

Effect Of Pegylated Recombinant Human Megakaryocyte Growth And Development Factor On Thrombocytopenia, Due To Induction Therapy Of Acute Myeloid Leukemia With High-Dose Ara-C And Idarubicin

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A. Study Purpose and Rationale

Acute myeloid leukemia (AML) is a clonal malignant disease of the myeloid component of hematopoietic tissue. It is characterized both by the proliferation of a clonal leukemic blast cell as well as by the impaired polyclonal production of normal blood cells. ANEL accounts for approximately 80% of new leukemias in adults and it appears not to predict particular races or sexes. AML is usually classified according to the French-American-British (FAB) system into 8 categories (M0 to M7) according to the phenotype of the leukemic cells. The FAB classification appears largely irrelevant in the treatment of AML except in the case of the M3 variant promyelocytic leukemia which has demonstrated marked responsiveness to differentiation therapy with all trans-retinoic acid as opposed to the more traditional cytotoxic therapies applied to other forms of AML.

Conventional therapy of AML includes the use of Cytarabine (Ara-C) and an anthracycline agent. Ara-C functions in the tri-phosphate form as a DNA chain terminator and synthesis inhibitor. In conventional doses (100-200 mg/m² /d) its dose-limiting toxicities are myelosuppression and neurologic toxicity. The nadir due to Ara-C occurs between days 7 and 14 and resolves between days 14 and 21. Of all the anthracycline compounds which function as topoisomerase inhibitors and DNA intercalators, Idarubicin has been shown to cause more frequent complete remissions following induction therapy. Its primary dose limiting toxicities include myelosuppression and cardiotoxicity.

Several recent studies have demonstrated enhanced antileukemic effects of chemotherapeutic regimens employing high-dose Ara-C (HDAQ at doses of 2-4 gm/m² every 12 hours in conjunction with conventional doses of an anthracycline. Findings have included both more frequent and more durable complete remissions. Unfortunately, severe myelosuppression remains the most important dose-limiting toxicity and leading cause of morbidity and mortality in patients treated with these regimens. The discovery of the hematopoietic cytokines GM- and G-CSF has improved the management of neutropenia. due to cytotoxic agents. Thrombocytopenia, however, remains a complicating effect of antitumor therapy.

The recent discovery of c-mpl ligand (thrombopoietin), a cytokine with profound megakaryopoietic properties, has made possible the treatment of chemotherapy-induced thrombocytopenia. By limiting the duration and magnitude of severe thrombocytopenia, thrombopoietin (TPO) may reduce the need for blood product transfusions as well as the incidence of life-threatening bleeding events following chemotherapy. Limiting platelet transfusions in patients with ANIL is desirable in order to preserve blood product supplies, to limit the costs associated with their use, and to prevent alloimmunization from repeated exposure to donor antigens that may make future allogeneic bone marrow transplantation more difficult.

The purpose of this study is to investigate the effects of the c-mpl ligand polyethylene glycol-conjugated recombinant human megakaryocyte growth and differentiation factor (PEG-rHuMGDF) on the duration and magnitude of thrombocytopenia in patients with de novo AML undergoing induction therapy with Idarubicin and High-Dose Ara-C (HDAC). By comparing treated and control groups we hope also to study the incidence of bleeding complications, the use of platelet transfusions, and the achievement of complete hematologic remission after induction therapy.

B. Study Design and Statistical Analysis

This will be a prospective, randomized placebo-controlled double-blind study comparing groups of AML patients treated either with or without PEG-rHuMGDF following induction therapy with Idarubicin and High-dose Ara-C. Patients will be recruited from the outpatient and inpatient clinical areas of the Columbia Presbyterian Medical Center. Pre-enrollment examination will be conducted and will include complete blood count determination, serum chemistry analysis, immunophenotyping and cytogenetic analysis of leukemic cells, bone marrow analysis, CMV status determination, HIA typing, chest radiographic imaging, MUGA examination and electrocardiogram analysis. Patients will be deemed appropriate for enrollment in the study if they meet the inclusion and exclusion criteria.

Once enrolled, patients will be randomized to one of two treatment arms in this study. Arm A includes patients who will receive PEG-rHuMGDF at a dose of 2.5 µg/kg/day. Patients in Arm B will receive only placebo diluent. All patients will undergo induction therapy with Cytarabine 3 gm/m²/q 12h for six days followed by Idarubicin 12 mg/m²/q 24h for three days. Beginning the day after completion of chemotherapy, the study drug (PEG-rHuMGDF or placebo) is administered daily by subcutaneous injection until the platelet count returns to baseline or 21 doses have been administered. All patients will receive GM-CSF 125 gg/m² administered twice daily by subcutaneous injection until the absolute neutrophil count rises above 500/mm³ for three consecutive days.

Patients will be monitored by daily complete blood count and serum chemistry determinations. Standard supportive care will be instituted as necessary, which includes but is not limited to the institution of prophylactic broad-spectrum antibiotic therapy for neutropenic fever and the transfusion of blood products. Packed red blood cells will be administered to maintain a blood hemoglobin concentration > 8 gm/dL. Platelet transfusions will be used to maintain a platelet count > 20,000/mm³ in asymptomatic patients or > 50,000/mm³ in bleeding patients. Patients who are CMV-negative will receive CMV-negative blood products. When possible HIA-matched single donor platelets will be given instead of pooled donor platelets to limit blood product alloimmunization. Transfusion of components donated by blood relatives will not be prohibited but will be strongly discouraged.

Patients will undergo repeat bone marrow analysis at day +30 following the completion of the first cycle of induction chemotherapy. Complete hematologic remission (CHR) defined as return of normal hematopoiesis and elimination of leukemic blasts from the bone marrow will be assessed by this bone marrow analysis. Patients who fail to achieve CHR following a first cycle of chemotherapy will receive a second, identical cycle of Idarubicin and HDAC. All patients receiving a second induction cycle will remain in their randomized treatment arms and will receive post-chemotherapy study drug (PEG-rHuMGDF or placebo) as outlined above. A third bone marrow analysis will be performed on these at day +30 following the completion of the second induction cycle. Patients will be discharged from the study after achieving CHR or after the second cycle of chemotherapy. They will follow up with their primary oncology physicians for appropriate post-remission or salvage care.

For the purposes of this study a total of 72 patients will be recruited (36 patients in each arm). This number was determined by an assessment of the number of subjects necessary to determine a statistically significant difference in effect of at least a 3 day reduction in the duration of thrombocytopenia. Variabilities of approximately 4 days have been determined by prior investigations of thrombocytopenia durations after chemotherapy for other malignancies followed by treatment with PEG-rHuMGDF vs. placebo.

Data that will be recorded for each subject include minimum nadir platelet count, the occurrence and magnitude of bleeding and thrombotic complications, the number of platelet transfusions needed, the occurrence of CHR after each cycle of induction therapy, and deaths during the study. In addition, the duration of platelet nadir will be measured and is operationally defined as the number of days inclusive between (1) the first day following an induction cycle that the platelet count falls below 85% of the baseline and remains below for 3 days and (2) the first day that the platelet count recovers beyond 85% of the baseline and remains above for 3 days.

The primary outcome in this study is the duration of thrombocytopenia. A mean duration will be calculated for each group after the completion of the first cycle of induction chemotherapy. The t-Test for

continuous data will be used to determine the presence of a significant difference in this statistic between the treatment groups. In addition, a subgroup of each treatment arm will require a second cycle of induction therapy. Mean durations of thrombocytopenia after a second cycle of induction therapy will be calculated for these two subgroups, and the t-Test will be applied to determine the significance of the difference between them.

A secondary outcome in this study will be the percentage of patients achieving CHR after one or two cycles of induction chemotherapy. The proportion of patients achieving CHR following one cycle in each treatment arm of the study will be compared by the Chi-square approximation for categorical data to determine the presence of a significant difference. The proportion of patients in CHR following either one or two cycles of therapy will likewise be compared for the two treatment arms.

C. Study Procedures

No special procedures beyond what is currently standard in the therapy of AML will be necessary. The patient will undergo 2 to 3 bone marrow aspirations with biopsy, one preceding enrollment and one following each cycle of induction chemotherapy. In addition each patient may undergo the placement of a long-term central venous catheter to facilitate both medication dosing and phlebotomy. The decision regarding central venous catheter placement will be left to the patient and his or her medical provider.

D. Study Drug

Idarubicin and Cytarabine (Ara-C) in combination are standard agents for the treatment of AML. High-dose administration of Ara-C has gained wide acceptance in the induction therapy of AML because it appears to increase the frequency and durability of hematologic remissions. Side effects of Idarubicin include myelosuppression, alopecia and cardiotoxicity leading to congestive heart failure. Myelosuppression, and cardiotoxicity are the dose-limiting side effects. Cytarabine has been associated with severe myelosuppression, gastrointestinal toxicity (nausea, vomiting, diarrhea, and mucositis), and neurologic toxicity (seizures, peripheral neuropathy, aphasia and cerebellar dysfunction). Peripheral neuropathy caused by Cytarabine appears not to be reversible. GM-CSF is a standard drug for the prophylaxis of neutropenia following chemotherapy for AML. It has been demonstrated in multiple studies to limit the duration of neutropenia without stimulating the regrowth of the leukemic clone. Its side effects include fevers, body aches and allergic reactions. PEG-rHuMGDF is an investigational drug developed by the Amgen Corporation of Thousand Oaks, CA. It is currently employed in a variety of Phase LM studies for the treatment of thrombocytopenia. It is administered by subcutaneous injection and has been associated with minimal side effects (fever and allergic reaction).

E. Medical Devices

No special medical devices will be used in this study. Central venous catheters placed under fluoroscopic guidance will be used at the discretion of the patient and provider. Their use has been associated with a limited risk of pneumothorax, line infection, and localized bleeding.

F. Study Questionnaires

None

G. Study Subjects

a. Inclusion Criteria:

1. Informed consent

2. Newly diagnosed and previously untreated acute myeloid leukemia (AML)
3. Adult patient (aged 20 or greater)
4. Karnofsky score of at least 60
5. Adequate renal function (Cr < 1.5 mg/dl)
6. Adequate hepatic function (bilirubin < 2.0 mg/dL)

b. Exclusion Criteria:

1. AML Subtype M3 (promyelocytic leukemia)
2. AML Subtype M7 (megakaryoblastic leukemia)
3. Presence of the t(15; 17) abnormality by cytogenetic analysis of leukemic cells
4. History of arterial or venous thrombosis Ischemic vascular disease
5. Allergy to E. coli products
6. Extensive prior radiation therapy to > 30% of bone marrow volume
7. Prior cytotoxic chemotherapy
8. Pregnancy or breast feeding
9. Unwillingness to accept blood product transfusions
10. Left ventricular ejection fraction < 50%
11. Peripheral neuropathy

H. Recruitment of Subjects

Patients will be recruited from the inpatient and outpatient areas of the ColumbiaPresbyterian Medical Center. They will be initially approached by their primary medical physician to determine willingness to enroll in investigational therapy. Enrollment appropriateness will be determined by a member of the study team.

I. Confidentiality of Study Data

Study data will be collected on forms and computer media separate from the official hospital record. Study data will be recorded under unique patient numbers that will not allow identification of individual results with enrolled patients. Results and conclusions will not be published or presented in any manner that might personally identify enrolled patients.

J. Potential Conflict of Interest

No investigators involved in this study have a proprietary interest in Amgen, Inc. or its PEG-rHuMGDF product. In addition, no investigator stands to benefit financially from Amgen, Inc. for carrying out this study.

K. Location of the Study

This study will be conducted within the inpatient clinical areas of the Milstein Hospital Building, and the Atchley Pavilion.

L. Potential Risks

Risks of enrollment in this study include the potential for stimulation of the leukemic clone by the study drug. Multiple in vitro studies of AML cell lines have demonstrated a positive growth effect of c-mpl ligand on these cells. Studies of GMand G-CSF effects on AML cell lines have shown similar stimulatory properties in vitro that have not been clinically significant when studied in vivo. Patients randomized to receive PEG-rHuMGDF are at risk for a reduction in the frequency and durability of complete remission following induction chemotherapy on the basis of leukemic cell stimulation by this

c-mpl ligand. To date, however, no evidence has been offered that c-mpl ligand used in vivo stimulates leukemic progression.

M. Potential Benefits

Benefits of enrollment include potential amelioration of thrombocytopenia following induction chemotherapy for AML. This result may reduce the occurrence of lifethreatening bleeding complications due to thrombocytopenia as well as limit the need for platelet transfusions. Reducing platelet transfusions may improve one's chance to successfully undergo allogeneic bone marrow transplantation should future need arise.

N. Alternative Therapies

Alternative therapies to this study include no therapy, conventional induction chemotherapy with platelet transfusion support, and other experimental protocols. Enrollment in this study will not preclude the patient from seeking alternative therapies should he or she fail to respond to this investigational regimen.

O. Compensation to Subjects

There is no compensation for enrollment in this study.

P. Costs to Subjects

There are no additional costs to the patient for enrollment in this study. The cost of the study drug, its administration, and laboratory examinations beyond those needed for routine AML treatment will be covered by the investigators.

Q. Minors as Research Subjects

Individuals less than 20 years of age are excluded from this study.

R. Radiation or Radioactive Substances

None.

S. References

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