Transfusion Practices In Advanced Cancer Patients

Sara Marote
Centro Hospitalar de Lisboa Central EPE
Joana Marinho
Centro Hospitalar de Vila Nova de Gaia Espinho EPE
Maria Cândida Silva
Instituto Português de Oncologia do Porto: Instituto Portugues de Oncologia do Porto Francisco Gentil EPE
José António Ferraz Gonçalves (ferrazg@ipoporto.min-saude.pt)
Instituto Português de Oncologia, Porto https://orcid.org/0000-0002-9506-7106

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Abstract

Purpose: Anemia is highly prevalent in patients with advanced cancer and adversely affects quality of life. There is limited data on the frequency, clinical utility and effectiveness of red blood cell transfusions (RBC), and no randomized controlled trials or clinical practice guidelines are available.

The aim of this study was to evaluate clinician practices on RBC transfusion in an oncologic palliative care service (PCS) and its impact in patients' symptoms, adverse events and overall survival.

Methods: Retrospective analyses of all advanced cancer patients who received RBC transfusions admitted, during a 3-year period. Pre-blood counts, reason for transfusion, subjective benefit and objective outcomes were listed.

Results: We identified 179 patients with a mean age of 67 years. A total of 435 RBC units, during 301 transfusion episodes were recorded. Asthenia/fatigue was the most frequent symptom (68%). The mean pretransfusion hemoglobin (Hb) was 6.85 g/dL and 48% patients had an Hb above 7 g/dL. Symptomatic benefit was achieved in 36% of patients. Adverse events were reported in 4%, with a 30-day survival rate of 57%. A statistically significant association between ECOG performance status (ECOG-PS) and symptomatic benefit was found (p=0.005). Hemoglobin level pre-transfusion, ECOG-PS and symptomatic benefit with transfusions were significantly associated with survival.

Conclusion: This study suggests that advanced cancer patients with a higher level of functioning may have a bigger benefit from RBC transfusion. Post-transfusion symptomatic benefit, and pre-transfusion ECOG-PS and hemoglobin levels seem to be independent predictors of survival. Further studies are needed to develop validated measures of objective functional changes to evaluate the clinical impact of transfusions and to identify patients most likely to benefit from it.

Introduction

The World Health Organization defines anemia as an Hemoglobin (Hb) level < 12 g/dL in women and < 13 g/dL in men [1]. Anemia is common in palliative care (PC) patients, affecting 77% of men and 68% of women [2] and, 50% of inpatients at any admission and 90% of inpatients in the last admission before death [3].

In this context, anemia is often multifactorial. Causes include iron deficiency that can result from chronic blood loss due to gastrointestinal and gynecological malignancies or surgery, chronic inflammation, erythropoietin deficiency, bone marrow infiltration, hematinic depletion and treatment effects [3]. Less frequently, anemia can also derive from nutritional deficiencies due to cancer-induced anorexia.

Anemia causes several symptoms that can influence the patient's physical and functional status, negatively affecting their quality of life [4].

Treatment options for anemia include red blood cell (RBC) transfusion, supplements when there is iron, folic acid or vitamin B12 deficiencies and erythropoiesis-stimulating agents.

Restrictive blood transfusion strategies (Hb level 7 and 8 g/dL) have been gradually adopted over the past years due to the lack of clinical evidence demonstrating an improved outcome when compared to more liberal practices. The European Society for Medical Oncology (ESMO) advocates a threshold of 7–8 g/dL and recommends that transfusions are only used in anemic patients with severe symptoms in need of rapid Hb improvement [5].

National Cancer Comprehensive Network (NCCN) guidelines states that the decision to offer RBC transfusion should not be made based on whether the Hb level of the patient has reached a certain threshold or “trigger”. Balance between transfusion risks and benefits should be evaluated on an individual basis [6].

For advanced cancer patients, there are no clinical practice guidelines or randomized controlled trials to assess the usefulness of transfusions or to identify groups of patients that are more likely to benefit.

The decision must be individualized and respect the bioethical principles: respect for autonomy, justice, non-maleficence and beneficence. Before deciding on transfusion, always inquire about ethical, cultural, and/or religious concerns that may lead patients to refuse blood products, then informed consent should be obtained. When a clinical deterioration is eventually expected, discuss expectations along with clinical signs that would suggest an appropriate timing to discontinue them [7]. RBC is a scarce and expensive resource. The decision of using it for a particular patient requires a consideration of who else might need the resource, as well as how much of it is available [8]. According to a recent review [9], adverse events occur in a minority of participants (3% to 7%), still RBC transfusion may result in adverse reactions, fluid overload and infection [10]. Additionally, RBC transfusions require frequent visits to healthcare facilities, which can impact on quality of life [7]. Studies on the beneficial effects of transfusions in advanced cancer patients are vastly inconclusive, and blood transfusion is highly individualized. Cochrane’s review [9] reported that 31% to 70% of advanced cancer patients showed an improvement in their fatigue, breathlessness or general well-being, with a limited duration of response of about 14 days or less. Timothy et al [3], evaluated PC patients seven days after receiving RBC transfusion, and found that in 49% of cases the primary target symptom improved and 78% of transfusions improved at least one of the target symptoms. Neoh et al [11], found that 18% patients had a clinical benefit maintained at 30 days; 31% had a transitory benefit for less than 14 days, and 11% of patients had no benefit from transfusion.

The main aim of this study was to assess clinician practices around RBC transfusion in an oncologic Palliative Care Service (PCS). The impact of RBC transfusion on patient’s symptoms, adverse events and post-transfusion overall survival were also studied.

Methods

Patients and study design

A retrospective cohort study was performed in a PCS from an Oncological Centre, from 1st January 2016 to 31st December 2018. All data was collected from electronic medical records.

Eligible population consisted of adults (≥18 years old) with a histologically confirmed malignant tumor, admitted to the PCS for symptomatic control as in-patients or as ambulatory, who received at least one RBC transfusion during the study period. No patients were receiving anti-cancer treatment. There were no exclusion criteria. Cancer staging was set in accordance with TNM Classification (AJCC 7th edition).

Since patients could have received RBC transfusions at different times, we designated each date associated with the transfusion of one or more units a transfusion episode (TE).

Patients and disease characteristics as demographic data (including age and gender), Charlson Comorbidity Index (CCI), primary cancer location and the presence of metastasis were collected. History of RBC transfusion in the previous 6 months, treatments used to treat or prevent anemia in the previous 6 months and number of TE, were recorded.

For each TE, drugs with impact on bleeding events (anticoagulants, antiplatelets, anti-inflammatory drugs and selective-serotonin-reuptake-inhibitors) administered in the previous 72h, pretransfusion patients symptoms, pretransfusion patients Eastern Cooperative Oncology Group Performance Status (ECOG-PS), pretransfusion report of active bleeding, pretransfusion Hb, local and professional responsible for the decision, number of RBC units administered, symptomatic benefit in the 15 days following TE, adverse events and survival, were collected.

A safety endpoint was to assess the number of adverse events.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations (SD), or medians and interquartile range (IQR) for variables with skewed distributions. Normal distribution was checked using skewness and kurtosis.

Variables (ECOG-PS, Hb level and symptomatic benefit) were compared using Chi-square test or Fisher's exact test. Survival curves were calculated using the Kaplan–Meier estimator and compared using the log-rank test. For multivariable analysis, Cox regression was used. The level of significance was deemed to be 0.05. Statistical analysis of the results was performed using IBM SPSS Statistics version 22.0.0.1 (IBM Corp., Armonk, NY) and MedCalc, version 17.7.2 (MedCalc Software, Ostend, Belgium). Missing data were dealt with by listwise deletion.

Compliance with ethical standards

The study was reviewed and approved by the ethics committee of the hospital, where the study was conducted. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki

declaration and its later amendments or comparable ethical standards. Since the study did not imply any contact with patients and all the rules of confidentially and respect for those involved were assured, no informed consent was required.

Results

During the study period, a total of 179 patients received RBC transfusions. The mean age of the participants was 67.0 years (SD ±12.9) and 60% were male (n=107). The mean CCI was 8.9 (SD ±2.3) (table 1).

The majority of patients had gastrointestinal (42%) and genitourinary (35%) primary tumors. The most common were colorectal cancer (17%), gastric cancer (17%) and prostate cancer (14%). Forty-seven percent of patients had advanced locoregional disease. In terms of distant metastasis, the most common sites of metastases were lymph nodes (48%, n=86), bone (35%, n= 62), and liver (30%, n=53) (table 1). Records of TE in the previous 6 months, were found in 56% of patients. Also, in the previous 6 months, at least 43% (n=77) were under other therapies to treat or prevent anemia as oral iron supplements (n=33), aminocaproic acid (n=28), folic acid supplement (n=22) and hemostatic radiotherapy (n=16) (table 2).

Drugs with impact on bleeding events, administered in the 72h prior every TE, were also analyzed and found in 59% (n=179) of TE. Anti-inflammatories (mainly corticosteroids) were used by 49% (n=146), anti-coagulants (mainly low molecular weight heparin) in 9% (n=27), antiplatelets in 2% (n=6) and selective-serotonin-reuptake-inhibitors in 8% (n=25) (table 3).

Over the 3-year period, 301 TE were recorded, with a median of 1.0 [Min 1 - Max 9]. Pretransfusion symptoms were recorded in 67% (n=202) TE. Asthenia/fatigue was the most frequent symptom, reported in 138 (68%) TE, followed by dizziness/lipothymia/syncope (n=29, 14%) and dyspnea (n=24, 12%). Before transfusions, the majority (n=169, 73%) had an ECOG-PS >2. In 68 TE the ECOG-PS was not recorded.

Evidence of active bleeding pretransfusion was recorded in 100 (33%) TE. The mean pretransfusion Hb was 6.85 g/dL (SD±1.15) with a range of 3.40-9.00 g/dL, and 145 (48%) patients had a Hb above the trigger threshold of 7 g/dL (table 4). The decision for transfusion was made by a PC physician in 86% of TE. In 13% of cases the physician on-call, usually not a PC doctor, was responsible for the decision on transfusion. Fifty-eight percent of TE concerned patients hospitalized in the PCS, while the remaining were relative to outpatients observed in the emergency room or in consultations. The median RBC units given per TE was 1.0, ranging between 1-3, and a total of 435 RBC units were transfused (table 5). Symptomatic benefit in the 15 days following transfusion was achieved in 36% (n=107), observed in 55 TE with fatigue/asthenia, 16 with dizziness/lipothymia/syncope and 9 with dyspnea. In 31% (n=93) TE there was no benefit, and in 34% (n=101) of cases the benefit of transfusion was not assessed (table 6). No serious adverse events were recorded. In 13 (4%) TE mild adverse events were documented: 11 cases of fever and two cases of volume overload (table 6).

Median time to death was 41 days (IQR 30.6-51.4 days), with a 15-day-survival rate of 70% and a 30-day-survival rate of 57% (figure 1).

There was a statistically significant association between pre-transfusion ECOG-PS and post-transfusion symptomatic benefit (p= 0.005), although there were only 9 patients with ECOG-PS ≤1, all with symptomatic benefit. No statistically significant correlation was found between Hb level before transfusion and symptomatic benefit (p= 0.151).

In an univariable analysis, pre-transfusion ECOG-PS and Hb level, as well as post-transfusion symptomatic benefit were significantly associated with survival (p<0.001) (table 7). In the multivariable analysis, the same variables tested in the univariable analysis (pre-transfusion ECOG-PS and Hb levels, and post-transfusion symptomatic benefit) were significantly associated with survival (table 8).

Discussion

Clinical practices

To the best of our knowledge, this study is one of the largest to analyze transfusion practices in a PC setting.

Almost half of the patients analyzed had a gastrointestinal malignancy, as bleeding events are common in these tumors. Although, hematologic malignancies are between the most reported advanced cancer diagnosis leading to RBC transfusion [12], we report only a few cases (4%) of oncohematologic patients. This is in accordance with the literature where oncohematologic patients can be nearly 7% of all oncologic patients [13,14].

There is evidence supporting that these patients behave as a special group in PC when compared with other tumors: there is a smaller number of referrals, with more advanced and symptomatic disease status, and less time between the last treatment date and the referral date or death [14].

We report that at least 56% of patients received RBC transfusion in the previous 6 months. Thus, most of the patients were already receiving RBC before being admitted by the PC team, which could have affected the decision to repeat the procedure. Only 43% were under other therapies to treat or prevent anemia, reflecting an inadequate investigation and treatment before transfusion.

More than half of the patients were under drugs with impact on bleeding events, which may have affected the decision to transfuse. Anti-inflammatory drugs were the most frequent. These drugs should be used carefully or suspended in patient at risk for bleeding.

We found a mean pretransfusion Hb level of 6.85 g/dL, lower than Neoh et al [11] (7.5 g/dL) and Timothy et al retrospective [10] (7.8 g/dL) and prospective [3] (7.2 g/dL) studies but higher than Sirianni et al [15] (6,5 g/dL). Neoh et al [11] report that 70% of patients had an Hb above the trigger threshold of 7.0 g/dL, while we found an inferior frequency of 42%. Also, we found a median of RBC units given per TE (1.0)

similar to Sirianni et al [15] and lower than Neoh et al [11] (2.0) and Timothy et al retrospective [10] (2.3) and prospective [3] (2.1) studies. These results may reflect doctors' effort to adopt a restrictive blood transfusion strategy in a PC setting.

Impact on symptoms

Symptoms were recorded in 67% of TE. It is likely that a higher number of patients had symptoms, but they were not registered in patient files. Similarly, to other studies [3,10,15] the most reported symptom was asthenia/fatigue.

Considering the overall number of TE in which it was possible to assess the 15-day symptomatic benefit, we observed a symptomatic benefit in more than half of the cases. However, symptomatic benefit was not assessed in nearly one third of the TE and no standardized tool was used to demonstrate or refute benefit, since no specific validated tools to assess the utility of transfusions exist. Additionally, symptoms as fatigue are multifactorial and very difficult to measure, and a single intervention targeting one of these factors is unlikely to have a widespread benefit. Pre-transfusion ECOG-PS association with symptomatic benefit suggests that patients with a higher level of functioning may have a bigger benefit from RBC transfusion.

Adverse events

No serious adverse events were documented and we found a lower frequency of adverse events (4%), comparing with other studies which reported 12% [3] and 12,5% [15] adverse events. The low frequency of adverse events may reduce concerns about potential harms.

Survival

Compared to Neoh et al prospective study [11], in which, 32% of patients died within 30 days, we found an inferior 30-day survival-rate (57%). Compared to Sirianni et al retrospective study [15] we found a longer median time to death. Their analyses only considered the first TE date, while we have included each TE, as in our opinion each TE results from an independent decision. Nonetheless, deterioration is expected in this population given the progressive nature of disease and cannot be attributed to RBC transfusions.

Univariable and multivariable analyses results suggest that pre-transfusion ECOG-PS and Hb levels, as well as symptomatic benefit are independent predictors of survival in advanced cancer patients who received RBC transfusions.

Limitations

Potential limitations of this study should be considered, as the retrospective design, and potential different criteria used by the assistant doctors to decide on transfusions. Moreover, as a single centre study it cannot be exclude possible selection biases accordingly to our transfusion practices.

Conclusion

In PC setting, transfusions seem to have a subjective symptomatic benefit and should be offered for symptom relief in patients with a higher level of functioning. They are well tolerated, but the lack of standardized pre/post assessment tools limits any ability to draw conclusions about utility. The duration and magnitude of the symptomatic benefit remain uncertain. According to a recent paper, most PC specialists consider red blood cell transfusion to have a role in symptom management, but many clinical and nonclinical factors influence their decisions to provide or discontinue transfusions [16].

Further studies are needed to develop tools to evaluate the clinical impact of transfusion, to identify patients most likely to benefit from transfusion, and to better understand the attitudes of physicians in PC setting.

Declarations

Funding

The authors did not receive support from any organization for the submitted work.

Conflicts of interest/Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This study was reviewed and approved by the ethics review committee from Instituto Português de Oncologia do Porto (IPO-Porto) [Ref. CES. 15/2021].

This retrospective chart review study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate

Since the study did not imply any contact with patients and all the rules of confidentially and respect for those involved were assured, no informed consent was required.

Consent for publication

Not applicable.

Availability of data and material (data transparency)

Available from the authors on request.

Code availability (software application or custom code)

Not applicable

Authors' contributions

All authors contributed to the study conception and design. Data collection was performed by Sara Marote, Joana Marinho and Maria Cândida Silva. Data analysis was performed by Sara Marote, Joana Marinho and José Ferraz Gonçalves. The manuscript was written by Sara Marote, Joana Marinho, and José Ferraz Gonçalves, and all authors commented on the versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1
Patients and disease characteristics.

		n = 179
Gender, n (%)	Male	107 (60)
	Female	72 (40)
Age, years	Mean±SD	67.0±12.9
	Min-Max	30–93
Charlson Comorbidity Index, score	Mean±SD	8.9±2.3
	Min-Max	3–15
Primary tumor location, n (%)	Colorectal	30 (17)
	Gastric	30 (17)
	Prostate	25 (14)
	Gynecological	22 (12)
	Other	14 (8)
	Head and neck	11 (6)
	Kidney	11 (6)
	Esophagus	9 (5)
	Lung	8 (4)
	Breast	7 (4)
	Hematologic	7 (4)
	Skin	5 (3)
Metastasis, n (%)	Lymph nodes	86 (48)
	Locoregional	84 (47)
	Bone	62 (35)
	Liver	53 (30)
	Peritoneum	43 (24)
	Lung	43 (24)
	Brain	7 (4)

Table 2
Therapies to treat or prevent anemia used in the 6 months prior to transfusion episode.

Treatments, n (%)	
RBC transfusion	100 (56)
Oral iron	33 (28)
Aminocaproic acid	28 (18)
Folic acid	22 (12)
Hemostatic radiotherapy	16 (9)
Intravenous iron	6 (3)
Vitamin K	5 (3)
Vitamin B12	4 (2)
Erythropoietin	3 (2)
Platelet transfusion	2 (1)
Angioembolization	1 (< 1)

Table 3

Drugs with impact on bleeding events, administered in the 72h prior to each transfusion episode.

Anti-inflammatories, n (%)	**Corticosteroids**	**137**	**(46)**
	Non-steroid anti-inflammatory	**6**	**(2)**
	COX-2 inhibitors	**3**	**(1)**
	None	**153**	**(51)**
	Unknown	**1**	**(< 1)**
Anticoagulants, n (%)	Heparins	25	(8)
	Vitamin K antagonists	2	(< 1)
	None	271	(90)
	Unknown	3	(1)
Antiplatelets, n (%)	Any	6	(2)
	None	293	(97)
	Unknown	2	(< 1)
Selective-serotonin-reuptake-inhibitors, n (%)	Any	25	(8)
	None	275	(91)
	Unknown	1	(< 1)

Table 4

Pre-transfusion hemoglobin levels (n = 301).

Hb (g/dL)	n (%)
⩽7.0	152 (50)
7.1–8.0	107 (36)
8.1–9.0	38 (13)
Not record	4 (1)

Table 5
Data collected by transfusion episode.

Transfusion episodes	**Total, n**	**301**
	Per patient	**1.0**
	Median	**1–9**
	Min-Max	
Pretransfusion symptoms, n (%)	Fatigue/asthenia	138 (46)
	Dizziness/lipothymia/syncope	29 (19)
	Dyspnea	24 (8)
	Other	11 (4)
	None	48 (16)
	Unknown	51 (17)
Pretransfusion ECOG-PS, n (%)	1	13 (4)
	2	51 (17)
	3	105 (35)
	4	64 (21)
	Unknown/not evaluated	68 (23)
Active bleeding, n (%)	Yes	100 (33)
	No	201 (66)
Pretransfusion hemoglobin, g/dL	Mean±SD	6.85±1.15
	Min-Max	3.40-9.00
RBC units received	Total, n	435
	Per transfusion episode	1.0
	Median	1–3
	Min-Max	

Table 6
Transfusion episodes assessment by symptomatic benefit, adverse events and survival.

		n = 301
Symptomatic benefit, n (%)	Yes	107 (36)
	No	93 (31)
	Unknown	101 (34)
Adverse events, n (%)	No	288 (96)
	Yes	14 (4)
Survival, days	Median	41.0
	IQR	30.6–51.4
	Min-Max	0-651

Table 7
Univariable analysis of factors influencing survival.

Factors	Median (days)	*p* value
ECOG-PS		
1	146	< 0.001
2	67	
3	37	
4	23	
Hemoglobin		
> 7	51	0.001
≤ 7	35	
Symptomatic benefit		
Yes	64	< 0.001
No	14	

Table 8
Multivariate analysis of factors associated with survival

	HR	95.0% CI	
		Lower	Upper
ECOG-PS			
1	0.18	0.08	0.40
2	0.16	0.09	0.28
3	0.53	0.35	0.79
4	1		
Hemoglobin			
> 7	0.56	0.39	0.81
≤ 7	1		
Symptomatic benefit			
Yes	0.59	0.42	0.83
No	1		