Phase II Study of the Combination of Mitoxantrone, Etoposide and Gemtuzumab Ozogamicin (MEGO) for Patients with Acute Myeloid Leukemia Refractory to Initial Standard Induction Therapy

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Version 5

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1.0 INTRODUCTION

1.1 Study objectives

Primary Objective: To evaluate the response rate and toxicity of the combination of mitoxantrone, etoposide and gemtuzumab ozogamicin as second line therapy in patients with acute myeloid leukemia (AML) who have failed the first induction therapy.

Secondary Objectives: To assess the progression-free survival, overall survival and treatment related mortality in patients with AML treated with the combination of mitoxantrone, etoposide and gemtuzumab ozogamicin.

To explore if age, cytogenetic status, percent of blast in the bone marrow prior to therapy or percent expression of CD33 in the leukemia blasts are predictive of complete remission, overall survival or progression-free survival in patients with AML treated with the combination of mitoxantrone, etoposide and gemtuzumab ozogamicin.

1.2 Background and Rationale

Acute myeloid leukemia (AML) is a disease characterized by a clonal proliferation of myeloid precursors with reduced capacity to differentiate into more mature cellular elements. As a result, there is an accumulation of leukemic forms in the bone marrow, peripheral blood and other tissues, with a marked reduction in red cells, platelets, and neutrophils. The increased production of malignant cells, along with reduction in these mature elements, results in a

variety of systemic symptoms and signs. These include anemia, bleeding and an increased risk of infection. If left untreated, AML can lead to death within weeks[1].

The standard treatment for newly diagnosed AML has not changed appreciably over the last few decades and consists primarily of an anthracycline (e.g. daunorubicin, idarubicin) combined with a nucleoside analogue, cytarabine. The goal of remission induction chemotherapy is the rapid restoration of normal bone marrow function[2]. Obtaining complete remission (CR) varies substantially depending on several factors, most notably age and cytogenetic abnormalities at the time of AML diagnosis. CR rates of 65-80% can be expected in younger patients (variably defined as < 55-60 years). CR rates decrease to 30% to 50% in older patients[3].

There is no agreed standard of care for AML patients that do not respond to initial first line induction therapy. Although remission after second-line therapy may occur, the CR rate is considerably lower. A number of chemotherapy regimens have been used in patients with resistant disease with overall CR rates of 20-40%. These regimens include different combinations and doses of agents that are effective in the treatment of AML such as fludarabine, cytarabine, etoposide, and mitoxantrone[4].

Gemtuzumab ozogamicin (GO) is an antibody drug conjugate consisting of a recombinant humanized antibody to CD33 which is linked to calicheamicin[5]. Calicheamicin is a potent antitumor antibiotic that cleaves double-stranded DNA at specific sequences[6]. Approximately 90% of AML patients have myeloid blast cells expressing the CD33 surface antigen[7]. Monotherapy with GO resulted in CR of 20-25% in adults with CD33 positive AML in first relapse[8]. GO was approved by the United States Food and Drug Administration (FDA) for use in patients age 60 or older with CD33+ AML in first relapse who were not considered candidates for cytotoxic chemotherapy in 2000[9]. However, due to early deaths in a prospective phase 3 randomized study which incorporated GO in the induction phase in one of the arms (SWOG S0106)[10] the manufacturer withdrew the product from the American market in 2010. The SWOG S0106 study used 6 mg/m^2 of GO on day 4 of induction with cytarabine, daunorubicin. The treatment-related mortality (TRM) was 5% on the GO arm vs 1% on the other arm. In 2017, FDA again approved GO for induction therapy in combination with chemotherapy based on a phase 3 prospective randomized, open-label study (ALFA-0701 trial[11]) and as monotherapy for patients unfit for intensive treatment based on the phase 3

randomized EORTC-GIMEMA AML-19 trial[12]. The ALFA-0701 trial randomized 280 patients 50-70 year-old to receive induction with daunorubicin and cytarabine or daunorubicin, cytarabine and GO 3mg/m^2 on days 1,4,7 of induction. It showed that the addition of GO to the induction chemotherapy improved event-free survival. The AML-19 trial randomized 237 patients unfit for induction chemotherapy to receive either best supportive care or GO 6mg/m^2 on day 1 and 3mg/m^2 on day 8. It showed that GO improved the overall survival in patients unfit for intensive treatment when compared to best supportive care with no difference in the adverse events. The NCRI AML17 trial[13] studied further the dose of GO with induction chemotherapy showing that 3mg/m^2 has the same efficacy but better safety profile than 6mg/m^2. The dosing regimen of GO as it is currently approved by the US FDA is 3mg/m^2 (maximum dose 4.5mg) on days 1,4,7 with induction chemotherapy or 6mg/m^2 on day 1 followed by 3mg/m^2 on day 8 if used as monotherapy.

The most important GO-associated hematologic toxicity is myelosuppression (thrombocytopenia, neutropenia). Infusion-related adverse reactions are similar to those of other monoclonal antibodies (fever, chills, cutaneous rash, hypotension, hypertension, dyspnea, nausea, emesis and headache). They are usually transient and respond well to symptomatic therapy[14].

Hepatic veno-occlusive disease or sinusoidal obstructive syndrome (VOD/SOS) is the most frequently reported life-threatening non-hematological adverse event. Overall, among all adult GO- treated AML patients evaluated in the clinical trial setting, SOS occurred at a rate of 3% when GO was administered as monotherapy at the initial FDA approved dose and schedule (for relapsed AML, 9 mg/m^2 on day 1 and 14); 7% when the drug was used in conjunction with other chemotherapeutic agents that are not known to be hepatotoxic; and 28% when GO was combined with thioguanine, a hepatotoxic chemotherapeutic agent. SOS rates were between 15% and 40% if stem cell transplantation was performed within 3 months of GO administration[15]. Another observational study showed an overall 9.1% risk of SOS with GO and 2.7% risk of death from SOS[16]. During the early 2000s when GO was used at higher doses it was observed that patients that received GO <3.5 months before allogeneic stem cell transplantation had much higher incidence of SOS[17], which was no longer observed in the modern era of lower GO fractionated doses[18].

Various clinical trials have evaluated the efficacy of GO as monotherapy in newly-diagnosed AML, refractory/relapsed AML and in combination with chemotherapy for induction. Different dosing schedules of GO were used in these trials. In addition to grade 3/4 neutropenia and thrombocytopenia some patients also develop transaminitis and VOD (Table 1).

Table 1: Clinical trials with gemtuzumab ozogamicin

Trial	***No. of pts***	***State of disease***	***GO Dosing***	***Therapy***	**Results**	***Ref***
EORTC-GIMEMA AML-19	237	New diagnosis, unwilling or unfit for treatment	Induction: 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8. Maintenance: 2mg/m^2 monthly up to 8 doses	Best Supportive Care GO +/-	CR/CRi 27% on the GO arm. OS improvement at 1 year with GO (4.9 vs 3.6 months, p=0.005)	12
LRF AML 14 and NCRI AML 16	495	New diagnosis, unfit for intensive treatment	5 mg (fixed dose) on day 1 of 42-day cycles for a maximum of four cycles	LDAC 20mg BID on days 1-10 of 42-day cycles +/- GO	Improved CR with GO (21% vs 11%, P= .002). No difference in OS. Patients in the GO arm had more nausea and vomiting, required more platelet transfusions and longer duration of antibiotics. No episodes of VOD were reported.	19
MRC AML-15	1113	New diagnosis	3mg/m^2 on the first day of induction.	DA or DAE or FLAG-IDA +/- GO	No difference is OS but improved 5-year OS in patients with favorable cytogenetics. No excess hematologic or liver toxicity on the GO arm	20
ALFA-0701	278	New diagnosis	Induction: 3mg/m^2 on days 1,4,7 Consolidation: 3mg/m^2 on day 1 for up to two cycles	Induction DA +/- GO Consolidation: DA +/- GO	Improved EFS, DFS on the intervention arm but no difference in OS. Prolonged thrombocytopenia and neutropenia on the GO arm.3 cases of VOD were reported on the GO arm.	11,21
NCRI AML16	1115	New diagnosis	Induction: 3 mg/m^2 on day 1	DA +/- GO	Improved OS on the treatment arm and similar TRM	22
SWOG S0106	595	New diagnosis	Induction 6 mg/m^2 on day 4	DA (with D at 60 mg/m2) vs DA (with D at 45mg/m2) plus GO	No difference in OS with increased TRM in the GO arm (6% vs 1%)	10

EORTC-GIMEMA AML-17	472	New diagnosis	Induction: 6mg/m^2 on days 1 and 15	MEC +/- GO	Similar CR rate and OS. Higher TRM with GO (22% vs 18%) mainly driven by patients >70 years old	23
NCRI	788	New diagnosis	Induction: randomization To 3 or 6 mg/m^2	Randomi- zation	No difference in OS. Increased TRM with higher	13
AML17			on day 1	to ADE or DA , both + GO	GO dose.	
HOVON-43	232	Consolidation	6 mg/m^2 every 4 weeks, up to 3 cycles	Observation vs GO	No difference in OS	24

Abbreviations: CR, complete remission; CRi, complete remission with incomplete hematologic recovery; GO, Gemtuzumab Ozogamicin; OS, overall survival; LDAC, low-dose cytarabine; VOD, veno-occlusive disease, DA, daunorubicin + cytarabine, DAE, daunorubicin + cytarabine + etoposide; FLAG-IDA, fludarabine + cytarabine + G-CSF + idarubicin; EFS, event-free survival; DFS, disease-free survival; TRM, treatment-related mortality; MEC, mitoxantrone + etoposide + cytarabine; ADE, cytarabine + daunarubicin + etoposide

Rationale

The combination of mitoxantrone and etoposide is an active regimen in refractory/relapsed AML patients[25]. In a retrospective study, we evaluated the efficacy and toxicity of mitoxantrone and etoposide in AML patients treated at our institution who did not respond to first induction therapy with cytarabine and an anthracycline. A total of thirty-five AML patients were treated with mitoxantrone (10 mg/m^2/d) on days 1-5 and etoposide (100 mg/m^2/d) on days 1-5. Thirteen of thirty-five patients (37%) achieved CR. There were no grade 3/4 hepatic toxicities. The median duration of neutropenia in patients achieving CR was 29 days after reinduction. 14% of patients died from infectious complications.

In order to increase the efficacy of mitoxantrone and etoposide as second line therapy in patients with AML we propose to conduct a phase II clinical trial evaluating the safety and efficacy of the combination of GO, mitoxantrone and etoposide. A similar trial was open in our institution before Pfizer withdrew the drug from the market in 2010[26]. Before the withdrawal 5 patients were treated with a regimen consisted of mitoxantrone 10 mg/m2 administered intravenously on days 1–3, etoposide 100 mg/m2 administered on days 1–5 and on day 6 GO 3 mg/m2. Three of the five patients achieved a CR. There were no treatment-related deaths. All patients developed grade 3–4 neutropenia and thrombocytopenia, with complete responders requiring a median of 19 days (range, 17–34 days) from the completion of

treatment to recover their neutrophils and a median of 24 days (range, 17–34 days) to recover their platelets. One patient developed grade 3 ALT transaminitis that resolved within 24 h and one patient developed a transient ischemic attack. No patient developed clinical signs or symptoms of veno-occlusive disease.

It has been demonstrated that high peripheral CD33-antigen load is an independent adverse prognostic factor in AML patients treated with GO. Data indicate that a high peripheral CD33antigen load consumes a large portion of the GO, which results in reduced GO penetration into the bone marrow [27]. As a consequence, CD33 saturation of AML blast cells present in the bone marrow is incomplete, which may hamper subsequent cell kill. Administration of GO may be more effective after reduction of the leukemic cell burden with conventional chemotherapy. Thus, we plan to administer the GO after the administration of mitoxantrone and etoposide. Furthermore, since enrolled patients in the study will already be treated with combination of cytarabine and an anthracycline (1st regimen) and mitoxantrone and etoposide (2nd regimen) and GO has been associated with neutropenia and thrombocytopenia, we plan to use a single dose of GO 3 mg/m^2 the day after the completion of the 5 days of etoposide and mitoxantrone.

2.0 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Eligibility Criteria

1. Able to understand and have the ability to provide written consent.
2. Age: ≥18 and ≤75 years old.
3. Patients with newly diagnosed AML based on the World Health Organization classification who have persistent disease after their first course treatment with an anthracycline and cytarabine (the diagnosis of persistent disease, which is defined as ≥10% blasts by morphology for this trial or >5% blasts if they have had an increase in blasts from the last bone marrow biopsy, will be based on their assessment after bone marrow aspiration and/or biopsy after initial treatment). The bone marrow aspiration and/or biopsy will be evaluated by the Hematopathology Division of the University of Pittsburgh. In order to prevent any delays in starting therapy for eligible patients, a preliminary evaluation of the bone marrow will be sent by the hematopathologist via e-mail to the investigator.

4. Patients with myelodysplastic syndrome (MDS) based on the World Health Organization classification who have persistent disease after their treatment with an anthracycline and cytarabine (the diagnosis of persistent disease, which is defined as ≥10% blasts by morphology for this trial or >5% blasts if they have had an increase in blasts from the last bone marrow biopsy, will be based on their assessment after bone marrow aspiration and/or biopsy after initial treatment).
5. CD33 expression in ≥ 30% of leukemic blasts on the bone marrow.
6. Eastern Cooperative Oncology Group Performance Status of 0 -2 (see Appendix I).
7. Patients must have the following laboratory values prior to beginning protocol treatment:
    - Calculated creatinine clearance ≥ 30 mL/min (using the Cockcroft-Gault equation CL creatinine = ((140-age) x body mass X 0.85 if female)/72 x creatinine where age is given in years, body mass is given in Kg and creatinine is given in mg/dl).
    - Aspartate aminotransferase (AST) ≤ 2.5 x upper normal limit.
    - Alanine aminotransferase (ALT) ≤ 2.5 x upper normal limit.
    - Total bilirubin ≤ 2 x upper normal limit.

Note: As many eligible patients will be pancytopenic secondary to their disease or prior treatments, hematologic abnormalities will not be used as criteria for entry or exclusion.

8. Left ventricular ejection fraction (LVEF) ≥50 %.
9. Females of child-bearing potential must have a negative pregnancy test during screening and all subjects must agree to use an effective method of contraception. A woman is eligible to enter and participate in the study if she is of:
    a. Non-childbearing potential (*i.e.*, physiologically incapable of becoming pregnant) including any female who has had a hysterectomy or has had a bilateral oophorectomy (ovariectomy).
    b. Childbearing potential, has a negative serum pregnancy test during the screening period and agrees to avoid sexual activity or use contraception from screening through follow-up (method of birth control if the patient is not neutropenic include the use of a diaphragm, intrauterine device, contraceptive sponge and/or usage of male condom with a spermicide from the partner). A man with a female partner of childbearing potential is eligible to enter and participate in the study if he has either had a prior vasectomy or agrees to avoid sexual activity or use adequate contraception (as described above) from screening through follow-up.

2.2 Exclusion criteria

1. Patients with a diagnosis of Acute Promyelocytic Leukemia (APL) as defined by the World Health Organization.
2. Relapsed acute leukemia.
3. Bi-lineage or bi-phenotypic leukemia.
4. Prior use of mitoxantrone or etoposide or GO.
5. Previous allogeneic hematopoietic cell transplantation.
6. First induction course of acute myeloid leukemia with CPX-351.
7. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of treating investigator.
8. Has known history of active Hepatitis B (HBsAg reactive) or Hepatitis C (detectable HCV RNA).
9. Uncontrolled, life-threatening infection that is not responding to antimicrobial therapy.
10. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
11. Patient may have not received any other investigational anti-neoplastic agents within 4 weeks from the start of therapy.
12. Concurrent active malignancy; exceptions include patients who have been disease free for 5 years, patients with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma, or patients with another malignancy with better prognosis than AML.
13. Women who are pregnant or breastfeeding.
14. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory or cardiac disease).

2.3 Eligibility evaluation

The following clinical and laboratory assessments must be performed for all eligible patients within 14 days of study enrollment and consent:

1. Complete medical history and physical examination, including height, weight, body surface area (BSA), ECOG performance status, and a neurological evaluation.
2. Echocardiogram to evaluate cardiac ejection fraction.
3. CBC with differential and platelets.
4. Complete metabolic panel (Na, K, Cl, CO2, glucose, BUN, Cr, Ca, total protein, albumin, total bilirubin, AST, ALT, and alkaline phosphatase) and magnesium level.
5. LDH, uric acid, and phosphorus levels.
6. PT/INR, PTT.
7. Urinalysis.
8. PA and lateral chest x-ray. If clinically indicated CT Chest/Abdomen/Pelvis can be performed.
9. EKG.
10. Urine pregnancy test for all women $\leq$ 60 years old.

The following clinical and laboratory assessments must have been performed for all eligible patients within 12 weeks from initiation of treatment:

1. Hepatitis B surface antigen.
2. Hepatitis C antibody and if positive HCV RNA.

3.0 STUDY IMPLEMENTATION

3.1 Study design and treatment plan

This study is an open-label, single arm phase II study which will examine the efficacy and toxicity of the combination therapy of GO, mitoxantrone and etoposide in patients who did not respond to first line induction therapy.

Treatment plan

Eligible patients will be treated at the UPMC Hillman Cancer Center inpatient leukemia service. Patients will receive mitoxantrone 10mg/m^2 administered intravenous piggyback

(IVPB) in 50ml 0.9% normal saline over 15 minutes on days 1-5 and etoposide 100 mg/m^2 administered intravenously in 500 ml of 0.9% sodium chloride over 2 hours on days 1-5.

On day 6, patients will receive a single dose of GO 3mg/m^2 (maximum dose 4.5mg). Patients will be pre-medicated 1 hour prior to the GO infusion with diphenhydramine 50mg administered orally or intravenously, acetaminophen 650 mg administered orally or intravenously and 1mg/kg methylprednisolone or an equivalent dose of alternative corticosteroid administered IV within 30 minutes prior to infusion of GO. GO will be administered intravenously in 50 ml (or other suitable volume resulting in a final GO concentration between 0.075 mg/mL to 0.234 mg/mL) of 0.9% sodium chloride over 2 hours. Doses of GO will be based on BSA calculated using actual body weight with a cap of 4.5mg. Vital signs will be recorded within one hour prior to the infusion and then every 30 minutes during the infusion and 30 minutes and one hour after completion of infusion. An additional dose of methylprednisolone 1 mg/kg IV may be given for any sign of infusion reaction, such as fever, chills, hypotension, or dyspnea occurring during the GO infusion or within 4 hours after the GO infusion.

For dose modifications based on kidney and liver function please see the treatment schema at the end of the study.

Supportive care including blood product transfusions, antiemetic medications, antiviral and antifungal medications, growth factor support, tumor lysis syndrome prophylaxis, or empiric antibiotics may be used at the clinical discretion of the provider.

3.2 Off study criteria for the study

1. Request by the patient at any time for any reason.
2. The patient may at any time be removed from the trial at the principal investigator's discretion if the principal investigator deems the patient to be at unacceptable risk to remain on the study. Reasons for this action may include (but are not limited to) diseaseprogression with declining organ function/performance status before treatment; inadequate family/caregiver support; noncompliance.

3.3 Off treatment criteria for the study

1. Unacceptable adverse event(s) due to the infusion of any of the three antineoplastic agents which necessitates the termination of the therapy.
2. Intercurrent disease that prevents the administration of treatment.

4.0 ON STUDY EVALUATION

All patients enrolled in the study will have the following evaluations:

1. History and physical examination will be performed daily during the hospital stay and then weekly (± 4 days) as an outpatient for 4 weeks after discharge and then every 2 weeks until count recovery (defined as ANC ≥1000 with or without PLT ≥ 100,000). Daily weight will be measured (if clinically possible) while in the hospital and at each outpatient visit.
2. If patients develop grade 3 or 4 non-hematologic toxicity during their treatment, they will be followed weekly after discharge until resolution of toxicity or improvement to grade 2 or less.
3. CBC with differential, complete metabolic panel (Na, K, Cl, CO2, glucose, BUN, Cr, Ca, total protein, albumin, total bilirubin, AST, ALT, and alkaline phosphatase), phosphorus, uric acid, magnesium level and LDH will be performed daily while in the hospital. After discharge, CBC with differential and complete metabolic panel as defined above will be obtained weekly (± 4 days) until count recovery (defined as ANC ≥1000 with or without PLT ≥ 100,000).
4. Bone marrow biopsy and/or aspirate will be performed no earlier than 7 days after the therapy completion to evaluate disease response.
5. Bone marrow biopsy/aspiration to test for remission will be performed once hematopoietic recovery (defined as ANC ≥1000 with or without PLT ≥ 100,000) has been achieved. It can be performed in the inpatient or outpatient setting. If the bone marrow is consistent with morphologic complete remission, minimal residual disease testing will be performed with flow cytometry. If, on diagnosis, the NPM1 mutation was detectable by PCR or next-generation sequencing, then NPM1 PCR will be performed as well if morphologic complete remission is achieved. If hematopoietic recovery has not been achieved by 5 weeks (± 7 days) after the completion of therapy, bone marrow biopsy and/or aspiration for disease evaluation will be

performed. If there is no evidence of leukemia, subsequent bone marrow biopsies will be performed based on count recovery.

6. After the assessment of the recovery marrow patients will be followed remotely from chart review to evaluate the disease-free survival and the overall survival. If information cannot be obtained from the chart patients may be contacted by telephone.

5.0 STATISTICAL CONSIDERATIONS AND METHODOLOGY

5.1 Number and evaluability of patients

This is a phase II study of the combination therapy of GO, mitoxantrone and etoposide as second line therapy in patients with acute myeloid leukemia. The study is designed to assess the therapeutic efficacy and the toxicity profile using Simon's optimal two-stage phase II design to permit early stopping of the trial if there is strong evidence that the studied treatment is inefficacious.

To be evaluable for clinical response, a patient must:

1. Receive a total of 5 days of mitoxantrone and etoposide,
2. Receive 1 dose of GO and
3. Have a follow-up bone marrow biopsy to evaluate the response to therapy.

Additional participants will be recruited to replace those who are not evaluable for clinical response. The accrual target is a maximum of 44 response-evaluable patients. All participants who begin treatment will be counted in the interim analysis for excess mortality.

5.2. Sample Size/Accrual rate

5.2.1 Sample size

This study is expected to require a minimum of 16 patients (at the interim evaluation of response) and a maximum of 44 response-evaluable patients unless undue toxicity is encountered. We anticipate accruing up to 9 additional patients (~20%) to account for patients who may prove unevaluable (i.e. ineligibility, cancellations, death or major violations). Therefore, our overall sample size will be a maximum of 53 patients.

5.2.2. Accrual time and study duration

Based on previous efforts in recruiting patients at the UPMC Hillman Cancer Center, it is anticipated that at least thirty patients per year will be enrolled in the protocol and the accrual will be completed within two years. The final evaluation of the study to assess overall survival will be conducted at 5 years or if all subjects expire, whichever comes first.

5.3. Study design

5.3.1 Definition of complete remission (CR): An evaluable patient will be classified as having complete remission if they meet the criteria in Appendix II.

Decision Rule (Simon two-stage design): The largest CR rate where the proposed treatment regimen would be considered ineffective in this population is 35%. Subsequent studies will be warranted if the CR rate is 50% or higher or the CR rates are similar to historical data but the disease-free survival and the overall survival are improved in comparison to our institution's historical cohort. The following optimal Simon two stage design uses 44 patients to test the null hypothesis that the true CR rate in the given patient population is at most 35%.

Stage 1: Enter 16 evaluable patients. If 5 or fewer patients have a CR in this timeframe, we will consider this early evidence that this treatment regimen is not sufficiently efficacious in this patient population, and the accrual of patients will be stopped. If 6 or more patients have a CR, then accrual will continue in the second stage of this trial.

Stage 2: Enter an additional 28 evaluable patients to the trial. If 19 or more patients achievea complete remission, the treatment will be promoted for further consideration. This design has $\alpha=0.15$ and $\beta=0.20$; the large value of α is appropriate in an early phase trial. If the probability of CR is 35%, the expected sample size is 30.3 patients, i.e., the probability that the trial will be halted after 16 patients is 48.9%.

5.3.2 Monitoring for treatment-induced mortality

The trial will be continually monitored to ensure that treatment-induced mortality is not excessive, defined as >0.20 of patients treated. A safety-evaluable patient is a patient

who was consented and started the protocol chemotherapy. All safety-evaluable patients, not just those evaluable for clinical response, are counted in the interim analysis for mortality. The cutpoints are listed in Table 2.

Table 2. Stopping rule for excessive mortality. The trial will be halted if, for the number of patients in the following table, the number of deaths is greater than or equal to the given number.

# Patients	# Deaths	# Patients	# Deaths
4	3	24	7
6	3	26	8
8	3	28	8
10	4	30	8
12	4	32	9
14	5	34	9
16	5	36	10
18	6	38	10
20	6	40	11
22	7	42	11

Justification of the stopping rule: It was assumed that under standard of care, the probability of death is $\pi=0.2$. A beta-binomial model is assumed with $\alpha=2$ and $\beta=8$. If the number of deaths, x, is greater than the value in the Stopping Rule table for the number of patients, n, then:

$$P(\pi>0.2|\alpha,\beta,x,n)>0.75.$$

Under different assumptions of the true probability of death (True P(Death)), the expected number of patients (E(n)) and the probability of the trial stopping early (P(Stop Early)) were determined by Monte Carlo simulation:

True P(Death)	E(n)	P(Stop Early)
0.20	28.3	0.513
0.25	22.9	0.720
0.30	15.8	0.900
0.35	11.5	0.973
0.40	8.4	0.994
0.45	6.9	0.996

5.4. Statistical analysis plan

5.4.1. Analysis of complete remission

The probability of complete remission (CR, Appendix II) will be estimated by the number of CR divided by the total number of patients evaluable for response. A 95% one-sided exact binomial confidence interval of the form (π_L,1) for the true probability of CR will be calculated.

5.4.2 Analysis of secondary endpoints

Overall and progression-free survival functions will be estimated by the product limit (Kaplan-Meier) method. The median survival and its 90% confidence interval will also be reported.

Proportional hazards (Cox) regression will be used to describe the relationship between age, cytogenetic status (poor, intermediate, favorable), percent of blast in the bone marrow prior to therapy and percent expression of CD33 in the leukemia blasts to overall and progression-free survival. Likelihood ratio tests will be used to identify statistically significant ratios and profile likelihood confidence intervals will be estimated for hazard ratios of statistically significant predictors. Logistic regression will be applied in a similar fashion to determine predictors of complete remission.

6. ADVERSE EVENT REPORTING

Definitions

The following definitions of terms apply to this section:

Adverse event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or *life-threatening suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or *serious suspected adverse reaction:* An adverse event or

suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death,

be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected adverse event or *unexpected suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Eliciting AE Information

Research subjects will be routinely questioned about AEs at study visits.

Recording Requirements

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s).

AEs or abnormal test findings felt to be associated with the investigational drug or study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

Abnormal Test Findings

An abnormal test finding will be classified as an *adverse event* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy.

  Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.
- The test finding leads to a change in study dosing or discontinuation of subject participation in the clinical study.

REPORTING OF SERIOUS ADVERSE EVENTS

All events meeting the definition of a serious adverse event, from the date of first dose of study drug until 30 days after last dose, should be reported according to the departmental SAE checklist and SAE form. The initial SAE form should be sent to the following within 24 business hours / 1 business day of the Principal Investigator becoming aware:

1. Robert Redner, MD
2. CRSSafetySubmissions@upmc.edu
3. Local Institutional Review Board when reporting requirements are met.
4. Pfizer Safety @ SAEFaxmailbox@Pfizer.com

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Sections B and C of the departmental SAE form:

- CTCAE(5.0) term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

Follow-up reports:

Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form.

Special Interest Serious Adverse Events

The following events also require reporting to Pfizer at the fax number provided above.

1. Exposure during Pregnancy, Exposure during Lactation, Occupational Exposure, and Lack of Effect. Even though there may not be an associated SAE, exposure to the Pfizer drug product during pregnancy, exposure to the Pfizer drug product during lactation, and occupational exposure to the Pfizer drug product are reportable, and lack of effect od rh Pfizer drug product may also be reportable. The term SAE is understood to include exposure during pregnancy, exposure during lactation, occupational exposure, and reportable instances of lack of effect.
2. Hy's Law Cases. Cases of potential drug-induced liver injury as assessed by laboratory test values are reportable. If a Subject develops abnormal lab values in aspartate transaminase (AST) or alanine transaminase (ALT) or both, concurrent with abnormal elevations in total bilirubin and no other known cause of liver injury, that event would be classified as a Hy's Law Case. The term SAE is understood to include Hy's Law Cases.

7. DATA SAFETY MONITORING PLAN

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet regularly in the disease center Data Safety Monitoring Board (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

Minutes from the disease center DSMB meetings are available to those who are unable to attend in person.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria Version 5.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC Hillman Cancer Center DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed bi-annually.

Both the UPMC Hillman Cancer Center DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

8. STUDY EVALUATION, TREATMENT SCHEMA AND FLOW CHART

Pre-treatment evaluation	
	Within last 6 weeks from day of consent
Anti-Hepatitis C antibody and if positive HCV RNA PCR	X

Hepatitis B surface antigen	X
	Within 14 days from day of consent
Medical history and physical examination	X
Height, weight, BSA, ECOG performance status	X
Toxicities from prior therapies	X
Cardiac echocardiogram	X
Bone marrow biopsy and aspiration	X
Urine βHCG in women ≤ 60 years old (pregnancy test)	X
PT/INR, PTT	X
Complete metabolic panel (Na, K, Cl, CO2, glucose, BUN, Cr, Ca, total protein, albumin, total bilirubin, AST, ALT and alkaline phosphatase)	X
Magnesium, Phosphorous, Uric Acid, LDH	X
CBC with differential	X
Urinalysis	X
Electrocardiogram (12 lead)	X
Chest radiograph	X
CT Chest, Abdomen and/or Pelvis if indicated	X

Treatment Schema						
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**
Mitoxantrone	X	X	X	X	X	
Etoposide *	X	X	X	X	X	
Gemtuzumab ozogamicin **						X

* Dose modification of etoposide for patients who develop elevated total bilirubin and/or AST or decrease in creatinine clearance

Adverse event	Dose modification of etoposide
CrCl 10 – 50 ml/min	administer 75% of normal dose
CrCl < 10 ml/min	administer 50% of normal dose
CrCl <50 ml/min AND Total bilirubin >3 mg/dL or AST >3 times ULN	Hold etoposide

**If enrolled patients on day 6 of therapy have levels of aspartate aminotransferase (AST) ≥ 2.5 x UNL or alanine aminotransferase (ALT) ≥ 2.5 x UNL or total bilirubin ≥ 2 x ULN the administration of GO will be on hold until recovery of total bilirubin to less than or equal to 2 × ULN and AST and ALT to less than or equal to 2.5 × ULN prior to each dose. Daily values of LFTs will be obtained. The GO dose can be delayed up to the 10th day after the initiation of therapy due to toxicity or unexpected events (ie infection). Doses of GO will be capped at 4.5mg. Administration of a FLT3 inhibitor will be prohibited until CR is achieved. The use of a FLT-3 inhibitor is not prohibited after CR has been achieved for patients with FLT3-ITD or FLT-TKD mutations.

ON STUDY EVALUATION	TIMING
History and physical examination	Daily during the hospital stay at UPMC Shadyside Hospital and then weekly as outpatient for 4 weeks, and then every 2 weeks until count recovery
CBC with differential	CBC with differential will be performed daily during the inpatient stay and weekly as outpatient until count recovery

Complete metabolic panel including LFTs	Complete metabolic panel including liver function tests (LFTs) will be performed daily during the admission. After discharge, they will be followed weekly as outpatient until count recovery
Bone marrow aspiration and biopsy (to evaluate disease status)	At least 7 days after the completion of treatment
Weight	Daily (if clinical possible) while in hospital and during each visit outpatient

Bone marrow biopsy, aspirate with flow cytometry studies, cytogenetics and molecular studies will be performed no earlier than 7 days after the completion of treatment. Once hematopoietic recovery has been achieved patients will undergo bone marrow biopsy and/or aspiration for disease evaluation which can be performed in the inpatient or outpatient setting. If the bone marrow is consistent with morphologic complete remission, minimal residual disease testing will be performed with flow cytometry. If on diagnosis the NPM1 mutation was detectable by PCR or next-generation sequencing then NPM1 PCR will be performed as well if morphologic complete remission is achieved If hematopoietic recovery has not been achieved by 5 weeks after the completion of therapy bone marrow biopsy and/or aspiration for disease evaluation will be performed.

Study Flow Chart										
Screening Period		Treatment Days						Post-treatment		
	Main Study Screening	1	2	3	4	5	6	Daily during Inpatient stay	Follow Up Visits	Survival Follow up[a]
Scheduling Window (Days)	-14 to 0	Can delay each dose up to 3 days.					Up to 5 days from the last dose of etoposide/ mitoxantrone[b]		Weekly[c]	
Informed Consent	X									
Inclusion/Exclusion Criteria	X									

Medication Review[d]	X	X	X	X	X	X	X	X		
Trial Treatment Administration		X	X	X	X	X	X			
Post-study anticancer therapy status										X
Survival Status										X
Review Adverse Events	X (from 1st induction therapy)	X	X	X	X	X	X	X	X	
Full Physical Examination	X								X	
Directed Physical Examination		X	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	
Urine or Serum β-HCG	X									
PT/INR and aPTT	X[e]									
CBC with differential	X[e]	X	X	X	X	X	X	X	X[f]	
Comprehensive Serum Chemistry Panel[g]	X[e]	X	X	X	X	X	X	X	X[f]	
Magnesium, Phosphorus, Uric Acid, LDH	X[e]	X	X	X	X	X	X	X		
Urinalysis	X[e]									
Chest Radiograph	X[e]									
Echocardiogram	X[h]									
EKG	X[e]									
Bone Marrow Biopsy	X[i]								X[j]	
Archival or Newly	X									
Obtained Tissue Collection										

[a] Survival will be assessed daily during inpatient stays and then in the follow up visits. After the assessment of the recovery marrow or the marrow after 5 weeks from the completion of therapy patients will be followed remotely from chart review to evaluate the disease-free survival and overall survival. If information cannot be obtained from the chart, patients may be contacted by telephone. [b] Administration of a FLT3 inhibitor will be prohibited until CR is achieved. The use of a FLT-3 inhibitor is not prohibited after CR has been achieved for patients with FLT3-ITD or FLT-TKD mutations.

[c] After discharge the patient will be followed weekly for 4 weeks and then every 2 weeks until count recovery (defined as ANC ≥ 1000 with or without PLT ≥ 100,000). If patients develop grade 3 or 4 nonhematologic toxicity during their treatment they will be followed weekly after discharge until resolution of toxicity or improvement to grade 2 or less. There is ± 4 days window for each visit. [d] Medication review will be performed from the day of screening until the day of discharge. [e] All screening laboratory assessment must occur within 14 days after consent is signed. [f] After discharge, CBC with differential and complete metabolic panel will be obtained weekly until count recovery (defined as ANC ≥ 1000 with or without PLT ≥ 100,000). [g] Includes Na, K, Cl, HCO3, BUN, Cr, glucose, Ca, total protein, albumin, total bilirubin, AST, ALT, alkaline phosphatase. [h] Transthoracic Echocardiogram must be performed after the administration of 7 days of cytarabine with 3 days of idarubicin and before the first day of the study treatment. [i] Bone marrow with persistent disease as described in eligibility criteria section and CD33 expression in ≥ 30% leukemic blasts on the bone marrow. [j] Bone marrow biopsy and/or aspirate will be performed no earlier than 7 days after the therapy completion to evaluate disease response. Bone marrow biopsy/aspiration to test for remission once hematopoietic recovery has been achieved will be performed in the inpatient or outpatient setting. If hematopoietic recovery has not been achieved by 5 weeks after the completion of therapy bone marrow biopsy/aspiration for disease evaluation will be performed. If the recovery bone marrow is consistent with morphologic complete remission, minimal residual disease testing will be performed with flow cytometry. If at AML diagnosis the NPM1 mutation was detectable by PCR or next generation sequencing then NPM1 PCR will be performed as well. [k] Blood will be collected prior to the initiation of therapy with mitoxantrone and etoposide, prior to the initiation of therapy with GO, after the administration of GO and weekly while in the hospital. Blood and bone marrow aspirate will be collected at the time of bone marrow evaluation following therapy and at the time of bone marrow evaluation following hematopoietic recovery or prolonged cytopenias.

APPENDIX I

Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

APPENDIX II

RESPONSE CRITERIA FOR ACUTE LEUKEMIA

Morphologic leukemia-free state

Bone marrow < 5% blasts in an aspirate with spicules

No blasts with Auer rods or persistence of extramedullary disease
Absolute neutrophil count < 1000/mcL AND platelets <100,000/mcL

Complete remission

Bone marrow < 5% blasts in an aspirate with spicules Absolute
neutrophil count > 1000/mcL

Platelets ≥100,000/mcL

No residual evidence of extramedullary disease
Morphologic CR - patient independent of transfusions
Cytogenetic CR - cytogenetics normal (in those with previously abnormal cytogenetics)
Molecular CR - molecular studies negative

Complete remission with incomplete hematologic recovery

Bone marrow < 5% blasts in an aspirate with spicules
No residual evidence of extramedullary disease
Absolute neutrophil count > 1000/mcL or platelets ≥100,000/mcL
No residual evidence of extramedullary disease

Partial remission

Decrease of at least 50% in the percentage of blasts to 5 to 25% in the bone marrow
Patients failing to achieve a complete remission are considered treatment failures

Relapse

Relapse following complete remission is defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause (eg, bone marrow regeneration after consolidation therapy)

Cheson BD, Bennett JM, Kopecky KJ et al. J Clin Oncol 2003;21 (24):4642-4649

9. DRUG INFORMATION

Gemtuzumab Ozogamicin

Other Names: Mylotarg

Classification: Antibody-drug conjugate

Mechanism of Action: Antibody-drug conjugate to CD33 antigen. Binding results in internalization of the antibody-antigen complex. Following internalization, the calicheamicin derivative is released inside the myeloid cell. The calicheamicin derivative binds to DNA resulting in double strand breaks and cell death. Pluripotent stem cells and nonhematopoietic cells are not affected.

Storage and Stability: GO is supplied as a sterile, pyrogen-free, unpreserved, white lyophilized powder in amber glass vials. The unopened vials of GO should be stored at 2 - 8° C (refrigerated) and protected from light and should be used within 8 hours of reconstitution. GO is light sensitive and should be reconstituted, prepared, and administered under protection from direct/indirect sunlight and Ultraviolet (UV) light.

Dose Specifics: GO will be administered at 3 mg/m^2 (cap at 4.5mg) on day 6. BSA will be calculated based on actual body weight.

Preparation: GO is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. ALL PREPARATION SHOULD BE DONE IN A BIOLOGIC SAFETY HOOD WITH FLUORESCENT LIGHT OFF. Prior to reconstitution, allow vials to come to room temperature for approximately 5 minutes. Reconstitute the contents of each vial with 5 mL sterile water for injection, USP, using sterile syringes. Gently swirl each vial. The final concentration is 1 mg/mL. Use reconstituted solution immediately or after being refrigerated at 2-8°C for up to 1 hour. Protect reconstituted solution from light. Do not freeze reconstituted solution. Dilute the desired volume of GO into a 50-milliliter

intravenous bag of 0.9% sodium chloride injection or other appropriate volume of 0.9% sodium chloride to make a final GO concentration between 0.075 mg/ml to 0.234 mg/mL. Gently invert the infusion container to mix the diluted solution. Do not shake. Following dilution with 0.9% sodium chloride injection, GO solution should be infused immediately. If not used immediately, store at room temperature (15–25°C; 59–77°F) for up to 6 hours, which includes the 2-hour infusion time and 1-hour, if needed, to allow the refrigerated diluted solution to equilibrate to room temperature. The diluted solution can be refrigerated at 2– 8°C (36–46°F) for up to 12 hours which includes up to 1-hour in the vial post-reconstitution.

Route of Administration: GO is administered as a 2 hour IV infusion. A 0.2-micron polyethersulfone filter is required on the IV line. The IV bag must be protected from light using a light-blocking cover during infusion. The infusion line does not need to be protected from light.

Compatibilities: No information; infuse via separate line.

Availability: Commercially available

Side Effects:

Common (occurs in more than 10% of people - more than 10 out of 100 people):
fever (79%), infection (42%), increased AST (40%), sepsis (32%), bleeding (23%), nausea and vomiting (21%), constipation (21%), mucositis (21%), headache (19%), increased ALT (16%), rash (16%)

Infrequent (occurs in 1% to 10% of people - from 1 to 10 out of 100 people):
pneumonia (7%), bleeding (7%), hyperbilirubinemia (7%), mucositis (4%), pain (4%), diarrhea (2%), headaches (2%), tachycardia (2%), lung edema (2%)

Rare (occurs in <1% of people, mainly identified in post-marketing surveillance):

neutropenic colitis, interstitial pneumonia, hemorrhagic cystitis

Nursing Implications: Patients should be premedicated prior to administration of GO with methylprednisolone 1 mg/kg IV, diphenhydramine 50 mg IV or PO and acetaminophen 650 mg PO 30 minutes prior to start of the infusion. Additional doses of acetaminophen and diphenhydramine may be administered every 4 hours after the initial pretreatment dose. Repeat with the same dose of methylprednisolone for any sign of an infusion reaction, such as fever, chills, hypotension, or dyspnea during the infusion or within 4 hours afterwards.

During and after the infusion patients will be monitored with vital signs recorded every 30 minutes during the infusion and for 1 hour after completion of the infusion.

GO should be administered in a setting where appropriate medical support, including life support equipment, is available in case of an unexpected adverse event.

Etoposide

Other Names: Toposar

Classification: Podophyllotoxin Derivative

Mechanism of Action: Etoposide has been shown to delay transit of cells through the S phase and arrest cells in late S or early G_2 phase. The drug may inhibit mitochondrial transport at the NADH dehydrogenase level or inhibit uptake of nucleosides into HeLa cells. It is a topoisomerase II inhibitor and appears to cause DNA strand breaks. Etoposide does not inhibit microtubular assembly.

Storage and Stability: Unopened vials of etoposide are stable for 24 months at room temperature (25 degrees Celsius). Vials of etoposide are stable at room temperature for 96

hours when diluted to concentrations of 0.2 milligrams/milliliter (mg/mL); stability is 24 hours with concentrations of 0.4 mg/mL at room temperature. The manufacturer does not recommend that etoposide be administered at concentrations greater than 0.4 mg/mL because time to precipitation is highly unpredictable and precipitate formation has been reported to occur earlier than the utility times listed above. Etoposide 20 mg/ml is stable in a plastic syringe for 5 days when stored at room temperature under fluorescent light.

Dose Specifics: Patients will receive etoposide 100 mg/m^2 administered intravenously in 500 ml of 0.9% sodium chloride over 2 hours on days 1-5 (for patients who have elevated total bilrirubin, AST or reduced creatinine clearance during the etoposide infusion see treatment schema for dose modification of the etoposide). BSA will be calculated based on actual body weight.

Preparation: Etoposide Injection must be diluted prior to use with either 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, to give a final concentration of 0.2 to 0.4 mg/mL . If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Route of Administration: Etoposide should be given as a diluted solution via the IV route.

Compatibilities: Variable stability (consult detailed reference) in D_5W, LR, NS.Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, cladribine, doxorubicin liposome, fludarabine, gemcitabine, granisetron, melphalan, ondansetron, paclitaxel, piperacillin/tazobactam, sargramostim, sodium bicarbonate, teniposide, thiotepa, topotecan, vinorelbine. Incompatible: Cefepime, filgrastim, idarubicin.

Compatibility when admixed: Compatible: Carboplatin, cisplatin, cisplatin with cyclophosphamide, cisplatin with floxuridine, cytarabine, cytarabine with daunorubicin, floxuridine, fluorouracil, hydroxyzine, ifosfamide, ifosfamide with carboplatin, ifosfamide

with cisplatin, ondansetron. Variable (consult detailed reference): Cisplatin with mannitol and potassium chloride, doxorubicin with vincristine.

Availability: Commercially available

Side Effects:

Common (occurs in more than 10% of people - more than 10 out of 100 people): Alopecia (8% to 66%), ovarian failure (38%), Nausea/vomiting (31% to 43%), anorexia (10% to 13%), diarrhea (1% to 13%), leukopenia (60 to 91%), thrombocytopenia (22% to 41%), anemia (up to 33%), mucositis

Infrequent (occurs in 1% to 10% of people - from 1 to 10 out of 100 people): Hypotension (1% to 2%), stomatitis (1% to 6%), abdominal pain (up to 2%), hepatic toxicity (up to 3%), peripheral neuropathy (1% to 2%), anaphylactic-like reaction (IV infusion 1% to 2%)

Rare (occurs in fewer than 1% of people – fewer than 1 out of 100 people): Congestive heart failure, hyperpigmentation, rash, radiation-recall reaction, StevensJohnson Syndrome, pruritus, toxic epidermal necrolysis, cyanosis, optic neuritis, transient blindness, diaphoresis, interstitial pneumonitis, pulmonary fibrosis, metabolic acidosis, thrombophlebitis, extravasation

Nursing Implications: For IV use only; may cause severe local tissue damage if extravasation occurs. Do not administer intrathecally; may cause serious and permanent neurologic damage. Should be administered under the supervision of an experienced cancer chemotherapy physician.

Mitoxantrone

Other Names: Dihydroxyanthracenedione, DHAD

Classification: Anthracenedione

Mechanism of Action: Analogue of the anthracyclines, mitoxantrone intercalates DNA; binds to nucleic acids and inhibits DNA and RNA synthesis by template disordering and steric obstruction; replication is decreased by binding to DNA topoisomerase II and seems to inhibit the incorporation of uridine into RNA and thymidine into DNA; active throughout entire cell cycle

Storage and Stability: Intact vials should be stored between 15 and 25 degrees Celsius (59 and 77 degrees Fahrenheit). DO NOT FREEZE. After penetration of the stopper, store the remaining solution of undiluted mitoxantrone for no longer than 7 days between15 to 25 degrees Celsius (59 to 77 degrees Fahrenheit) or for no longer than 14 days under refrigeration (2 to 8 degrees Celsius or 36 to 46 degrees Fahrenheit). Mitoxantronemust be further diluted for infusion.

Dose Specifics: Patients will receive mitoxantrone 10mg/m^2 administered IVPB in 50ml 0.9% sodium chloride over 15 minutes on days 1-5. (Refer to Treatment Plan of Phase I and II sections). BSA will be calculated based on actual body weight.

Preparation: MITOXANTRONE CONCENTRATE MUST BE DILUTED PRIOR TO USE. Dilute the dose with at least 50 milliliters (mL) of 0.9% sodium chloride or 5% dextrose in water. Dilution in volumes greater than 50 mL may be done in 5% dextrose in water, 0.9% sodium chloride, or dextrose 5% with 0.9% sodium chloride. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Route of Administration: Mitoxantrone should be given as a diluted solution via the IV route.

Compatibilities: Stable in D_5NS, D_5W, NS Y-site administration: Compatible: Allopurinol, amifostine, cladribine, etoposide phosphate, filgrastim, fludarabine, gatifloxacin, gemcitabine, granisetron, linezolid, melphalan, ondansetron, sargramostim, teniposide, thiotepa, vinorelbine. Incompatible: Amphotericin B cholesteryl sulfate complex, aztreonam, cefepime, doxorubicin liposome, paclitaxel, piperacillin/tazobactam, propofol.

Compatibility when admixed: Compatible: Cyclophosphamide, cytarabine, fluorouracil, hydrocortisone sodium succinate, potassium chloride. Incompatible: Heparin. Variable (consult detailed reference): Hydrocortisone sodium phosphate.

Availability: Commercially available

Side Effects:

Common (occurs in more than 10% of people - more than 10 out of 100 people): Arrhythmia (3% to 18%), ECG changes (11%), fatigue (up to 39%), fever (6% to 78%), headache (6% to 13%), alopecia (20% to 61%), nail bed changes (11%), amenorrhea (28% to 53%), menstrual disorder (26% to 61%), hyperglycemia (10% to 31%), abdominal pain (9% to 15%), anorexia (22% to 25%), nausea (26% to 76%), constipation (10% to 16%), diarrhea (14% to 47%), GI bleeding (2% to 16%), mucositis (10% to 29%), stomatitis (8% to 29%), vomiting (6% to 11%), urinary tract infection (7% to 32%), neutropenia (79% to 100%), leukopenia (9% to 100%), lymphopenia (72% to 95%), anemia (5% to 75%), thrombocytopenia (33% to 39%), petechiae/bruising (6% to 11%), alkaline phosphatase increased (37%), transaminases increased (5% to 20%), creatinine increased (13%), hematuria (11%), dyspnea (6% to 18%), upper respiratory tract infection (7% to 53%), fungal infection (9% to 15%), infection (4% - 18%), sepsis (31% to 34%)

Infrequent (occurs in 1% to 10% of people - from 1 to 10 out of 100 people): LVEF decreased (≤5%), CHF (2% - 5%), depression (5%), seizure (2% - 4%), hypocalcemia

(10%), hypokalemia (7% - 10%), hyponatremia (9%), menorrhagia (7%),impotence (7%), jaundice (3% to 7%), myalgia (5%), arthralgia (5%), conjunctivitis (5%), blurred vision (3%), renal failure (8%), proteinuria (6%), rhinitis (10%), pneumonia (9%), sinusitis (6%), diaphoresis (9%)

Rare (occurs in fewer than 1% of people – fewer than 1 out of 100 people):
Blue skin discoloration, rash, interstitial pneumonitis, hypersensitivity, extravasation

May cause myocardial toxicity and potentially-fatal congestive heart failure (CHF); risk increases with cumulative dosing. Predisposing factors for mitoxantrone-induced cardiotoxicity include prior anthracycline therapy, prior cardiovascular disease, concomitant use of cardiotoxic drugs, and mediastinal/pericardial irradiation. Not recommended for use when left ventricular ejection fraction (LVEF) <50%.

Nursing implications: For IV use only; may cause severe local tissue damage if extravasation occurs. Do not administer intrathecally; may cause serious and permanent neurologic damage. May cause urine, saliva, tears, and sweat to turn blue-green for 24 hours post infusion. Whites of eyes may have blue-green tinge. Has been associated with the development of secondary acute myelogenous leukemia and myelodysplasia. Should be administered under the supervision of an experienced cancer chemotherapy physician.

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