

## RESEARCH ARTICLE

# Use of Blood Transfusion at the End of Life: Does it Have Any Effects on Survival of Cancer Patients?

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### Abstract

**Background:** Treatment of anemia is an important issue in the palliative care setting. Blood transfusion is generally used for this purpose in supportive care. However the place of blood transfusion in terminally ill cancer cases is less far established. **Objective:** We aimed to outline the use of transfusions and to find the impact of blood transfusion on survival in patients with advanced cancer and very near to death. **Design:** Patients dying in 2010-2011 with advanced cancer were included in the study. We retrospectively collected the data including age, type of cancer, the duration of last hospitalisation, ECOG performance status, Hb levels, transfusion history of erythrocytes and platelets, cause and the amount of transfusion. The anaemic patients who had transfusion at admission were compared with the group who were not transfused. Survival was defined as the time between the admission of last hospitalisation period and death. **Results:** Three hundred and ninety eight people with solid tumours died in 2010-2011 in our clinic. Ninety percent of the patients had anemia at the time of last hospitalisation. One hundred fifty three patients had erythrocyte transfusion at admission during the last hospitalisation period (38.4%). In the anaemic population the duration of last hospitalisation was longer in patients who had erythrocyte transfusion (15 days vs 8 days,  $p < 0.001$ ). **Conclusions:** Patients who had blood transfusion at the end of life lived significantly longer than the anaemic patients who were not transfused. This study remarks that blood transfusions should not be withheld from terminal cancer patients in palliative care.

**Keywords:** Blood transfusion - terminally ill cancer

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### Introduction

Anemia is the most frequent hematologic manifestation in patients with cancer (Calabrich and Katz, 2011). The European Cancer Anemia Survey (ECAS) reported that approximately 40% of the patients had haemoglobin levels  $< 12$  g/dl (Ludwig et al., 2004). Anemia causes several symptoms that can influence the physical and functional status of the patients, negatively affecting their quality of life (Ludwig and Strasser, 2001). It is also associated with worse treatment outcomes (Vamvakas and Blajchman, 2001). Cancer related anemia is often multifactorial including: bone marrow infiltration, malnutrition, bleeding, renal insufficiency, toxicity related with chemotherapy/radiotherapy, anemia of the chronic disease (Schrijvers, 2011). Present treatment options for anemia include blood transfusions, iron supplementation when there is iron deficiency or erythropoiesis-stimulating agents (ESAs).

The use of blood transfusions to correct anemia is a therapeutic modality for which there is less literature available for patients with cancer. The chief aim of

transfusion is to immediately correct the signs or symptoms resulting from anemia (Barrett- Lee et al., 2000). However, there is evidence in the literature that blood transfusion may have a negative impact on the progression of disease. Meng J had demonstrated that allogeneic blood transfusion increased the postoperative tumor mortality, local recurrence and distant metastasis in patients with colon cancer ( Meng et al., 2013).

Treatment of anemia is an important issue in the palliative care setting. Dunn et al reported that 77% of men and 68% of women in the palliative care had anemia (Dunn et al., 2003). As erythropoiesis stimulating agents has some disadvantages including; cost, efficacy in only some patients, and the 4-8 weeks delay before maximum benefit is achieved (Eagleton and Littlewood, 2003), most of the guidelines recommends their usage only in the treatment of chemotherapy related anemia (Bokemeyer et al., 2007; Rizzo et al., 2010). Blood transfusion is used in the treatment of anemia in supportive care. However the place of blood transfusion in terminally ill cancer is less far established.

Blood transfusion is usually used in patients with

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terminal illness when there is acute blood loss, in patients with respiratory and cardiac symptoms, in chemotherapy related anemia (Leibovitz et al., 2004). However the trigger level of Hb has not been determined and varies between the guidelines and the physicians views (Leibovitz et al., 2004; Bokemeyer et al., 2007; Rizzo et al., 2010). Most of them give a cut of value of Hb <9 g/dl in asymptomatic patients; cut-off values may be lower depending on the patients symptoms and cardiac status (Bokemeyer et al., 2007; NCCN Guideline on Cancer- and Chemotherapy-Induced Anemia, Version 2, 2011; Rizzo et al., 2010; Schrijvers, 2011).

There are no systematic reviews or randomised controlled trials to assess the usefulness of transfusions in advanced cancer or to identify which groups of patients are more likely to benefit from them (Preston et al., 2012).

Here we aimed to outline the use of transfusions at the end of life and to find the impact of blood transfusion on survival in patients with advanced cancer and very near to death.

## Materials and Methods

Patients diagnosed with solid tumours and died in 2010-2011 in the medical oncology clinic were included in the study. Patients with hematologic malignancies who were treated in the haematology service were not included. We retrospectively collected the data including age, type of cancer, the duration of last hospitalisation, ECOG performance status, Hb levels, transfusion history of erythrocytes and platelets. Cause and the amount of transfusion were also recorded. Anemia was defined as a Hb level of <12g/dl in women, and <13 g/dl in men according to the WHO classification (Beutler and Waalen, 2006). The anaemic patients who had transfusion at admission were compared with the group who were not transfused. Survival was defined as the time between the admission of last hospitalisation period and death.

Descriptive statistics methods were used for the statistical analysis of the data. The comparisons between the study groups were performed using the Chi-square test for categorical and Mann-Whitney test for continuous variables.  $p < 0.05$  was considered significant.

## Results

Three hundred and ninety eight people with solid tumours died in 2010-2011 in our clinic. The median age was 61 (range 20-90). There were 248 men (62.3%), and 150 women (37.7%). The most common diagnoses were non-small cell lung cancer (27%), pancreas and biliary tract cancers (10%), colon cancer (8.8%), gynaecologic cancers (7.3%) and breast cancer (6.5%).

Ninety percent of the patients had anemia at the time of last hospitalisation. Mean Hb level was 9.9 g/dl. One hundred fifty three patients had erythrocyte transfusion at admission during the last hospitalisation period (38.4% of all patients, 42.3% of the anaemic patients). Hb level was significantly lower in patients who were transfused. 52.2% of patients had multiple courses of transfusion. Average 4.37 units (1-24) of erythrocytes were transfused.

**Table 1. A) Comparison of Survival and Hb in Anaemic Patients between the Transfusion Group and No Transfusion Group and B) Comparison of Patients who had Platelet Transfusion and Who Did Not**

A)	RBC transfusion (n: 153)	No RBC transfusion (n:206)	p
Survival	15 (1-67)	8 (1-58)	<0.001
Hemoglobin (g/dL)	8.5±1.2	10.3±1.4	<0.001
B)	Platelet transfusion (n: 55)	No platelet transfusion (n: 343)	p
Duration of last hospitalisation	16 (2-67)	10 (1-60)	0.001

The most frequent cause of transfusion was low Hb, either solely or in conjunction with symptoms (73.9% low Hb, 26.1% acute bleeding). In the anaemic population the duration of last hospitalisation was longer in patients who had erythrocyte transfusion (15 days vs 8 days,  $p < 0.001$ ).

Nearly fourteen percent of the patients (13.8%) had platelet transfusion. The cause of platelet transfusion was bleeding prophylaxis in 77.5%, and acute bleeding in 22.5% of the patients. The duration of last hospitalisation was longer in patients who had platelet transfusion (16 days vs 10 days,  $p < 0.001$ ).

## Discussion

In our series the transfusion rate was %38.4. This is higher than the rate observed in other studies (Greer et al., 1986; Monti et al., 1996). In the National Hospice Study it has been documented that terminal cancer patients in conventional care settings are five times more likely to be transfused than the patients in hospital-based hospices. The transfusion rate during the last 4 weeks of life was significantly higher (27%) in the conventional care sample than in home-based (4%) and hospital-based hospices (8%) (Greer et al., 1986). Our hospital is a university teaching hospital, and we do not have a palliative care unit so the patients are treated by medical oncologist until death. This may explain our high rate of transfusion.

In the anaemic population survival was longer in patients who had transfusion (15 days vs 8 days). To our knowledge there are no randomised prospective studies to assess the survival of patients with advanced cancer who had blood transfusion. Monti et al examined 246 terminally ill cancer patients; the transfusion rate was 12.6%. Sixty percent of patients who had transfusion died during the same hospitalisation period, a median of 49 days after transfusion. Time before death was significantly shorter in patients who did not report any improvement in well-being after transfusion (Monti et al., 1996). Brown et al had reported a median survival of 42 days following first transfusion for palliative care patients (Brown and Bennett, 2007). In the Cochrane review a significant proportion of participants (23% to 35%) with advanced cancer died within 14 days of transfusion (Preston et al., 2012). They argued that in patients with advanced cancer, blood transfusion may have resulted in increased morbidity and mortality perhaps because of fluid overload or higher plasma viscosity. In our study group, patients

who had transfusion had a median survival of 15 days but it was longer than the ones who had anemia and did not have transfusion. One possible explanation is getting enough oxygen to vital organs may cause this survival benefit. Another is that this was a non-homogenous group of patients and these participants were terminally ill and would have died with or without transfusion. The effect of blood transfusion on survival in terminally ill cancer needs further investigation.

Cancer-related fatigue is the most prevalent cancer symptom, reported in 50%-90% of patients and severely impacts quality of life and functional capacity. Anemia is one of the main reversible causes of fatigue (Campos et al., 2011). It has been shown that an Hb level >12 g/dl improves fatigue and quality of life, and even in mild anemia (Hb level between 10-12 g/dl) there is a marked increase in fatigue (Cella, 1997). In our study the data of symptom relief in patients who were transfused were not recorded. Mercadante had reported that haemoglobin values and well-being significantly increased after transfusion, maintaining acceptable values 15 days afterward. Significant changes in fatigue and dyspnea were found immediately after transfusion, although the effect was partially lost 15 days after transfusion (Mercadante et al., 2009). In the Cochrane review 31% and 70% of participants appeared to show some symptomatic response to blood transfusion between day two to seven, with scores (where measured) returning to near baseline levels by day 14. On the other hand Dunn et al. (2003) did not find a significant association between anemia and presence of fatigue (Dunn et al., 2003). Monti had reported that transfusions administered during the last 4 weeks of life were likely to prove a useless procedure that does not influence the quality of life (Monti et al., 1996). Further prospective studies should be done monitoring the efficacy of blood transfusion on symptom relief in patients very near to death.

There are no well-defined guidelines for terminal cancer patients, therefore transfusion decisions in the setting of terminal cancer are greatly influenced by the attitudes of the medical team and not infrequently regarded as unnecessary (Wachtel and Mor, 1985; Mozes et al., 1989; American College of Physicians, 1992; Monti et al., 1996). Leibovitz had reported views of 500 physicians and nurses on blood transfusion to terminally ill cancer patients. There was broad agreement that blood transfusions should not be withheld from terminal cancer patients. Responders tended to regard terminal cancer patients as a separate group, and slight but a significant majority had the opinion that transfusions to these patients do not prolong suffering (Leibovitz et al., 2004).

Platelet transfusion is also an important issue in patients with advanced cancer. Platelets are transfused to stop active bleeding due to thrombocytopenia and for the prophylaxis of bleeding. However platelet transfusion threshold of prophylactic platelet transfusion is not clear. For many years a platelet level of  $20 \times 10^9$  per liter was used as a trigger for prophylactic platelet transfusion (Gaydos et al., 1962; Lozano and Cid, 2007). An increasing body of evidence suggests that a transfusion trigger of  $10 \times 10^9$  per liter is safe as higher levels for

patients without additional risk factors (Heckman et al., 1997; Rebulla et al., 1997; Zumberg et al., 2002; Diedrich et al., 2005). However most of these studies are conducted in leukemic patients or in stem cell transplantation. Our clinical practice is to transfuse in patients with a platelet level lower than  $20 \times 10^9$  per liter. The duration of last hospitalisation was longer in patients who had platelet transfusion (16 days vs. 10 days,  $p < 0.001$ ). None of the patients who did not have platelet transfusion were reported to die due to active bleeding. Further studies are needed to examine the prophylactic platelet threshold and effectiveness of platelet transfusion in terminally ill cancer patients with solid tumours.

In conclusion, patients who had blood transfusion at the end of life lived significantly longer than the anaemic patients who were not transfused. This study remarks that blood transfusions should not be withheld from terminal cancer patients in palliative care. We need prospective studies defining the exact role of blood transfusion in terms of survival and symptom relief in patients with advanced cancer.

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