Cover Page

Outpatient Induction Chemotherapy in Treating Patients With Acute Myeloid Leukemia or Advanced Myelodysplastic Syndrome

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Study Protocol with Statistical Analysis Plan

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Title: Feasibility of Outpatient Induction Chemotherapy for Adult Patients with Acute Myeloid Leukemia or Advanced Myelodysplastic Syndrome

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Study Overview
This study will be a pilot trial for the feasibility of outpatient induction chemotherapy for diagnosed acute myeloid leukemia (AML) or advanced myelodysplastic syndrome (MDS) for those ages ≥18 years of age.

1. Objectives
Assess the feasibility of outpatient induction therapy for acute myeloid leukemia (AML) or advanced (MDS) by examining whether:
1.) >50% of patients treated as outpatients can complete chemotherapy without being admitted to hospital.
2.) <5% of patients die within 14 days of beginning outpatient chemotherapy.

2. Background and Study Rationale
Medical practice over the past 20 years has tried to curb health care costs by increasing outpatient treatment and care for common medical procedures in patients with mainstream conditions. An example of this would be the establishing of "day surgical procedure units". Little focus has been on the "outlier healthcare consumer", those patients that make up a fraction of the population, but disproportionately consume resources [1]. Those patients can drive up healthcare cost with a rare, life threatening disease.

Little research has been done to look at the health care economics of acute myeloid leukemia (AML). Commonly today, acute myeloid leukemia (AML) is treated with induction and consolidation chemotherapy in an inpatient hospital setting. Feasibility of outpatient consolidation chemotherapy has been examined [2], but induction chemotherapy to induce remission in an outpatient setting has not been done.

Research has shown that it is not the LOS (length of stay) fueling the cost of hospital admissions, but front loaded costs; the cost that occur during the "early stage of admission when resource consumption is most intense" [3]. We have already shown that patients can be safely early discharged once induction therapy is complete. This can be done without an increase in "treatment-related mortality" (TRM) provided the patients are doing well at discharge, live in proximity to UW/SCCA, have an outpatient caregiver, and are committed to return for outpatient follow-up [4]. While we have not quantified the effects of early discharge on cost or quality-of-life, it seems likely that these effects are favorable. We have also shown that, regardless of neutrophil count, patients can be discharged from the hospital after successful treatment of "neutropenic fever" without increase in mortality or admission to the ICU [5]. We have addressed patient safety and early discharge and now want to look one step further. We want to go beyond cost containment of early stage hospital admission and take a look at the feasibility of moving induction chemotherapy for AML patients to an outpatient treatment setting.

This protocol is an extension of our early discharge experience. Specifically it will examine the feasibility of administering to selected outpatients an induction chemotherapy regimen that would usually be administered to inpatients, as will still be the case for most patients. Although administration of the regimen requires only 4-7 days, there could be great cost savings per patient multiplied by many patients and the same seems highly plausible as applied to a patients' quality-of-life.

We will use 2 criteria to assess "feasibility". The first is whether an excessively high proportion of patients need to be admitted to hospital during administration of chemotherapy because of complications such as vomiting, infection etc. The need to admit a high proportion of patients would at the very least increase work required by providers. Our unpublished experience with outpatient induction is that 15% of a series of 13 patients with relapse were admitted prior to completion of therapy. We propose these data as our historical control, but any specific number will be arbitrary. Certainly the relevance and utility of outpatient therapy would be in doubt were the proportion much above 50%, so we have chosen this number. The 2nd and more important criterion is TRM attributable to administration of typically inpatient chemotherapy to outpatients. "Attributable" is also somewhat nebulous but TRM within 14 days of beginning chemotherapy seems reasonable. Current TRM rates for patients receiving chemotherapy as inpatients are <5% [6]. Hence it would require many patients given chemotherapy as outpatients to be confident that the outpatient TRM rate is similarly low. Such hypothesis testing is not our intent. We merely intend to enter a maximum of 25 patients stopping early should it become likely that our 2 criteria for feasibility will not be met. Our statistical section (see section 7.0) provides the rationale supporting our stopping rules, briefly stated that the study if 7 of 10 patients are hospitalized, or if 3 patients die.

3. Eligibility

Our eligibility requirements have been selected to minimize the chance of TRM and, probably, the need for admission to hospital during the days of chemotherapy administration.

3.1. Inclusion Criteria

1.) Signed Written Informed Consent a.)

The signed informed consent.

b.) The benefits / risks of the induction chemotherapy regimen will be reviewed, and a second consent may be necessary if the regimen will be administered according to a separate protocol.

2.) AML (APL excepted) or high-risk MDS (10-19% blasts in marrow by morphology or flow cytometry or blood).

3.) Meet the eligibility criteria for the selected inpatient protocol that they will receive as an outpatient.

To receive the treatment as an outpatient they must:

a.) Treatment-related mortality (TRM) score (ref) <9.21 corresponding to a TRM rate of 3% when chemotherapy of similar intensity as proposed here is administered to inpatients.

b.) Ages ≥18 years of age

c.) Blast count ≤ 10,000

d.) Fibrinogen > 200

e.) Afebrile with clear chest imaging and no signs of active viral, bacterial, fungal infection unless determined to be, at the discretion of the investigator, not clinically significant in the context of this study.

f.) Adequate cardiac function as demonstrated by LVEF of 45% or greater, by MUGA or echocardiogram. No ongoing cardiac issues such as uncontrolled arrhythmias or unstable angina or congestive heart failure.

g.) Patient must have an outpatient caregiver available.

h.) Patient must live within 30 minutes of the treating physician's office during outpatient treatment.
i.) Patient must be willing to return to the treating physician's office for outpatient follow-up once outpatient treatment is completed.
j.) Logistical requirements:
1. Space available in infusion room.
2. Outpatient infusion pump available if continuous infusion required.
3. Case discussed with infusion room nursing staff.

Note: age and white blood count are already components of the TRM score, but are included here for safety purposes

4. Treatment Plan
1.) Patients will be treated according to the operative inpatient induction chemotherapy regimen for which they will also provide informed consent.
2.) Treatment must begin on Monday, Tuesday, Wednesday, Thursday, or Friday after discussion with the 5th floor Infusion Room staff.
3.) If treatment includes ara-C at a daily dose of ≥ 1g/m2 patients will receive steroid eye drops and prednisone 100 mg daily or its IV equivalent.
4.) Patients must be followed daily during administration of chemotherapy. Evaluation will be until completion of chemotherapy.

Evaluation will include:
a.) Daily weight
b.) Daily CBC and platelet count (ordered as "S2D"), chemistries (ordered as S9), and uric acid, LDH, Mg, phosphate
5.) Change in weight of +/- 1.5 kg , hematocrit < 24, platelet count < 10, sodium < 130 or > 145, potassium < 3.2 or > 4.8, fever, or development of fever will mandate a call to the patient's mid level provider or attending physician.
6.) Patient will receive prophylactic oral levofloxacin, fluconazole and acyclovir.

4.1. Indications for Hospitalization While On Study
1.) Fever (≥101.0 F)
2.) Infection requiring IV antibiotics.
3.) Shortness of breath not promptly responsive to red cell transfusion and/or associated with new infiltrate on chest X-ray.
4.) Bleeding not easily halted by platelet transfusion.
5.) Any grade 3-4 toxicity (NCI Common Toxicity Criteria) other than myelosuppression, nausea/vomiting controlled by antiemetics, asymptomatic metabolic abnormalities, or skin rash, diarrhea of volume unable to be compensated by oral and IV fluids, pain not controlled by analgesics.

4.2. Mechanism For Care "After Hours" Patients will proceed directly to the local hospital.

5. Study Procedures

All laboratory and radiographic testing mentioned in this protocol will be done as a part of standard of care for patients undergoing induction chemotherapy for AML or advanced MDS.

5.1. Screening Evaluations

1.) Complete physical examination.
2.) Medical history: Detailed documentation of disease and treatment history with outcomes in standard medical record.
3.) ECOG performance status.
4.) Concurrent medical conditions.
5.) Hematology: CBC with differential and platelet count and peripheral blood smear.
6.) Serum chemistries: Electrolytes (sodium, potassium, chloride, and bicarbonate), blood urea nitrogen (BUN), creatinine, glucose, and liver function tests (aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, DIC panel (includes fibrinogen)
7.) Initial standard of care diagnostic bone marrow reports, including hematopathology, cytogenetics/FISH, and flow cytometry.
8.) Chest imaging within 7 days of consent.
9.) MUGA or echocardiogram within 28 days of consent.
10.) Informed consent.

5.2. On Study Evaluations

1.) Daily weights during induction chemotherapy administration.
2.) Provider (physician or advanced practice provider) visit including elicitation and documentation of adverse events as well as symptom-focused physical exam on days 1, 3, and 5 of induction chemotherapy.
3.) Hematology: CBC with differential and platelet count daily during induction chemotherapy then as standard of care; DIC panel days 1 and 2 of induction chemotherapy and then as needed.
4.) Serum chemistries: Electrolytes (sodium, potassium, chloride, and bicarbonate), BUN, creatinine, glucose, and liver function tests (AST, ALT, ALP, total bilirubin, LDH) and tumor lysis labs (Ca, Mag, phos, uric acid, LDH) daily during induction chemotherapy.
5.) Hospitalization and reason for hospitalization during induction will be monitored.
6.) Mortality during the first 14 days will be monitored.

6. Regulatory and Reporting Requirements

6.1. Adverse Event Monitoring and Reporting

The principal investigator is responsible for monitoring the safety of patients who enroll in the study. This protocol will not dictate the choice of chemotherapy regimens. The sole research focus of this study is the feasibility of using an outpatient setting for administration of chemotherapy for AML or advanced MDS. For purposes of this study, only the following AEs will be recorded:
1.) Reasons for hospitalization during planned outpatient administration of chemotherapy.
2.) Causes of any deaths that occur within 14 days of start of outpatient chemotherapy (expedited reports).

6.2. Data and Safety Monitoring Plan

Ongoing trial oversight is carried out by the principal investigator, Dr. Becker and the primary research nurse. These individuals will meet regularly to review recently acquired data, and adverse events. Institutional support of trial monitoring is provided in accordance with the FHCRC Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, the FHCRC research Trials Office coordinates monitoring of data accuracy and compliance 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. In addition, protocols are reviewed at least annually by the Protocol and Data Monitoring Committee (PDMC) and the Institutional Review Board (IRB). The PDMC reviews accrual, adverse events, stopping criteria, and adherence to the data and safety monitoring plan. The PHCRC IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of both committees is necessary to continue the study.

7. Statistical Considerations

A maximum of 25 patients will be entered. Stopping earlier would happen under 2 circumstances:

1.) Excess probability that patients have to be admitted to hospital during the 4-7 days of outpatient chemotherapy.
2.) Excess probability that patients die during the 14 days after beginning outpatient treatment.

For both 1 and 2 the case for stopping will be evaluated using the program "predictive probabilities" freely available from the Statistics Department at MD Anderson Cancer Center (https://biostatistics.mdanderson.org/softwaredownload/). In particular stopping will occur based on the Bayesian inequality probability $Pr[\pi_i > \pi_j] > 0.90$ where Pr= probability, π_I is the posterior probability for rate of admission to the hospital with current management and π_j the probability of rate of admission with former management. We will assume that π is distributed $\beta(a,b]$ where "a" is the number of successes (no admission) and "b" the number of failures (admission) with management approach i (current) or management approach j (previous). We will assume a prior of $\beta[25,25]$ for the previous approach corresponding to a 50% need for hospital admission with prior outpatient management in 50 patients and a prior of $\beta(5,1)$ with the current approach corresponding to our data indicating that 5 patients have been treated as outpatients without need for inpatient admission while 1 has been admitted. As patients up to a maximum of 25 are entered on the current approach its prior will be updated and compared to the $\beta[25,25]$ distribution using the inequality probability 0.90 noted above. With this configuration here are the predictive probabilities that the current approach (called A) is truly better than the previous approach $\beta[25,25]$ denoted B given various numbers of successes (no admission during days 4-7) and failures (admission).

Successes (No admission)	Failures (Admission)	Predictive Probability A (current) better than B (Previous)
1	0	0.95
0	1	0.74
0	2	0.51
0	3	0.31
0	4	0.16
0	5	0.07
1	6	0.05
1	5	0.12
2	6	0.09
3	6	0.15
3	7	0.06

We would stop accrual should the predictive probability be < 0.10, for example in the 3 success / 7 failure scenario noted above. In this case 7 patients of 10 patients would have been admitted contrasted with the maximum acceptable rate of 4 admitted / 6 not.

For the death within 14 days endpoint our prior for the current (inpatient) approach will be $\beta[49, 1]$ corresponding to a 2% (1/50) death rate and will be $\beta[5, 0]$ for the outpatient approach, corresponding to 0 deaths in the 5 patients who would have met eligibility criteria for the proposed protocol. These data will be updated as patients (up to the maximum of 25) are enrolled and the resultant beta distribution compared to the $\beta[49, 1]$ distribution noted above, using the inequality probability 0.9 noted in the section on admission to the hospital. With this configuration here are the predictive probabilities that the current approach (called A) is truly worse than the previous approach $\beta[49, 1]$ denoted B given various numbers of successes (no deaths days 1- 14) and failures (deaths days 1- 14).

Success (No death within 14 days)	Failure (death within 14 days)	Predictive Probability A (current) worse than B (Previous)
1	0	0.05
0	1	0.28
0	2	0.97
1	2	0.95
4	2	0.90
5	2	0.88
21	3	0.99

We would stop accrual should the predictive probability be > 0.90, for example in cases where there are 2 failures and < 5 successes, or in any case where there are 3 deaths.

8. References

1. Moroney SD. Understanding Health Care Cost Drivers. National Institute of Health Policy. 2003.
2. Saini L,Minden MD, Schuh AC, Yee KWL, Schimmer AD, Gupta V, Atenafu EG, Murray C, Nixon S, Brandwein JM. Feasibility of outpatient consolidation chemotherapy in older versus younger patients with acute myeloid leukemia. Am J Hematol. 2012 Mar; 87(3):323-6.
3. Taheri PA, Butz DA, Greenfield LJ. Length of Stay Has Minimal Impact on the Cost of Hospital Admission. J Am Coll Surg. 2000; 191:123-130.
4. Walter RB, Othus M, Borthakur G, Ravandi F, Cortes JE, Pierce SA, Appelbaum FR , Kantarjian HA, and Estey EH. Prediction of Early Death After Induction Therapy for Newly Diagnosed Acute Myeloid Leukemia With Pretreatment Risk Scores: A Novel Paradigm for Treatment Assignment. J Clin Oncol. 2011; 29:4417-4423.
5. Walter RB, Lee SJ, Gardner KM, Chai X, Shannon-Dorcy K, Appelbaum FR, Estey EH. Outpatient management following intensive induction chemotherapy for myelodysplastic syndromes and acute myeloid leukemia: a pilot study. Haematologica. 2011 Jun; 96(6):914-7.
6. Othus M, Hagop K, Petersdorf S, Ravandi F, Cortes J, Pierce S, Erba H, Faderl S, Appelbaum F, Estey E. Declining Rates of Treatment-Related Mortality in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) Given "Intensive" Induction Regimens: A Report from the Southwest Oncology Group (SWOG) and MD Anderson Cancer Center (MDA). (presented at the oral session at the ASH Annual Meeting 2012).

9. Appendix A

PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

10. Appendix B

TREATMENT RELATED MORTALITY SCORE

Treatment Related Mortality Score								
Patient I.D.	Age	Performance Status	Platelet Count ($x10^3$/ul)	Albumin (g/dL)	Secondary AML (yes=1,no=0)	WBC Count ($x10^3$/ul)	Blast Peripheral Blood (%)	Creatinine (mg/dL)

* Data collection for calculating the TRM Score