Strategy for the Use of Erythropoetin Alpha to Maintain Hemoglobin Level in Breast Cancer Patient Treated with Anthracycline-base of Adjuvant Chemotherapy

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Abstract

Objective: To evaluate the value of erythropoietin alpha (epoetin) administration, as an alternative treatment of anemia in the operable breast cancer patients.

Methods: This is a multicenter phase III randomized clinical trial to evaluate the value of epoetin administration among anemic breast cancer patients who are undergoing anthracyclin-based adjuvant chemotherapy. Sixty four patients were incuded in this trial with initial hemoglobin (Hb) level of 10–12 g/dL. The patients were randomly distributed into two groups: one group received aministration of 40,000 IU epoetin/week for six times a week after operation and the other did not. In the third week after the operation, both groups were started on a 6 cycles of adjuvant chemotherapy with three weeks intervals. Hb levels were evaluated during every chemotherapy cycle.

Results: The Hb levels in the epoetin group were always above 10 g/dL up until the end of the sixth chemotherapy cycle or until the twenty first week post operation without blood transfusion.

Conclusions: The administration of epoetin 3 weeks prior and 3 weeks after the first cycles of chemotherapy, maintains a sufficient/normal Hb level in breast cancer patients receiving anthracycline-based chemotherapy.

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Introduction

In the management of operable breast cancer with histopathologically proven lymph nodes metastasis, adjuvant chemotherapy has to be given.[1] For optimal adjuvant chemotherapy result, drug type accuracy, dosage and consistent schedule have to be obtained. However, the inconsistency in therapy sometimes occured due to the side effects of chemotherapy on the hematopoietic system, causing a decrease in the hemoglobin level.

In several studies, some researchers reported that anthracycline-based chemotherapy could lead to 4–63% of anemia, depending on the number of chemotherapy cycles.[2] It is also reported that 25% patients who received 21-day cyclophosphamide, epirubicin, 5-fluorouracil (CEF) regiment [600/60/600 mg/m^2] developed anemia.[3] Other researchers have reported that anemia occurred at the beginning of the first week of chemotherapy in 88.3% patients receiving adriamycin-cyclophosphamide (AC) regiments [60/600 mg/m^2, three weekly].[3] Blood transfusion is the recommended treatment for chemotherapy related anemia. The result is fast achieved but the side effect of blood transfusion should not be ignored. These side effects ranging from allergic reaction to anaphylactic shock with possible risks for viral infections such as hepatitis and human immunodeficiency virus (HIV) infections.[4]

In 2002, the American Society of Clinical Oncology (ASCO) has recommended the usage

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of erythropoietin alpha (epoetin) as a therapy for chemotherapy induced anemia.[5] Epoetin boosts erythrocyte production by proliferating and differentiating the erythroid precursor in the bone marrow. It also stimulates reticulocyte release from bone marrow and increases cellular hemoglobin (Hb) synthesis due to colony forming unit-erythroid (CFU-E) differentiation into erythroblast.[6-10] ASCO recommended that epoetin treatment should be started when the Hb level is ≥10 g/dL but also in mild anemia where the Hb level is 10–12 g/dL. The recommended dosage is 150 IU/kg, three times a week or 40,000 IU once a week.[5] Del Mastro and Venturini reported that in 20–40% cases of patients with Hb <10 g/dL, transfusion was still required even after epoetin alpha was given.[6] This failure may account to the delay in treatment, since epoetin response in cancer patients occurred in a range of 3–12 weeks.

An alternative strategy that can be selected is to use epoetin to prevent the occurence of severe anemia in patients with normal Hb level or mild anemia. The goal of this third phase clinical trial, which was to understand the role of epoetin alpha in maintaining Hb levels in breast cancer patients who was receiving anthracycline-based adjuvant chemotherapy. Positive results of this clinical trial would suggest the use of epoetin alpha to replace blood transfusion and may also be used as a consideration in developing treatment protocols for operable breast cancer patients treated with anthracycline-based adjuvant chemotherapy.

Methods

Research Subjects

This trial involved two groups of operable breast cancer patients, the erythropoietin and control groups. The inclusion criteria were having undergone a modified radical mastectomy with an Hb level ranging from 10 to 12 g/dL and receiving doxorubicin(A)-cyclophosphamide/ fluorouracil-doxorubicin-cyclophosphamide (AC/FAC) or epirubicin-cyclophosphamide/ fluorouracil-epirubicin-cyclophosphamide (EC/ FEC) adjuvant chemotherapy. Patients with anemia due to other causes such as nutritional deficiency, renal malfunction, vitamin (iron, folic acid and B12) deficiency and hypersplenism were excluded from the trial.

This is a multicenter third phase clinical trial study in Department of Surgical Oncology, Dr. Hasan Sadikin General Hospital, Bandung, West Java; Dr. Kariadi General Hospital, Semarang, Central Java; and Dr. Soedarso General Hospital, Pontianak, Kalimantan with paralleled design, 1:1 randomize-controlled. Approval was gained from the Ethical Committee of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

Subjects who met the inclusion criteria were recorded and randomly distributed into the group receiving epoetin or control group. One week folowing the radical matectomy surgery, the epoetin group was given 40,000 IU/week epoetin alpha for 6 times. In the 3rd week both groups underwent adjuvant chemotherapy for 6 cycles with 3 weeks intervals. Hb levels were evaluated in every chemotherapy cycle.

Table 1 Patient Characteristics

Characteristics	Epoetin alpha (n=32)	Control (n=32)
Age (yrs.)		
Mean±SD	43.63±8.167	45.13±8.393
Range	30–63	24–61
Stage		
IIA	30 (93.7%)	2 (6.25%)
IIB	-	29 (90.6%)
IIIA	2 (6.3%)	1 (3.12%)
Hemoglobin (g/dL)		
Mean±SD	11.1±0.67	11.16±0.74
Median	10.9	10.9

SD, Standard Deviation

The level of hemoglobin in the 3rd, 6th and 21st week in both groups were analyzed statistically by using unpaired t-test technique. Data analysis was performed using SPSS for Windows version 13.0. with 95% degree of confidence with a p-value of ≤ 0.05.

Results

Effectiveness and safety evaluation

Sixty four patients were recruited from three centers (Bandung, Semarang, and Pontianak) where 32 patients were given epoetin alpha and 32 patients were included in the control group. The demographic and characteristic distributions of the patients were generally equal in both groups (Table 1).

Need of transfusion

No transfusion was needed during chemotherapy in the epoetin alpha group. In contrast, 9 (28.1%) patients in the control group needed transfusion. Transfusion was mostly required after the 4th cycle or the 12th week post-operation (5 patients, 15.6%) (Table 2).

Hematopoetic responses

It shows the mean level of hemoglobin from the beginning of the clinical trial up to the 21st week in both groups (Fig. 1). Patients in the epoetin alpha group showed a gradual elevation in the mean hemoglobin level, visible in the 3rd week, and reached the hemoglobin level of 12 g/dL after the 6th week and maintained the level of around 11.5 g/dL until the 21st week. There were significant differences from the 3rd week onward (Table 3).

Discussion

Anemia is a common condition found among cancer patients, caused by either the cancer itself, blood loss in the operating procedure, chemotherapy or radiation anemia which will affect the whole organ and tissue function, prognosis of therapy, morbidity, and survival rates of the patient. The common cause of anemia in cancer patients is the cancer itself that causes inadequate production of erythropoietin and vitamin deficiencies (iron, folic acid, and B12), infiltration of cancer cells to the bone marrow, excessive bleeding during the operation, and bone marrow suppression after chemotherapy or radiation. Previous randomized double blind clinical trials with larger sample numbers had shown that recombinant epoetin alpha was effective in treating anemia and was safe for cancer patients.[7,8] However, these earlier studies were generally focused in correction of anemia on patients with hemoglobin levels below 10.5

Table 2 The Need of Transfusion During Chemotherapy

Chemotherapy periods	Weeks	Epoetin group (n=32)	Control group (n=32)
1st chemotherapy	3	-	-
2nd chemotherapy	6	-	2
3rd chemotherapy	9	-	1
4th chemotherapy	12	-	5
5th chemotherapy	15	-	1
6th chemotherapy	18	-	-
Percentage (%)		0 (0%)	9 (28.1%)

Table 3 Statistical Analysis of Hemoglobin Level at Week 3, 6 and 21

	Week	Mean Hb (g/dL)	95% CI	p value
Hemapo Group Control Group	3	11.7 11	0.33–1.11	<0.001
Hemapo Group Control Group	6	12.5 10.9	1.05–2.08	<0.001
Hemapo Group Control Group	21	11.8 10.7	0.71–1.34	<0.001

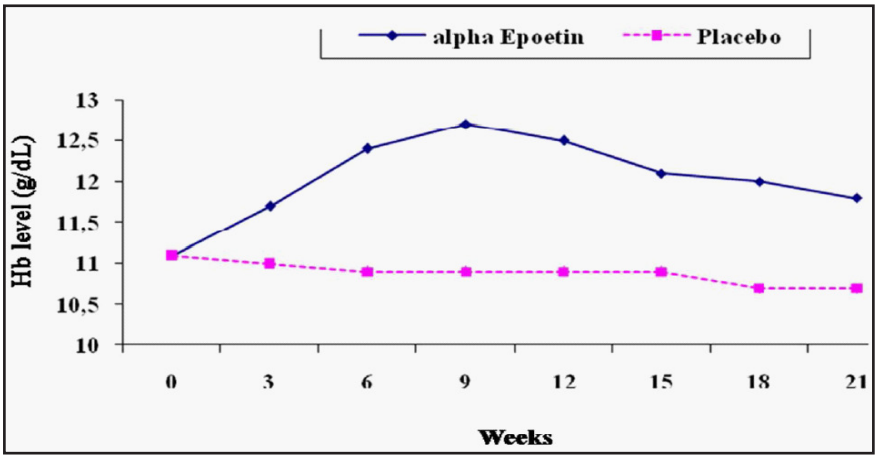

Fig. 1 Mean Level of Hemoglobin During the Clinical Trial

or 11 g/dL, thus circumventing the need for blood transfusion. The benefit of epoetin as a prophylaxis againts anemia in patients undergo chemotherapy has not been fully attested.

Savonije *et al*.[9] compared the admistration of epoetin alpha to supportive therapy on cancer patients who underwent chemotherapy with a goal of evaluating hematologic parameters and the need for transfusion. The study involved 316 patients with hemoglobin stratification baseline <9.7 g/dL, 9.7–10.5 g/dL, 10.5–11.3 g/dL and >11.3 g/dL. The study has shown that erythropoietin increased the Hb level significantly and decreased the need of transfusion. Patients with mild anemia in the epoetin group were able to maintain their Hb level steady and decrease the need for transfusion, which was also seen among patients with a higher initial Hb level. In this study 40,000 IU epoetin alpha was given per week to each patient, started 2 weeks prior to anthracycline-based chemotherapy up to the 2nd cycle or for 6 weeks. It showed that patients receiving epoietin were able to maintain their Hb level above 10 g/dL until the end of the 6th cycle of chemotherapy or until the 21st weeks after the operation without blood transfusion.

Six weeks adminstration of epoetin alpha therapy, three weeks prior and three weeks after the first cycle of anthracyclin-based chemotherapy, maintains the hemoglobulin level in breast cancer patients receiving anthracycline-based chemotherapy.

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Author disclosure statement

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