indicate that with therapy similar to what we are testing in this protocol, the great majority of long-term survivors (alive for > 2 years after starting therapy) achieve CR. Given this background, we are unwilling to accept a **decline** in CR rate.

d) **Performance of the design under various clinical scenarios**

Assuming independence between OS6 and CR, we simulated the operating characteristics of the design and summarize results in the table below. In reality, OS6 and CR may not be independent, but we believe this is a conservative assumption for evaluating properties of the design.

The design's operating characteristics in are shown below:

Scenario	Probability stop after 10 patients	Probability stop after 20 patients	Probability stop early	Probability positive trial
Alternative, no decrease in CR OS6 = 80% CR = 45%	6%	3%	9%	90%
Alternative with improved CR OS6 = 80% CR= 60%	4%	2%	5%	94%
Null, decrease in CR OS6 = 65% CR = 25%	42%	28%	71%	17%
Null, no decrease in CR OS6 = 65%	27%	20%	47%	41%

CR = 45%				
Too toxic, worse OS and no decrease in CR OS6 = 50% CR = 45%	62%	26%	89%	4%

If OS6 is improved and the CR rate is the same as the historical rate, this design has 90% power. If both OS6 and the CR rates are improved, this design has 94% power. If OS6 is not improved and the CR rate is worse than the historical rate, the probability of incorrectly concluding the trial is positive and the regimen warrants further study is 17%. If OS6 is not improved and the CR rate is the same as the historical rate, the probability of incorrectly concluding the trial is positive and the regimen warrants further study is 41%. If the OS6 is worse than the historical rate and the CR rate is the same as the historical rate, the probability trial incorrectly has a positive result is 4% and the probability of stopping accrual early is 89%.

Regulatory and Reporting Requirements

Adverse Event Reporting

Many, if not most of the patients to be treated here, would presumably receive anthracycline + ara-C, for example as in "3+7". Expectations for grade 3-4 organ toxicity with idarubicin + ara-C have been reported (see Table 1 below).(22) We will use these as a control for our 10-day decitabine + 10-day ara-C regimen.

Grade ≥3 adverse events other than hematologic toxicities will be recorded, graded, and reported as appropriate. AEs will be collected for the duration that the patients remain on protocol. AEs that do not meet the requirement for expedited reporting will be reported to the IRB as part of the annual renewal of the protocol. Myelosuppression and associated complications are expected events during leukemia therapy; therefore, myelosuppression and associated simple complications such as fever, infections, bleeding, and related hospitalizations will not be reported as individual AEs but will be summarized in the annual report to the IRB.

Toxicities will be graded using the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.03. Information on these criteria can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

Grade 3-4 toxicity expectations

Table 1 Percent Grade 3-4 toxicity expectations with Idarubicin + Cytarabine (21)

Toxicity	***Percent of Patients Affected (%)***
Anemia	67
Thrombocytopenia	70
Neutropenia	94
Fever of Unknown Origin	31
Documented Infection	61
Hospitalization	92
Renal	2
Hepatic	22
Cardiac	4
Dialysis	6
Intensive Care Unit Admission	27
Mechanical Ventilation	14
Hyponatremia	14
Hypokalemia	38

Data and Safety Monitoring Plan

Ongoing trial oversight is carried out by the Principal Investigator and the research staff. They will meet frequently to review recently acquired data and adverse events. The data recorded within the research charts and protocol database will be compared with the data that is available from the medical record and/or clinical histories. All investigators on the protocol have received formal training in the ethical conduct of human research. The Principal Investigator will receive monitoring support as described below. Institutional support of trial monitoring is provided in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP. In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC), and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to asses continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study. The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

Data Management/Confidentiality

The investigator will ensure that data collected conform to all established guidelines. Each patient is assigned a unique patient number to assure confidentiality. Patients will not be referred to by this number, by name, or by any other identifier in any publication or external presentation. The licensed medical records department, affiliated with the

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institution where the patient received medical care, maintains all original inpatient and outpatient chart documents. Patient research files are scanned and stored in a secure database. Access is restricted to personnel authorized by the Division of Clinical Research.

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APPENDIX: Treatment-Related Mortality (TRM) Score

Calculation of Simplified Treatment-Related Mortality (TRM) Score

Includes covariates: performance status (PS), age, platelet count, albumin, secondary AML, white blood cell count (WBC), peripheral blood blast percentage, and creatinine.

Score = $100/(1+e^{(-x)})$, with x = -4.08 + 0.89*PS + 0.03*age – 0.008*platelet count – 0.48*albumin + 0.47*(have secondary AML) + 0.007*WBC-0.007*(peripheral blood blast percentage) + 0.34*creatinine

Probability of TRM Above and Below Various Simplified TRM Score Cut-offs

TRM Score Interval	Patients below/ within/above TRM Score Interval (%)	TRM Probability if below TRM Score Interval (%)	TRM Probability if within TRM Score Interval (%)	TRM Probability if above TRM Score Interval (%)
0 – 1.9	0/20/80	-	1	12
1.91 – 3.9	20/20/60	1	2	16
3.91 – 6.9	40/20/40	1	7	20
6.91 – 9.2	60/10/30	3	7	24
9.21 – 13.1	70/10/20	4	12	31
13.11 – 22.8	80/10/10	5	20	41
22.81 – 100	90/10/0	6	41	-

From: Walter RB, Othus M, Borthakur G, Ravandi F, Cortes JE, Pierce SA, APpelbaum FR, Kantarjian HM< Estey EH. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk socres: a novel paradigm for treatment assignment. *J Clin Oncol.* 2011;29(33):4417-4424.