

Clinical and economic effect of administration of red blood product transfusions in an outpatient supportive care cancer service

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Abstract. Patients with cancer may develop disease- or treatment-associated anemia, requiring red blood product transfusions. In Italy, transfusions are usually administered in a day hospital service or in inpatient wards. Since 2013, a dedicated supportive care service for outpatients has been implemented in Pisa, where red blood product transfusions are administered. The present study evaluated the patients that received red blood product transfusions at the dedicated supportive care service for outpatients in 2016. The clinical features of patients were analyzed, and the procedural cost was evaluated by comparing its administration with a hypothetical scenario in which transfusions were provided via day hospital services or inpatient wards. The results revealed that the dedicated supportive care service for outpatients avoided the hospitalization of patients, allowing them to receive prompt and timely transfusions, with a rapid resolution of symptoms. Avoiding hospitalization was also estimated to decrease transfusion-associated costs by €48,805-177,805.

Introduction

Anemia occurs following the decrease of hemoglobin (Hgb) concentrations below that of normal levels. Although severity may differ due to age, sex and race, it is a frequent symptom of patients with cancer. It is more commonly observed in patients with hematological malignancies (60-80% in myelodysplastic syndromes) compared with non-hematological tumors (~40%

of all patients) (1-3). The causes of anemia in patients with cancer are heterogeneous and may be associated with patient characteristics, the type of cancer itself or the administration of oncological treatment (4,5). The principle causes of anemia in patients with cancer are summarized in Table I.

Anemia can be graded according to its severity. Version 4.3 of the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) is the international system for adverse event grading, which categorizes symptoms as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) or fatal (grade 5). The NCI-CTCAE criteria for the grading of anemia is presented in Table II (6).

Patients with solid tumors most commonly develop mild anemia (30% of all patients with cancer). However, a minority of patients also develop moderate (9%) or severe anemia (1%) (2). When mild, anemia is often asymptomatic, but can be characterized by various symptoms, including pallor of the skin and mucous membranes, tachycardia, tachypnea, asthenia and fatigability, chest pain, syncope and lethargy (2,3).

When a patient with cancer presents symptoms of anemia, a thorough evaluation of their condition is mandatory. In addition to recording patient history and performing a physical examination, it is important to perform a complete blood examination, which includes a total blood count, reticulocyte count, renal function tests and the evaluation of iron, ferritin, transferrin saturation, folate, vitamin B12 and C-reactive protein levels. It is also important to assess the presence of blood loss in urine and stool. Furthermore, other tests, including bone marrow biopsy, should be considered as a second-level assessment tool in selected patients (4).

Iron deficiency is common in patients with cancer (6). Whilst some patients exhibit absolute iron deficiency, with ferritin levels <200 ng/ml and transferrin saturation <10%, most have functional iron deficiency, where ferritin levels are normal, but transferrin saturation is low (10-20%). The latter condition results in insufficient iron mobilization and consequently causes iron-restricted erythropoiesis (7).

The treatment of anemia in patients with cancer is selected based on the cause of anemia and the general condition of the patient, where symptoms, possible comorbidities and the

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Table I. Causes of anemia in patients with cancer.

Disease-associated	Treatment-associated	Patient-associated
Bone marrow infiltration	Extensive radiotherapy	Thalassemia
Bleeding	Bone marrow and renal toxicity secondary to chemotherapy	Other hereditary diseases
Hypersplenism	Drug-induced hemolysis	Renal insufficiency
Hemolysis	Hemoglobinopathies	Diminished nutritional status
Anemia of chronic disease	-	-

Adapted from ESMO Guidelines (3).

necessity/speed of treatment are taken into consideration. The two major therapies of anemia include red blood cell transfusions (RBCTs) and erythropoiesis-stimulating agents (ESAs), the latter only being available to patients receiving chemotherapy. Aside from these, it is also important to consider possible iron supplementation (4,8).

According to international guidelines, such as those of the National Comprehensive Cancer Network (8), treatment with RBCTs is considered in symptomatic, high-risk patients; for example, those with a progressive decline of Hgb who have been recently treated with intensive chemotherapy or radiation. Treatment with RBCTs is also considered in asymptomatic patients with various comorbidities including cardiac, chronic pulmonary and cerebrovascular disease.

RBCTs result in the rapid increase of Hgb levels and a rapid improvement of anemia-associated symptoms. However, this procedure has certain risks, including transfusion reactions, circulatory and iron overload, and a potential decrease of survival (9). Due to these risks, RBCTs performed in Italy are administered in inpatient medical wards or emergency rooms. In late 2012, at the St. Chiara Hospital (Pisa, Italy), an outpatient supportive care service (OSCS) was created to assist patients experiencing any symptoms associated with cancer or cancer treatments (10).

The aim of the present study was to evaluate and confirm the use of RBCTs for anemia treatment in patients with cancer in everyday clinical practice. The present study also aimed to assess the safety and feasibility of RBCTs in a dedicated supportive care service for outpatients as opposed to other hospital settings. Additionally, as a secondary objective, the present study estimated the potential economic effect of this service.

Materials and methods

Patients. The present study retrospectively collected the data of patients who received RBCTs at the OSCS of the St. Chiara Hospital (Pisa, Italy) from January until December 2016 (12 months). Demographical data was collected, and various clinical features were analyzed, including patient disease, treatments that were administered at the time of RBCT, hemoglobin levels, the presence of anemia-associated symptoms, possible iron deficiency, any supplements that were administered and the resolution of the patients' acute condition.

Assessments. Patients were later interviewed to record the improvement of symptoms or their resolution, the time taken to improvement or resolution, and the time to subsequent anti-cancer therapy.

Cost analysis. Additionally, the economic costs associated with RBCTs were analyzed. Costs were recorded, checked and analyzed by cross-checking the tax codes of each patient and the median cost per transfusion was calculated. The cost of a single transfusion was calculated, taking into consideration the cost of a single RBC unit, the materials, the blood group and cross-matching tests and the work time of every health-care professional involved (oncologist, nurse and transfusion center staff). The median cost of a single RBCT was therefore determined to be €373. These costs were then compared with the average daily fee of the blood product in combination with the costs associated with hospitalization in other wards (emergency room, inpatient ward and emergency medicine unit). The economic costs were obtained from the Regional Health System of Tuscany (Italy) where the study was performed. The two institutions were then compared, and the net reduction of costs obtained by performing blood transfusions at the OSCS was analyzed. An independent t-test was performed to determine the significance of the data, considering a two tailed test with an α error=0.05 and a standardized effect size=0.15.

Results

Patients' characteristics. In 2016, >1,400 patients were referred to the OSCS. Of these, 125 patients received an RBCT for the treatment of anemia. In total, 215 red cell concentrates (RCCs) were administered.

Of the patients admitted to the OSCS, the majority presented with gastrointestinal tract tumors (15.2% esophageal or gastric, 12% colorectal and 10.4% pancreatic), head and neck tumors (9.6%) and urinary tract tumors (9.6%). The majority of patients also had metastatic disease and were treated in a palliative, non-curative setting (96.8%). A total of 30 (24%) patients received exclusive supportive care and were not treated with any further form of active oncological therapy. The median Hgb level, determined at OSCS admittance was 7.8 g/dl (range, 6.3-8.7 g/dl). The majority of patients were asymptomatic (78.4%); however, 21.6% exhibited anemia-associated symptoms. Only 27.2% of patients had at least one comorbidity, including cardiac or cerebrovascular disease, which made the patient more at risk

Table II. National Cancer Institute-Common Toxicity Criteria for Adverse Events v.4.3 grading of anemia.

Grade	Definition
1	Hgb <LLN-10.0 g/dl (6.2 mmol/l)
2	Hgb <10.0-8.0 g/dl (<6.2-4.9 mmol/l)
3	Hgb <8.0 (<4.9 mmol/l), transfusion indicated
4	Life-threatening consequences; urgent intervention indicated
5	Death

Hgb, hemoglobin; LLN, lower limits of normal.

of anemia. The aforementioned demographical and clinical characteristics of the 125 patients included in the present study are summarized in Table III.

Iron deficiency investigations. An iron deficiency evaluation was performed in 28 patients (22.4%) prior to OSCS admittance. Among these patients, 5 (4%) had absolute iron deficiency, demonstrated by low ferritin and transferrin saturations, whereas 9 (7.2%) exhibited functional iron deficiency, defined as the presence of normal ferritin blood levels and low transferrin saturation. All patients were treated with iron supplementation, with the majority (13 of 14 patients) receiving oral iron formulation. Only 1 patient was treated with intravenous iron.

Complications. During the administration of RBCT, only one adverse reaction to the infusion was observed. It was characterized by fever (temperature of 38.5°C) and mild shivering. This reaction was treated successfully with 1 g of intravenous paracetamol and of intravenous 500 mg hydrocortisone. Following resolution, RCC administration was restarted with a slower infusion rate and the patient ended treatment without any additional problems.

Median time of treatment. The service provided a prompt treatment for patients. A median waiting time of 2 h was observed from the time the patient was admitted until the time RBCT was started. The median transfusion time was 1.5 h (range, 1-3 h) and the median time of stay was 3 h (range, 2-5 h). Patients were interviewed in the days following RBCT. The median time to the clinical interview was 4 days (range, 1-9 days).

Symptom resolution. Among all symptomatic patients (27; 21.6% of the whole study population), 20 demonstrated an improvement of symptoms (74.1%) and among these, 8 exhibited a complete resolution of their anemia-associated symptoms (29.6%). The median time to improvement or resolution of symptoms, calculated from the end of the RBCT, was 1 day (range, 0.5-3 days). Furthermore, the time to subsequent anticancer therapy was 6 days (range, 4-26 days). No patient that was admitted to the OSCS for RBCT required hospitalization for the treatment of anemia or for any complications following the procedure.

Table III. Demographical and clinical characteristics of the patient cohort.

Demographical and clinical characteristics	Number of patients (%)
Total number of patients	125 (100)
Age	
Median	69
Range	18-89
Tumor primary site	
Esophagus and stomach	19 (15.2)
Colon/rectum	15 (12)
Pancreas	13 (10.4)
Head and neck	12 (9.6)
Urinary tract	12 (9.6)
Prostate	9 (7.2)
Liver/biliary tract	9 (7.2)
Lung	8 (6.4)
Kidney	8 (6.4)
Breast	7 (5.6)
Melanoma	5 (4)
Sarcoma	5 (4)
Ovary and uterus	3 (2.4)
Setting	
Curative	4 (3.2)
Palliative	121 (96.8)
Cancer treatment	
Patients on active treatment	95 (76)
Patients in best supportive care	30 (24)
Median Hgb levels at the time of access (range)	7.8 (6.3-8.7)
Presence of anemia-associated symptoms	
Yes	27 (21.6)
No	98 (78.4)
Presence of comorbidities	
Yes	34 (27.2)
No	91 (72.8)

Cost reduction. Finally, the present study analyzed the economic effect of the RBCTs, which was a primary objective of the study. The administration of RBCTs at the OSCS decreased costs, with an estimated net reduction of €48,805-177,805 (P<0.001). Table IV presents the effective costs, the hypothetical costs of administration in other hospital settings and the net reduction of costs at the OSCS.

Discussion

Anemia is a frequent occurrence in patients with cancer. In this setting, patients must be evaluated to determine the cause of anemia and to provide an appropriate and prompt treatment for symptoms, improving the quality of life and positively affecting their prognosis (11-13).

Table IV. Economic analysis of crude costs associated with the service and hypothetical net reduction of these costs.

Setting	OSCS	Inpatient medical ward	Emergency room	Emergency medicine ward
Cost per single RCC	€373	€600	€900	€1,200
Effective costs ^a	€80,195	-	-	-
Hypothetical costs	-	€129,000	€193,500	€258,000
Net reduction of costs	-	€48,805	€113,305	€177,805
P-value	-	<0.001	<0.001	<0.001

^aEffective costs include costs associated with the RCC unit, other possible administered drugs, staff remuneration, and outpatient visiting costs. OSCS, outpatient supportive care service; RCC, red cell concentrates.

RBCTs are important for the treatment of anemia in patients with cancer, as stated in both international and national guidelines (8). They rapidly increase Hgb levels and thereby improve anemia-associated symptoms. Therefore, RBCTs should be offered to symptomatic or high-risk patients that require rapid treatment. However, though this treatment should be offered promptly to patients with cancer, in clinical practice, RBCTs are only offered to patients via emergency rooms and subsequent admission to inpatient wards.

In 2012, an OSCS was created at the St. Chiara Hospital in Pisa for the purpose of treating cancer- or treatment-associated symptoms. RBCTs were therefore offered for the treatment of anemia. The service began in 2016, 4 years after its creation, due to authorization problems.

A total of 125 patients were treated with RBCTs in 1 year. Patients who received this treatment were heterogeneous and included patients affected by several different types of cancer, at different stages, receiving different treatments.

The present study determined that there was a lack of attention to iron deficiency in patients. Following this observation, the OSCS evaluated the patients accessing the day hospital ward and the treatment of anemia that was provided. Subsequently, iron supplementation, primarily oral, was offered to any patient with an absolute or functional iron deficiency. Internal educational meetings were also planned to recognize the importance of anemia and its evaluation, iron supplementation and the role of RBCTs.

RBCTs were administered a few hours following admittance, meaning patients received prompt treatment. This allowed for the rapid relief of anemia-associated symptoms. The symptom improvement rate was high (74.31%), with almost one of three symptomatic patients experiencing symptom resolution. Furthermore, the time to improvement or symptom resolution was short (median time, 1 day).

No particular safety concerns emerged during the present study. The sole infusion reaction that was observed was mild and its management was handled with no particular concern. The OSCS also allowed patients to avoid admission to an emergency room or any other inpatient medical ward, maintaining a direct connection with the medical oncology unit and ward.

In conclusion, the OSCS had both clinical and economic benefits. As a positive result, access to OCSC was rapid and direct, meaning there was no need for patient hospitalization and the long waiting hours associated with emergency rooms were avoided. Patients also experienced a rapid improvement

in possible anemia-associated symptoms and in the majority of cases, this allowed them to continue anticancer treatment, which could be resumed within <1 week. Economically, a marked decrease in the costs associated with RBCTs was observed, with a net reduction of ~one-third of the total expense. This is consistent with the results of a previous Italian OSCS evaluation by Ripamonti *et al* (14). In future studies, the assessment of patient quality of life via a questionnaire and the real quantitative and qualitative effect of this OCSC activity should be performed.

The present study confirmed that RBCTs should be considered as a primary treatment for patients with cancer experiencing anemia. It was also demonstrated that RBCTs may be safely administered in an OSCS, creating positive clinical and economic effects.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AS and AA conceived the present study. All authors collected data. AS, AA and EV analyzed the data. FP, FB, MD, LG, IMB, SR and AF were involved in the acquisition and analysis of the data. AS wrote the manuscript, with contribution from all the authors. All authors read and approved of the final manuscript.

Ethics approval and consent to participate

The present study was performed according to the principles of the Declaration of Helsinki 2000 and was approved by the Local Ethic Committee of the University Hospital of Pisa. As per the policy of the Ethics Committee, patients, when

applicable, were asked to provide oral consent for the use of their data and such consent was recorded in their clinical files.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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