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ORIGINAL ARTICLE

A randomized trial of anemia correction with two different hemoglobin targets in the first-line chemotherapy of advanced gastric cancer

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Abstract
Purpose To evaluate if raising baseline and maintaining hemoglobin (Hb) levels with red blood cell (RBC) transfusion could improve the outcomes of chemotherapy for advanced gastric cancer (AGC).
Methods Patients were randomized to receive RBC transfusion to maintain their Hb levels ≥10 g/dl (arm 1) or ≥12 (arm 2) before the start of their 5-fluorouracil-based first-line chemotherapy. Objective response, KPS and quality of life (QOL) data were measured.
Results For 87 patients enrolled, mean baseline Hb was 10.1 g/dl, and 54 patients received RBC prior to chemotherapy initiation. Despite transfusion, we failed to maintain the Hb level above the predefined target range. Eighteen patients experienced brief and reversible adverse events during transfusion, including two patients with acute pulmonary edema. KPS was improved from baseline to post-chemotherapy in both arms. QOL data showed improvement in some symptom scores, but there was no difference in the QOL scores between the two arms at baseline and all four cycles of treatment. Similar response rates were observed in both arms (arm 1, 30%; arm 2, 35%). Both arms showed similar chemotherapy duration (3.8 and 4.1 months, respectively), progression-free survival (4.0 and 4.1 months) and overall survival (9.9 and 9.3 months).
Conclusions Red blood cell transfusion achieving Hb level above 10 g/dl might contribute to the improvement of the KPS and QOL seen in patients with AGC. The observation of equivalent outcomes at the two target Hb levels supports the feasibility of anemia correction to Hb 10 g/dl, which merits further evaluation.

Keywords Anemia · Transfusion · Chemotherapy · Stomach cancer

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Introduction

Anemia, in the presence or absence of treatment, is common among cancer patients [1]. A number of factors contribute to the high incidence of cancer-related anemia [2]. These include not only chemotherapy and radiation-induced myelosuppression, but also bleeding, hemolysis, marrow infiltration by tumor, nutritional deficiencies, and cytokine-mediated anemia of chronic disease. Approximately 41% of patients with advanced gastric cancer (AGC) had a hemoglobin (Hb) level <10 g/dl at presentation [3], and most of the remainder would develop anemia during their initial chemotherapy. In a retrospective survey of patients with solid tumors being treated with chemotherapy, 33% of patients required at least one red blood cell (RBC) transfusion [4]. Over 60% of patients included in the European Cancer Anaemia Survey (ECAS) who developed anemia did not receive treatment for this condition [5]. In addition to its negative impact on health-related quality of life (QOL) in patients with cancer [6–9], anemia is associated with reduced tumor control and reduced survival [10].

For patients with AGC, standard chemotherapeutic agent for several decades has been 5-fluorouracil (FU) [11, 12]. In vitro studies have demonstrated that cancer cells responding to FU became resistant under hypoxic conditions [13, 14]. Hypoxia-derived proteome and

genome changes in tumors can lead to a more aggressive phenotype and malignant progression [15–17]. Furthermore, anemia has been shown to have an adverse effect on patients' treatment outcomes. In patients with AGC, baseline Hb level was one of the most important adverse prognostic factors for chemotherapy response and survival [3]. As well as the adverse effect of tumor hypoxia, the underlying presumption is that anemia may reduce the ability to respond to chemotherapy. Anemia may also result in a lower level of performance whereby, less chemotherapy is tolerated or more toxicity develops. It is also possible that patients with anemia receive less chemotherapy overall.

To date, no data of randomized trials were available that indicated whether the correction of anemia before initiating chemotherapy can enhance the effectiveness of chemotherapy in AGC patients. In our previous observation [3], RBC transfusion prior to chemotherapy had no prognostic role in terms of response rate or survival. Although Hb level may be prognostic, it is unclear whether raising baseline Hb level can directly impact treatment outcomes. It is also questionable whether anemia itself is the direct cause of poor outcomes or is instead a surrogate marker for other adverse prognostic factors. To clarify this, we designed a randomized study to evaluate if raising baseline and maintaining Hb levels (targets, 12 vs. 10 g/dl) with RBC transfusion could enhance the effectiveness and tolerability of FU-based first-line chemotherapy for AGC. Target Hb level of 12 g/dl was used based on the maximum QOL benefits observed in patients who achieve Hb levels of 12 g/dl [18], and the European Organisation for Research and Treatment of Cancer (EORTC) guidelines [19]. Our goal was to conduct a pragmatic study with broad entry criteria that did not require specialized regimens or procedures, thus providing results widely applicable to a routine clinical practice.

Patients and methods

Eligibility

This study was a single-center, randomized phase II trial. Adult patients with a confirmed diagnosis of measurable AGC and scheduled to receive FU-based first-line chemotherapy for metastatic/recurrent disease were enrolled. The only requirements for participation were that patients be receiving palliative chemotherapy and that be free of evidence of ongoing blood loss at study entry. Exclusion criteria included clinically significant dysfunction of major organs not attributable to the malignancy or chemotherapy that would likely result in early withdrawal from the study, known history of adverse events with blood products and relevant acute or chronic bleeding. The possible benefit and harm of RBC transfusion were fully discussed with each patient, and all patients gave written informed consent before randomization. The protocol was reviewed and approved by Gil Medical Center (Incheon, South Korea) institutional review board.

Medical history and physical examination, determination of Karnofsky performance status (KPS), complete blood counts (CBC), serum chemistry, chest X-ray, computed tomography scan of abdomen and pelvis, and upper gastrointestinal endoscopy to rule out ongoing bleeding were obtained before treatment.

Treatment and evaluation

The chemotherapy regimen to be used was determined by the treating physician but restricted to FU-based. Chemotherapy was repeated every 3 or 4 weeks according to the regimen. Dosage of the subsequent cycles was adjusted according to the toxic effects that developed during the preceding cycle. All patients received standard supportive regimen but no prophylactic administration of hematopoietic growth factors, including colony stimulating factors or erythropoietic growth factors, was allowed. Although measurements of serum ferritin and iron level were not mandatory, patients with baseline transferrin saturation <20% and/or serum ferritin level <100 ng/ml were allowed to receive oral iron supplements at the discretion of the physician. Subsequently, they were randomly assigned to receive RBC transfusion to raise their baseline and to maintain Hb levels $\geq$10 g/dl (arm 1) or $\geq$12 g/dl (arm 2) during chemotherapy cycles. However, before the enrollment of first patient, protocol was amended that RBC transfusion was given for four cycles of chemotherapy. Only outcomes that were achieved during the first four cycles were analyzed, because clinical responses generally occur within the first few cycles of chemotherapy and to avoid possible cumulative complications of transfusion. The number of RBC units administered was calculated according to the guideline provided by American Association of Blood Banks [20]. According to current department policy, all patients had to be admitted to the hospital during transfusion and chemotherapy administration and the routine use of leukodepleted RBC was given. Patients' baseline CBC were measured and recorded 1 or 2 days before the initiation of chemotherapy. In cases requiring RBC transfusion, Hb levels were measured repeatedly after the completion of transfusion. However, no more transfusions were allowed if the patient's Hb level did not reach the predefined target.

Objective response rate was the primary endpoint and was evaluated according to World Health Organization criteria. In brief, a complete response was defined as

disappearance of all known cancer, whereas a partial response was a decrease of 50% or more in the sum of the largest diameters of all lesions. Progressive disease was defined as a 25% or more increase in the size of at least one measurable lesion or the appearance of a new lesion. All tumor measurements were assessed after every two cycles of chemotherapy and reviewed by an independent investigator, blinded to the study results, later at the time of analysis. The secondary endpoints were chemotherapy duration, survival and the impact of treatment on KPS and QOL. The starting point of various time intervals was the day of randomization.

Quality of life was measured with the EORTC QLQ-C30 questionnaire, which was completed at baseline and the end of each chemotherapy cycles. Validated Korean versions of EORTC QLQ-C30 questionnaires were used [21, 22]. EORTC QLQ-C30 contains 30 questions addressing various aspects of QOL. Missing items were analyzed using the method advocated by the EORTC QOL Study Group [23]. If at least half of the items from a scale were completed, the values of missing ones were imputed as the mean value of the completed items. All questionnaires were distributed and collected by a research nurse. Adverse events were recorded regardless of their relationship to transfusion or chemotherapy itself.

Statistical consideration

The random allocation sequence was generated by a table made from the permuted block method. A permuted block size of four was used but there was no stratification. This randomized phase II trial was treated, statistically, as two simultaneous phase II studies and the Fleming's single-stage design was applied separately for each treatment group. The sample size estimation was based on the assumption that the absolute difference in response rates would be 15% or greater. With a significance level set at 0.05, a power of 0.80, and a dropout rate of 10%, 43 patients per group were required. Hb levels, KPS and QOL scores are presented as means ± SD. In this design, the target Hb level with the higher response rate is to be selected, irrespective of the difference. Since a selection design was chosen, no formal statistical comparisons between arms were planned. Within-arm comparisons were made using the Wilcoxon matched-pairs test, where appropriate. To determine the impact of clinical and treatment variables on chemotherapy response, multiple logistic regression, fixed and stepwise, models were used. All analyses were performed on the intent-to-treat population, defined as all randomized patients who signed informed consent. Only the hypothesis regarding the primary endpoint was statistically tested with a two-sided level of significance of 5%.

Results

Patients

Eighty-seven patients who received FU-based first-line chemotherapy for AGC were registered between January 2004 and August 2005. Three patients were not evaluable for responses: one patient in arm 1 did not receive chemotherapy because he declined the consent before treatment, and two patients in arm 2 discontinued after receiving their first cycle of chemotherapy due to a rapid clinical deterioration. Baseline patient and disease characteristics are summarized in Table 1. Although there were some discrepancies between arms in terms of patients' age ($P = 0.169$) and the use of anthracyclines ($P = 0.129$), no differences reached statistical significance. A majority of patients (73%) had two or more metastatic disease sites, mostly involving peritoneum and abdominal lymph node. The most commonly used chemotherapy regimen was the combination of cisplatin and infusional FU or capecitabine (30 patients for both arms), followed by taxane plus 5-day FU (27 patients). As expected, 89% of patients had baseline Hb < 12 g/dl and approximately 44% had Hb < 10 g/dl at baseline.

Transfusion requirements

At baseline, 54 patients received RBC transfusion (36 units in arm 1 and 73 units in arm 2; $P < 0.001$) prior to chemotherapy initiation. Despite pretreatment transfusion, 7 patients in arm 1 (16 RBC units) and 21 in arm 2 (45 RBC units) had transfused again before the start of their second cycle of chemotherapy (Fig. 1).

Red blood cell transfusion was well tolerated. The overall incidence of adverse events and the incidence of individual toxicities were generally similar between the two arms (Table 2). Eighteen patients experienced brief and reversible adverse effects during transfusion, which were predominantly febrile non-hemolytic transfusion reactions. Two patients in arm 2 experienced acute pulmonary edema which was reversed with diuretics. Development of new alloantibody was detected in three patients. No patient discontinued the study because of transfusion-related adverse events.

Quality of life

When the baseline KPS was compared with that recorded at the end of third cycle, there was a significant improvement in KPS in both arms ($P < 0.001$; Fig. 2). A significant improvement in KPS became apparent by the start of second cycle. For patients in arm 1, KPS was improved, but not maintained after third cycle. There was a trend toward a

Table 1 Patient and treatment characteristics

	Arm 1 (Hb ≥ 10 g/dl)	Arm 2 (Hb ≥ 12 g/dl)
Number of patients	44	43
Treated	43	43
Age (years)		
Median	55	61
Range	28–74	32–75
Male gender	23	30
Karnofsky performance status		
Median	80	80
Range	70–100	70–100
Site(s) of metastatic disease[a]		
Abdominal lymph node	27	29
Peritoneum	17	18
Liver	14	11
Lung and/or malignant pleural effusion	6	7
Ovary	4	5
Bone	1	2
Supraclavicular lymph node	6	4
Brain	1	0
Type of fluoropyrimidine		
Protracted infusional 5-fluorouracil	18	16
5-day Infusional 5-fluorouracil ± folinic acid	19	20
Capecitabine	6	7
Concomitant drug(s)		
Cisplatin	19	17
Taxanes	13	14
Anthracyclines	2	6
Baseline hemoglobin level (g/dl)		
Mean ± SD	10.33 ± 1.79	10.20 ± 1.27
Mean corpuscular volume (fl)		
Mean ± SD	89.5 ± 7.87	89.6 ± 6.79

[a] Because patients could have metastases at multiple sites, the total numbers of metastases are greater than the number of patients

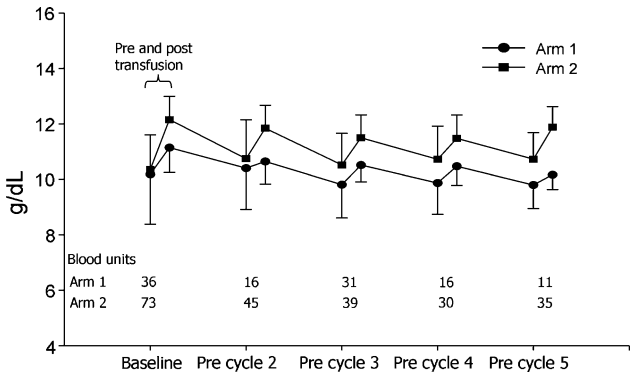

Fig. 1 Mean (SD) hemoglobin levels before and after transfusion. Arm 1, hemoglobin target ≥10 g/dl; arm 2, hemoglobin target ≥12 g/dl. At all time point post-transfusion, there was significant ($P < 0.001$) difference between the two arms

sustained improvement in duration of improvement in KPS for arm 2.

Quality of life questionnaires were completed by 49 patients at baseline, 35 at the end of third cycle and 31 at the end of fourth cycle (Table 3). The highest scores of the symptoms scales and single items were assigned to fatigue (45) and constipation (36). The QOL data indicated that the global, functional and symptoms scores were almost identical for the two arms at baseline, and also after the completion of subsequent cycles of chemotherapy.

Over this period, analyses of mean changes from baseline in the QOL scores demonstrated clinically meaningful (≥10 points) improvements including fatigue, pain, dyspnea, constipation and diarrhea. However, no relevant difference between arms was detected in the proportion of

Table 2 Transfusion- and treatment-related adverse events (all grade)

	Arm 1		Arm 2	
	No. of patients	Percentage	No. of patients	Percentage
Transfusion related				
Hemolysis, acute or delayed	0	0	0	0
Fever	8	19	10	23
Allergy with urticaria	8	19	9	21
Pulmonary edema, acute	0	0	2	5
Viral infection	0	0	0	0
New alloantibodies	2	5	1	2
Chemotherapy related				
Neutropenia	28	65	23	54
Neutropenic infection	7	16	8	19
Thrombocytopenia	10	23	11	26
Fatigue	11	26	9	21
Nausea and vomiting	25	58	23	54
Oral mucositis	12	28	16	37
Diarrhea	13	30	14	33
Constipation	11	26	9	21

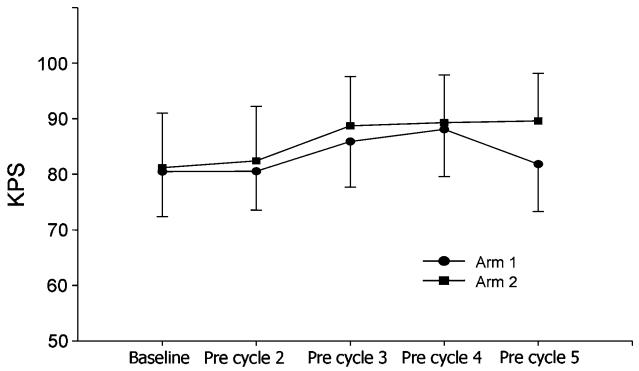

Fig. 2 Pre-chemotherapy mean (SD) Karnofsky performance status, measured before each chemotherapy cycles

patients reporting QOL improvements from baseline to post-chemotherapy.

Treatment outcomes

There was no significant difference in the number of chemotherapy cycles ($P = 0.537$), with 188 cycles given for arm 1 (median 4, range 0–9) and 203 cycles for arm 2 (median 5, range 1–12). The duration of chemotherapy also was similar for both arms (median 3.8 vs. 4.1 months, respectively; $P = 0.773$). Reasons for discontinuation of chemotherapy were equally distributed in both arms, the main reason being progressive disease (61% in arm 1 vs. 65% in arm 2).

The overall response rate was 37% (95% confidence interval, 27–47%). The overall response rate in an intent-to-treat analysis was similar between both arms (30 vs. 35%; $P = 0.350$). As expected, when we grouped patients according to the baseline Hb levels, significant difference in the response rate was observed: 45% for patients with baseline Hb ≥ 10 g/dl vs. 19% for patients with Hb < 10 g/dl ($P = 0.011$). Both arms also showed similar progression-free (4.0 and 4.1 months) and overall survival (9.9 and 9.3 months).

The different transfusion strategy, age, KPS, chemotherapy regimen and baseline Hb level were considered predictors for clinical response. In a fixed logistic regression analysis with these five variables, only the baseline Hb level (odds ratio, 0.249 in cases where Hb ≥ 10 g/dl) and age (odds ratio, 1.066 per year) were independently related to the probability of response to chemotherapy. To investigate whether some interactions were also related to this probability a stepwise logistic regression was done. Again, only the baseline Hb level (odds ratio, 0.289) and age (odds ratio, 1.064) were significantly related to the probability of response.

Discussion

Because anemia is associated with reduced QOL, reduced performance status and resistance to anti-cancer therapy, an active approach to anemia management is essential to improve the overall quality of care in patients with cancer. American Society of Clinical Oncology and the American Society of Hematology (ASCO/ASH) guidelines recommended starting anemia treatment when Hb levels declined to 10 g/dl or less [24]. Treatment initiation in patients with

Table 3 Patients mean scores on EORTC QLQ-C30

	Baseline		Post cycle 1		Post cycle 2		Post cycle 3		Post cycle 4	
	Arm1 (n = 26)	Arm2 (n = 23)	Arm1 (n = 26)	Arm2 (n = 23)	Arm1 (n = 20)	Arm2 (n = 23)	Arm1 (n = 19)	Arm2 (n = 16)	Arm1 (n = 16)	Arm2 (n = 15)
Global health/QOL[a]	63	66	57	63	63	77	65	71	70	70
Functional scales[a]										
Physical	77	81	73	78	77	79	78	82	77	85
Role	69	74	74	78	71	74	64	80	73	71
Emotional	71	75	73	80	78	78	77	72	78	73
Cognitive	77	80	85	91	85	88	76	84	81	80
Social	73	72	69	76	67	72	54	63	59	60
Symptom scales[b]										
Fatigue	45	44	36	27	26	37	27	22	21	24
Nausea/vomiting	18	17	22	19	17	33	15	17	15	12
Pain	28	28	15	11	14	15	24	17	19	21
Dyspnea	32	31	24	32	18	26	19	13	12	19
Insomnia	26	25	22	13	16	18	26	15	16	21
Appetite loss	25	21	44	23	39	26	36	31	42	22
Constipation	36	32	20	20	13	22	19	18	12	33
Diarrhea	17	22	16	7	9	8	9	9	11	9
Economic impact	30	35	27	18	30	44	40	48	38	47

[a] Scores range from 0 to 100, with a higher score representing a higher level of function

[b] Scores range from 0 to 100, with a higher score representing a higher level of symptom

Hb between 10 and 12 g/dl, and symptomatic due to anemia, was left to the discretion of the physician. More recently, EORTC published evidence-based guidelines for the management of anemia in cancer patients [19]. The guidelines endorse early initiation of treatment with erythropoietic growth factor at Hb levels of 9–11 g/dl, with the aim of achieving and maintaining Hb levels of 12–13 g/dl. Although transfusion is the fastest way to alleviate symptoms, the present guidelines would encourage that erythropoietic growth factor is started simultaneously in such patients.

However, there are inconclusive evidences suggesting that anemia may have an adverse impact on treatment outcomes in cancer patients undergoing chemotherapy. EORTC concluded that there are currently insufficient data available to determine the impact of erythropoietic growth factors on tumor growth or survival in cancer patients [19]. We recently reviewed retrospectively the association between baseline Hb level, tumor control and survival in 511 patients with AGC who were treated with FU-based first-line chemotherapy for metastatic disease [3]. Patients with baseline Hb level < 10 g/dl had significantly lower response rate and overall survival than those with Hb 10 g/dl or more. Although the results suggested that anemia had a detrimental effect on chemotherapy outcomes, it is unclear whether there is a point during chemotherapy at which it is most critical to maintain patients' Hb levels. Another study found that the nadir Hb level was the most predictive factor for treatment failure, whereas baseline Hb level was insignificant [25]. On the other hand, it has been suggested that an earlier Hb response leads to better clinical outcomes [26].

The results of this study demonstrate that RBC transfusion with two different Hb targets can be safely and effectively performed in first-line chemotherapy of AGC. Although we planned initially to maintain patients' Hb level throughout the chemotherapy period, the relevance of this maintenance of nadir Hb levels was hampered by the transient effect of transfusion on Hb levels and amelioration of anemia. There was a significant improvement in KPS in both arms, and the number of chemotherapy cycles given was similar. The KPS, QOL and chemotherapy response are correlated [27]. However, when we further compared the response rate, there was no difference between the two arms (30 vs. 35%). The results of the current study demonstrated the possible benefit in terms of improved KPS but questionable acceptability of the correction of Hb to near-normal levels with RBC transfusions. While it is possible that a negative interaction occurred between transfusion and chemotherapy, the improved KPS and the absence of significant transfusion-related toxicity makes this an unlikely explanation. Another explanation might be that the patient population studied is not only anemic at baseline but is also prone to develop anemia during chemotherapy.

Despite RBC transfusions, pre-transfusion Hb levels at each chemotherapy cycles were still low (Fig. 1). It is still questionable whether anemia is a prognostic factor that cannot be altered simply by RBC transfusion or simply a marker of patients with more aggressive and advanced disease.

The compliance of patients in the QOL analysis was generally poor for both arms (65% at baseline and 48% at the end of third cycle). The low compliance rate makes interpretation of the results difficult and raises the risk of bias owing to ill patients being unable to complete QOL questionnaires or staff being unwilling to approach them. However, there was no significant difference in QOL scores over time between two arms. Symptom resolution was impressive and comparable in both arms particularly in fatigue, pain, dyspnea, constipation and diarrhea. This is encouraging, although no further improvement with a higher Hb target, for this group of patients who frequently present with such anemia-related symptoms. One may argue that the positive effect of transfusion on KPS and QOL could be an overestimate since it is not possible to determine whether the improvements in these parameters were due to anemia correction or simply due to other confounding factors such as the clinical response to chemotherapy. The only way to truly answer this question would have been to have "no" transfusion arm.

It was also interesting to note, in addition to the high prevalence of anemia in patients with AGC, the significantly high symptoms scores at baseline. In particular fatigue is a main component of anemia symptomatology, but that is under-recognized by physicians [28]. This demonstrates the absolute requirement to use patient-assessed QOL in studies in which evaluation of symptoms is a major end point.

Anemia in cancer patients is often treated with RBC transfusion or administration of erythropoietic growth factors. Erythropoietic growth factors effectively raise Hb levels and decreases transfusion requirements in 50–60% of anemic cancer patients [8, 29]. However, it takes some patients the relatively long time to achieve a hematopoietic response (up to 12 weeks) [30]. In the present guidelines [19, 24], there was inconclusive evidence available on the safety of erythropoietic growth factors, namely incidence of thromboembolic events and hypertension. The requirement for frequent injection schedule necessitates frequent patient visits to oncology clinics, which may not coincide with routine clinical practice. Furthermore, many patients do not respond to erythropoietic growth factors when given at recommended dosages, and currently there are no reliable means of predicting whether a patient will respond. In this study, RBC transfusion was chosen to correct anemia because we wanted to know whether raising baseline Hb level can directly impact chemotherapy response. Within the limitations of some perceived risks such as infections and hemolytic reactions, RBC transfusion was considered to provide immediate and consistent increase in Hb level. Furthermore, transfusion therapy was found to be cost-effective relative to erythropoietic growth factors [31]. This would suggest that physicians should tailor treatment based on patients' needs and conditions.

In this study, RBC transfusion corrected anemia to a predefined target level rapidly but this was not sustained in the long-term. It is possible that adequate Hb levels could be better maintained in these patients with the appropriate use of erythropoietic growth factors, with a further improvement in their QOL. A recent meta-analysis suggested that erythropoietic growth factor may have improved survival in cancer patients [32]. The use of erythropoietic growth factor has become more attractive in light of evidence-based recommendations concerning adult cancer patients receiving chemotherapy whose Hb level is 10 g/dl or less [19, 24]. However, two large studies which were attempting to treat patients prophylactically to keep Hb levels normal (i.e., >12 g/dl) reported that erythropoietic growth factor therapy might actually be harmful in certain groups of cancer patients [33, 34]. Despite a solid rationale for the correction of anemia in cancer patients, meticulous anemia correction may not have the intended effect, particularly when corrected to a normal Hb level.

In conclusion, RBC transfusion achieving Hb level above 10 g/dl might contribute to the improvement of the KPS and QOL seen in patients with AGC. We showed that with RBC transfusion, the KPS and QOL were improved in anemic patients receiving FU-based first-line chemotherapy. The observation of equivalent outcomes at the two target Hb levels supports the feasibility of anemia correction to Hb 10 g/dl. Within the limitation of difficulty in successfully achieving and maintaining the predefined target Hb levels, there was no clear advantage of raising Hb levels to 12 g/dl or more in terms of chemotherapy response or QOL. Further adequately powered, incorporating the use of erythropoietic growth factors, randomized trials are required to establish the role of anemia correction in this potentially deadly disease.

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