Cancer Chemother Pharmacol (2006) 57: 91–96
DOI 10.1007/s00280-005-0027-2

ORIGINAL ARTICLE

**Se Hoon Park · Jeeyun Lee · Se Hoon Lee
Joon Oh Park · Kihyun Kim · Won Seog Kim
Chul Won Jung · Young Suk Park · Won Ki Kang
Keunchil Park · Seonwoo Kim · Soo Mee Bang
Eun Kyung Cho · Dong Bok Shin · Jae Hoon Lee**

Anemia is the strongest prognostic factor for outcomes of 5-fluorouracil-based first-line chemotherapy in patients with advanced gastric cancer

Received: 6 December 2004 / Accepted: 23 February 2005 / Published online: 9 August 2005

Abstract *Objective*: To examine the prevalence of anemia and its impact of hemoglobin (Hgb) levels in predicting outcomes of 5-fluorouracil (FU)-based first-line chemotherapy for patients with advanced gastric cancer (AGC). *Methods*: We collected data retrospectively from 511 consecutive patients treated with FU-based first-line chemotherapy as a routine clinical practice for AGC and followed up in two centers from 1995 to 2003. FU was given in combination with cisplatin (61%), taxanes (12%), anthracyclines (24%) and/or folinic acid (50%). *Results*: Hgb values were <10 g/dl in 41%, and patients with baseline Hgb levels <10 g/dl had significantly lower response rates (9%) than patients with Hgb$\geq$10 g/dl (53%; $P<0.001$). In addition, Hgb <10 g/dl served as a predictor for disease progression (RR, 1.77; 95% CI, 1.42–2.21) and death (RR, 1.85; 95% CI, 1.48–2.32) along with chemotherapy response and performance status. *Conclusion*: Low baseline Hgb level is a strong and independent prognostic factor for the outcomes of AGC patients receiving FU-based first-line chemotherapy. This results strongly suggest that Hgb level, along with performance status, may be considered as a stratification variable in subsequent studies of AGC.

Keywords Gastric cancer · Chemotherapy · 5-Fluorouracil · Anemia

S. H. Park · S. M. Bang · E. K. Cho · D. B. Shin (✉)
J. H. Lee
Division of Hematology and Oncology,
Department of Internal Medicine,
Gachon Medical School Gil Medical Center,
Incheon, 405-760 Korea
E-mail: dbs@ghil.com
Tel.: +82-32-4603817
Fax: +82-32-4603233

J. Lee · S. H. Lee · J. O. Park · K. Kim · W. S. Kim
C. W. Jung · Y. S. Park · W. K. Kang · K. Park
Division of Hematology and Oncology,
Department of Internal Medicine, Samsung Medical Center,
Sungkyunkwan University, Seoul, Korea

S. Kim
Center for Biostatistics, Samsung Biomedical Research Institute,
Seoul, Korea

Introduction

Gastric cancer remains the most common cause of cancer-related death in Korea [1]. For patients with unresectable, recurrent, or metastatic disease, chemotherapy can provide significant palliation of symptoms [2, 3]. A variety of chemotherapeutic agents such as 5-fluorouracil (FU), anthracyclines, cisplatin and mitomycin C as well as newer agents including taxanes (paclitaxel or docetaxel), oxaliplatin and irinotecan have been proposed to have a place in the treatment of gastric cancer. Most trials using varied combinations of these drugs have provided durations of survival ranging from 6 months to 10 months in patients with recurrent or metastatic gastric cancer [4]. None of these regimens, however, has been recognized as a standard or superior to FU alone in the treatment of advanced gastric cancer (AGC) [5, 6].

Fu is a cycle-active antimetabolite which has been used as a standard chemotherapeutic agent for gastrointestinal malignancies for several decades. In vitro studies have demonstrated that cancer cells responding to FU became resistant under hypoxic conditions [7, 8]. Hypoxia-derived proteome and genome changes in tumors can lead to a more aggressive phenotype and malignant progression [9–11]. Experimental results in animal model have shown that tumoral tissues are hypoxic in the presence of anemia [12].

In patients with AGC, anemia is a common feature. However, there is little data to support or refute the assertion that gastric cancer is particularly aggressive in anemic patients. Many factors may contribute to anemia in patients with AGC. These include tumor bleeding, malabsorption, poor oral intake, and prolonged pretreatment illness, all of which can be either iatrogenic or related to tumor pathology.

Studies performed in patients with cervical and head and neck cancer have indicated that anemia at the time of presentation may be associated with decreased response rates and survival [13–18]. However, the impact of anemia on treatment responsiveness has not been evaluated in patients with AGC. Despite the lack of evidence for benefit associated with raising hemoglobin (Hgb), it is a common practice to transfuse anemic patients prior to the administration of cytotoxic chemotherapy for AGC. 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 better understand the impact of anemia on the outcomes of chemotherapy in patients with AGC, we performed a retrospective analysis of AGC patients treated with FU-based first-line chemotherapy. The present evaluation was also done with the intent to plan and develop improved therapeutic strategies for anemic patients with AGC.

Patients and methods

Eligibility and patient selection

We collected the data retrospectively from 511 consecutive patients with metastatic or recurrent adenocarcinoma of stomach, treated with FU-based first-line chemotherapy as a routine clinical practice and followed in two tertiary centers (Gachon Medical School Gil Medical Center, Incheon, Korea and Sungkyunkwan University Samsung Medical Center, Seoul, Korea) from 1995 to 2003. We excluded patients who were enrolled in clinical trials to ensure the normal Hgb level was not a prerequisite for their chemotherapy regimens. No prior chemotherapy or only adjuvant chemotherapy which had been completed more than 6 months prior to registration were allowed. Only patients who had their complete blood counts measured and recorded just prior to the initiation of chemotherapy were included in this analysis. Patients with any evidence of ongoing blood loss were excluded. Written informed consent was given by all patients prior to receiving chemotherapy, according to institutional guidelines.

Hgb level of 10 g/dl was used as a cut-off value for further analyses based on the following observations: (1) preliminary data from the first 88 patients revealed that a median Hgb value was 10.2 g/dl, (2) this definition is consistent with the Hgb value required in many cancer clinical trials, (3) the guidelines published by American Society of Clinical Oncology and the American Society of Hematology for the treatment of cancer-related anemia recommended Hgb < 10 g/dl as a treatment threshold [19]. In cases requiring red blood cell transfusion, Hgb levels were measured repeatedly after the completion of transfusion.

Treatment

All patients received FU-based first-line chemotherapy for metastatic and/or recurrent AGC. FU was, in 3/4 of cases, given by 4- or 5-day continuous infusion in combination with cisplatin (310 patients, 61%), taxanes (61, 12%), anthracyclines (124, 24%) and/or folinic acid (254, 50%). Protracted infusional FU via ambulatory pump (26%) was also used as part of the ECF (epirubicin, cisplatin and FU) regimen, or as a single agent.

Assessment

Tumor response was evaluated according to World Health Organization criteria [20] and was assessed by abdominopelvic computed tomography (CT) scan and other tests that were used initially to stage the tumor. All tumor measurements were assessed after every two or three courses of chemotherapy and reviewed by an independent investigator later at the time of analysis. The starting point of various time intervals was the first day of chemotherapy. Response duration was the time from the first date of chemotherapy to progression in responding patients. The date of disease progression or death from causes other than AGC was used in calculating rogression-free survival (PFS). Time to death, whatever the cause, was used to calculate overall survival (OS).

Statistical considerations

Chi-square test was used for comparison of categorical variables. Continuous variables were encoded as categorical after dichotomization, using the median or known prognostic values as the cut-off. PFS and OS were estimated according to the Kaplan-Meier method and the statistical significance of survival curves between the two groups was tested with a log-rank test. To examine the impact of clinical and treatment variables on the outcomes of chemotherapy, multiple logistic regression and Cox regression models were used. Covariates included were concomitant chemotherapeutic agents (cisplatin vs. anthracyclines vs. taxanes), methods of FU administration (continuous infusion and modu-

lation with folinic acid), age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (0–1 vs. ≥2), weight loss before treatment, disease status (recurrent vs. primarily metastatic), adjuvant treatment, number of involved site(s), presence of peritoneal dissemination, liver metastasis, second-line chemotherapy, red blood cell transfusion, and Hgb levels. All P values were two-sided, with $P < 0.05$ indicating statistical significance.

Results

Patient characteristics

Patient characteristics are given in Table 1. Men constituted 70% of the patients. The median age was 57 years with a range of 23–77 years. Twenty-three percent of the patients had ECOG performance status of two or more. A majority of patients (78%) had two or more metastatic disease sites, mostly involving peritoneum and liver. Approximately half of the patients (46%) received at least one cycle of second-line chemotherapy.

As expected, 73% of patients had baseline Hgb < 12 g/dl and approximately 41% of patients had Hgb < 10 g/dl at presentation for chemotherapy. Despite pretreatment transfusion of a total of 73 units of red blood cells in 35 patients (7%), 39% of the patients received their first cycle of chemotherapy with Hgb < 10 g/dl. When the groups were stratified according to Hgb < 10 g/dl or ≥10 g/dl, except for gender, red blood cell transfusion and performance status, there were no differences in prognostic variables including age, weight loss, disease status, adjuvant treatment, number of metastatic sites, peritoneal dissemination, liver metastasis and concomitant chemotherapeutic agents given (Table 2). No patient received erythropoietic growth factors.

Table 1 Patient characteristics

Characteristic	No. of patients	Percentage
Age (years)		
Median	57	
Range	23–77	
Male gender	356	70
ECOG performance status		
0–1	396	77
≥ 2	115	23
Weight loss	226	44
Disease status at registration		
Recurrent	195	38
Primary metastatic	316	62
Adjuvant treatment		
Chemotherapy	132	26
Chemoradiotherapy	57	11
Metastatic sites		
Solitary metastasis	115	22
Peritoneal dissemination	232	45
Liver metastasis	174	34

Response rate

Of a total of 511 patients, 177 could not be evaluated for responses because of the absence of any measurable lesion or early discontinuation of treatment. Responses to chemotherapy were noted in 117 evaluable patients (35%; 95% confidence interval [CI], 30–40%) out of which 8 were complete responses. The median response duration was 7.8 months (95% CI, 6.8–8.9 months).

Patients who had Hgb < 12 g/dl and Hgb < 10 g/dl were significantly less likely to respond to chemotherapy (27%, $P < 0.001$ and 9%, $P < 0.001$, respectively) compared to those with Hgb≥12 g/dl (58%) and Hgb≥10 g/dl (53%). Other factors associated with lack of optimal response were prior exposure to chemotherapy as adjuvant treatment (23% vs. 39%, $P = 0.004$) and multiple metastatic sites (32% vs. 45%, $P = 0.030$). Response rate was not significantly influenced by age, gender, weight

Table 2 Comparison of groups relative to baseline Hgb < 10 g/dl

Characteristic	Hgb < 10 g/dl ($n = 207$)	Hgb≥10 g/dl ($n = 304$)	P value
Age≥60 years	35%	41%	0.129
Male gender	59%	77%	< 0.001
ECOG performance status≥2	30%	17%	0.001
Weight loss	49%	41%	0.086
Primary metastatic disease	59%	64%	0.265
Adjuvant treatment given	30%	23%	0.079
Solitary metastasis	20%	24%	0.274
Peritoneal dissemination	45%	46%	0.859
Liver metastasis	33%	35%	0.778
Transfusion given prior to chemotherapy	17%	0	< .001
Pretreatment Hgb level (mean ± SD)			
Before red cell transfusion	8.97 ± 0.84	11.83 ± 1.12	< 0.001
After red cell transfusion	9.32 ± 0.07	11.83 ± 1.12	< 0.001
Concomitant chemotherapeutic agent			
Taxanes	16%	12%	0.053
Anthracyclines	22%	26%	0.374
Cisplatin	55%	60%	0.054
Folinic acid	44%	48%	0.071
Protracted infusion of FU	26%	26%	0.923
Single agent FU	6%	2%	0.005

Hgb hemoglobin, *ECOG* Eastern Cooperative Oncology Group, *FU* 5-fluorouracil

loss, disease status, peritoneal dissemination, liver metastasis, performance status, or concomitant chemotherapeutic agents. Using a multiple logistic regression model, only Hgb < 10 g/dl was significantly associated with the lower response rates (odds ratio = 6.77; 95% CI, 3.46 to 13.25; $P < 0.001$).

Survival

Of the 511 patients analyzed in the study, 442 (87%) died. The estimated median PFS was 5.2 months (95% CI, 4.6 to 5.8 months) and median OS was 10.2 months (95% CI, 9.3 to 11.1 months). The estimated PFS was significantly shorter for patients with baseline Hgb < 10 g/dl (median, 3.4 months vs. 6.7 months; $P < 0.001$). Similarly, OS was shorter for Hgb < 10 g/dl (median, 6.6 months vs. 12.7 months; $P < 0.001$). The median follow-up of the patients was 69.5 months (95% CI, 66.9–72.1 months). The Kaplan-Meier estimates of PFS and OS are illustrated in Fig. 1.

In the proportional hazards regression analysis, independent prognostic variables for PFS and OS were response to chemotherapy, performance status and Hgb level. These data are summarized together in Table 3. This model suggests that patients with Hgb < 10 g/dl and poor performance status prior to the initiation of chemotherapy have a risk of death that is 3.8 times that of patients with Hgb≥10 g/dl and ECOG performance status of 0 or 1.

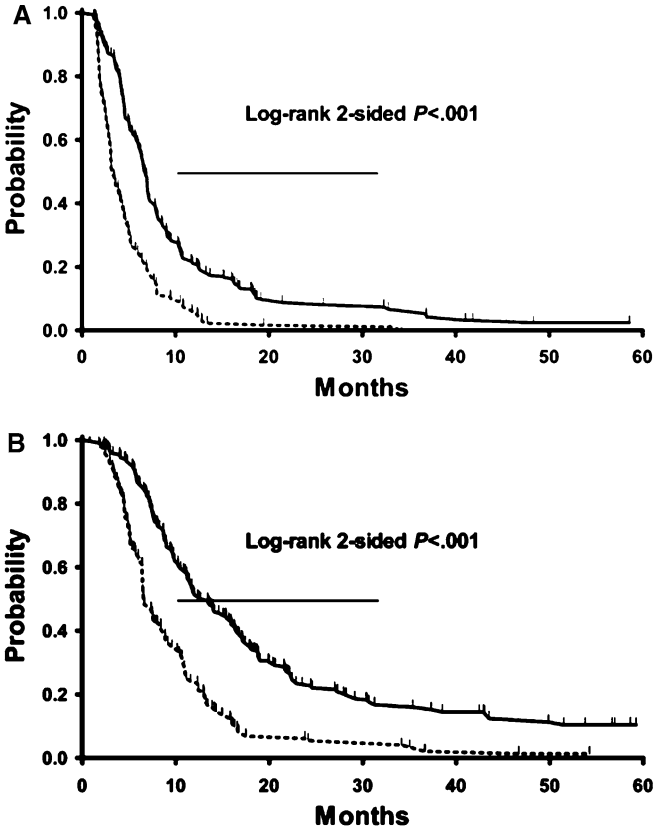

Fig. 1 Progression-free survival (**a**) and overall survival (**b**). Baseline Hgb≥10 g/dl (198 patients, *solid line*) and Hgb < 10 g/dl (136 patients, *dotted line*) are shown, along with 2-sided *P* value

Discussion

Anemia, in the presence or absence of treatment, is common among cancer patients. A number of factors contribute to the high incidence of cancer-related anemia. 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. In a review of the European Cancer Anemia Survey (ECAS), Ludwig and colleagues cited a 50% baseline anemia rate (Hgb < 12 g/dl) among 3,010 patients with hematologic malignancies and a 41% baseline anemia rate among 11,453 patients with solid tumors [21].

A relationship between anemia and treatment outcomes in various forms of cancer has been established by several authors, primarily in a retrospective fashion. One characteristic retrospective analysis found that 5-year survival rates for Canadian women receiving radiotherapy for cervical cancer were higher (74% vs. 45%) when the average weekly Hgb was 12 g/dl or greater, compared with women whose Hgb was < 10 g/dl [13]. Similar benefits were reported when combination chemoradiotherapy was employed [15]. Studies of patients treated for head and neck cancers have shown

Table 3 Multivariate analysis in relation to PFS and OS

Characteristic	PFS			OS		
	P value	RR	95% CI	*P* value	RR	95% CI
Second line Chemotherapy				0.454	1.08	0.88–1.32
Weight loss				0.053	0.81	0.66–1.00
Adjuvant treatment	0.457	0.88	0.63–1.23	0.806	1.04	0.74–1.47
Disease status	0.302	1.16	0.87–1.55	0.087	1.29	0.96–1.73
Multiple metastasis	0.210	0.86	0.67–1.09	0.187	0.85	0.67–1.08
Response	< 0.001	1.44	1.16–1.79	< 0.001	1.37	1.10–1.72
Poor performance	< 0.001	0.57	0.46–0.72	< 0.001	0.49	0.39–0.63
Hgb≥10 g/dl	< 0.001	1.77	1.42–2.21	< 0.001	1.85	1.48–2.32

RR risk ratio

similar benefits when a higher Hgb level was maintained [16, 18]. This relationship between anemia and treatment outcome, and the association between increased levels of hypoxia and chemoresistance in animal models, has led to the belief that anemia increases tumor resistance and decreases responsiveness to treatment in humans.

The present analysis of 511 patients with AGC treated with FU-based first-line chemotherapy has demonstrated a strong association between anemia and reduced response rates, PFS and OS. The response rate achieved with FU-based first-line chemotherapy was 35%. Overall, in anemic (Hgb < 12 g/dl) and severely anemic (Hgb < 10 g/dl) patient subsets, objective response rates were only 27% and 9%, respectively. This adverse impact was not reversed by red blood cell transfusion. Patients with Hgb≥10 g/dl prior to initiating chemotherapy had approximately a 77% decreased risk of progression and a 85% decreased risk of death. The strength of this analysis lies in a uniform patient population. Survival data are mature as 87% of patients died. All patients received FU-based first-line chemotherapy for their recurrent or metastatic gastric cancer. In addition, we excluded patients who were enrolled in clinical trials to better reflect the patients seen in routine clinical practice. To the authors' knowledge, this is the first report describing the association between anemia and inferior outcomes in AGC patients treated with chemotherapy.

This retrospective analysis also demonstrates a high incidence of anemia in patients with AGC. Overall, 41% (207/511) patients presented with severe anemia (Hgb level < 10 g/dl). One may, however, argue that the percentage of anemic subjects in this population could be an overestimate since other causes of anemia such as bleeding and/or nutritional deficiencies are also quite common in AGC patients. Within the limitations of a retrospective analysis, the present study suggests that AGC patients without anemia, at least those with Hgb level≥10 g/dl, achieve a significantly higher response rates and improved survival with FU-based first-line chemotherapy. Also, the impact of the study on survival may be better reflected by PFS since this parameter is not influenced by subsequent therapies.

The results of the present analysis strongly suggest that Hgb level, along with performance status, may be considered as a stratification variable in subsequent studies of AGC. It was evident that anemia was more associated with a poorer performance status and more likelihood of receiving single agent FU. An interesting finding in this analysis is the observation that red blood cell transfusion prior to chemotherapy had no prognostic role in terms of response rates or survival. Unlike other pretreatment variables Hgb level can often be modified before treatment. In patients with metastatic testicular cancer, frequent use of red blood cell transfusions has been shown to achieve median Hgb nadirs of 7.5–8.0 g/dl [22]. This reflects the difficulty in excluding the possibility of ongoing blood loss, even in the absence of any predefined target Hgb values to determine whether the patient should be transfused or not.

Whether raising Hgb levels with red blood cell transfusion or erythropoietic growth factors is advantageous in improving the outcomes after chemotherapy is another important factor to be considered. Although Hgb level may be prognostic, it is unclear whether raising Hgb levels can directly impact treatment outcomes. Animal studies have demonstrated that hypoxia cannot be completely eliminated by transfusion or by erythropoietic growth factors [12, 23]. Human studies are consistent with these results, as only 50% of patients with cervical cancer demonstrate an increase in tumor oxygenation following transfusion [24]. Transfusion of the most profoundly anemic patients may improve oxygen delivery, but does not necessarily improve treatment results. If anemia *per se* reduces response to chemotherapy, simple and proven means of anemia correction could become important adjuncts to treatment. However, the literature suggests that the pros and cons of anemia correction in this population, either with transfusion or with erythropoietic growth factors, have not been adequately explored to date. In recently published guidelines from European Organisation for Research and Treatment of Cancer (EORTC), they do not recommend the prophylactic use of erythropoietic growth factors to prevent anemia in patients who have normal Hgb values at the start of treatment [25]. A randomized controlled trial is currently in progress to determine whether there is a causal relationship between low Hgb levels and outcomes of first-line chemotherapy for AGC, and whether raising Hgb levels can overcome the negative impact of anemia.

Conflict of interest

The Authors indicated no potential conflicts of interest to declare.

References

1. Bae JM, Won YJ, Jung KW, Park JG (2002) Annual report of the Korean central cancer registry program 2000. Cancer Res Treat 34:77–83
2. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M (1995) Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 71:587–591
3. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden PO, Haglund U, Svensson C, Enander LK, Linne T, Sellstrom H, Heuman R (1997) Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 8:163–168
4. Van Cutsem E (2004) The treatment of advanced gastric cancer: new findings on the activity of the taxanes. Oncologist 9(Suppl 2):9–15
5. Cullinan SA, Moertel CG, Wieand HS, O'Connell MJ, Poon MA, Krook JE, Mailliard JA, Tschetter LK (1994) Controlled evaluation of three drug combination regimens versus fluoro-

uracil alone for the therapy of advanced gastric cancer. North Central Cancer Treatment Group. J Clin Oncol 12:412–416
6. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, Yamamichi N, Miyata Y, Ikeda N, Yamamoto S, Fukuda H, Yoshida S (2003) Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol 21:54–59
7. Teicher BA, Holden SA, al-Achi A, Herman TS (1990) Classification of antineoplastic treatments by their differential toxicity toward putative oxygenated and hypoxic tumor subpopulations in vivo in the FSaIIC murine fibrosarcoma. Cancer Res 50:3339–3344
8. Tannock IF (1987) Toxicity of 5-fluorouracil for aerobic and hypoxic cells in two murine tumours. Cancer Chemother Pharmacol 19:53–56
9. Cuvier C, Jang A, Hill RP (1997) Exposure to hypoxia, glucose starvation and acidosis: effect on invasive capacity of murine tumor cells and correlation with cathepsin (L + B) secretion. Clin Exp Metastasis 15:19–25
10. Graham CH, Forsdike J, Fitzgerald CJ, Macdonald-Goodfellow S (1999) Hypoxia-mediated stimulation of carcinoma cell invasiveness via upregulation of urokinase receptor expression. Int J Cancer 80:617–623
11. Hockel M, Schlenger K, Aral B, Mitze M, Schaffer U, Vaupel P (1996) Association between tumor hypoxia and malignant progression in advanced cancer of the uterine cervix. Cancer Res 56:4509–4515
12. Hill RP, Bush RS, Yeung P (1971) The effect of anaemia on the fraction of hypoxic cells in an experimental tumour. Br J Radiol 44:299–304
13. Girinski T, Pejovic-Lenfant MH, Bourhis J, Campana F, Cosset JM, Petit C, Malaise EP, Haie C, Gerbaulet A, Chassagne D (1989) Prognostic value of hemoglobin concentrations and blood transfusions in advanced carcinoma of the cervix treated by radiation therapy: results of a retrospective study of 386 patients. Int J Radiat Oncol Biol Phys 16:37–42
14. Grogan M, Thomas GM, Melamed I, Wong FL, Pearcey RG, Joseph PK, Portelance L, Crook J, Jones KD (1999) The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. Cancer 86:1528–1536
15. Obermair A, Cheuk R, Horwood K, Janda M, Bachtiary B, Schwanzelberger B, Stoiber A, Nicklin JL, Perrin LC, Crandon AJ (2001) Impact of hemoglobin levels before and during concurrent chemoradiotherapy on the response of treatment in patients with cervical carcinoma: preliminary results. Cancer 92:903–908
16. Lee WR, Berkey B, Marcial V, Fu KK, Cooper JS, Vikram B, Coia LR, Rotman M, Ortiz H (1998) Anemia is associated with decreased survival and increased locoregional failure in patients with locally advanced head and neck carcinoma: a secondary analysis of RTOG 85–27. Int J Radiat Oncol Biol Phys 42:1069–1075
17. Dubray B, Mosseri V, Brunin F, Jaulerry C, Poncet P, Rodriguez J, Brugere J, Point D, Giraud P, Cosset JM (1996) Anemia is associated with lower local-regional control and survival after radiation therapy for head and neck cancer: a prospective study. Radiology 201:553–558
18. Kumar P, Wan J, Viera F (1997) Analysis of survival outcome and prognostic factors in the treatment of unresectable head and neck squamous cell carcinoma using supra-dose intra-arterial targeted cisplatin and concurrent radiotherapy. Proc Am Soc Clin Oncol 16:390a (abstr 1394)
19. Rizzo JD, Lichtin AE, Woolf SH, Seidenfeld J, Bennett CL, Cella D, Djulbegovic B, Goode MJ, Jakubowski AA, Lee SJ, Miller CB, Rarick MU, Regan DH, Browman GP, Gordon MS (2002) Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. J Clin Oncol 20:4083–4107
20. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214
21. Ludwig H, Van Belle S, Barrett-Lee P, Birgegard G, Bokemeyer C, Gascon P, Kosmidis P, Krzakowski M, Nortier J, Olmi P, Schneider M, Schrijvers D (2004) The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer 40:2293–2306
22. Bokemeyer C, Oechsle K, Hartmann JT, Schoffski P, Schleucher N, Metzner B, Schleicher J, Kanz L (2002) Treatment-induced anaemia and its potential clinical impact in patients receiving sequential high dose chemotherapy for metastatic testicular cancer. Br J Cancer 87:1066–1071
23. Kelleher DK, Matthiensen U, Thews O, Vaupel P (1995) Tumor oxygenation in anemic rats: effects of erythropoietin treatment versus red blood cell transfusion. Acta Oncol 34:379–384
24. Sundfor K, Lyng H, Kongsgard UL, Trope C, Rofstad EK (1997) Polarographic measurement of pO2 in cervix carcinoma. Gynecol Oncol 64:230–236
25. Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Osterborg A, Repetto L, Soubeyran P (2004) EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. Eur J Cancer 40:2201–2216