A Combination Chemotherapy Trial of Relapsed Acute Myelogenous Leukemia with Gemtuzumab Ogozamicin and Escalating Dose Mitoxantrone

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A. Background

Chemotherapy in patients with relapsed acute myelogenous leukemia *(ANM)* results in low rates of complete remission (CR, 30-40%) and disease free survival rates less than 6 months. Mylotarg (Gemtuzumab ogozamicin), a recently approved treatment for relapsed *ANM* is a recombinant humani zed anti-CD33 monoclonal antibody conjugated with the antibiotic calicheamicin. CD33 is a surface antigen expressed by leukemic blasts in 80-90% of patients with AML but it is not expressed by pleuripotent hematopoietic stem cells. Once the antibody binds the CD33 antigen, it is internalized and the antibiotic released destroys the leukemic cells. Since the stem cells are spared, they regenerate a normal myeloid population. In three single-arm open label studies with CD33 positive AML in first relapse Mylotarg, as a monotherapy achieved results comparable to combination chemotherapy (16% CR and a median survival of 5.9 months).

Mtoxantrone is an agent that has also been found to have efficacy in relapsed AML. Mylotarg and mitoxantrone make an excellent combination to test in relapsed AML because they have different toxicity profiles and mechanisms of action. However, mitoxantrone is hepatically cleared, and mylotarg is known to have transient, reversible hepatotoxicity and thus may affect clearance of mitoxantrone. Here, we propose a study to assess the safety and feasibility of combining these agents and secondarily, the efficacy of this combination as compared to historical controls.

B. Methods

a. Outcomes:

i. Toxicity

- will be graded according to the common toxicity criteria of NCI (grade 0-4); serious and unexpected side effect will be reported to sponsor (Wyeth-Ayerst)

ii. Efficacy

- complete hematologic remission: YV`BC 3.0 * 10^9 (writhout blasts), Bg >10.0 * 10^9/1, p1t >100*10^9

Complete remission: as above + BM < 5% blasts

Complete remission P: as above but plt < 100* 1 OA9

Cytogenetic response - in patients with initially abnormal cytogenetics, now no abnormalities detected

b. Study design

single institution, single-arm, prospective pilot study for safety and efficacy

The approved dosing of mylotarg is 9 mg/m2 on day I and day 14. Mtoxantrone dosing is approved at 12 mg/ra.2 and will be given on day 2 or 2+3 or 2+3+4. Group 1 will receive mylotarg on day I and mitoxantrone on day 2with serial measurements of mitoxantrone serum levels at time 0, 3 0 min, 60 min, 2 hrs, 4 hrs, 6 hrs, 24 hrs, and 48 hours (note that mitoxantrone has a prolonged half-life). If this single dose of mitoxantrone is tolerated, then Group 2 will also receive mitoxantrone on day 3 with additional measurements of drug levels at 72 and 96 hours. Finally, should no toxicity be seen with group 2, mitoxantrone will be given to Group 3 on days 2, 3, and 4 with an additional serum level to be drawn at 120 hours. A "3+3 " design will be followed wherein each group will consist of three patients. If more than one patient in a group experiences significant toxicity, that dose will be considered a toxic dose and

three patients will be enrolled again in the group receiving a lower dose. If only one patient experiences significant toxicity, the dosage used in that patienfs group will be repeated with another three patients. Both drugs will be prepared according to the manufacturers instructions.

Standard prophylaxis for the post infusion syndrome seen with Mylotarg includes acetaminophen 650-1000 mg, one hour prior to administration with additional doses pm at 4 and 8 hours. In light of acetaminophen's known effect on reducing glutathione levels in the liver and heart, 25-50 mg diphenhydramine IV/po and 400-600 mg ibuprofen will be substituted to minimized potentiation of mitoxantrone toxicity. Patients enrolled in the study will also receive fidl supportive care including isolation procedures until neutrophil engraftment, transfusions of irradiated blood products, antibiotics, etc. GM-CSF will be used only >48 hours after the second Mylotarg dose and only in febrile patients requiring broad spectrum antibiotics.

C. Subject selection

- patients will be referred from Columbia and its collaborating network
- Eligibility: patients aged 18 - physiologic 75 with AML, CNIL in blast crisis, or MDS in leukemic transformation who have relapsed after standard induction chemotherapy
- Inclusion criteria: bilirubin <1.5, creatinine < 2.0, CD33+ ANIL by flow, WBC <30k
- Exclusion criteria: active CNS leukemia, EF <50% or active CBF, pregnancy
- Informed consent must be signed by patients who meet the above criteria and wish to participate

D. Risks/Drug Side effects

a. Mylotarg

Mylotarg is associated with a post infusion syndrome (fever, chills, hypotension, and dyspnea), which is easily treated with fluids and pre-medication. Hematological effects include severe myelosuppression and therefore severe infections and bleeding. Gastrointestinal side effects include transient, reversible hepatotoxicity characterized by elevations of transaminases in 50% of patients (though only 2% were grade 4 i.e. >20 * ULN) and bihrubin elevations (25% of which were grade 4 i.e. >1 0 * ULN). There have been infrequent reports of seizures, nausea, and immune reactions.

b. Mitoxantrone

Approximately 10- 15% of patients develop cardiotoxicity manifested by arrythmias or congestive failure. Also less than I 01/o of patients develop reversible renal insufficiency.

c. Mylotarg + Mitoxantrone

In combination the drugs may produce mild to moderate anorexia, vomiting, diarrhea, and abdominal discomfort. Sterility, disruption of menses, and fetal damage can also occur. Finally, virtually all patients will experience alopecia but typically reversible.

d. Benefits

These drugs with their differing mechanisms of action may result in improved outcomes as stated earlier (complete remission or disease free survival).

e. AlternativeTtherapies

Patients could theoretically receive either drug alone or complete, other chemotherapeutic agents (with known or unknown efficacy), and /or supportive care.