Gynecologic Oncology 116 (2010) 522–525

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

# Blood transfusion reduction with intravenous iron in gynecologic cancer patients receiving chemotherapy

Penkae Dangsuwan, Tarinee Manchana *

*Gynecologic Oncology Division, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand*

ARTICLE INFO

*Article history:*
Received 21 October 2009
Available online 3 January 2010

*Keywords:*
Anemia
Blood transfusion
Gynecologic cancer
Intravenous iron
Quality of life

ABSTRACT

*Objective.* To compare the incidence of repeated red blood cell (RBC) transfusion in anemic gynecologic cancer patients receiving platinum-based chemotherapy comparing intravenous and oral iron.

*Materials and methods.* Forty-four anemic gynecologic cancer patients (hemoglobin level below 10 mg/dl) who required RBC transfusion were stratified and randomized according to baseline hemoglobin levels and chemotherapy regimen. Study group received 200 mg of intravenous iron sucrose and control group received oral ferrous sulphate 600 mg/day. RBC transfusion requirement in the consecutive cycle of chemotherapy was the primary outcome. Quality of life was evaluated by validated Thai version of the Functional Assessment of Cancer Therapy–Anemia (FACT-An).

*Results.* In a total of the 44 patients, there were 22 patients in each group. Five patients (22.7%) in the study group and 14 patients (63.6%) in the control group required RBC transfusion in consecutive cycle of chemotherapy ($p=0.01$). No significant difference in baseline hemoglobin and hematocrit levels was demonstrated in both groups. Significantly higher mean hemoglobin and hematocrit levels after treatment were reported in the study group ($10.0\pm0.8$ g/dl and $30.5\pm2.4\%$) than the control group ($9.5\pm0.9$ g/dl and $28.4\pm2.7\%$). No significant change of total FACT-An scores was noted between before and after treatment in both groups. No serious adverse events were reported and there was no significant difference among adverse events between both groups.

*Conclusion.* Intravenous iron is an alternative treatment for anemic gynecologic cancer patients receiving platinum-based chemotherapy and reduces the incidence of RBC transfusion without serious adverse events.


## Introduction

Anemia is a common complication in cancer patients which affects patients' physical, functional and emotional well-being and impairs quality of life [1]. A negative correlation between anemia and survival has been reported in anemic cancer patients including gynecologic cancer patients [2]. The etiology of cancer-related anemia is multifactorial, such as bleeding, hemolysis, impaired iron absorption, nutritional deficiency, renal dysfunction resulting in decreased erythropoietin synthesis, bone marrow metastasis, and myelosuppression from cancer treatment. Another common cause is anemia of chronic disease which is a cytokine-mediated disorder. Tumor cells can produce proinflammatory cytokines resulting in erythroid progenitor cell suppression, impaired erythropoietin production, impaired iron utilization, and decreased erythrocyte's half-life [3]. Inflammatory cytokines, such as interleukin-6, induce the hepcidin synthesis by hepatocytes. Hepcidin will inhibit iron transport across cell membranes by down-regulated ferroportin expression, a transmembrane iron exporter. As this result, it decreases both iron release from the reticuloendothelial cells and duodenal enterocytes to the circulation [4]. These effects cause functional iron deficiency, which is characterized by insufficient available iron at the site of erythroblast production (iron restricted erythropoiesis) but adequate iron stores [3].

Anemia is defined as a hemoglobin level below 12 g/dl [5]. Red blood cell (RBC) transfusion is usually administered to patients with moderate (8–10 g/dl) to severe (below 8 g/dl) anemia. Treatment options for chemotherapy-related anemia usually include oral iron supplementation and RBC transfusion. However, oral iron has gastrointestinal side effects, which affects patient compliance, and only a small amount of oral iron can be absorbed from the gastrointestinal tract. Compliance issues may be greater in the patients receiving chemotherapy. Although RBC transfusion is widely used as a rapid and effective treatment, it has the risks of blood transfusion reaction and blood transmitted disease. Intravenous iron has been used in cancer patients with chemotherapy-related anemia. It may overcome a block of iron absorption and iron recycling induced by hepcidin. A few studies reported significant improvement in hemoglobin level and reduced RBC transfusion with this therapy [6]. However, these reports investigated the effectiveness of intravenous iron in combination with erythropoiesis stimulating agents (ESAs).

* Corresponding author. Fax: +66 2 2549292.
*E-mail address:* T_manchana@hotmail.com (T. Manchana).

0090-8258/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2009.12.004

ESAs can prevent chemotherapy-induced anemia and can reduce the need of RBC transfusions when administered concomitantly with chemotherapy regimens that produce a high incidence of anemia [7]. However, they have been reported to increase the risk of thromboembolism and stimulate tumor growth with a negative effect on survival [8,9]. Furthermore, high expense may limit their usage especially in a low resource setting. In our clinical practice guidelines, ESAs are not prescribed routinely and RBC transfusion will be given when the hemoglobin level is below 10 g/dl. At least one-fourth of our gynecologic cancer patients, receiving chemotherapy, met criteria for RBC transfusion. Almost all of them developed anemia after the second or third cycles of chemotherapy. Up to 80% of these patients required RBC transfusions in the consecutive cycles. Therefore, we conducted this randomized trial aiming at exploring whether intravenous iron could reduce RBC transfusions in anemic gynecologic cancer patients receiving platinum-based chemotherapy.

## Materials and methods

A prospective randomized study was conducted. Eligible patients had ovarian cancer, endometrial cancer, or synchronous ovarian and endometrial cancer. They underwent primary surgery and were receiving first-line platinum-based chemotherapy during August 2008 to July 2009. Chemotherapy regimens included single agent carboplatin and combinations of carboplatin with paclitaxel or docetaxel. All of them met criteria for RBC transfusion which was defined as hemoglobin level below 10 g/dl. Inclusion criteria were patients aged 20–65 years, normal liver and kidney function, no prior radiotherapy or having received radiotherapy, and had at least 1 remaining cycle of chemotherapy. Patients with iron hypersensitivity, risk of iron overload such as chronic renal failure or thalassemia major, progressive disease, bone marrow metastasis, and inability to monitor weekly complete blood counts were excluded. The study profile is shown in Fig. 1.

This study was approved by the ethics committee of Chulalongkorn University. Informed consent was obtained from all patients before participation into this study. Primary outcome was the incidence of RBC transfusion at the consecutive cycle of chemotherapy between oral and intravenous iron. Secondary outcomes were hemoglobin and hematocrit increment, number of RBC transfusion units, and adverse events in both groups. Quality of life (QOL) was evaluated by validated Thai version of the Functional Assessment of Cancer Therapy–Anemia (FACT-An, version 4). FACT-An is a 47-item cancer-specific questionnaire consisting of a core 27 items general questionnaire (FACT-G) and a 20-item anemia additional concerns subscale. The general questionnaire includes 4 subscales: physical, social/family, emotional, and functional well-being. Each item score ranges from 0 to 4. Higher FACT-An score represents a better quality of life [10].

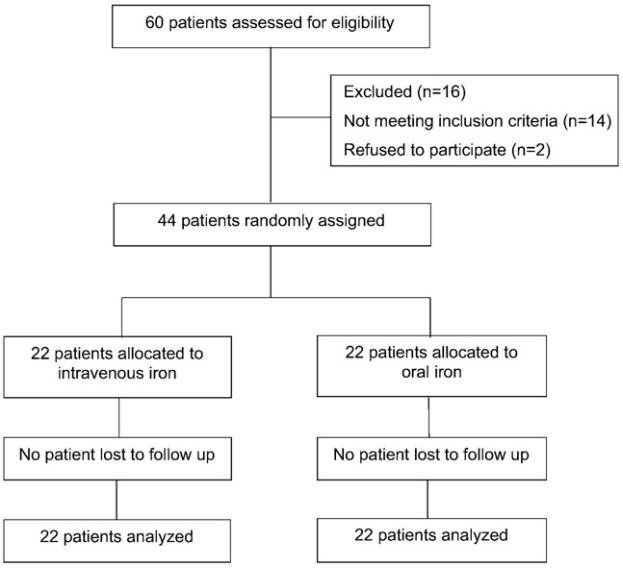


**Fig. 1.** The study profile.

All patients received RBC transfusion before chemotherapy infusion according to the standard protocol of our gynecologic oncology division. The units of RBC transfusions depended on the hemoglobin level as follows: 1 unit if hemoglobin 9–9.9 g/dl, 2 units if hemoglobin 8–8.9 g/dl, and one additional unit will be added for every 1 g/dl decline of hemoglobin level. The patients were stratified and randomized according to baseline hemoglobin level and chemotherapy regimen. Randomization was done using a random table. The study group received 200 mg of iron sucrose (Venofer®) by intravenous drip over 30 minutes. The control group received 200 mg of oral ferrous three times a day. FACT-An questionnaires were completed at before and after treatment. A complete blood count was monitored weekly in both groups. RBC transfusion requirements in the consecutive cycle of chemotherapy and adverse events were recorded.

Data were analyzed using parametric and nonparametric statistics. $\chi^2$ Test was used to compare categorical data, and continuous variables were evaluated by Student's *t*-test. Median values were compared using Mann–Whitney *U* test. A difference was considered significant when the probability of being due to random chance was below 5% ($p<0.05$).

## Results

Forty-four patients were included in this study with 22 patients in each group. Patients' characteristics, such as age, type of cancer, histology, chemotherapy regimen, pretreatment hemoglobin and hematocrit, and number of RBC transfusion units were not significantly different between both groups (Table 1).

Five patients (22.7%) in the study group and fourteen patients (63.6%) in the control group required RBC transfusion in consecutive

**Table 1**
Patients' characteristics.

| | Control ($N=22$) | Study ($N=22$) | *p* value |
|---|---|---|---|
| Mean age ± SD (years) | 53.0 ± 8.7 | 49.6 ± 8.1 | 0.19 |
| Diagnosis | | | |
| CA ovary | 19 (86.3%) | 19 (86.3%) | 0.55 |
| CA corpus | 0 (0%) | 1 (5%) | |
| Two primary | 3 (13.6%) | 2 (9.1%) | |
| Histology | | | |
| Endometrioid | 6 (27.3%) | 8 (36.4%) | |
| Clear cell | 6 (27.3%) | 4 (18.2%) | 0.67 |
| Serous | 5 (22.7%) | 5 (22.7%) | |
| Mucinous | 2 (9.1%) | 1 (4.5%) | |
| Other | 3 (13.6%) | 4 (18.2%) | |
| Surgical outcome | | | 1.00 |
| Optimal debulking | 14 (63.6%) | 13 (59.1%) | |
| Suboptimal debulking | 8 (36.4%) | 9 (40.9%) | |
| ECOG performance status | | | |
| 0 | 3 (13.6%) | 1 (4.5%) | 0.50 |
| 1 | 14 (63.6%) | 17 (77.3%) | |
| 2 | 5 (22.7%) | 4 (18.2%) | |
| Regimen | | | |
| Carboplatin and paclitaxel | 18 (81.8%) | 19 (86.4%) | 0.84 |
| Carboplatin | 2 (9.1%) | 2 (9.1%) | |
| Carboplatin and docetaxel | 2 (9.1%) | 1 (4.5%) | |
| Hemoglobin level | | | |
| 8.0–8.9 g/dl | 9 (40.9%) | 8 (36.4%) | 0.76 |
| 9.0–9.9 g/dl | 13 (59.1%) | 14 (63.6%) | |
| Mean pretreatment hemoglobin ± SD (g/dl) | 9.0 ± 0.6 | 8.9 ± 0.6 | 0.76 |
| Mean pretreatment hematocrit ± SD (%) | 27.6 ± 1.9 | 27.3 ± 1.8 | 0.45 |
| Median unit of RBC transfusion before treatment (range) | 1 (1–2) | 1 (1–2) | 0.91 |