Blood Transfusion Has An Adverse Impact On The Prognosis of Patients Receiving Chemotherapy For Advanced Colorectal Cancer: Experience From a Single Institution With a Patient Blood Management Program

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Abstract

Purpose: Perioperative blood transfusion in early stage cancer patients had a negative effect on the prognosis of patients, but the prognostic impact of transfusion in advanced cancer patients remains unclear. To minimize transfusion, a institutional patient blood management (PBM) program was launched, and we evaluated the new program has changed practice and impacted on prognosis of advanced cancer patients.

Methods: We investigated the medical records of colorectal cancer patients who received chemotherapy from 2015 to 2020. The amount and frequency of transfusion, iron replacement and laboratory findings, and overall survival were compared before and after implementation of PBM.

Results: The rate of transfusion in colorectal cancer patients was significantly decreased from 23.5/100 person-quarter in 2015 to 1.2/100 person-quarter in 2020, but iron supplementation therapy was frequently used and the proportion of patients who received transfusion under haemoglobin 7 g/dL significantly increased from 15.9% in 2015 to 55.3% in 2020. Multivariate analysis revealed that transfusion was a significant risk factor affecting the overall survival of patients (HR 2.70, 95% CI: 1.93–3.78, $p < 0.001$). Kaplan–Meier analysis revealed that overall survival was significantly longer in non-transfused patients than in transfused patients (11.0 versus 22.4 months; HR 0.69, 95% CI: 0.56–0.86, $p < 0.001$).

Conclusions: This study shows that minimized transfusion through an institutional PBM can positively affect the prognosis of patients who are receiving chemotherapy for advanced colorectal cancer.

Introduction

The Anemia is a common problem in patients with cancer, particularly among those receiving cytotoxic chemotherapy. The prevalence of anemia in patients with cancer varies according to clinical factors, including the type of malignancy, stage, duration of disease, and chemotherapy regimen. The prevalence of anemia in cancer patients ranges from 30–90% [1], and one study reported that approximately 40% of cancer patients are already anaemic prior to treatment [2]. The aetiology of cancer-related anemia is multifactorial, including gastrointestinal bleeding, iron deficiency, malnutrition, metastatic bone marrow infiltration, and chemotherapy-induced myelosuppression [3, 4]. Patients receiving chemotherapy frequently report fatigue, nausea, loss of appetite, and dyspnoea, but these symptoms of anemia are often mistaken for cancer-related symptoms. Uncorrected anemia has a significant impact on the patient's physical, functional and emotional well-being [5, 6] and results in decreased adherence to treatment. Therefore, it is important to proactively correct anemia in patients receiving chemotherapy to achieve an optimal clinical outcome.

Current guidelines recommend the active correction of anemia in cancer patients by erythropoiesis-stimulating agents (ESA) and iron supplementation [7, 8]. Red blood cell (RBC) transfusion is reserved for patients who are hypovolemic from acute blood loss and refractory with adequate fluid resuscitation or

patients with chronic anemia unresponsive to iron supplementation. However, blood transfusion has been used to correct anemia for patients with advanced stage cancer in Korea. Considering the recent evidence suggesting the adverse effects of blood transfusion on the prognosis of early stage cancer patients [9–12], rational application of blood transfusion in advanced cancer patients should be explored.

The implementation of the patient blood management (PBM) program was suggested by World Health Organization in 2010 to reduce RBC transfusion and maintain the quality and safety of transfusions [13]. The PBM program has been standardized as routine practice in the United States and most European countries [14, 15], as well as in a few Asian countries [16]. The Korea University Anam Hospital launched an institutional PBM program in early 2018 [17]. In line with the institutional program, management guidelines for anemia in cancer patients were established and shared with young doctors in the educational programs [17]. As the PBM program became more widely implemented throughout the hospital's system, it was expected that there would be reductions in blood transfusion and practice in cancer care has also been changed. In this study, we examined the impact of the implementation of PBM in cancer care on the patterns of anemia management in the real world setting and evaluated if it affects the prognosis of patients who are receiving chemotherapy for advanced cancer.

Materials And Methods

Patients

We conducted a retrospective study by the review of medical records of colorectal cancer patients who received chemotherapy at the cancer centre of the Korea University Anam Hospital from January 2015 to December 2020. Patients were eligible if they were treated with at least one regimen of standard chemotherapy backbone: either leucovorin, fluorouracil, and irinotecan hydrochloride (FOLFIRI) or leucovorin, fluorouracil, and oxaliplatin (mFOLFOX6). Agents (cetuximab or bevacizumab) that target the epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) were combined with chemotherapy according to the patient's *KRAS* mutation status.

Data collection

Demographic and disease characteristics such as age at diagnosis, gender, primary tumour location (ascending colon, descending colon, or rectum), metastatic sites at diagnosis, number of total chemotherapy regimens, tumour histology (adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, adenosquamous carcinoma, squamous cell carcinoma), molecular biomarkers (*KRAS*, *NRAS*, *BRAF* mutation), the status of microsatellite instability (MSI), and survival status were collected from electronic health records.

To identify the changes in pattern of anemia management over time, records for the amount and frequency of blood transfusion, iron replacement therapy, and relevant laboratory findings were collected. The data were summarized by quarter-year from the first quarter of 2015 to the fourth quarter of 2020. The rate of RBC transfusion over time was assessed by the percentage of patients transfused. The total

amount of transfused RBC was assessed by the number of units transfused per patient during hospital admission. Our analytic unit was per 100 person-quarter. Pre-transfusion Hb value was obtained as the latest Hb recorded on the database before the transfusion time. The proportion of transfused patients stratified by the pre-transfusion Hb value was calculated to examine the proportion of patients who received blood transfusions under Hb 7.0 g/dL, the institutional indication for transfusion. Also, in our study cohort, the pre-transfusion Hb value > 9.0 g/dL was considered as an over-transfusion, except in special clinical condition such as acute blood loss.

The overall incidence of anemia at the time of diagnosis was calculated in the study population. To investigate changes in the prescription of iron replacement for anemia management, the proportion of patients receiving oral or intravenous iron supplement therapy was evaluated. We calculated the mean Hb level for each quarter-year for the entire cohort.

Overall survival (OS) was assessed from date of diagnosis of metastatic cancer to death from any cause or censoring.

Anemia definition

In this study, anemia was defined according to the WHO classification of anemia. Anemia is defined as a Hb level of <12 g/dL in women and <13 g/dL in men.

Statistical analysis

All statistical analyses were conducted using SPSS version 20.0 (Statistical Package for the Social Sciences for Windows software, Chicago, IL, USA). Descriptive statistics are presented as the mean, standard deviation for numerical variables, and as number and percentage for categorical variables. Numerical variables between two independent groups were analysed with student t-test in case of normal distribution and with Mann–Whitney U test otherwise. The comparison of the rates between the groups was performed by chi square analysis. Survival analyses were performed with Kaplan–Meier analysis. We used Cox regression to identify determinant factors that were associated survival. Backward stepwise model was used with parameters with a p-value below 0.050. An overall 5% alpha error level was used to infer statistical significance.

Results

Patient characteristics

The demographic and clinical characteristics of the colorectal cancer patients are presented in Table 1. A total of 871 colorectal cancer patients were treated at the Division of Medical Oncology from January 2015 to December 2020. The number of colorectal cancer patients increased over time. The distribution of characteristics such as age, gender, primary tumour location, pathology, and molecular biomarkers were similar before and after the implementation of PBM in 2019.

Table 1
Patient characteristics before and after implementation of the PBM program

	Total (n = 871)	Pre-PBM* (n = 509)	Post-PBM (n = 362)	p-value
Age, years (range)	61.9 (23-89)	62.1 (23-89)	61.5 (25-87)	0.412
Gender, n (%)				0.268
Male	554 (63.6)	316 (62.1)	238 (65.7)	
Female	317 (36.4)	193 (37.9)	124 (34.3)	
Primary location, n (%)				0.723
Ascending colon	194 (22.2)	112 (22.0)	82 (22.7)	
Descending colon	268 (30.8)	162 (31.8)	106 (29.3)	
Rectum	409 (47.0)	235 (46.2)	174 (48.1)	
Metastatic site, n (%)				0.612
0	181 (20.8)	98 (19.3)	83 (22.9)	
1	316 (36.3)	187 (36.7)	129 (35.6)	
2	232 (26.6)	138 (27.1)	94 (26.0)	
More than 2	142 (16.3)	86 (16.9)	56 (15.5)	
Number of total chemotherapy regimens in a lifetime, n (%)				<0.001
1	478 (54.9)	221 (43.4)	257 (71.0)	
2	219 (25.1)	135 (26.5)	84 (23.2)	
More than 2	174 (20.0)	153 (30.1)	21 (5.8)	
Pathology, n (%)				0.242
Adenocarcinoma	800 (91.8)	472 (92.7)	328 (90.6)	
Mucinous adenocarcinoma	60 (6.9)	31 (6.1)	29 (8.0)	
Others**	11 (1.2)	6 (1.2)	5 (1.4)	
PBM, Patient blood management; MSI, Microsatellite instability.				
* Analyzed patients before (pre-PBM) and after (post-PBM) the implementation of PBM.				
** These include signet ring cell carcinoma, adenosquamous carcinoma, squamous cell carcinoma.				
*** Data not from all patients available.				

	Total (n = 871)	Pre-PBM* (n = 509)	Post-PBM (n = 362)	p-value
Molecular biomarker, n (%)***				
<i>KRAS</i> mutation	378 (43.4)	225 (44.2)	153 (47.2)	0.099
<i>NRAS</i> mutation	19 (2.2)	12 (2.4)	7 (1.9)	<0.001
<i>BRAF</i> mutation	32 (3.6)	18 (3.5)	14 (3.9)	<0.001
MSI high	17 (2.0)	12 (2.4)	5 (1.4)	0.203
PBM, Patient blood management; MSI, Microsatellite instability.				
* Analyzed patients before (pre-PBM) and after (post-PBM) the implementation of PBM.				
** These include signet ring cell carcinoma, adenosquamous carcinoma, squamous cell carcinoma.				
*** Data not from all patients available.				

Among the 871 patients, 554 (63.6%) were male and 317 (36.4%) were female. The median age was 61.9 years (range, 23–89). The main anatomical sites of the primary tumour at diagnosis were as follows: rectum (47.0%), descending colon (30.8%), and ascending colon (22.2%). At the time of diagnosis, the most common histologic type was adenocarcinoma (92.5%) and the number of metastatic sites varied (20.8% none, 36.3% 1 site, 26.6% 2 sites, and 16.3% more than 2 sites). With the increase use of precision medicine, the detection rate of mutational status of biomarkers increased accordingly.

RBC transfusion rates

The rate of RBC transfusion significantly decreased in the study population over time, from 23.5/100 person-quarter in the 4th quarter of 2015 to 1.2/100 person-quarter in the 4th quarter of 2020 (Fig. 1). The total amount of transfused RBC decreased from 100.0 units/100 person-quarter in the 4th quarter of 2015 to 3.7 units/100 person-quarter in the 4th quarter of 2020. Hb levels before transfusion were evaluated among the patients who were transfused. The proportion of patients who received blood transfusions under 7 g/dL, the institutional indication for transfusion, significantly increased yearly during the study period: 15.9%, 23.7%, 28.7%, 32.3%, 52.2% and 55.3% for the study periods. Conversely, the proportion of patients receiving RBC transfusion at Hb $\geq$ 9 g/dL significantly decreased yearly over the study period: 12.3%, 5.3%, 2.0%, 5.2%, 2.2%, and 0% (Fig. 2).

Pattern of anemia treatment

The overall incidence of anemia at the time of diagnosis was 67.3% in the study population. The proportion of patients receiving iron supplementation therapy significantly increased after implementation of PBM: from 0.4% in 2015 to 20.8% in 2020. Oral iron supplements were more commonly prescribed and steadily increased, from 4.0/100 person-year in 2015 to 13.1/100 person-year in 2020. Use of intravenous iron also increased over several years (Fig. 3).

Hemoglobin data by quarter-year

During the study period, the mean hemoglobin level of the patients was 11.2 ± 2.1 g/dL in the 1st quarter of 2015 and this value significantly increased to 11.9 ± 1.6 g/dL in the 4th quarter of 2020 (Supplement Fig. 1).

Overall survival based on transfusion

During the entire study period, 20.2% (176/871) of patients received at least one unit of RBC transfusion. The prognostic impact of transfusion on OS was evaluated at the median follow-up of 34.1 months (range, 3.0 to 169.7 months).

Univariate analysis for OS revealed that age (≥ 61.9 years), number of distant metastatic sites, presence of biomarkers (*KRAS* mutation, MSI), and history of transfusion were the unfavourable predictors for OS. In multivariate analysis, history of transfusion during chemotherapy was a significant risk factor for decreased OS (hazard ratio (HR) = 2.696, 95% confidence interval [CI], 1.925 to 3.776, $P < 0.001$) after number of distant metastatic sites > 1 (HR = 4.616) (Table 2). Kaplan–Meier analysis estimated that the median OS among patients who received transfusion was 22.4 months (95% CI, 16.6 to 34.0) compared with 11.0 months (95% CI, 8.3 to 14.3) among patients who did not receive transfusion (HR for death, 0.69; 96.4% CI, 0.56 to 0.86; $p < 0.001$) (Fig. 4).

Table 2
Univariate and multivariate analysis for overall survival

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (≥ 61.9 vs. < 61.9)*	1.03	1.01-1.04	0.001	1.03	1.02-1.05	<0.001
Gender (Female vs. Male)	0.73	0.52-1.01	0.059			
Primary location						
Ascending colon			0.158			
Descending colon	0.93	0.60-1.42	0.726			
Rectum	0.69	0.45-1.06	0.088			
Metastatic site						
0			<0.001			<0.001
1	5.40	2.13-13.68	<0.001	4.62	1.81-11.75	0.001
2	11.23	4.46-28.3	<0.001	9.94	3.93-25.13	<0.001
More than 2	18.46	7.34-46.46	<0.001	14.33	5.63-36.48	<0.001
Total Chemotherapy regimens						
1			<0.001			0.486
2	1.67	1.04-2.67	0.033	0.74	0.45-1.23	0.245
More than 2	2.80	1.87-4.20	<0.001	0.89	0.54-1.46	0.638
Pathology						
Adenocarcinoma			0.714			
PBM, Patient blood management; MSI, Microsatellite instability.						
* 61.9 years is median age.						
** These include signet ring cell carcinoma, adenosquamous carcinoma, squamous cell carcinoma.						
*** Data not from all patients available						

Factor	Univariate analysis			Multivariate analysis		
Mucinous adenocarcinoma	0.57	0.27-1.22	0.146			
Others**	0.00		0.963			
Molecular biomarker***						
<i>KRAS</i> mutation	0.97	0.70-1.36	0.032	0.85	0.60-1.18	0.372
<i>NRAS</i> mutation	0.94	0.61-1.45	0.79			
<i>BRAF</i> mutation	0.92	0.68-1.25	0.109			
MSI status						
Stable			0.013			0.540
Low	1.96	1.12-3.43	0.019	0.66	0.09-4.86	0.685
High	1.20	0.68-2.11	0.528	1.01	0.43-2.35	0.986
PBM (Post-PBM vs. Pre-PBM)	0.91	0.58-1.40	0.628			
Transfusion status (Transfused vs. Nontransfused)	3.61	2.60-5.01	<0.001	2.70	1.93-3.78	<0.001
PBM, Patient blood management; MSI, Microsatellite instability.						
* 61.9 years is median age.						
** These include signet ring cell carcinoma, adenosquamous carcinoma, squamous cell carcinoma.						
*** Data not from all patients available						

Discussion

Correction of anemia in patients who are receiving systemic chemotherapy has important clinical value, as anemia negatively impacts the patient's quality of life and compliance of treatment in the oncology clinic. In this retrospective study, we showed that the pattern of anemia management in colorectal cancer patients receiving chemotherapy was significantly changed after implementation of the PBM program in oncology practice. The number of patients receiving RBC transfusion as well as the amount of transfused RBC decreased after the specific guideline for cancer patients was implemented. Instead, iron supplementation was significantly increased to minimize blood transfusions. As a result, the mean hemoglobin levels increased gradually over the study period, while the baseline clinical characteristics of

patients remained consistent. Of note, we also observed that blood transfusion was a significant unfavourable factor influencing OS along with the number of metastatic sites at diagnosis in advanced colorectal cancer patients.

In patients with anemia receiving myelosuppressive chemotherapy for advanced cancer, it is recommended to correct anemia with iron replacement and/or ESA to reduce transfusion [7, 8]. However, blood transfusion has also been frequently used in clinical practice alone or in combination with pharmaceutical measures. Many studies showed that perioperative blood transfusion in early stage cancer patients had a negative effect both on short-term surgical outcome and long-term prognosis of patients [18–21]. Most of all, colon cancer was the prototype of disease that was proven the relevance of transfusion and clinical outcome [22, 23]. The negative impact of blood transfusion was documented in multiple cancer types after extended follow-up investigations [24, 25], supporting restrictive transfusion in early stage cancer patients. However, the prognostic impact of transfusion in advanced cancer patients had not been sufficiently investigated. Patients with malignancy in the gastrointestinal tract are more likely to have anemia at the time of cancer diagnosis because of chronic blood loss, insufficient food intake, or chronic inflammatory condition. Moreover, anemia is aggravated with repeated cycles of chemotherapy. In the oncology clinic, however, correction of anemia is not a priority issue compared with the choice of treatment, management of side effects from chemotherapy, and pain control. In this study, patients who were transfused using packed RBC showed an inferior survival time irrespective of chemotherapy or initial tumour burden.

In the current analysis, blood transfusion was required in 20% of the patients (175 out of 871). Patients who required at least one unit of transfusion were characterized by more metastatic sites at diagnosis (more than 2 sites, 53 of 175 [30.3%] vs. 89 of 696 [12.8%]; $p < 0.001$) and more chemotherapy regimens over the lifetime (more than 2 courses, 75 of 175 [42.8%] vs. 99 of 696 [14.2%]; $p < 0.001$) (Supplementary Table 1). The increased probability of transfusion in patients with a high tumour burden could be explained by the fact that advanced cancer induces functional iron deficiency mediated by inflammatory mediators; hepcidin [26–29]. Thus, standard oral iron supplementation or ESA might not be effective for this patient group as in patients with benign conditions. Nevertheless, considering the limited therapeutic options for advanced colorectal cancer patients, better supportive care like restricting transfusion for anemia correction might be a valuable strategy to improve clinical outcome.

There are several well-known adverse events from blood transfusion, including blood-borne infections, hemolytic reactions, transfusion-related acute lung injury (TRALI), and transfusion-related immunomodulation (TRIM) [30]. TRIM is one of the major mechanisms underlying the negative impact of blood transfusion on clinical outcome in cancer patients. TRIM is mediated by residual leukocytes, apoptotic cells, and microparticles in blood components. Upon transfusion, the components of transfusion can modify immune functions, including decreasing the number of lymphocytes, CD4 cells, the CD4/CD8 T-cell ratio, NK cells and the lymphocyte response to mitogens. These effects might contribute to cancer growth and dissemination by compromising immune surveillance [31, 32]. The prognostic impact on patients receiving immune checkpoint inhibitors is not known. Indeed, there is

sufficient clinical evidence to support the practice of restrictive transfusion and proactive correction of anemia in both early and advanced stage cancer patients.

Implementation of PBM at the institutional level is usually challenging, especially for high volume clinical settings like oncology clinics. The recognition of the potential hazards of blood transfusion and change in practice by young doctors who are responsible for primary care takes time. Good availability and low cost of transfusion were additional hurdles in building up the new culture in Korea. With institutional level educational programs and continuous feedback to faculty physicians, the use of blood transfusion dramatically decreased and the mean hemoglobin level in patients significantly increased in a short period. Moreover, the increased awareness of anemia by the treatment team was reflected by the increase in iron replacement. For the continuity of care pattern in anemia, cancer patient-specific guidelines were established and shared with rotating residents. Encouraged by the results from this study, a new practice of attentive care of anemia with restrictive transfusion is now the standard of care for all cancer types in our institution.

There are several limitations in our study. First, this is a retrospective study, and thus the prognosis of the patients might be inherently affected by unrecognized confounding variables. In oncology patients, the prognosis of patients is usually improved with the implementation of new agents and better supportive care. To investigate the prognostic impact of anemia correction, we selected metastatic colorectal cancer, as the standard of care has not significantly changed over recent years. Second, the results presented here are based on a single cancer type from a single institutional experience. Thus, the value of restrictive transfusion should be further evaluated in other cancer types and the clinical context in a multicentre or national database setting. Despite these limitations, we demonstrated that the implementation of restrictive transfusion by the implementation of PBM program were feasible to change practice patterns. Through these changes, we observed many valuable benefits in the oncology clinic, not only saving the costs of blood transfusion and reducing the burden of time-consuming and high-risk medical practice of caregivers, but also improving patient prognosis.

In conclusion, allogenic blood transfusion is an independent adverse prognostic factor in patients receiving chemotherapy for advanced colorectal cancer. Increased awareness of anemia and proactive use of medicinal strategies should be considered rather than transfusion for better prognosis of these patients.

Declarations

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of the Korea University Anam Hospital (IRB number: 2021AN0457, date of acceptance 16 September 2021).

Consent to participate: Informed consent was waived because of the retrospective nature of the study and there were minimal risks to subjects.

Consent for publication: Not applicable.

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Figures

Figure 1

RBC Transfusion trend: (a) Number of patients transfused/100 person per year-quarter and (b) total unit of RBC transfusion/100 person per year-quarter from 2015 to 2020. RBC, red blood cell

	2015 (n = 138)	2016 (n = 114)	2017 (n = 101)	2018 (n = 96)	2019 (n = 90)	2020 (n = 76)
Hb < 7	22 (15.9%)	27 (23.7%)	29 (28.7%)	31 (32.3%)	47 (52.2%)	42 (55.3%)
7 ≤ Hb < 8	73 (52.9%)	55 (48.2%)	57 (56.4%)	50 (52.1%)	32 (35.6%)	32 (42.1%)
8 ≤ Hb < 9	26 (18.8%)	26 (22.8%)	13 (12.9%)	10 (10.4%)	9 (10.0%)	2 (2.6%)
Hb ≥ 9	17 (12.3%)	6 (5.3%)	2 (2.0%)	5 (5.2%)	2 (2.2%)	0 (0.0%)

Figure 2

Yearly number of patients transfused stratified by pre-transfusion Hb levels from 2015 to 2020. Pre-transfusion Hb level was obtained as the latest Hb recorded on the database before the transfusion time. Hb, hemoglobin.

	2015 (n = 222)	2016 (n = 207)	2017 (n = 213)	2018 (n = 233)	2019 (n = 314)	2020 (n = 404)
Incidence of anemia	78.1 %	69.1 %	67.4 %	61.9 %	68.0 %	63.2 %
Total iron supplement	1 (0.4 %)	6 (2.9 %)	13 (6.1 %)	19 (8.1 %)	61 (19.4 %)	84 (20.8 %)
PO iron	1 (0.4 %)	6 (2.9 %)	13 (6.1%)	14 (6.0%)	39 (12.4%)	53 (13.1%)
IV iron	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.1%)	22 (7.0%)	31 (7.7%)

Figure 3

Proportion of use of PO/IV iron replacement therapy by year-quarter from 2015 to 2020: Incidence of anemia [in cluded patients with Hb levels <13 g/dL (males) or <12 g/dL (females)] and total (PO/IV) iron supplement during study period. PO, per os/orally; IV, intravenous.

Figure 4

Kaplan-Meier curve for overall survival according to RBC transfusion status. Median overall survival of transfused patients (dashed line) was significantly lower than that of untransfused patients (solid line).

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