Transfusion plaquettaire en fin de vie chez des patients atteints d'hémopathie maligne : une revue

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End-of-life platelet transfusion in haematological malignancies: a review

transfusion plaquettaire, médecine palliative, fin de vie, hémopathies malignes
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Résumé

L'unedes complexités spécifique à la prise en charge de la prise en charge des patients atteints d'hémopathies malignes en fin de vie est la transfusion sanguine. Parmi les produits sanguins labiles, les concentrés plaquettaires forment un cas particulier. Leur utilisation est sujette à débat, en dehors même de la fin de vie, sur de nombreux aspects. Ce débat est exacerbé à une période où la qualité de vie l'emporte sur la quantité. De plus, le nombre de concentrés plaquettaires alloués ne cesse d'augmenter chaque année, rendant nécess-

Abstract

One of the specificities and complexities of palliative care in haematology is the issue of platelet transfusion. Platelet concentrates constitute a particular kind of transfusion product. Debate is ongoing about their utilisation and some transfusion parameters even outside the end-of-life context. This debate is exacerbated in patients also can be young patients when quality of life takes precedence. Moreover, the number of allocated platelet concentrates every year continues to increase, making their optimal use

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aire l'optimisation de leur utilisation. Les données actuellement disponibles sont insuffisantes pour proposer un consensus dans ce contexte particulier de la fin de vie. Cette revue, réalisée à partir d'articles publiés après 2011, vise à poser et alimenter ces débats, tant dans leurs aspects pratiques qu'éthiques.

crucial. The information currently available is insufficient to reach a consensus over their use at the end of life. This review of articles published after 2011 aims to contribute towards both the practical and ethical aspects of this debate.

The transfusion of platelet concentrates from donor to recipient is a time-consuming process. It was developed following the demonstration by Gaydos of the link between the extent of thrombocytopenia and the occurrence of bleeding [1]. This demonstration, dating from 1962 and based on a prospective cohort of 92 patients with acute leukaemia, undeniably improved patients' quality of life by limiting haemorrhagic episodes. It led to significant therapeutic advances, making it possible to carry out aplastic chemotherapies which were transfusion-dependent. However, this ground-breaking study did not define a precise threshold above which transfusion would be systematically indicated.

Since then, the role of prophylaxis and the threshold at which transfusion is indicated remain under discussion, as do other parameters that are not addressed here [2]. In 2003, the French Agency for the Safety of Health Products (*l'Agence française de sécurité sanitaire des produits de santé*) stated that *"the problem posed is not the use of platelet transfusions in absolute terms, but rather the methods by which they are used: should transfusions be conducted prophylactically, to prevent the onset of bleeding that could have sufficiently severe or life-threatening clinical consequences, or should transfusions be used curatively, to stop an actual haemorrhagic episode? In the case of prophylactic transfusions, below what threshold would withholding a transfusion pose a significant risk to the patient?"* [3]. A meta-analysis was published on the subject in 2018. It was unable to reach a conclusion on the non-inferiority of an exclusively curative approach as compared to a prophylactic approach, due to the weakness of the data [4]. This meta-analysis excluded patients receiving haematopoietic stem cell transplantation or intensive chemotherapy. It probably explains why the prophylactic approach was maintained for the most part [5], including during palliative care, with a threshold of 10×10^9/L [6].

However, by changing the paradigm, the end of life lends a new angle to this issue. In this situation, quality of life is prioritised rendering patient safety key and putting aside the objectives of prophylaxis, threshold and measurement of reponse to platelet transfusion. The French *Haute Autorité de Santé* advocates a case-by-case policy, which is not backed up by any grade of recommendation [7]. However, the decision to transfuse or not to transfuse platelet concentrates can be complex. A review, published in 2011 by Uceda Torres, focused on blood transfusion at the end of life in oncology and haematology. End-of-life transfusions were described as one of the most difficult dilemmas for healthcare teams, involving medical, ethical and organisational issues. The term "precarious" has also been mentioned about this under explored topic, [8]. While Torres's review pointed out relevant elements such as the specificity of the transfusion of platelet concentrates in haematology (versus oncology or other departments) and the debated prophylactic indication, these data, rarely quantified, were too weak and disparate, according to the author, to contribute towards decision-making.

We would like to explore these issues once more, from the specific angle of end-of-life patients with haematological malignancies, through an updated review of literature published since 2011.

A little-explored subject

Thirteen quantitative and seven qualitative research articles using the key words "platelet transfusion(s)", "hematologic malignancies" and "palliative care" or "end

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of life care" or "terminal care" from databases including Pubmed, the Cochrane Library and Google Scholar were selected *(Table 1*).
Included studies explicitly addressed platelet concentrate transfusion in patients with haematological malignancies who died or who were treated in a palliative care unit or palliative medical setting. The quantitative studies represented a total of 9,937 patients. Methodologically, there were no randomised studies, only one prospective cohort, and most of the time the included size population per article was small.
Although a majority of studies show that haematology patients are transfused with platelets at the end of their lives [9-17], the percentage of such patients ranges from 0% [18, 19] to 100% [20]. As outlined below, these studies are rarely comparable, depend on a multitude of variables, and do not allow for a generalisation of results. All of these variables are summarised in *Table 2*.

Period and objective

There is no consensus around what is referred to as the "end-of-life" period. While several studies focus on the last seven days of life [9, 11, 12, 16, 21], the palliative care in others extended over several months [20]. The definition of "advanced haemopathies" given by the French Haematology Society may be helpful but dates from 2005 and therefore does not take into account the latest therapeutic advances. [22].
Of the studies on terminal cares, four address the criteria for aggressive end-of-life treatment [13, 16, 19, 21]. This relatively recent concept, a legacy of Earle [23], was not explored in the previous review. It is generally defined as:

– administration of chemotherapy during the last 14 days of life or the decision to undertake new chemotherapy during the last month of life,
– more than one hospitalisation in an intensive care unit or emergency room during the last month of life or the occurrence of dying in an acute care setting,
– being hospitalised more than once during the last month of life and being admitted to a hospice (or palliative care unit) for fewer than three days.

In general, patients with haematological malignancies are more likely die in intensive care units [9] and less likely to die in palliative care units [9, 10] than patients with solid tumours. Patients with haematological malignancies also have have fewer consultations with palliative care teams and more aggressive end-of-life treatment [21]. They also receive more platelet concentrates [9, 11, 12]. No difference is observed for red blood cell transfusions. [11, 15].
Several problems can be identified with these criteria. Firstly, they are not suitable for patients with haematological malignancies, since they are derived from solid tumour patients. [13, 24]. Second, these administrative indicators do not directly reflect patients' quality of life. They show that hospitalisation in palliative care [15] or the implementation of a palliative care service [21] reduces the number of platelet concentrates administered to patients, without studying other causes. Hospitalisation in palliative care increases the time between the last blood transfusion and death by 30 days. The implementation of a palliative care service leads to a decrease in the number of patients transfused with platelets (only for four patients but statistically significant) during the last seven days of life. In our opinion, the selection and randomisation biases in the first study, and the confounding factors of the second (decrease in the aggressiveness of treatment between the two periods, particularly the administration of chemotherapy), do not allow us to conclude that palliative care has a beneficial impact on these patients. Thirdly, these criteria may be at odds with the daily practice of haematologists, for whom it may not be acceptable to forego hospitalisation in the emergency department or intensive care unit [24]. This can create tension in the collaboration

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Table 1

Selected articles since since 2011 concerning the transfusion of platelet concentrates (PC) at the end of life in patients with hematologic malignancies disorders.

Author	Type of study	Population	Objective	Key findings on platelet transfusion
Capodanno (2019) [20]	Retrospective cohort	44 deceased adult patients with haematological malignancies from a haematology department in Emilia-Romagna (Italy) who were treated at home under a specific programme, Haematological Home Care, from 2012 to 2015.	To evaluate three years of programme experience. Comparison with a "historical" cohort before the programme was implemented.	All patients received at least one transfusion of platelet concentrates (PCs). On average, patients received a median of 1.4 PCs for 113 days (range: 1–426). There were no recipient adverse events among the 67 patients receiving PCs. Antihistamines were routinely prescribed before each platelet transfusion. No deaths due to cataclysmic haemorrhage were reported.
Kihara (2018) Abstract [21]	Retrospective cohort	351 adult patients with haematological malignancies who died (all departments) at Kamaki Hospital (Japan) between 2007 and 2017.	To measure the aggressiveness of end-of-life care. Comparison between two periods (2007–2012 and 2012–2017).	PC transfusion during the last seven days of life occurred in 18 patients in the first period and 14 patients in the second period (an absolute difference of four patients between the two periods). 9% of patients received PCs in the last week of life. Patients with lymphoma who had palliative care consultation had fewer platelet transfusions during the last seven days of life. This difference was not seen for those with leukaemia.
Lowe (2018) [17]	Prospective cohort	33 adult patients with haematological malignancies starting chemotherapy at Duke Hospital (USA) between 2014 and 2015 and who died before June 2016 (at Duke Hospital or elsewhere, including six who died in palliative care units).	To collect information on patient-related outcomes, palliative care use and blood transfusion use.	The number of patients transfused with PCs during the last six months of life was 23 (70%). Patients received a median of: 12 PCs during the last six months, one PC between six and four months before death, and five PCs during the last month of life. The number of PCs allocated increased as death approached, while the number of red blood cell concentrates allocated remained stable. Patients dying in hospital were transfused more often than those cared for in a hospice, all blood products combined. Six patients (out of 16 or 37.5%) experienced a "moderate to severe" haemorrhagic event during the last month of life, which had an impact (along with other symptoms) on their quality of life.
Sirianni (2018) [18]	Retrospective cohort	2,065 adult patients with or without cancer, including 12.5% of haematological malignancies, treated in two palliative care units: Sunnybrook Health Sciences Center (1069 patients) and Baycrest Hospital (996 patients) in Toronto, Canada between April 2015 and March 2017.	To observe the indication, frequency and characteristics of the patients being transfused.	No PC transfusions were performed (including in solid oncology patients), as the indication was exclusively curative. No haemorrhagic events were found, but the grade at which haemorrhagic events were considered was not documented. The cause of death was unknown, but long survival times of more than 35 days in 50% of cases were noted.

Table 1
(*Continued*)

Author	Type of study	Population	Objective	Key findings on platelet transfusion
Wang (2018) [15]	Retrospective cohort	116 adult patients with haematological malignancies and with allogenic or autogenic stem cell transplantation who died in a palliative care unit at a cancer centre in San Diego, USA, between January 2011 and December 2015.	To determine the average difference in days between last transfusion and death. Comparison between a group treated in a hospice (16 patients) versus a group treated at a cancer centre (100 patients).	Patients not treated in a hospice received more platelet transfusions, while the number of red blood cell concentrates remained stable between the two groups. PC transfusion in the last 96 hours of life involved four (25%) hospice patients compared to 78% for non-hospice patients.
Dasch (2017) [9]	Retrospective cohort	532 adult cancer patients, 20.3% of whom haematological malignancies and died at the University Hospital of Munich (Germany) in 2014, all departments combined.	To describe the clinical and demographic characteristics of patients at the end of life.	Patients with haematological malignancies received more PC transfusions (19.1% *vs* 5%) during the last seven days of life than patients with solid cancers. The same was observed in the last 30 days of life (48.2% *vs* 9.2%). End-of-life treatment allocation was more intensive for haematology patients.
Hoell (2017) [10]	Retrospective cohort	65 paediatric patients with solid tumours or malignant haemopathies (15) who died and were treated in a paediatric outpatient palliative care unit at the University Hospital of Dusseldorf (Germany) between 2008 and 2016.	To determine the proportion of haematology patients in a palliative care unit, characteristics and symptoms.	Seven patients with haematological malignancies received 16 PCs (median: 2.3 per patient) compared to 27 PCs (median: 3 per patient) for the nine patients with solid tumours. The proportion of patients transfused with platelets was 46.6% in the haematology department versus 18% in the oncology department. None of the children had extensive external haemorrhaging.
Argyrou (2016) Abstract [11]	Retrospective cohort	211 adult patients with or without cancer, including 11 haematological malignancies, who died in two cancer centres between April and June 2015 in Greece.	To observe transfusion practice at the end of life.	Eight (73%) patients with haematological malignancies received platelet transfusions. These eight patients received 158 (53.5%) PCs for a median of 4.66 transfusions per patient (compared to 2.5 in the oncology department and 0 for non-cancer patients). Patients with haematological malignancies received more PC transfusions than patients with solid tumours or without tumours while there was no difference compared to other blood products. All haematology patients had a pretransfusion blood sample test.
Fletcher (2016) [13]	Retrospective cohort	6,955 patients over 65 years of age with non-acute myelodysplastic syndromes who died (irrespective of department or hospital) in the United States (Medicare data) between 2006 and 2011.	To measure the aggressiveness of end-of-life care.	3% of patients were dependent exclusively on PC transfusion and 23% of patients were tranfusion-dependent. Patients dependent on blood transfusions were less likely to be admitted to a hospice and more likely to be admitted to intensive care units during the last month of life (OR: 1.8) and received more chemotherapy during the last 14 days of life (OR: 2.54).
Cheng (2013) [16]	Retrospective cohort	21 adult patients with haematological malignancies who died in the palliative care unit at Grantham Hospital (Hong	To measure the aggressiveness of end-of-life care.	10 patients received platelet transfusions (47%) during their last seven days of life. 68 PCs were allocated over 17 transfusions, *i.e.* four PCs per episode. The indication was prophylactic in 14 (82.3%) transfusions. The grade of haemorrhages

Table 1
(*Continued*)

Author	Type of study	Population	Objective	Key findings on platelet transfusion
		Kong) between 2012–2013.		are unknown. The mean platelet transfusion threshold was 9.3 × 10^9/L.
Bruck (2012) [12]	Retrospective cohort	177 adult cancer patients, including 156 with haematological malignancies, who died in the haematology department or in the intensive care unit at Frankfurt hospital (Germany) between 2005 and 2008	To measure the aggressiveness of care and certain prescriptions at the end of life.	120 (69.8%) patients were transfused with platelets during the last seven days of life. There were 1,388 PCs allocated, with an average of 11.57 per patient; 60% of haemorrhagic complications were ungraded; 20% of deaths were due to haemorrhage (Grade 4). Haemorrhage localisations were cerebral, pulmonary or gastrointestinal.
Kodama (2011) [19]	Retrospective cohort	346 adult cancer patients, including 14 with haematological malignancies, treated in several clinics specialising in home care. Patients joined a home-based care programme in several areas in Japan during 2007.	To describe the factors that lead to discontinuation in home care.	11 patients received red blood cell concentrates but none received PC transfusions (including those with solid cancers). Factors causing discontinuation at home were not linked to related to blood transfusion.
Linquist (2011) [14]	Retrospective cohort	1,864 patients over 66 years of age with myelodysplastic syndromes at diagnosis, data from Medicare (USA). Diagnoses was reached in 2001 or 2002 and followed until death or the end of the collection period in 2005.	Study the prevalence of cytopenias. To measure the intensity of end-of-life care. To characterise the relationship between cytopenias, health care utilisation and mortality.	46 (2%) patients received platelet transfusions; 8% of patients were hospitalised for a haemorrhagic event (grade unknown). Thrombocytopenia appeared after a median of 15 months of follow-up (whereas anaemia appeared at five months). Thrombocytopenia occurred in 40% of patients (81% anaemic and 25% neutropenic). PC transfusions occurred at a median of 16 months of follow-up compared to four months for red cell concentrates. Haemorrhagic events occurred at a median of 14 months of follow-up. Thrombocytopenia was the second leading predictor of death (after hospitalisation), ahead of anaemia and neutropenia.
Gergi (2018) [29]	*Fast fact and concept*	12 publications between 1958 and 2017	Articles on the outcomes of transfusion-dependent patients.	To study the issues of platelet transfusion at the end of life. The transition from a prophylactic transfusion policy to an exclusive curative policy may be misunderstood and perceived as a form of euthanasia by patients and their relatives. A restrictive platelet transfusion strategy does not appear to hasten death. Patients need to have a discussion and receive information from an experienced health care provider around stopping or spacing out transfusions.
Odejide (2017) [24]	Qualitative	20 haematologists divided into four focus groups from the Dana-Farber/Harvard Cancer Center (United States), interviewed between Septem-	To explore the perceptions of haematological oncologists and their decision-making processes regarding end-of-life care.	Abstention from PC transfusions in the last seven days of life would be more acceptable to haematologists (50%) than abstention from emergency department visits in the last month or abstention from ICU deaths. The criteria for measuring end-of-life quality of life for haematologists are

Table 1
(*Continued*)

Author	Type of study	Population	Objective	Key findings on platelet transfusion
		ber 2013 and January 2014.		therefore different from those for oncologists. The inability to continue PC transfusions in hospices is a barrier to haematologists, who do not refer their patients to these units.
Mannis (2016) [26]	Editorial	Case reports of two elderly patients with acute myeloid leukaemia, transfusion-dependent, and managed in a haematology department in San Francisco (USA).	To discuss the inadequacy of palliative care facilities for transfusion-dependent patients.	The authors describe the difficulty in transferring a transfusion-dependent patient to a palliative care unit and the difficulty for the patient to forego platelet transfusions. There is a paradox: transfusion prevents patients from being taken into palliative care whereas they are the most in need and symptomatic. The need for tools to determine when to initiate the palliative phase, to integrate palliative management into the training of haematologists, and to encourage Medicare to cover the costs of transfusions is noted.
Sherbeck (2016) [31]	*Case report*	One paediatric patient (aged 5), with acute lymphocytic leukaemia in post-transplant relapse at the University of Michigan (USA).	To discuss paediatric end-of-life PC transfusion.	Biomedical ethics must be taken into account (distributive justice). The authors advocate the use of non-HLA-compatible and close-to-expired PCs and the promotion of local haemostasis. An ethics consultation for complex situations is recommended. Similarly, improving communication between clinicians and biologists is encouraged.
Bordessoule and Moreau (2014) [37]	Book chapter	Not suitable	To present palliative care in haematology in France.	The symbolism of blood paradoxically represents life and death. To identify the transport constraints for the patient and the weariness that sets in over time. The exclusively symptomatic transfusion of PCs is difficult for patients and their relatives to accept. The principle of distributive justice is not well accepted by relatives. It is not unethical to transfuse at the end of life given the trauma of bleeding and the representation of "life ebbing away". There is a need for collegiality, which can be based on factors shared by haematologists and palliative care physicians such as the patient-physician relationship; ethics or emotional burden. A patient-centred approach rather than a morning platelet count approach should be adopted. Training of teams in palliative medicine but also in ethics is required.
Bordessoule (2012) [6]	Forum for ethical reflection	Not suitable	To reflect on the management of patients with transfusion-dependent haematological malignancies in France.	End-of-life PC transfusion is still usually preformed at a threshold of 10×10^9/L, despite recommendations. Doctor-patient consultation is essential, as is collegial decision-making. Patients and their relatives find abstention difficult to accept. Patients' reluctance or refusal to be admitted to palliative care units due to technical and economic constraints is a reality. Home transfusion of PCs has been discontinued

Table 1
(*Continued*)

Author	Type of study	Population	Objective	Key findings on platelet transfusion
				due to organisational and regulatory constraints.
Smith (2012) [30]	*Case report*	Four paediatric patients, including one with a haematological malignancy (10 years old) and acute myeloid leukaemia in post-transplant relapse, at the University of Michigan (USA).	Ethical discussion on the allocation of blood transfusion at the end of life with suggested guidelines.	End-of-life PC transfusion should exclude crossmatched and HLA-matched PCs distributional justice). It is necessary to limit platelet transfusions to significant bleeds it's to say distressing for the patient. The emotional burden for all those involved should be taken into account. It may be important to develop physicians' training sessions to improve ethical and end-of-life discussions. The importance of allowing some form of flexibility to adapt on a case-by-case basis is emphasised.

HLA: human leukocyte antigen. PC: platelet concentrate.

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between haematologists and palliative care physicians, which is already complex. [25].

Finally, transfusion, and especially transfusion-dependency, is not a consensual criteria for aggressiveness [21, 26]. Transfusion dependency is defined as at least two blood transfusions during the last 30 days of life [13]. It affects between 23% [13] and 78% of patients [17] and varies according to haemopathy (myelodysplasia compared to acute leukaemia). It should be noted that quality of life, as measured by aggressiveness criteria, decreases for transfusion-dependent patients [17]. Aside from the nature of the haemopathy, the causes of this dependence are unknown. Only its association with the intensity of care at the end of life is noted. Overall, despite advances in palliative medicine in recent years, there is no definition of "end of life" in haematology. Quality of life measured through administrative indicators is poorer for haematology patients than for oncology patients. Quality of life decreases even further for transfusion-dependent patients. The incorporation of palliative medicine into haematology with the objective of increasing quality of life is, therefore, desirable [27] but requires the creation of specific criteria for these patients [26].

National policies

In France, the transfusion of platelet concentrates at home has been discontinued due to organisational and regulatory constraints [6]. The aim of home transfusions was to reduce the number of emergency hospitalisations, which are often unpleasant for patients, and to allow death at home when desired. The approach to home transfusions fell short due to the absence of home care workers and opposition from some healthcare professionals [19]. It should be noted that safety regarding the use of the products was not in question [20]. Other countries have also discontinued this practice. Thus, nine of the articles reviewed by Uceda Torres et al. with home-based care, compared to only two in our review.

Conversely, only one case report used the term "hospice" in the last review in 2011, compared to 10 which dealt with palliative care in 2019, demonstrating the expansion of this discipline. However, hospice or palliative care units do not have the same legislative constraints according to the country they are located. In

Table 2

Fluctuation in the number of patients receiving platelet concentrates (PCs) based on quantitative studies as a function of different variables.

Author, country	Percentage of patients transfused with platelets	Median end-of-life period studied	Number of PCs per patient or transfusion dependence	Percentage of bleeding events	Indication for platelet transfusion	Type of care and place of death	Number of patients with haematological malignancies	Affiliation
Capodanno Italy [20]	100 %	113 days (range: 1–426)	1.5 transfusion episodes on average, range (0–16)	0% Grade 4, no data on other grades	Prophylactic and curative	Palliative care at home based on a haematological programme. Death at home or in hospital.	44 with several acute leukaemias	Haematologist
Wang United States [15]	78% outside palliative care unit 25% in a palliative care unit	96 hours	No information	No information	No information	Comparison between patients who died in palliative care vs. other departments	27 acute myeloid leukaemias 27 non-Hodgkin's lymphomas 19 myelomas 15 myelodysplastic syndromes 12 acute lymphatic leukaemias 6 Hodgkin's lymphomas 10 others	Intern
Argyrou Greece [11]	73%	7 days	19.75 PCs per patient, or 4.66 transfusions per patient	No information	No information	Patients who died in two cancer centres	No information	Oncohaematologist
Lowe United States [17]	No information (78.8% of patients transfused with all labile blood products combined)	30 days	7.7 PCs (average) or 5 PCs (median; range: 0–26)	37.5 %moderate to severe grades without detailed classification.	No information	Patients who died in various departments including a palliative care unit	33 acute myeloid leukaemias	Biostatistician affiliated with a haematology department
Bruck Germany [12]	69.8 %	7 days	11.57 PCs on average per patient, maximum 58 units for one patient (minimum unknown)	20% Grade 4 (death) 60% all grades	Prophylactic and curative	Patients who died in the intensive care unit or in haematology	60 acute myeloid leukaemias 16 acute lymphatic leukaemias 45 non-Hodgkin's lymphomas 11 myelomas 19 others	Haematologist
Dash Germany [9]	48.2% in the last 30 days 19.1 % in the last 7 days	7 or 30 days	No information	No information	No information	Patients who died in any department of the hospital	30 acute myeloid leukaemias 11 acute lymphatic leukaemias 18 myelomas	Palliative care physician

(*Continued*)

Table 2
(*Continued*)

Author, country	Percentage of patients transfused with platelets	Median end-of-life period studied	Number of PCs per patient or transfusion dependence	Percentage of bleeding events	Indication for platelet transfusion	Type of care and place of death	Number of patients with haematological malignancies	Affiliation
Cheng China [16]	No information	7 days	6.8 PCs on average or 1.7 transfusions per patient	14 % unknown grade	Prophylactic (82.3%) and curative	Patients who died in palliative care units	7 acute myeloid leukaemias 6 lymphomas 8 myelomas	Palliative care physician
Hoell Germany [10]	46.6 %	12 days (range: 6–122)	2.3 PCs on average	0% Grade 4 no data on other grades	Exclusively curative, but grade for indicated transfusion unknown	Patients who died in a palliative care unit or at home	11 acute leukaemias 4 lymphomas	Paediatric oncohaematologist
Kihara Japan [21]	10.2% over the first period 8% over the second period	7 days	No information	No information	No information	Patients who died in any hospital department	150 non-Hodgkin's lymphomas 113 acute myeloid leukaemias 63 myelomas 11 acute lymphatic leukaemias 8 chronic lymphatic leukaemias 5 Hodgkin's lymphomas	No information, member of the American Society of Hematology
Fletcher United States [13]	No information	30 days	23% of transfusion-dependent patients (all blood products combined). 3% of patients dependent only on PCs	No information	No information	Medicare data, deaths in the United States.	6,955 myelodysplastic syndromes	Oncohaematologist
Linquist United States [14]	No information	No information	29% over three years of cumulative treatment	8 % no grade given	No information	Medicare data, deaths in the United States.	1,864 myelodysplastic syndromes	Methodologist affiliated with authors (oncohaematologists)
Sirianni Canada [18]	0%	87 days (range: 37–166)	0	0%	Exclusively curative, but grade for indicated transfusion unknown	Deceased patients in two palliative care units	258 acute leukaemias	Palliative care physician
Kodama Japan [19]	0%	47 days (range: 0–2712)	0	No information	No information	Patients who died at home receiving home care	14, no information	Social Communication System Research Department

HLA: human leukocyte antigen. PC: platelet concentrate.

English-speaking countries, up to 40% of hospices do not carry out transfusions [17, 18], which is not the case elsewhere in Europe [9-12, 20]. In some studies, the indication for platelet concentrates may be prophylactic [16, 20], while others have adopted an exclusive curative platelet transfusion policy [10, 18]. In the latter case, the grade of haemorrhage for which transfusion would be indicated is unknown, making it impossible to define a medically acceptable haemorrhagic threshold.

This lack of a transfusion policy leads haematologists in English-speaking countries to believe that palliative units or hospices are not appropriate for their patients [13]. It can explain the low percentage of patients referred to them [15, 16]. These findings are consistent with those of a meta-analysis of palliative care for haematology patients [28]. This policy may also explain the delay in admission (one to three days) of patients [9], as well as the selection of patients at low risk of bleeding in some studies [18, 19]. Transfusion-dependent patients may therefore face difficulties in accessing palliative care. However, they are probably the patients with the most disabling symptoms and in greatest need of this type of care [26]. Indeed, the difference between the number of blood transfusions allocated to hospice patients and those allocated to patients treated elsewhere is solely due to the quantity of platelet concentrates, without the exact causes being mentioned [15]. Wang suggests that the main reason for this difference is that hospice patients are willing to forego transfusions.

We believe that only individualised, palliative patient-centered care is able to adapt blood transfusions to what is strictly necessary. However, some hospices appear to refuse transfusion-dependent patients, leading to selection and randomisation bias that prevents generalisation of results. This acts as a barrier to access to palliative care. In addition, platelet transfusions seem to be a more significant barrier to palliative care than that of red blood cell transfusions.

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Protagonists

Representations on platelet transfusions shared by patients and their relatives are conditioned by information previously received about the risk of massive bleeding, particularly if this morning platelet count falls below a certain threshold [6, 29]. The transition from prophylactic to curative transfusion and the discontinuation of laboratory tests may be a source of misunderstanding [29]. The transfusion threshold is an important consideration for haematologists and their patients. The latter is 9.3 $\times$ 10^9/L on average during the last seven days of life [16]. In addition, 100% of haematology patients have a pre-transfusion test compared to 70% of solid oncology patients and 45% of those without an oncohaematological pathology, reflecting a common practice at the end of life in haematology [11].

The views of healthcare professionals are influenced by patients' suffering [30, 31], and have an impact upon the prescription of platelet concentrates. This may be explained by the lack of "institutional guidelines" [30] or the lack of consensus regarding the use of labile blood products at the end of life [16]. It forces physicians to take a position based on their personal ethics. For some professionals, the impossibility of delivering platelet concentrates due to technical or economic constraints or related to the place of care is prohibitive. [6, 22, 24, 26]. Mannis describes the transfusion of platelet concentrates as "tethered" [26] in haematology, "improving the well-being and prolonging the lives of patients dying from hematologic cancers" and is a less expensive to face the symptom burden. Of course, transfusion at the end of life are not unethical or illegitimate. Bleeding can be physically, psychologically and emotionally traumatic for patients and their relatives. [24].

However, the impact of the platelet transfusion on the well-being and quality of life of patients has not been demonstrated and appears to be negative [29].

Patient-related outcomes show poor end-of-life quality for patients with acute myeloid leukaemia. Haemorrhages contribute to this low quality of life for 42.9% of such patients [17]. Quality of life is not impacted by the safety of platelet concentrate transfusion, as the number of recipient adverse events reported at the end of life (in this review [20] and in the previous one in 2011) is low. This should be reassuring without legitimising the practice. Quantity of life does not seem to be affected by an exclusively curative platelet transfusion policy [18]. Patients (adult and paediatric with acute leukaemia and lymphoma) on this restrictive approach do not present more bleeding, including Grade 4, and may survive for several months (within the limits of the above biases) [10, 18]. Finally, although costs were not investigated it should be noted that the average cost per platelet concentrate is 400 euros in France.

The symbolism of blood is strong, paradoxically linked to both life and death. Gergi uses the word "euthanasia" to refer to the perception that patients and their relatives have when the transfusion of platelet concentrates is stopped [29]. Could stopping these transfusions appear like murder or a "death sentence" from some points of view? We propose conducting a study to better understand and take into account the impact of the representation of end-of-life platelet transfusion on all those involved in patient management (NCT03806712).

Haematological malignancies

Myeloid pathologies are identified as being more at risk of haemorrhage, due to their natural tendency to evolve towards cytopenias and myeloablative treatment. This probably explains why 9,141 patients in this review had myeloid pathologies. Only seven studies included multiple haematological malignancies, representing 813 patients [9, 10, 12, 15, 16, 20, 21]. Thus, there is a wide disparity in the study of end-of-life platelet transfusion in haematology. The following points should be noted:

Myelodysplastic syndrome

This is the biggest population with only two studies (with one excluding acutisation) [13, 14]. The prevalence of platelet transfusion is the same between the two studies. The first study showed that of the 23% of patients dependent on blood transfusions, only 3% were dependent exclusively on platelets [13]. The second study showed that of the 26% of patients transfused, only 2% were transfused exclusively with platelets [14].

Thrombocytopenia is reported as a poor prognostic factor (HR = 2.27), the second most common after hospitalisation (HR = 6.54), and before anaemia or neutropenia [14]. Platelet transfusion due to thrombocytopenia tends to occur during the last six months of life (at 15 and 16 months, respectively, based on a median follow-up of 22 months). This is not the case with red blood cell transfusions, which takes place much earlier in the history of the disease (at four months).

These patients are often considered to be "stable", *i.e.* at low risk of bleeding, and effectively present only 8% of haemorrhages. Haemorrhages are the cause of hospitalisation in 12% of cumulative cases over three months and 41% of cumulative cases over three years [14]. It should be noted that some authors do not recommend platelet transfusion in these patients, even for thresholds below 10×10^9/L [32], due to few and non-severe haemorrhages.

Patients dependent on blood transfusion are less likely to be admitted to a hospice and more likely to be admitted to intensive care units during the last month of life (OR: 1.8) and receive more chemotherapy during the last 14 days of life (OR: 2.54) [13].

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Acute leukaemia

The prevalence of platelet concentrate allocation appears to be random. Its importance was confirmed by one study with a median of five platelet concentrates during the last 30 days of life [17], but was negated by another study reporting no transfusions during the last 87 days of life (median follow-up) [18].

Dependency on platelet transfusion increases as death approaches in patients with acute myeloid leukaemia [17], while the number of red blood cell transfusions remains stable. This finding is consistent with another study for which the pathology is unknown [11].

Haemorrhagic events during the last month of life occur in 37.5% of cases (graded as moderate to severe) [17]. Death by haemorrhage (Grade 4) occurred in 0% of patients in one study based in a hospice [18].

All haematological malignancies combined

For other pathologies, the data cannot be individualised, and only a link with aggressiveness of treatment is observed. When comparing two identical study periods, for example, the last seven days of life, the results range from 6.8 platelet concentrates allocated in a palliative care unit [16] to 19.75 in a cancer centre [11].

The largest numbers of haemorrhagic events (60%) and related deaths (20%; Grade 4) [12] were found in patients hospitalised in intensive care.

Could it be, beyond the nature of the haemopathy, that aggressive end-of-life treatment is a determining factor in the allocation of platelet concentrates? Haematologists [26] have called for tools to help determine "the optimal timing" for palliative care referral. Could the development of thrombocytopenia in myelodysplastic patients or the increased need for platelet concentrates in those with acute leukaemia be one such tool?

Areas for improvement

Currently, 67% of platelet concentrates are intended for haematology patients [33]. Their use has been steadily increasing in recent years due to the rising incidence of haematological malignancies and the ageing population. In the United Kingdom, there was a 25% increase in the use of platelet concentrates between 2007 and 2008 and 2014 and 2015 [33]. In France, 2016 figures from the *Etablissement Français du Sang* showed a 0.7% increase compared to the previous year [34]. In response to this growing need, studies are looking at multiple ways to save resources [35]. Recommendations, although not targeting end-of-life care, have been published [36].

- This review reveals a number of non-innovative recommendations for optimising the allocation of platelet concentrates.

Managment of end-of-life bleeding should include medications (sedative, anxiolytics...) as comfort measures (compression, black towel, reassurance...) The effectiveness of this approach remains under debate [2].

- The use of products that are close to the expiry date and non-HLA compatible, that are not derived from rare groups or mixtures or from apheresis in accordance with the principle of justice, should be encouraged [29-31]. This is limited by the seldom inclusion of palliative status in patient records and its absence in the transfusion communication record, when such a document exists. This information could, in our opinion, enable professionals working in blood banks to better allocate certain types of products and to improve collaboration.
- Improving collaboration between blood bank physicians, haemovigilance physicians, haematologists and multidisciplinary teams is recommended. Using ethics committees in complex situations or conflicts is also recommended but poorly implemented in practice [30, 31, 37].

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- Discussing the appropriateness of platelet transfusions with the patient is recommended [8, 29]. In our view, this discussion reflects the value of a case-by-case policy advocated by palliative medicine. However, the level of incorporation of palliative medical training into the professional training of haematologists and haematology teams [37] remains low. Patient information could also be better developed with personalised transfusion plans [40].
- Limiting transfusions to bleeding that are "significant", i.e. distressing for patients is often suggested [6, 11, 16, 30]. This remains a complex issue since there is currently no complete consensus on the grading of bleeding events [2, 38]. In addition, clinical or biological severity factors (anticoagulation, renal failure [39]) that may encourage bleeding, as well as the risk factors for poor transfusion performance (fever, infections, *etc.*) have been poorly studied. Only one study based on our review reported that neither age nor type of allograft had an impact on the number of transfusions of platelet concentrates [15]. This could lead to an adjusted haemorrhagic risk score at the end of life for all haemopathies, based on criteria that have already been identified [2].
Studies specifically targeting end-of-life platelet transfusion in haematology from a clinical and biological perspective are needed. We thus propose to monitor such cases with regards to efficacy and tolerance (NCT03814486).

Conclusion

Since 2011, little progress has been made in research into end-of-life platelet transfusion. The elements identified by Uceda Torres with regard to clinical, organisational and ethical issues persist [8]. Platelet transfusion policies differ according to a multitude of variables, and still do not allow for tools to be established in order to support decision-making.
Based on this review, we can conclude that platelet concentrates are frequently transfused at the end of life in haematology patients. The indication admission to for such transfusions, although variable, appears to be linked to aggressive end-of-life treatment, may be a barrier to admission to a hospice cares, and may be of prognostic value. As such, platelet transfusion is different from other blood products.
Some potential measures for optimising platelet concentrate use can be identifed. Improved information, collaboration with other areas of expertise and appropriate delivery at the end of life are all possibilities. In our opinion, only a palliative, patient-centred approach is relevant due to the individual nature of clinical situations encountered. Further studies are needed, however, to determine whether and how this has an impact upon patients' quality of life.

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