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PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

Transfusion as a Palliative Strategy

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Abstract

Purpose of Review The palliative care population is a complex and heterogeneous one. While transfusion therapy is a readily available intervention for many patients, inadequate knowledge for accurately identifying which patient subsets at end-of-life will benefit from a transfusion, along with an unclear understanding of the magnitude of attendant risks of transfusion in those receiving palliative care, complicates the risk-benefit assessment of this therapy. In this brief review, the current literature surrounding transfusion of red cells and platelets in the palliative care patient population will be reviewed and recommendations provided.

Recent Findings Benefits of transfusion therapy include subjective relief of fatigue and dyspnea, and improved sense of wellness, amongst other findings. However, these responses are not durable and there are currently no validated, objective metrics that correlate with symptomatic improvements. It is clear that transfusion-associated adverse reactions are underestimated in those receiving palliative care, with reaction rates similar to the general patient population. Additionally, based on the high mortality rates reported soon after transfusion, the impact of these blood components must be considered as an exacerbating or causative factor of mortality when evaluating declining condition or death. Hematinics are rarely assessed in anemic palliative care patients or, when measured, are often not corrected. The decision to transfuse palliative care patients is multifactorial, and benefits, risks, patient wishes, blood component inventories, and alternatives to transfusion should all be considered.

Summary There are many unknowns regarding transfusion in palliative care. Critical next steps for optimizing blood component therapy in this population include high-quality trials that help to identify validated measures of objective functional changes that parallel patient-reported outcomes and subsets of patients receiving end-of-life care that will most likely be positively impacted by transfusion therapy.

Keywords Palliative care · Transfusion · Red cells · RBC · Platelets · End-of-life

Introduction

The World Health Organization defines palliative care as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual" [1]. The palliative care population is a complex and heterogeneous one, and the single category under which these patients are placed does not effectively characterize their different diseases, treatments, comorbidities, and nutritional and functional statuses. Nor does the palliative care designation clearly communicate a patient's health care setting, support systems, and access to resources outside of the hospital.

Cytopenias, particularly anemia and thrombocytopenia, are common in palliative care patients. During the care of this diverse group of patients receiving end-of-life treatments, transfusion of blood components, such as red cells or platelets, might provide symptomatic relief and subjective improvements. However, the paucity of factors reliably identifying which patient subsets will benefit from a transfusion, along with an unclear understanding of the magnitude of the attendant risks of transfusion in those receiving palliative care, complicates the risk-benefit assessment of this therapy [2]. Additionally, the lack of validated measures of objective functional changes that mirror patient-reported outcomes further confounds this issue. Last but not the least, the fact that blood components are a finite and expensive resource needs to be considered. In this brief review,

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the current literature surrounding transfusion of red cells and platelets in the palliative care patient population will be reviewed and suggested guidelines provided.

Ethics of Blood Transfusion in Palliative Care

Red cell and platelet units are produced via the altruistic acts of healthy blood donors. As such, they are finite resources with measurable expenses on the order of hundreds to thousands of dollars per transfused unit. Despite their importance in routine medical care, collection and utilization of blood components are decreasing, at least in part, due to increased adherence to evidence-based transfusion guidelines and restrictive transfusion strategies [3, 4•, 5•]. Combined with the facts that red cell units have a shelf-life of up to 42 days and platelet units only a mere 5–7 days, responsible allocation of these precious therapeutic agents is necessary.

Ethical principles can assist in guiding decision making for allocating blood components to those patients with terminal illnesses [2, 6–9]. When consulting on clinical care team requests in which a finite resource, like red cells or platelets, is considered for use in this patient population, the ethical tenets of autonomy (i.e., patient consent or refusal of care), nonmaleficence (i.e., do no harm), and beneficence (i.e., act in the patient's best interest)—principles that advocate for an individual patient—can be balanced with justice (i.e., fairness for all patients) [10]. Each request for blood components to the Blood Bank is evaluated on its merits with a risk-benefit assessment performed. While it may be easy to simply assert that the needs of the many outweigh the needs of the few, particularly those few whose prognoses are unfavorable, careful consideration is necessary. Difficulties lie in the facts that the benefits of red cell or platelet transfusion in these palliative care patients may be difficult to characterize. Additionally, risks of blood component therapy in this diverse, unwell population are poorly described [11, 12, 13•]. However, depending on the goals of transfusion therapy, the patient's specific blood component needs, and the ability of the Blood Bank to provide the requested blood components, resolutions between demand and supply can be possible.

Possible Benefits of Transfusion Therapy in Palliative Care

Anemia is a common finding at the end of life, with 7% of those admitted to a palliative care unit being transfused with red cells [11]. Transfusion has been shown to be critical in a variety of settings to acutely correct symptomatic anemia [5•, 14, 15]. The ability to improve deficits in oxygen-carrying capacity in the setting of anemia to assist in patients' overall medical recoveries is clear. In almost all of these different patient populations, transfusions are being administered alongside other interventions with the underlying goal of returning a patient's status as close to their baseline as possible. In the palliative care setting, however, goals are individualized and clinical endpoints are usually short-term alleviation or abrogation of signs and symptoms associated with anemia in patients with a limited lifespan. Thus, the red cell and platelet transfusion thresholds used in other patient populations may not necessarily apply to those receiving palliative care [2].

It has been previously shown that red cell transfusion for common patient-reported symptoms, such as fatigue, dyspnea, and decreased well-being, in those receiving palliative care had marked short-term improvements of these subjective findings. In a prospective observational study of all palliative care patients to assess the benefit of receiving red cell transfusions, the most common indications for transfusion were weakness and dyspnea [16]. Using a visual analogue scale with scores from 0 to 10 for well-being, strength, and breathing, patients reported their change in symptoms over 14 days after transfusion. At 2 and 14 days post-transfusion, significant improvements in all three categories were noted. In another prospective observational study, 61 patients admitted to a palliative unit were recruited and transfused with 133 units of red cells for anemia and/or anemia-associated symptoms including decreased well-being, fatigue, or dyspnea [17]. Using the Edmonton Symptom Assessment Scale, all three parameters significantly improved immediately after transfusion, but only improvement in well-being significantly persisted at 2 weeks post-transfusion. In a retrospective review of 31 palliative care unit patients who received 44 transfusions for primarily fatigue and breathlessness, 39 of the transfusions were associated with subjective benefit by the observing clinicians and 29 of the patients expressed symptomatic benefit [18].

Recently, a multi-center prospective observational study identified 141 palliative care patients undergoing transfusion for a defined target symptom and, if present, secondary symptoms; 101 patients had data up to day 7 post-transfusion [19]. Of the various symptomatic indications being targeted, 49% of patients had benefit in the target symptom, with 78% having benefit in any symptom. In an unadjusted analysis, patients with an Australia-modified Karnofsky Performance Scale of 40–50% responded to red cell transfusion more frequently; however, after logistic regression, no baseline factors in these transfusion recipients were associated with an improvement in the worst symptoms. In a prospective U.K. study of 465 transfusion episodes in hospices for patients with anemia, breathlessness, and/or fatigue, clinician-reported outcomes showed that only 83 (18%) patients were deemed to have sustained benefit at 30 days post-transfusion [20••].

With regard to platelet transfusions, these components are typically administered to inpatients when counts are less than 10,000/μL in order to prevent spontaneous bleeding or to assist in providing hemostasis in the presence of active,

clinically significant bleeding [4•]. There is no reason to believe that, in the absence of an anatomic abnormality causing persistent blood losses, these criteria would not be medically applicable to palliative care patients. In one retrospective analysis of 469 adult and pediatric palliative care outpatients with advanced hematological malignancies, 123 (26%) of patients had 232 bleeding episodes [21]. In 188 of these episodes (81%), bleeding was corrected with the use of platelet transfusion. In another retrospective analysis of pediatric palliative care patients, 32 platelet transfusions were administered to 12 patients with oral bleeding, epistaxis, rectal bleeding, and/or hematuria [22]; there was complete resolution of bleeding with the majority of transfusions (30/32, 94%). While catastrophic, life-threatening bleeding may not be able to be remedied with platelet transfusions, its use in correcting less severe hemorrhage in palliative care patients appears to be as effective as in recipients from other groups [23].

In addition to any observed and reported subjective benefits from blood component therapy, routine transfusions involve coordination and requisite interactions with a variety of health care professionals. These include phlebotomists, technologists, medical assistants, administrative staff, nurses, physician assistants, physicians, and other health care providers. This caregiver network has been reported to be an important source of routine interaction and socialization that benefits particularly those palliative care patients receiving chronic, intensive transfusion support [24].

It is important to note, however, that these reported positive effects were not durable and typically abated after a couple of weeks [11, 12, 13•]. Additionally, no validated and objective measures, neither through the lens of traditional provider-assessed outcome measures nor through the lens of patient-reported outcomes, were found to significantly correlate with these symptomatic improvements. Nevertheless, despite the subjective nature of the majority of these benefits of blood transfusion, improvements which may enhance the quality of life in those with remaining lifespan of days to months cannot be discounted if it is in keeping with a patient's and family's wishes and is medically feasible.

Possible Risks of Transfusion Therapy in Palliative Care

Similar to the issues of applying red cell and platelet transfusion thresholds studied in the non-palliative care setting to palliative care populations, the same concern arises when discussing transfusion risks for these patients at end-of-life. In these individuals with admittedly complex and heterogeneous diseases who have received various treatments, factors such as other underlying comorbidities, poor dietary intake, nutritional deficiencies, deconditioning, and expected survival time all confound traditional transfusion risk assessments. However, the fact that there is a paucity of high-quality evidence to guide or support transfusion therapy in palliative care patients cannot be overlooked [11, 12, 13•]. Additionally, no validated, objective measures have been identified that correlate with symptomatic improvements [19]. The risks of transfusion in this specific population have also been poorly characterized. The combination of unclear, subjective benefits in conjunction with the much more explicit and measured potential for adverse reactions complicates the task of conducting a proper risk-benefit analysis by ordering providers [2].

Transfusion reactions in general patient populations have been well characterized and protocols for their identification and reporting have been discussed previously [25•]. Rates for common reactions, such as febrile non-hemolytic transfusion reactions, allergic reactions, and transfusion-associated circulatory overload, have been reported to occur in < 1 to 8% of transfusions [26, 27]. Interestingly, complications resulting from transfusions in palliative care patients have been reported to occur seldomly [28]. When combining the palliative care patient cohorts from 6 different transfusion studies involving a total of 306 patients that conservatively received an estimated 554 units, 25 associated adverse events possibly related to blood components were documented (reported reaction rate range of 0–16.7% per transfused patient) [16, 18, 19, 22, 29, 30]. These included 5 febrile non-hemolytic transfusion reactions, 3 transfusion-associated circulatory overload reactions, 3 allergic transfusion reactions, 1 hemolytic transfusion reaction, 1 hypotensive transfusion reaction, 7 unspecified transfusion reactions, and 5 other adverse events associated with but not necessarily caused by transfusion. Collectively, this represents reaction rates per patient and per transfused unit of 8.2% and 4.5%, respectively, which is surprisingly similar to reported reaction rates in non-palliative care patient populations.

It is noteworthy that in an analysis of hospices transfusing red cells, 85% of patients were not weighed and 84% had at least two units transfused [20••]; these would almost certainly place a subset of palliative care patients at increased risk for development of transfusion-associated circulatory overload, the primary cause of transfusion-related fatalities [31]. Such quantification of the risks of transfusion for palliative care populations and may help to better inform ordering providers that hazards of transfusion for their patients are similar, both in frequency and variety of reactions, to other groups. Additionally, active surveillance and prompt recognition of transfusion reactions that can be fatal, particularly in palliative care patients, should be part of routine evaluation; these would include reactions such as transfusion-associated circulatory overload, severe allergic, septic, and hemolytic reactions [31].

The high rates of death reported after transfusion may reflect the severe underlying diseases of these palliative care patients. Indeed, when combining the palliative care patient cohorts from 8 different studies involving transfused recipients that died within 30 days, a total of 326 deaths out of 833

transfusion recipients were documented (overall 30-day mortality rate of 39.1%) [16–18, 20••, 29, 30, 32, 33]. However, given that the rate of transfusion reactions appears to be similar to that observed in non-palliative care populations and is not as rare and innocuous as previously reported, a fraction of these deaths could be due to or hastened by unrecognized transfusion reactions [20••, 26, 27]. Death rates at post-transfusion times of 7 days, 14 days, and 30 days were approximately 69% (105/153), 29% (38/130), and 33% (183/550), respectively; with such high rates of mortality, especially within the first week after transfusion, complications associated with blood transfusion must be considered as an exacerbating or causative factor of mortality when evaluating declining condition or death in these severely ill patients.

Last but not the least, costs of red cell and platelet transfusion must be considered. It has been reported that the cost of a routine red cell unit transfusion can be at least $1,183, whereas the average cost incurred by transfusing a platelet unit has been calculated to be as high as $4,436 [24, 34, 35]. In patients with red cell alloimmunization and/or platelet refractoriness, both conditions that would require antigen negative or matched blood components, the costs are even higher. These reported values likely underestimate the true total expenses, as the costs of ordering, obtaining, and delivery of components from a blood supplier, the accessioning, storage, manipulations, issuing, and release of a blood unit from the Blood Bank, and then the receipt, observation, documentation, infusion, and disposal by the transfusing health care providers are not all necessarily included in these estimates (not to mention the extra costs associated with a transfusion reaction evaluation). While monetary factors alone cannot dictate the decision to offer or withhold transfusion, it is an important consideration that should not be ignored.

Given its relatively short-term benefits, greater than expected risks, inherent costs, and an unclear understanding of which specific palliative care subpopulations would most benefit from blood therapy, use of transfusion in palliative care patients should not be indiscriminately offered to those with anemia and thrombocytopenia, but rather given to individuals that are predicted to have the greatest benefit from use of such a limited resource. This advice is consistent with recommendations from international guidelines [5•, 14, 15, 36, 37•].

Alternatives to Transfusion Therapy in Palliative Care

The etiology of anemia is variable, and transfusion is not necessary to correct all causes of anemia. Erythrocytosis-stimulating agents, intravenous iron, and correction of other hematinics can be utilized in lieu of transfusion (or at least to decrease transfusion) to care for those with sequelae of anemia. In one retrospective study, 72 episodes of care for treatment of anemia were analyzed in those receiving chemotherapy in the palliative care setting [38]. Forty-three (60%) patients were anemic at the initiation of chemotherapy. Iron status was assessed in 39 (54%) patients and a deficiency was identified in 25 (64%) of these patients. Interestingly, only 13 of the 25 iron-deficient patients (52%) received therapy with intravenous iron. In addition, of the 15 cases of iron deficiency that were deemed to be eligible for treatment with erythrocytosis-stimulating agents, only 6 (40%) patients actually received them. Other hematinics such as vitamin B12 and folate were also assessed in 33 (46%) and 34 (47%) patients, respectively; only 2 cases of vitamin B12 deficiency were identified, and there were no cases of folate deficiency. The most frequent mechanisms for correcting anemia were red cell transfusion (92%), followed distantly by intravenous iron (18%) and erythrocytosis-stimulating agents (8%) [38]. Notably, it was estimated that up to 26% of patients would have required fewer to no transfusions if strict adherence to international guidelines had occurred [39••, 40•].

In a prospective UK study of 465 transfusion episodes in 83 hospices caring for anemic patients, anemia of chronic disease was present in 176 individuals (38%) and was the most common etiology of anemia [20••]. Surprisingly, hematinics such as iron, vitamin B12, and folate were not assessed in 70% of patients. Regarding iron status, 310 of the 465 (67%) episodes were not assessed. Of the 149 patients with documented iron deficiency or possible iron deficiency, only 37 of them (24.8%) received iron supplementation (4 others were intolerant of iron). Of the 102 individuals (22%) assessed for vitamin B12 status, 12 of them (12%) would have benefited from vitamin B12 injections; remarkably, only 1 of these patients received such treatment. Similarly, of the 105 individuals (23%) assessed for folate status, 43 (41%) of them with detectable deficiencies would have benefited from supplementation, but only 10 were on treatment with folate. Erythrocytosis-stimulating agents were only administered in three patients, even though at least 66 were eligible. Overall, these two studies demonstrate that etiologies of anemia are inadequately investigated prior to transfusion. Correction of deficient hematinic parameters can result in increased hemoglobin values within 7 days [41], and use of intravenous iron can decrease need for red cell transfusions and the associated risk of transfusion-associated circulatory overload [20••], the primary cause of death in transfusion recipients [31]. These alternatives to red cell transfusion should be considered in palliative care patients, particularly for those that are anticipated to live longer than 7 days.

With regard to alternatives for platelet transfusion, recommendations are more general. Useful maneuvers include reversal of any underlying non-iatrogenic coagulopathies, optimization of any anticoagulant or antiplatelet agents, and exerting pressure at local bleeding sites. Another reported strategy for improving platelet function in anemic thrombocytopenic patients, particularly if platelet therapy is not readily available, is to transfuse these individuals with red cells to achieve a hematocrit as high as

35% [42, 43]. This has been shown to improve bleeding time and normalize thromboxane B2 levels, but other mechanisms, such as measurable increases in platelet reactivity with tests measuring the adenosine diphosphate-P2Y12 receptor pathway, may also contribute to this effect [44]. A recent systematic review revealed insufficient evidence for thrombopoietin (TPO) mimetics for preventing bleeding in patients with thrombocytopenia due to chronic bone marrow failure [45•]. Additionally, there is no high-quality evidence for artificial platelet substitutes, platelet-poor plasma, fibrinogen concentrate, recombinant FVIIa, recombinant FXIII, recombinant IL-6, recombinant IL-11, antifibrinolytics, or DDAVP in these settings. However, two randomized trials, the TRial to EvaluAte Tranexamic Acid Therapy in Thrombocytopenia (TREATT) and the American Trial Using Tranexamic Acid in Thrombocytopenia (A-TREAT), are currently recruiting patients. TREATT will answer whether giving antifibrinolytic therapy with tranexamic acid to patients receiving treatment for blood cancers reduces the risk of bleeding or death and the need for platelet transfusions [46]. A-TREAT will address the usefulness of tranexamic acid in preventing bleeding in patients who are thrombocytopenic due to primary bone marrow disorders or chemotherapy, immunotherapy, and/or radiation therapy [47]. Findings from these two important studies will certainly assist in the management of thrombocytopenic palliative care patients who may require platelet transfusion. Lastly, discontinuation of platelet therapy despite persistent or worsening thrombocytopenia is an option. While concerns for catastrophic hemorrhaging often accompany discussions over discontinuing platelet transfusions, it has been reported that most dying patients who stopped platelet therapy did not suffer significant bleeding, and those who were previously dependent on transfusion support lived over 7 days after cessation of transfusions [48, 49].

Determining Whether or Not to Transfuse a Palliative Care Patient

When addressing the question of whether or not to transfuse a palliative care patient, multiple factors must be considered simultaneously. The benefits of transfusion therapy to specifically correct worrisome signs or symptoms have to be viewed against the risks of such therapy in these patients approaching end-of-life. Informed consent on this matter is necessary, as it is impractical to have a meaningful conversation about transfusion therapy without addressing its risk-benefit profile as accurately as possible. The ethical principles of autonomy, beneficence, and nonmaleficence that advocate for the individual patient also have to be appropriately balanced against the tenet of justice for other patients [2, 9, 10].

With blood components being finite resources with measurable costs, clear discussions with the patient, family, and all caregivers regarding indications for transfusion, goals of treatment, expectations of the impact of transfusion therapy, when to continue red cell and/or platelet transfusions, and when to discontinue them are critical [49]. Regarding goals of treatment, both the patient's and family's goals, as well as health care providers' goals, have to be considered when entertaining transfusion therapy. Similarly, outcomes need to be carefully defined so that all parties view interpretations of "success" and "failure" after transfusions clearly and consistently [6, 7]. This definition should ideally incorporate both provider-assessed and patient-reported outcomes to fully capture the effects of transfusion. In cases where agreement cannot be reached on a therapeutic plan of action, when special components with unique manipulations are requested, or when component shortages require triaging of blood orders, consultation with the hospital ethics committee (or equivalent body in the outpatient

Table 1 Suggested guidelines for considering red cell and platelet transfusion in palliative care patients

Estimate duration of survival
- In patients that are predicted to live > 7 days, investigate causes of cytopenias and correct any underlying abnormalities

Investigate cytopenias
- Explore causes of anemia, thrombocytopenia, and bleeding
- Implement corrections in lieu of or in addition to transfusion

Consider risk-benefit profile of transfusion therapy
- Health care providers should clearly explain benefits versus risks of transfusion therapy, particularly the hazard of transfusion associated circulatory overload, as part of obtaining informed consent
- Suggest alternatives to transfusion (e.g., supplemental oxygen, antifibrinolytic therapy, et cetera)
- Clearly define expectations and goals of transfusion, and use tangible endpoints after transfusion to guide whether or not to continue therapy with blood components

Use restrictive transfusion thresholds based on high-quality recommendations
- In patients without cardiac disease, implement a red cell transfusion threshold of < 7 g/dL
- In patients with cardiopulmonary disease, implement a red cell transfusion threshold of < 7–10 g/dL
- In patients without active bleeding, implement a platelet transfusion threshold of < 10,000/μL
- In patients with active bleeding or who are at high risk of bleeding, implement a platelet transfusion threshold of < 20,000-50,000/μL

Perform the transfusion safely
- If a patient is at risk of transfusion associated circulatory overload, discuss strategies to minimize risks with the Blood Bank
- Transfuse weight-appropriate doses of blood components slowly (over up to 4 h per unit)
- Only transfuse one blood components unit at a time, and reevaluate impacts after each unit
- Unnecessarily large blood components volumes that are transfused can cause iatrogenic injury via transfusion associated circulatory overload and other reactions

Evaluate outcomes after transfusion
- After transfusion, repeat laboratory testing within 24 h for red cells and within 1 h for platelets
- Perform a functional assessment no later than 7 to 14 days after red cell transfusion and as soon as possible after platelet transfusion
- Based on impacts of transfusion (if any), reassess need for additional blood components

setting) may be beneficial [2, 6, 7, 9]. Lastly, policies of transfusing facilities should also include mutually agreed-upon language by all healthcare stakeholders that address concerns involved in transfusing palliative care patients [8, 9]. This will assist in proactively handling issues such as poly-transfusion, medical futility, special manipulations of blood components, inventory shortages, and other issues involved in the transfusions of these critically ill patients. See Table 1 for points to consider when making the decision to transfuse a palliative care patient.

Conclusions

The decision to transfuse palliative care patients can be complex. Any potential benefit of red cell or platelet transfusion, including honoring individual patient goals, must be weighed against the attendant risks of these blood components. Additionally, evaluation and correction of anemias by any applicable mechanisms other than transfusion, such as erythrocytosis-stimulating agents, intravenous iron, and correction of other hematinics, needs to be performed. Ethical considerations regarding utilization of blood components, a finite resource, must also be considered. However, as investigations continue in this unique yet heterogeneous patient population, evidence-based improvements involving transfusion therapy in palliative care will allow for a better selection of patients that are more likely to have therapeutic benefits, decrease adverse reactions, and ultimately ameliorate the signs and symptoms necessitating transfusion. Critical next steps include identifying validated measures of objective functional changes that parallel patient-reported outcomes and using these to identify subsets of patients receiving end-of-life care that will most likely be positively impacted by transfusion therapy.

Compliance with Ethical Standards

Conflict of Interest The author declares that there is no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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when such investigations are performed, and the practice of red cell transfusion is too liberal.

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