Principal Investigator

First Name: Elizabeth
Last Name: Wright
Degree: phD
Primary Affiliation: NIDDK/NIH
E-mail: wrightel@niddk.nih.gov
Phone number: 301-402-8729
Address: 6707 Democracy Blvd, room 777

City: Bethesda
State or Province: MD
Zip or Postal Code: 20892
Country: USA
SCOPUS ID: 7401796129

General Information

Key Personnel (in addition to PI):
First Name: Daniel
Last name: Wright
Degree: MD
Primary Affiliation: NIDDK/NIH

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Scientific Publication

Conflict of Interest

http://yoda.yale.edu/system/files/coi_ecw.pdf
http://yoda.yale.edu/system/files/coi_dgw.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training
Associated Trial(s):

1. NCT00211133 - A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Impact of Maintaining Hemoglobin Using Eprex (Epoetin Alfa) in Metastatic Breast Carcinoma Subjects Receiving Chemotherapy
2. NCT00270127 - Double-Blind, Placebo-Controlled Study to Assess the Effect of Early Intervention and/or Treatment With Epoetin Alfa on Anemia in Cancer Patients Receiving Non-Platinum-Containing Chemotherapy
3. NCT00270166 - A Placebo-Controlled Study on the Effect of Epoetin Alfa in Patients With Malignancy Receiving Chemotherapy
4. NCT00269997 - The Effect of Subcutaneous r-HuEPO in Patients With Chronic Anemia Secondary to Cisplatin Chemotherapy
5. NCT00266617 - The Effect of Subcutaneous r-HuEPO in Patients With Chronic Anemia Secondary to

Chemotherapy

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Neutropenia in myelosuppressed cancer patients treated with recombinant human erythropoietin (EPO)

Narrative Summary:

Erythropoietin (EPO), a hormone that promotes red blood cell production, has been used for over 25 years to treat anemia. When first used clinically, there were concerns that EPO treatment might cause neutropenia, since EPO had been observed to suppress neutrophil production in marrow cell cultures. While there has been no evidence that EPO suppresses neutrophil production in individuals with normal marrow function, several clinical trials of EPO treatment in cancer patients receiving myelosuppressive chemotherapy have suggested that EPO may exacerbate neutropenia in such patients. Availability of clinical trial data through YODA now provides an opportunity to examine this issue in detail.

Scientific Abstract:

Background: Recombinant human erythropoietin (EPO) has been used extensively for nearly 3 decades to treat various forms of anemia, including anemia associated with cancer treatment. Several randomized, placebo controlled clinical trials have found that EPO can ameliorate anemia, reduce transfusion requirements, and improve quality of life measures in cancer patients receiving myelosuppressive chemotherapy. Results from several of these trials have suggested that EPO may also exacerbate neutropenia in these patients. However, this possible side effect of EPO has not been studied, nor reported, in detail.
Objective: To review primary clinical trial data to determine whether EPO may affect the degree and duration of neutropenia in myelosuppressed cancer patients.
Study Design: Analysis of data from 5 clinical trials of EPO treatment in cancer patients to compare serial blood neutrophil counts (ANCs) of study subjects randomly assigned to either EPO or placebo treatment.
Participants: 1673 study subjects with various forms of cancer enrolled in 5 clinical trials of EPO treatment during myelosuppressive cancer therapy.
Main Outcome Measures: The primary outcome is the number of patients who have at least one ANC value <500/mm3 during 12 weeks of treatment. Secondary outcomes include the number with at least 1 value <250/mm3, mean decreases in ANC, the number of ANC values <500/mm3 and <250/mm3, and the duration of nadirs <500/mm3 and <250/mm3.
Statistical Analysis: Individual patient data meta-analysis will be used to compare ANC changes in the EPO and placebo groups.

Brief Project Background and Statement of Project Significance:

Recombinant human erythropoietin (EPO) was approved by the FDA for treatment of the anemia of chronic renal failure in 1989 and anemia associated with cancer chemotherapy in 1993, based on clinical trial findings that EPO ameliorated anemia, reduced blood transfusions, and improved quality of life. During the past 21/2 decades, EPO treatment has been used widely in the management of both renal failure and cancer treatment, although its use for these indications has decreased in recent years because of concerns about toxicities(1,2).

It was anticipated that EPO treatment might suppress the production of blood cells other than erythrocytes because all blood cell lineages were known to originate from a common pool of bone marrow stem cells(3,4), raising the possibility that lineage competition might occur if one differentiation pathway was pharmacologically amplified. Moreover, it had been observed that EPO had reciprocal effects on erythroid and myeloid cell production in vitro when added to long-term marrow cell cultures(5-7). However, no evidence emerged from extensive clinical experience that EPO treatment alters production of blood cells other than erthrocytes in individuals with normal

marrow function.

Nonetheless, some studies of EPO treatment in individuals with compromised marrow function, e.g. premature newborns(8) and adults undergoing myelosuppressive cancer chemotherapy(9), have suggested that EPO treatment could be associated with an exacerbation of neutropenia. Findings reported from a multicenter trial of EPO treatment in cancer patients, published in 1993(9), serves as an example. Although “no significant (P>0.005) between group differences” were reported for neutrophil or platelet counts in trial participants assigned to EPO treatment vs. placebo in this study, severe neutropenia (ANC <500/mm3) occurred more frequently in trial participants randomized to EPO treatment than in those assigned to placebo, 41% (32 of 79) vs. 31% (23 of 74; Table 5). Moreover, a detailed study of subjects treated at one of the trial’s centers suggested that ANC nadirs were on average lower and delays in successive chemotherapy cycles due to persistent neutropenia more frequent in individuals receiving EPO than in those on placebo(10).

Most published trials of EPO treatment of anemia in cancer patients have provided little or no information about blood counts other than hemoglobin and hematocrit measurements. Detailed adverse event reporting has also been limited. However, two trials reported granulocytopenia (not defined) as an adverse event that was more frequent in patients randomized to the EPO treatment arm than among controls (20% vs. 13%(11,12); and 35% vs. 26%(13)).

A detailed study of the effects of EPO treatment in myelosuppressed cancer patients, as outlined here, will be valuable for a fuller understanding of the biology of EPO-driven erythropoiesis in the setting of compromised hematopoietic reserves and of potential clinically relevant side effects associated with EPO treatment.

Specific Aims of the Project:

To determine whether cancer patients randomized to receive EPO while undergoing myelosuppressive chemotherapy in 5 prospective controlled trials (NCT00211133, NCT00266617, NCT00269997, NCT00270127, and NCT00270166), compared with trial participants randomized to receive placebo, experience nadirs of neutropenia that:
1. Are more common (i.e. more patients with at least one ANC value <500/mm3 or <250/mm3).
2. Are more severe (i.e. greater frequencies of ANC values <500/mm3 or <250/mm3).
3. Are more prolonged (i.e. greater numbers of days with ANC measurements <500/mm3 or <250/mm3).
4. Are associated with lower ANC values on average when expressed as a difference from pre-treatment values.
5. Are associated with more frequent delays in the administration of chemotherapy because of persistent neutropenia following prior cycles of treatment.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment safetyParticipant-level data meta-analysisParticipant-level data meta-analysis uses only data from YODA ProjectOther

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

All randomized patients in the following 5 clinical trials will be included:

NCT00211133, A double-blind, randomized, placebo-controlled study to evaluate the impact of maintaining normal hemoglobin using EPREX® in Metastatic breast cancer patients receiving chemotherapy, N=939, 12 months of treatment.(14)

NCT00266617, A Study to Evaluate the Safety and Effectiveness of Epoetin Alfa in Patients With Anemia as a Result of Advanced Cancer and Treatment With Aggressive Chemotherapy, 12 weeks of treatment, N=86.(9)

NCT00269997, A double-blind, placebo-controlled study to determine the safety and efficacy of r-HuEPO, administered subcutaneously, in patients with anemia secondary to advanced cancer and cisplatin therapy, 12 weeks of treatment, N=72.(15)

NCT00270127, A double-blind, placebo-controlled study to access the effect of early intervention and/or treatment with epoetin alfa on anemia in cancer patients receiving non-platinum containing chemotherapy, 12 – 24 weeks of

treatment, N=375.(11)

NCT00270166, A placebo controlled study of the effect of r-HuEPO in patients with malignancy receiving chemotherapy, 12 weeks of treatment, N=201.

Main Outcome Measure and how it will be categorized/defined for your study:

The main outcome measure is the change in ANC during the 12 weeks following randomization.

For the primary outcome, patients will be categorized into two groups according to whether they develop severe neutropenia, defined as one or more ANC values <500/mm3.

Secondary outcome measures include the following:
1. One or more ANC values <250/mm3
2. Number of ANC values <500/mm3 or <250/mm3,
3. Number of days with ANC values <500/mm3 or <250/mm3,
4. Minimum ANC value, and
5. Maximum change in ANC from baseline during 12 weeks following randomization.

The frequency of delays in administration of chemotherapy because of persistent neutropenia following a prior cycle of treatment and the patterns of ANC decline over 12 months of therapy (NCT00211133 only) are exploratory outcomes.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The main predictor variable is the random assignment to EPO or placebo.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Other independent variables include trial, age, gender, race, type of cancer, EPO dose and frequency, type of chemotherapy, dose and timing of chemotherapy, hemoglobin and CBC at baseline and during follow-up, RBC transfusions, and adverse events. These variables will be included in the analysis of the predictors of severe neutropenia.

Statistical Analysis Plan:

Data will be analyzed using SAS via the remote, secure, password protected data sharing platform. SAS will be used to create analysis data sets from the original form data sets. We anticipate the following analysis data sets:
• Baseline: age, gender, race, type of cancer, hemoglobin, CBC, previous chemotherapy and transfusions
• Laboratory data during follow-up: date of test, hemoglobin, CBC
• EPO: Dose and frequency of administration
• Chemotherapy: Dates and doses for each cycle
• Transfusions
• Adverse events
• Withdrawals from the study.

The primary analysis will use the first 12 weeks of follow-up because data from all studies are available for this time. We will quantify changes in ANC as follows:
• At least one ANC <500/mm3 (<250/mm3)
• Time to first ANC <500/mm3 (<250/mm3)
• Number of ANC <500/mm3 (<250/mm3)
• Number of days with ANC <500/mm3 (<250/mm3)
• Mean change in ANC from baseline to 12 weeks

We estimate that there will be 1673 patients available for analysis. The first three trials randomized patients in a 1:1 ratio, but the last 2 randomized 2:1, EPO to placebo, so we estimate 935 EPO patients and 738 placebo patients. We have used the ClinicalTrials.gov enrollment numbers for NCT00266617 (N=86) and NCT0026997 (N=72), rather than the 157 and 132 included in the linked summaries and the publications. Both publications(9,15)

combined data from 3 trials; it is possible that data are only available for some of the trials.

We have estimated power for a comparison between EPO and placebo groups in the percent of patients with at least one ANC <500/mm3 using PASS.(16) We assumed a two-sided type I error of 5%, a normal approximation to the two-sided z-test, a sample size of 1673 with 55.9% in the EPO group, and placebo rates varying from 10% to 30%. We have calculated the effect sizes that can be found with 95% power since the actual power will be reduced due to missing data and the clustering of patients within studies. The odds ratios that can be detected with 95% power vary from 1.45 (Epo 38%, placebo 30%) to 1.70 (EPO 16%, placebo 10%) depending on the placebo rate. One of the trials, NCT00211133, has a sample size of 939 patients randomized 1:1. It has power to detect odds ratios varying from 1.63 (Epo 41%, placebo 30%) to 1.99 (EPO 18%, placebo 10%) with 95% power. The publication for this trial(14) did not report the incidence of neutropenia during the trial.

Publications are available for 4 of the 5 trials. We will first try to replicate the results of the linked summaries and the publications for each trial.

We will use independent participant data (IPD) meta-analysis to summarize the results of the five trials.(17-21) Our primary approach will be a one-stage analysis, taking into account the clustering of patients within trials, but we will also report the results of two-stage analyses. We will also report results of both random and fixed intercepts (trials), but random effects will be the primary analysis were feasible. We will use SAS PROC GLIMMIX for binary and count data, SAS PROC MIXED for continuous outcomes, and SAS PROC PHREG for time to event data.

Secondary analyses will adjust for baseline variables including age, gender, race, type of cancer, type of chemotherapy, initial EPO dose, hemoglobin and CBC. Exploratory analyses will look at the effect of the dose and timing of chemotherapy and EPO.

We will test for interactions using standard procedures and will use multiple imputation for missing data if needed.

Project Timeline:

Project start date: February 2018
Analysis completion date: July 2018
Manuscript drafted and submitted for publication: October 2018
Results reported back to the Yoda project: January 2019

Dissemination Plan:

The target audience is academic and clinical Hematologists. We expect to produce one publication describing the results of these analyses. The suggested journals are Blood and Experimental Hematology

Bibliography:

1. Leyland-Jones B; BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. Lancet Oncol. 2003 Aug;4(8):459-60.
2. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006 Nov 16;355(20)
3. Till JE, McCulloch EA. A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. Radiat Res. 1961 Feb;14:213-22.
4. Till JE, McCulloch EA. Hemopoietic stem cell differentiation. Biochim Biophys Acta. 1980 Nov 26;605(4):431-59.
5. Dexter TM, Testa NG, Allen TD, Rutherford T, Scolnick E. Molecular and cell biologic aspects of erythropoiesis in long-term bone marrow cultures. Blood. 1981 Oct;58(4):699-707.
6. Salvado AJ, La Russa VF, Kessler SW, Wright DG. Effects of erythropoietin in human long-term marrow cultures. Blood. 1988 Nov; 72 (5, suppl 1): 101a, 1988.
7. Mayani H, Guilbert LJ, Janowska-Wieczorek A. Modulation of erythropoiesis and myelopoiesis by exogenous erythropoietin in human long-term marrow cultures. Exp Hematol. 1990 Mar;18(3):174-9.
8. Beck D, Masserey E, Meyer M, Calame A. Weekly intravenous administration of recombinant human erythropoietin in infants with the anaemia of prematurity. Eur J Pediatr. 1991 Sep;150(11):767-72.
9. Case DC Jr, Bukowski RM, Carey RW, Fishkin EH, Henry DH, Jacobson RJ, Jones SE, Keller AM, Kugler JW, Nichols CR, et al. Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. J Natl Cancer Inst. 1993 May 19;85(10):801-6.

10. Wright DG, St Germaine D, Jacobson RJ. Evidence that recombinant human erythropoietin may exacerbate neutropenia in myelosuppressed cancer patients. Clin Res 1991; 39(2):171a.
11. Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B; Epoetin Alfa Study Group. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2001 Jun 1;19(11):2865-74.
12. Littlewood TJ, Nortier J, Rapoport B, Pawlicki M, de Wasch G, Vercammen E, Schuette W, Wils J, Freund M; Epoetin Alfa Study Group. Epoetin alfa corrects anemia and improves quality of life in patients with hematologic malignancies receiving non-platinum chemotherapy. Hematol Oncol. 2003 Dec;21(4):169-80. Granulocytopenia 20% EPO, 13% PCB. NCT00270127.
13. Grote T, Yeilding AL, Castillo R, Butler D, Fishkin E, Henry DH, DeLeo M, Fink K, Sullivan DJ. Efficacy and safety analysis of epoetin alfa in patients with small-cell lung cancer: a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2005 Dec 20;23(36):9377-86.
14. Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski T, Tjulandin S, Manikhas G, Makhson A, Roth A, Dodwell D, Baselga J, Biakhov M, Valuckas K, Voznyi E, Liu X, Vercammen E. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncol. 2005 Sep 1;23(25):5960-72.
15. Henry DH, Brooks BJ Jr, Case DC Jr, Fishkin E, Jacobson R, Keller AM, Kugler J, Moore J, Silver RT, Storniolo AM, Abels RI, Gordon DS, Nelson R, Larholt K, Bryant E, Rudnick S. Recombinant human erythropoietin therapy for anemic cancer patients receiving cisplatin chemotherapy. Cancer J Sci Am. 1995 Nov-Dec;1(4):252-60.
16. PASS 14. Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.
17. Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. Stat Med. 2017 Feb 28;36(5):855-875.
18. Debray TP, Moons KG, van Valkenhoef G, Efthimiou O, Hummel N, Groenwold RH, Reitsma JB; GetReal Methods Review Group. Get real in individual participant data (IPD) meta-analysis: a review of the methodology. Res Synth Methods. 2015 Dec;6(4):293-309.
19. Simmonds M, Stewart G, Stewart L. A decade of individual participant data meta-analyses: A review of current practice. Contemp Clin Trials. 2015 Nov;45(Pt A):76-83.
20. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF; PRISMA-IPD Development Group. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA. 2015 Apr 28;313(16):1657-65.
21. Thomas D, Platt R, Benedetti A. A comparison of analytic approaches for individual patient data meta-analyses with binary outcomes. BMC Med Res Methodol. 2017 Feb 16;17(1):28.