

A randomized trial of recombinant human interleukin-11 following high dose chemotherapy and autologous stem cell transplantation in patients with metastatic breast cancer

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A. Study purpose and rationale

Thrombocytopenia is a common toxicity of chemotherapy, especially when given at higher than conventional doses. While transplantation of bone marrow or peripheral blood stem cells after chemotherapy may prevent or shorten the duration of thrombocytopenia, many patients still develop thrombocytopenia severe enough to increase the risk of bleeding. In the past platelet transfusions were the only way of treating severe thrombocytopenia. Recently, however, recombinant human interleukin-11 (IL-11) has been developed as a thrombopoietic growth factor that causes the proliferation of hematopoietic stem cells and induces megakaryocytic maturation. Several randomized placebo-controlled trials have shown that IL-11 shortens the duration of severe thrombocytopenia and reduces the requirement for platelet transfusions in cancer patients receiving chemotherapy (1, 2). One study has shown IL-11 to accelerate platelet recovery when given after high dose chemotherapy and autologous bone marrow transplantation in 18 patients with high risk breast cancer (3). However, another randomized placebo-controlled study of 80 breast cancer patients receiving high dose chemotherapy with autologous stem cell rescue failed to show any significant reduction in platelet transfusion requirements in patients receiving IL-11 compared to those receiving placebo. In retrospect, however, it was realized that there were 12 patients in the IL-11 group who were already alloimmunized at study entry compared to only one such patient in the placebo group (4).

Several clinical trials involving high dose chemotherapy with autologous stem cell rescue are ongoing at New York Presbyterian Hospital, including CAMP 007 for patients with metastatic breast cancer. While G-CSF is incorporated in the standard protocol, IL-11 still is not routinely used, despite data showing an average of 3 to 5 platelet transfusions required for each patient after transplant. Insofar as platelet transfusions are associated with high cost and the risk of infection, transfusion reactions, and alloimmunization, the purpose of this study is to determine whether the use of IL-11 in these patients can reduce their requirement for platelet transfusions and to assess the magnitude of this potential reduction.

B. Study design and statistical analysis

CAMP 007 is an ongoing protocol for patients with metastatic breast cancer consisting of three cycles of high dose chemotherapy, each followed by peripheral blood stem cell rescue and G-CSF (at 5 mcg/kg/day SQ) given until ANC > 1000. The first cycle uses paclitaxel at a dose of 825 mg/m² given as a continuous IV infusion over 24 hours. The second cycle occurs at least 14 days after completion of paclitaxel when ANC > 1000 and platelets > 50,000 and involves melphalan at a dose of 90 mg/m²/day IV x 2 days. The third cycle takes place at least 21 days after completion of melphalan when ANC > 1000 and platelets > 30,000 and involves: cyclophosphamide 1500 mg/m²/day IV x 4 days on days -7 to -4; thiotepa 125 mg/m²/day IV x 4 days on days -7 to -4; carboplatin 200 mg/m²/day IV x 4 days on days -7 to -4; and mesna 1500 mg/m²/day IV x 5 days on days -7 to -3.

This study will be a single-center prospective trial which randomizes subjects admitted for the third cycle of CAMP 007 to receive IL-11 at a dose of 50 mcg/kg given daily as a subcutaneous injection or placebo, to begin four hours after stem cell infusion (day 0) and to continue until the platelet count is > 20,000 for 2 consecutive days, independent of platelet transfusions. Patients will be transfused 6 units of random-donor, pooled platelet which are irradiated and administered through a PAL leukocyte filter when platelet counts are < 20,000. Patients may also be given platelet transfusions when the platelet count

is >20,000 in the presence of bleeding or at the discretion of the bone marrow transplant team. Single-donor HLA-matched platelet transfusions will be used for patients who are alloimmunized,

In addition, prior to randomization patients will be stratified according to: 1.) the amount of CD34+ stem cells/kg they receive (1 to 2.5×10^6 stem cells/kg vs. $>2.5 \times 10^6$ stem cells/kg); and 2.) alloimmunization status. The latter will be determined prior to study entry by testing each patient's blood for titers of lymphocytotoxic antibodies (included in an HLA typing screen); those with antibodies will be considered alloimmunized.

The primary endpoint of this study will be the total number of platelet transfusions required by each patient after high dose chemotherapy and stem cell transplantation. Based on historical data, the median number of platelet transfusions required by patients receiving 1 to 2.5×10^6 stem cells/kg was 5, with a range of 2 to 10. In patients receiving $>2.5 \times 10^6$ stem cells/kg, the median number of platelet transfusions required was 3, with a range of 2 to 9. In order to detect a mean reduction of at least 2 platelet transfusions with IL-11 compared to placebo with >80% power, using a significance level $p = 0.05$, the study will require at least 36 patients (at least 18 patients in each group). In addition, this study will look at the following secondary endpoints: time to platelet recovery ($>20,000$ for 2 consecutive days independent of transfusions), the development of alloimmunization, and the costs associated with IL-11 administration compared with costs associated with platelet transfusion.

C. Study procedures

The study will not involve any additional procedures aside from those outlined in the CAMP 007 protocol (i.e., peripheral blood stem cell harvesting via leukapheresis after mobilization with G-CSF with or without a cycle of induction chemotherapy, performed prior to initiation of the first cycle of CAMP 007).

D. Study drugs

In addition to the chemotherapy and G-CSF which are part of the CAMP 007 protocol (see CAMP 007 protocol for details regarding these drugs), this study will involve the administration of recombinant human IL-11, also known as oprelvekin and *Neumega*. Recombinant human IL-11 is a 177-amino acid polypeptide produced in *E.coli* by recombinant DNA technology and only differs from native IL-11 in lacking the amino-terminal proline residue. It is supplied as a lyophilized powder in vials of 5 mg intended for reconstitution with 1 ml of sterile water to a final concentration of 5 mg/ml. It is FDA-approved to increase platelet counts and decrease the need for platelet transfusions in patients with severe thrombocytopenia caused by chemotherapy for nonmyeloid malignancies (5).

E. Medical devices

This study will not require the use of any medical devices.

F. Study questionnaire

This study will not require the use of any questionnaires.

G. Study subjects

The study will include patients enrolled in the CAMP 007 protocol, according to the eligibility criteria it outlines: Nonpregnant, nonlactating women, age 18 to physiologic 60, with histologically confirmed breast cancer, stage 4, that is in a state of ongoing objective response to cytotoxic chemotherapy, who have completed at least 3 cycles of chemotherapy prior to study entry. They must have no evidence of brain metastases, have no prior history of brain irradiation, have adequate cardiac

(LVEF \geq 45%), renal (Cr <1.5 x normal), and liver function (bilirubin <2 x normal, SGOT <2.5 x normal), with WBC \geq 3000/ul, ANC \geq 1500/ul, and platelets \geq 100,000/ul, and with ECOG performance status 0-1. Patients who have other serious medical conditions, including HIV infection, or psychiatric comorbid disease are excluded. In addition, this study will exclude: patients with a history of thromboembolic disease, stroke, or transient ischemic attacks within the past 6 months; patients with atrial fibrillation or any condition known to increase the risk of atrial arrhythmias; patients with congestive heart failure; patients with any significant bleeding episodes in the past 6 months; patients taking anticoagulants, aspirin, or other NSAIDS within 1 week of study entry. All patients enrolled will sign informed consent, indicating full understanding of the potential risks and benefits of participating in the study.

H. Recruitment of subjects

Study subjects will be recruited from all patients admitted to Milstein Hospital for the third cycle of CAMP 007.

I. Confidentiality of study data

In order to safeguard the confidentiality of the study data and the identity of study subjects, each subject will be assigned a unique study code number. Data will be secured in a locked file in the oncology offices at Milstein Hospital, accessible only to study investigators.

J. Potential conflict of interest

No investigators involved with this study will have any proprietary interest in IL-11 or in its manufacturer, Genetics Institute, Cambridge, MA.

K. Location of the study

The study will be conducted on the bone marrow transplant service at Milstein Hospital, 177 Fort Washington Avenue, New York, NY 10032.

L. Potential risks

In addition to the risks associated with the chemotherapy and stem cell transplant (outlined in CAMP 007), this study has risks associated with the potential toxicity of IL-11. Prior studies have found that patients receiving IL-11 commonly experience fluid retention which is reversible upon discontinuation of the drug. This fluid retention may be associated with mild to moderate generalized edema, dyspnea, increased size of preexisting pleural effusions, as well as a reversible dilutional anemia. Transient atrial tachyarrhythmias have been observed in patients receiving IL-11, which is also presumably related to fluid retention. Other reported side effects of IL-11 include conjunctival injection, arthralgias, and myalgias. Increased levels of C-reactive protein, fibrinogen, and circulating von Willebrand factor have been associated with IL-11, but there have been no observed effects on platelet function or coagulation. In addition, one of 16 patients in a phase I study of IL-11 developed anti-IL-11 antibodies, with no apparent adverse effect (6).

M. Potential benefits

Those patients randomized to receive IL-11 may require a significantly fewer number of platelet transfusions, which may carry the risk of infection, transfusion reactions, and alloimmunization. As its efficacy in reducing the requirement for platelet transfusions has not yet been established in patients

undergoing high dose chemotherapy and stem cell transplantation, this study will help determine if there is any benefit to its standard use in this setting.

N. Alternative therapies

This study will not involve the use of any other experimental therapies to ameliorate chemotherapy-related thrombocytopenia.

O. Compensation to subjects

Subjects will not receive any financial compensation for participation in the study.

P. Costs to subjects

Subjects will not incur any additional costs as a result of participating in the study.

Q. Minors as research subjects

This study will not involve any minors as subjects.

R. Radiation or radioactive substances

This study will not involve radiation or any radioactive substances.

S. References

- 1 Tepler I, Elias L, Smith JW, et al. A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. *Blood* 87:3607-3614, 1996.
- 2 Isaacs C, Robert NJ, Bailey FA, et al. Randomized placebo-controlled study of recombinant human interleukin-11 to prevent chemotherapy-induced thrombocytopenia in patients with breast cancer receiving dose-intensive cyclophosphamide and doxorubicin. *Journal of Clinical Oncology* 15:3368-3377, 1997.
- 3 Champlin RE, Mehra R, Kaye JA, et al. Recombinant human interleukin-11 (rhIL-11) following autologous BMT for breast cancer. *Blood* 84:385a, 1994 (absr, suppl 1).
- 4 Vredenburgh JJ, Hussein A, Fisher D, et al. A randomized trial of recombinant human interleukin-11 following autologous bone marrow transplantation with peripheral blood progenitor cell support in patients with breast cancer. *Biology of Blood and Marrow Transplantation* 4:134-141, 1998.
- 5 Recombinant interleukin-11 for chemotherapy-induced thrombocytopenia. *The Medical Letter* 40:77-78, 1998.
- 6 Gordon MS, McCaskill-Stevens WJ, Battiato LA, et al. A phase I trial of recombinant human interleukin-11 (Neumega rhIL-11 growth factor) in women with breast cancer receiving chemotherapy. *Blood* 87:3615-3624, 1996.