Coagulopathy and blood abnormalities in cancer and inflammation

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Chapter 6

Lifetime transfusion burden and transfusion-related iron overload in adult survivors of solid malignancies

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Abstract

Background: Limited data exist on transfusion burden and transfusion-related iron overload in adult survivors of solid malignancies.

Methods: Hospital-specific cancer registry data of solid tumor patients receiving systemic anti-cancer treatment between January 2008 and September 2009 at the Oncology department of the Leiden University Medical Center (The Netherlands) were retrieved and cross-referenced with red blood cell (RBC) transfusion records. Individual lifetime transfusion burden was captured in April 2015. Multitransfused long-term survivors with serum ferritin > 500 μg/L were subsequently screened for hepatic and cardiac iron overload using 1.5 Tesla magnetic resonance imaging.

Results: The study population consisted of 775 adult solid cancer patients (45.2% male, median age: 58 years, > 75% chemotherapy-treated), 423 (54.6%) of whom were transfused with a median of 6.0 RBC units (range 1-67). Transfusion triggers were symptomatic anemia or hemoglobin < 8.1 - 8.9 g/dl prior to each myelosuppressive chemotherapy cycle. We identified 123 (15.9%) patients across all tumor types with a lifetime transfusion burden ≥ 10 RBC units. In the absence of a hemovigilance program, none of these multitransfused patients were screened for iron overload despite a median survival of 4.6 years. In 2015 at disclosure of transfusion burden, 26 multitransfused patients were alive. Six (23.1%) had hepatic iron overload: 3.9 - 11.2 mg Fe/g dry weight. No cardiac iron depositions were found.

Conclusions: Patients with solid malignancies are at risk for multitransfusion and iron overload even when adhering to restrictive RBC transfusion policies. With improved long-term cancer survivorship, increased awareness of iatrogenic side effects of supportive therapy and development of evidence-based guidelines are essential.

Implications for Practice

In the presence of a restrictive transfusion policy, ~ 30% of transfused adult solid cancer patients are multitransfused and ~ 50% become long-term survivor, underscoring the need for evidence-based guidelines for the detection and management of transfusion-related iron overload in this group of patients. In each institution, a hemovigilance program should be implemented which captures the lifetime cumulative transfusion burden in all cancer patients, irrespective of tumor type. This instrument will allow timely assessment and treatment of iron overload in cancer survivors, thus preventing organ dysfunction and decreased quality of life.

Introduction

Transfusion-related iron overload (TRIO), also referred to as transfusional iron overload, occurs when red blood cell (RBC) transfusions are given in the absence of iron deficiency.[1] Each unit of RBCs contains 200 – 250 mg of iron, which is released upon erythrocyte death and accounts for 100 – 250 times the normal uptake through duodenal enterocytes. As the maximum iron excretion is capped at 1 – 2 mg per day, regular RBC transfusions may result in hepatic, cardiac, and endocrine organ dysfunction over time because of iron accumulation unless the patient is bleeding.[2] Diagnostic workup includes measurement of serum ferritin and assessment of total body iron stores through biopsy or noninvasive T2-weighted magnetic resonance imaging (MRI).[3]

Patients with solid malignancies receive blood transfusions for cancer-related anemia caused by chronic release of inflammatory cytokines, therapy-induced myelosuppression, metastatic bone marrow infiltration, microangiopathic hemolysis, nutritional iron or vitamin B11/B12 deficiency, and blood loss.[4-6] In contrast to blood transfusion and iron overload literature in hematological diseases (e.g., thalassemia, sickle cell anemia, myelodysplastic syndrome, acute leukemia) and pediatric cancers, data on TRIO in adult patients with solid malignancies are lacking. Guidelines are available in countries outside the U.S., but in the U.S. the only extant guidelines are the Children's Oncology Group Long-Term Follow-Up Guidelines, which do not address TRIO outside the hematopoietic stem cell transplantation (HSCT) setting and are developed for childhood cancer survivors. Although most guidelines recommend treatment in patients with a life expectancy of > 1 year and a lifetime transfusion burden of ≥ 10 – 20 RBC units, serum ferritin levels > 1,000 – 2,500 μg/L, and/or liver iron content (LIC) ≥ 7 mg Fe/g dry weight (dw), some guidelines advocate early assessment and treatment after transfusion of 8 RBC units, serum ferritin levels > 500 μg/L, or LIC > 2 – 3 mg Fe/g dw.[7-13] Other guidelines also include transfusion dependence of ≥ 2.0 RBC units per month as a trigger for initiation of iron chelation therapy.[12,14,15]

With improved survivorship of patients with cancer because of new treatment strategies, screening for iatrogenic complications becomes increasingly important.[16] As the risk of TRIO increases with older age,[17] adult patients may benefit from early assessment and low thresholds for screening.

To gain more insight in the occurrence of TRIO in adult patients with solid malignancies and identify those at risk, we performed a real-world study involving 775 adult patients who were scheduled to receive systemic anticancer treatment.

Methods

Study Design and Definitions

Hospital-specific cancer registry data of all patients aged ≥ 16 years visiting the in- and outpatient clinic of the Department of Medical Oncology of the Leiden University Medical Center in the period January 1, 2008, to August 31, 2009, were retrieved and cross-referenced with real-time RBC transfusion records. Patients only in follow-up via outpatient consultations were excluded. Patients with lung cancer in The Netherlands fall under the responsibility of pulmonologists and were thus not included.

In total, 775 patients were identified who had received or were scheduled to receive systemic anticancer treatment (e.g., single agent or combination chemotherapy, concomitant chemoradiotherapy, immunotherapy, endocrine or targeted therapy in combination with parenteral bone resorption inhibitors).

In 405 patients, initial cancer diagnosis and start of anticancer treatment dated from before 2008, whereas in 370 patients, cancer diagnosis and treatment initiation dated from 2008 to 2009. We refer to this latter group as "newly diagnosed patients." Observation of all patients ended on April 1, 2015, thus allowing acquisition of more contemporary transfusion data from newly diagnosed patients during an observation period > 5 years. At censoring, lifetime transfusion burden and overall survival were assessed for all 775 patients.

Overall survival was calculated from cancer diagnosis to censoring on April 1, 2015, or upon death. Long-term survivorship was defined by the general definition of survival beyond 5 years. Lifetime transfusion burden, the cumulative number of RBC units received during life, was extracted from real-time institutional transfusion logs at the end of the observation period. Multitransfusion was defined as lifetime transfusion of ≥ 10 RBC units. Transfusion intensity, which reflects the level of transfusion dependence, was reported as the yearly equivalent number of RBC units administered.

Transfusion Policy

Transfusion triggers were symptomatic anemia (e.g., fatigue, dyspnea, palpitations, and dizziness) or hemoglobin levels < 8.1 – 8.9 g/dL (< 5.0 – 5.5 mmol/L) on day 1 of each chemotherapy cycle if myelosuppressive cytostatic agents were administered.

The hemoglobin threshold was slightly lower (i.e., more restrictive) than advised in the national 2004 and 2011 consensus guidelines on transfusion published by Centraal Begeleidingsorgaan voor Intercollegiale Toetsing, an organization for hospital quality assurance in The Netherlands. As all patients treated with intravenous single or multiagent chemotherapy were discharged after administration, oncologists in general adhered to a double unit transfusion strategy taking into account upcoming hemoglobin nadir, comorbidity, age, and ambulant status of the patient. During the study period, almost no patients were treated with erythrocytestimulating agents in line with warnings released by the Committee for Medicinal Products for Human Use of the European Medicines Agency stating that "in cancer patients with a reasonably long life expectancy, the benefit of using epoetins to avoid blood transfusions does not balance the risks of tumor progression and shorter survival" and that "transfusion should be the preferred method for correcting anemia in cancer patients" (Doc. Ref. EMEA/CHMP/333962/2008).[18]

Measurement of Iron Overload

Screening for biochemical, hepatic, and cardiac iron overload occurred at the treating physician's discretion, and real-world data were captured. Serum ferritin, a marker for

biochemical iron overload, was measured in accordance with local laboratory standards (reference values: 10 – 150 μg/L for women, 35 – 260 μg/L for men).
The presence of hepatic and cardiac iron overload was established using a 1.5 Tesla magnetic resonance scanner (Philips, Amsterdam, The Netherlands). LIC was estimated from the patient's liver magnetic resonance (MR) image using the method described by Gandon et al.,[19] which is based on the correlation between the biochemical hepatic iron concentration and the liver to muscle intensity ratio calculated from MR images (highly T2-weighted gradientrecalled-echo sequence: repetition time 120 ms, time echo 21 ms, pulse angle 20°). LIC was reported as μmol Fe/g dw and converted to mg Fe/g dw using the formula 17.8 μmol Fe/g dw = 1 mg Fe/g dw. Values of < 2.0 mg Fe/g dw were considered normal.

Cardiac MR images were acquired using StarQuant (Philips, Best, The Netherlands) and analyzed with Medis Suite MR software (Medis, Leiden, The Netherlands). Cardiac iron content was measured as T2* value in milliseconds from multiecho decay curves and converted to mg Fe/g dw using the formula [Fe] = 45.0 × (T2*) − 1.22. Values of T2* > 20 ms (< 1.1 mg Fe/g dw) correspond with low risk of cardiac complications and were considered normal.[20-22] Left ventricular ejection fraction (LVEF) was retrieved from MRI volumetric data (reference values: 55% – 74%).

Statistical Analysis

Data analyses were conducted using Prism version 7.04 (GraphPad Software, San Diego, CA, USA). The Mann–Whitney *U*-test was applied for nonparametric univariate analysis. Differences between independent categories were established using the Kruskal–Wallis test and reported as H(df). The Wilcoxon matched-pairs signed-rank test was used to compare repeated measurements at different time points.
Correlations were determined using the Spearman's rho (r_s) method. Statistical significance was set at $P < 0.05$.

Table 1. Baseline patient characteristics of patients selected from the Academic Hospital Cancer Registry (n=775)

Age (years)		
Median	58	
Range	16-90	
Sex, n (%)		
Male	350	(45.2)
Female	425	(54.8)
Tumor type, n (%)		
Gastrointestinal cancers	160	(20.6)
Breast cancers	153	(19.7)
Genitourinary cancers	128	(16.5)
Gynecological cancers	99	(12.8)
Bone tumors	57	(7.4)
Soft tissue sarcomas	50	(6.5)
Head and Neck cancers	40	(5.2)
Skin cancers	27	(3.5)
Endocrine cancers	11	(1.4)
Cancers of unknown primary	9	(1.2)
Miscellaneous malignancies	3	(0.4)
Multiple primary malignancies	38	(4.9)
Date of cancer diagnosis, n (%)		
Before January 1st 2008 *	405	(52.3)
Newly diagnosed (since January 1st 2008)	370	(47.7)
Treatment type at inclusion, n (%)		
Chemotherapy ± any other systemic therapy	585	(75.5)
Radiotherapy ± concomitant chemotherapy	86	(11.1)
Targeted therapy only †	60	(7.7)
Miscellaneous systemic treatments #	26	(3.4)
Best supportive care only	18	(2.3)
Survival status at censoring, n (%)		
Alive	276	(35.6)
Deceased	498	(64.3)
Unknown	1	(0.1)
Cause of death, n (%)		
Cancer-related	414	(83.1)
Not cancer-related	37	(7.4)
Unknown	47	(9.4)

*: Median time elapsed since first cancer diagnosis: 1.7 years (range: 1 day to 41.3 years).

†: Predominantly multi-receptor tyrosine kinase, mammalian target of rapamycin inhibitors.

#: Amongst others: adoptive T-cell therapy, interferons, checkpoint-inhibitors, endocrine therapy, parenteral bone resorption inhibitors.

Results

Patient Characteristics

The study population included 775 patients, 45.2% male, with a median age of 58 years (range 16 – 90) who were diagnosed with a wide range of solid malignancies (Table 1). Newly diagnosed patients constituted 47.7% of the population. The other patients (52.3%) were known to have cancer for a median of 1.7 years (interquartile range [IQR] 0.5 – 5.0; range 0.0 – 41.9) before enrollment. Only 55 patients were diagnosed before the year 2000.

Patients received a multitude of systemic treatments during the course of their disease. The majority (75.5%) of patients were treated with at least one single or multiagent chemotherapy regimen, whereas 11.1% were initially treated with concomitant chemoradiotherapy or radiotherapy alone, and 7.7% received targeted therapy only. In a small proportion of patients (2.3%), the planned treatment was canceled, and patients received best supportive care (Table 1).

Overall survival ranged from 15 days to 43.5 years (median 5.8 years). By April 2015, 498 patients had died, and 414 deaths were confirmed to be cancer related. One multitransfused long-term survivor was lost to follow-up.

Lifetime Transfusion Burden

At the end of the observation period, 423 of 775 (54.6%) patients across all tumor types had received at least 1 unit of RBC transfusion during their life (Figure 1, Table 2). In general, transfusion dependence was low, as reflected by a median transfusion intensity of < 2.0 RBC units per year diagnosed with cancer. A total of 123 (15.9%) of patients qualified as multitransfused patients; only eight (6.5%) had a short cancer-specific survival of less than 1.0 years and received 12 – 26 RBC units in that short period of time. Only two multitransfused patients were highly transfusion dependent; these patients died within 1.7 years from cancer diagnosis after receiving 33 – 48 RBC units.

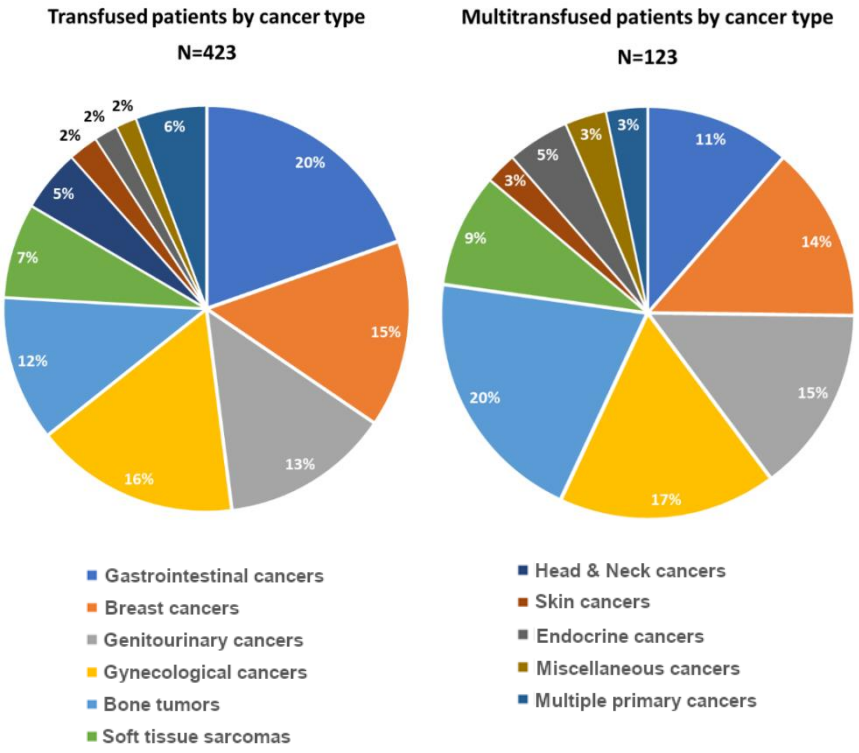

Figure 1. Distribution of cancer types in red blood cell (RBC) transfused patients. The left pie chart shows that RBC transfusions were administered across all cancer types. The right pie chart shows that multitransfused patients could be identified among all cancer types with the exception of head and neck cancers (■). A relatively large proportion of patients with bone tumors (■) was multitransfused.

Despite low transfusion intensity, the mean and median lifetime transfusion burden of the 423 transfused patients were 8.7 and 6.0 RBC units, respectively (range 1 – 67 RBC units). The proportion of patients receiving RBC transfusions was higher in the group diagnosed with cancer before 2008 compared with the group diagnosed in 2008 – 2009 (57.1% vs. 49.5%). Lifetime transfusion burden was also higher in the group diagnosed before 2008 (mean, 9.6; median, 6.0 RBC units; n = 240) than in the group of patients newly diagnosed with cancer (mean, 7.5; median, 4.0 RBC units; n = 183; $P = 0.0014$). Nevertheless, there was no correlation between lifetime transfusion burden and the time elapsed since cancer diagnosis. In addition, no correlation was found between

lifetime transfusion burden and age (r_s – 0.062; P = 0.0863; n = 775) or gender (median, 1.5 RBC units in males vs. 2.0 RBC units in females; P = 0.1146; n = 775).

Patients at risk for based on a lifetime transfusion burden of ≥ 10 RBC units constituted 123 of 423 (29.1%) transfused patients (Figure 1). Of these multitransfused patients, 44 had received ≥ 20 RBC units. The prevalence of multitransfusion was highest for intensive combination chemotherapy regimens (e.g., the Euro-Ewing trial regimen),[23] but overall patients who received ≥ 10 RBC units could be identified across all tumor types (Table 2) and types of anticancer treatment at inclusion (Figure 2). In contrast, none of the patients in the best supportive care group, who did not receive any anti-cancer treatment, were multitransfused. High-dose chemotherapy followed by autologous stem cell rescue was administered to only 4 of 775 patients (breast cancer, n = 1; Ewing sarcoma, n = 1; nonseminoma, n = 2) and only resulted in high lifetime transfusion burden when patients previously received intensive chemotherapy regimens.

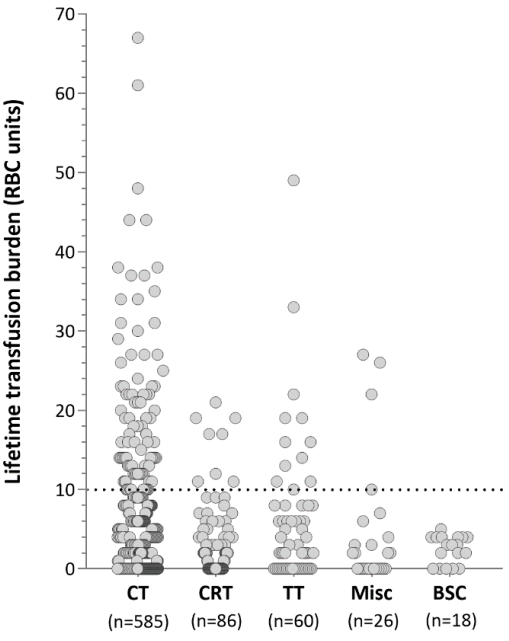

Figure 2. Lifetime RBC transfusion burden of all 775 patients grouped according to anti-cancer treatment received at inclusion. Subsets were defined as follows: single or multi-agent chemotherapy (CT: 52.1% transfused), concomitant chemo-radiotherapy or radiotherapy only (CRT: 61.6% transfused), targeted therapy only (TT: 65.0% transfused), miscellaneous systemic treatment only (Misc: 50.0% transfused) or best supportive care only (BSC: 72.2% transfused). For the 423 transfused patients, median lifetime transfusion burden was 6.0 RBC units in the CT-group (n=305), 4.0 RBC units in the CRT-group (n=53), 6.0 RBC units in the TT-group (n=39), 4.0 RBC units in the Misc-group (n=13), and 4.0 RBC units in the BSC-group (n=13). The majority (84.1%) of patients who received ≥20 RBC units were found in the group of patients treated with chemotherapy.

Table 2. Lifetime RBC transfusion burden of all 775 solid cancer patients on April 1st 2015 or death

Cancer type	Age (years) median (range)	Transfused patients n (%)	Units ECs median (range)	Multitransfused n (%)
All cancer patients (n=775)	**60 (18-90)**	**423/775 (54.6)**	**2 (0-67)**	**123/775 (15.9)**
Gastrointestinal cancers (n=160)	**65 (30-90)**	**83/160 (51.9)**	**1.5 (0-26)**	**14/160 (8.8)**
Lower GI cancer (n=87)	65 (30-83)	52/87 (59.8)	2 (0-22)	11/87 (12.6)
Upper GI cancer (n=46)	67 (46-90)	21/46 (45.7)	0 (0-19)	2/46 (4.3)
Pancreatic cancer (n=18)	53.5 (40-75)	5/18 (27.8)	0 (0-26)	1/18 (5.6)
Cholangiocarcinoma (n=2)	57.5 (56-59)	2/2 (100)	2.5 (2-3)	0/2 (0.0)
Anal cancer (n=7)	62 (56-84)	3/7 (42.9)	0 (0-6)	0/7 (0.0)
Breast cancers (n=153)	**61 (31-87)**	**63/153 (41.2)**	**0 (0-67)**	**17/153 (11.1)**
Genitourinary cancers (n=128)	**57 (21-81)**	**57/128 (44.5)**	**0 (0-61)**	**18/128 (14.1)**
Seminoma (n=35) *	49 (21-71)	7/35 (20.0)	0 (0-61)	1/35 (2.9)
Non-seminoma (n=30) *	39 (25-71)	10/30 (33.3)	0 (0-44)	5/30 (16.7)
Rete testis carcinoma (n=1)	59 (59)	1/1 (100)	12 (12)	1/1 (100)
Prostate cancer (n=17)	71 (49-80)	10/17 (58.8)	4 (0-22)	2/17 (11.8)
Urothelial cancer (n=5)	64 (52-73)	3/5 (60.0)	10 (0-13)	3/5 (60.0)
Renal cancer (n=40)	67 (48-81)	26/40 (65.0)	2 (0-22)	6/40 (15.0)
Gynecological cancers (n=99)	**55 (27-84)**	**69/99 (69.7)**	**4 (0-38)**	**21/99 (21.2)**
Ovarian/tubal cancer (n=40) †	63.5 (34-84)	26/40 (65.0)	3.5 (0-38)	8/40 (20.0)
Cervical cancer (n=38)	49.5 (27-83)	29/38 (76.3)	4 (0-22)	9/38 (23.7)
(Carcino)sarcoma (n=8)	53 (41-65)	7/8 (87.5)	8 (0-24)	3/8 (37.5)
Vulva/vagina cancer (n=6)	65 (38-84)	3/6 (50.0)	1 (0-4)	0/6 (0.0)
Endometrial cancer (n=2)	62 (47-77)	1/2 (50.0)	1 (0-2)	0/2 (0.0)
Germline tumor (n=5)	39 (30-51)	3/5 (60.0)	2 (0-14)	1/5 (20.0)

Table 2 (Continued) *Lifetime RBC transfusion burden of all 775 solid cancer patients on April 1st 2015 or death*

Cancer type	Age (years) median (range)	Transfused patients n (%)	Units ECs median (range)	Multitransfused n (%)
Bone tumors (n=57)	**34 (18-81)**	**49/57 (86.0)**	**8 (0-38)**	**25/57 (43.9)**
Ewing sarcoma (n=19)	28 (19-68)	18/19 (94.7)	17 (0-38)	13/19 (68.4)
Osteosarcoma (n=32)	39.5 (18-81)	29/32 (90.6)	6 (0-23)	11/32 (34.4)
Other bone tumor (n=6)	43.5 (26-54)	2/6 (33.3)	0 (0-13)	1/6 (16.7)
Soft tissue sarcomas (n=50)	**51.5 (20-83)**	**32/50 (64.0)**	**4 (0-49)**	**11/50 (22.0)**
GIST (n=19)	59 (28-83)	13/19 (68.4)	5 (0-49)	5/19 (26.3)
Other STS (n=31)	47 (20-78)	19/31 (61.3)	4 (0-21)	6/31 (19.4)
Head and Neck cancers (n=40)	**65 (50-80)**	**21/40 (52.5)**	**1 (0-9)**	**0/40 (0.0)**
Skin cancers (n=27)	**60 (42-80)**	**10/27 (37.0)**	**0 (0-16)**	**3/27 (11.1)**
Melanoma (n=24)	59 (42-80)	9/24 (37.5)	0 (0-16)	3/24 (12.5)
Non-melanoma (n=3)	71 (63-75)	1/3 (33.3)	0 (0-3)	0/3 (0.0%)
Endocrine cancers (n=11) *	**50 (31-77)**	**8/11 (72.7)**	**10 (0-25)**	**6/11 (54.5)**
Unknown primary (n=9)	**70 (39-77)**	**6/9 (66.7)**	**2 (0-17)**	**3/9 (33.3)**
Miscellaneous cancers (n=3)	**60 (37-63)**	**1/3 (33.3)**	**0 (0-10)**	**1/3 (33.3)**
2nd / 3rd primary cancers (n=38)	**66.5 (27-83)**	**24/38 (63.2)**	**2 (0-44)**	**4/38 (10.5)**

*: Seminoma and non-seminoma included gonadal and extragonadal germ cell tumors. Endocrine cancers consisted of adrenocortical carcinoma (n=7) and thyroid cancer (n=4).
†: Two patients had tubal carcinoma and both were multitransfused receiving 34-38 RBC units

Adherence to Guidelines

In the absence of a strict hemovigilance program within our institution, oncologists were unaware of the lifetime cumulative transfusion burden of their patients. Thus, serum ferritin was usually measured at the treating physician's discretion as part of routine laboratory testing. During the inclusion period of 2008 – 2009, serum ferritin was determined in 146 (40.6%) transfused patients and in 165 (39.7%) nontransfused patients. Despite active cancer and treatment, ferritin levels increased significantly with transfusion burden ($H(2) = 51.22$, $P < 0.0001$). Patients who had received ≥ 10 RBC units had higher median serum ferritin levels (1,121 µg/L; IQR 510 – 2,095; n = 38) than patients who received 1 – 9 RBC units (445 µg/L; IQR 235 – 850; n = 108; $P < 0.0001$) and patients who had not received any transfusions (241 µg/L; IQR 125 – 399; n = 165; $P < 0.0001$).

Elevated ferritin levels were typically attributed to the increased cancer-associated inflammatory state, and ferritin measurements were often not repeated after completion of anticancer treatment. Thus at the end of the observation period in 2015, none of the 123 multitransfused patients was screened for biochemical, hepatic or cardiac hemosiderosis despite having survived for a median of 4.6 years (IQR 1.9 – 7.0; range 0.1 – 26.4 years) since cancer diagnosis.

Multitransfused Survivors and Iron Overload

By April 2015, only 276 of the original 775 patients (35.6%) were alive, and only 26 of 123 (21.1%) patients who received ≥ 10 RBC units survived. These 26 multitransfused long-term survivors had been diagnosed with the following cancers for a median of 7.0 years (range 5.5 – 22.6): malignant germ cell tumors (n = 7), osteosarcoma (n = 6), Ewing sarcoma (n = 5), ovarian cancer (n = 2), esophageal cancer (n = 2), sigmoid cancer (n = 1), breast cancer (n = 1), cervical cancer (n = 1), and adrenocortical cancer (n = 1). One multitransfused patient was also treated with an erythrocyte-stimulating agent (ESA) and iron supplements.

Upon disclosure of lifetime transfusion burden, treating physicians initiated screening for biochemical iron overload. Seven patients had serum ferritin levels above the threshold 500 µg/L (563 – 1,769 µg/L), 3 had a slightly elevated serum ferritin (284 – 463 µg/L), and 14 had normal ferritin levels (29 – 250 µg/L). Two patients had been referred back to their general practitioner after being cured from cancer and were not tested.

Serum ferritin at end of treatment was available from 21 of 26 multitransfused survivors, allowing us to study the evolution of ferritin levels over a longer period of time (Figure 3). Interestingly, over a more than 5-year time period, ferritin levels had decreased with 331 – 2,350 µg/L in 14 multitransfused patients, whereas one patient with metastatic cancer demonstrated a 10-fold increase in serum ferritin after having received 15 RBC units.

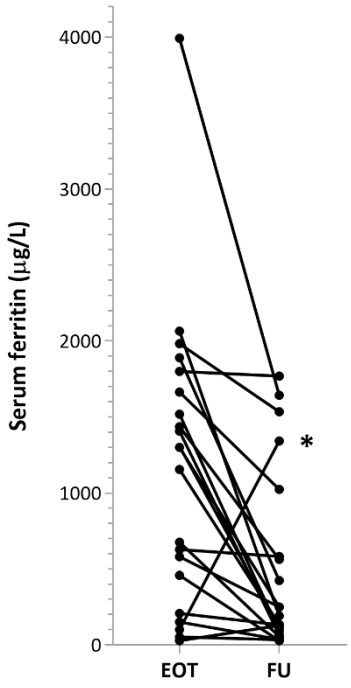

Figure 3. Evolution of serum ferritin levels in multitransfused survivors during follow-up. Serum ferritin was measured at the treating physician's discretion and was available at two time points for 21 of 26 multitransfused survivors: end of treatment, which corresponds with the serum ferritin determined immediately after end of anticancer therapy, and at end of follow-up more than 5 years later in 2015.
Median serum ferritin was significantly lower at end of follow-up (192 µg/L, interquartile range [IQR] 78.5 – 803.5) than at end of treatment (1,300 µg/L, IQR 332.5 – 1,733; $P = 0.0004$).
One patient with metastasized disease (*) demonstrated a 10-fold increase in serum ferritin after having received 15 red blood cell units. Abbreviations: EOT, end of treatment; FU, follow-up.

Seven multitransfused survivors had persistently elevated serum ferritin levels of > 500 µg/L. As one of these patients was diagnosed with a cancer relapse shortly after screening for biochemical iron overload, six of seven patients were screened for hepatic and cardiac hemosiderosis.

MRI-assessed LIC was elevated in all six (23.1% of multitransfused) patients and ranged from 3.9 to 11.2 mg Fe/g dw (Table 3). In five of six patients, the last RBC transfusion had been administered ≥ 6.5 years ago. One patient with a slightly elevated serum ferritin (583 µg/L), who received 13 RBC units, demonstrated the second highest LIC. The patient with the highest LIC had elevated liver enzymes, which normalized upon treatment with phlebotomies. Although two of six patients developed nonischemic deterioration of LVEF from ~70% to 50% in the absence of cardiovascular risk factors or cardiotoxic chemotherapy, which fully normalized after phlebotomies, none of the patients showed evidence of cardiac hemosiderosis on MRI.

Because serum ferritin may not reflect total body iron accurately, four of seven patients with high transfusion burden (≥ 19 RBC units) and ferritin levels that had dropped into the normal range were also screened for transfusional hemosiderosis. No signs of hepatic or cardiac iron overload were found (LIC 0.0 – 1.8 mg Fe/g dw, cardiac iron content < 1.1 mg Fe/g dw, LVEF 57% – 61%).

Table 3. Transfusion-related iron overload in multitransfused patients alive in April 2015 with serum ferritin >500 µg/L

ID	Sex	Age	Diagnosis	Treatment	Blood loss	Trf burden (RBC units)	Time since Trf (yrs)	Ferritin (µg/L)	Liver iron content (Fe mg/g d.w)	Cardiac iron content (Fe mg/g d.w)	LVEF (%)
1	M	33	Ewing sarcoma	6x VIDE, radiotherapy, surgery, 8x V(A)I	No	38	6.8	1769	11.2*	<1.1	50%
2	M	53	Extragonadal seminoma	Orchidectomy, 1x EP, 4x VIP	Yes	61	7.8	1643	7.3*	<1.1	50%
3	M	24	Ewing sarcoma	6x VIDE, surgery, 8x VAI	No	27	6.5	1535	5.1*	<1.1	66%
4	F	65	Papillary ovarian cancer	6x Carbo/Tax, rechallenge at relapse, Carbo/Pld	No	18	0.7	1342	5.3*	<1.1	63%
5	M	29	Non-seminoma testis	Orchidectomy, 4x VIP, lymph node dissection	Yes	13	8.5	583	9.0*	<1.1	62%
6	M	45	Non-seminoma testis	Orchidectomy, 6x (B)EP, 4x VIP, 4x Cis/Tax/Gem	Yes	44	7.0	563	3.9*	<1.1	56%
7	M	44	Non-seminoma testis	Orchidectomy, 4x BEP, Gem/Txt/Cis, IE, CE, CTC, ASCT	No	31	2.8	1024	n.a.	n.a.	n.a.

Findings in all seven multitransfused survivors who were alive on April 1st 2015 and had a serum ferritin > 500 µg/L are reported: patient characteristics, lifetime transfusion burden, time elapsed since last RBC transfusion, MRI-assessed iron content and left ventricular ejection fraction.
Reference values: Serum ferritin 10-150 µg/L for women vs. 35-260 µg/L for men. Liver iron content: <2.0 mg Fe/g dry weight (dw). Cardiac iron content <1.1 mg Fe/g dw corresponds with low risk of cardiac complications and is considered normal. Left ventricular ejection fraction: 55-74%.
*Liver iron content above the upper limit of normal indicating hepatic iron overload.
Abbreviations: ASCT: *autologous stem cell transplantation*. LVEF: *left ventricular ejection fraction*. n.a.: *not assessed* (patient relapsed and urgently needed to restart treatment). RBC: *red blood cell.* Trf: *transfusion.* **Chemotherapeutic treatment:** BEP: *bleomycin, etoposide, cisplatin*. Carbo: *carboplatin*. CE: *carboplatin, etoposide*. Cis: *cisplatin.* EP: *etoposide, cisplatin.* CTC: (*high dose) carboplatin, thiotepa, cyclophosphamide*. Gem: *gemcitabine.* IE: *ifosfamide, etoposide.* Pld: *pegylated liposomal doxorubicin.* Tax: *paclitaxel.* Treo: *treosulfan.* Txt: *docetaxel.* VAI: *vincristine, actinomycin D, ifosfamide*. VIDE: *vincristine, ifosfamide, doxorubicin, etoposide*. VIP: *etoposide, ifosfamide, cisplatin.*

Discussion

This is the first study examining lifetime transfusion burden and the occurrence of TRIO in a large cohort of 775 adults treated for a wide variety of solid tumors. Almost 30% of all transfused patients received ≥ 10 RBC units. Multitransfusion occurred across all tumor types, predominantly outside the HSCT setting. Without a hemovigilance program that actively reports the cumulative number of RBCs transfused, oncologists were unaware of the lifetime transfusion burden of their patients. Guidelines typically advise treatment of iron overload in patients with a life expectancy of > 1 year, which is often difficult to predict in patients with solid malignancies. The uncertain patient outcome and the notion that patients with solid malignancies receive the bulk of transfusions close to time of death may have contributed to the belief that TRIO is not clinically relevant in this patient population.

This study shows that 50% of multitransfused patients with solid cancer have a considerable median life expectancy of 4.6 years or more since cancer diagnosis. A large proportion (75%) of multitransfused patients survived ≥ 1.9 years and, according to existing guidelines, met the > 1.0-year life expectancy criterion for the initiation of chelation therapy.

Although their numbers were small, when surviving multitransfused patients in our institution were finally tested after more than 5 years, 23% demonstrated serum ferritin levels > 500 μg/L and hepatic iron overload ranging from 3.9 to 11.2 mg Fe/g dw. Incidental or retrospective discovery of TRIO in patients with solid cancer outside the HSCT setting has also been reported in pediatric oncology,[24,25] stressing the need for routine cancer survivor screening.

The lack of awareness is further illustrated by assessment of transfusion records from a large regional nonacademic hospital in The Netherlands, showing that although 58 of 171 (33.9%) patients with solid cancer transfused within a 6-year time period had a lifetime transfusion burden of ≥ 10 RBC units (data not shown), none was screened for iron overload. These patients (median age, 68 years; range, 27 – 96; 40.4% male) were

comparable to our academic hospital study population. Cancer diagnoses encompassed a similar variety of solid malignancies (albeit no germ cell tumors, bone tumors, or endocrine cancers), and a similar median lifetime transfusion burden of 6.0 RBC units (range 2–80) was found.

Serum ferritin is a widely available inexpensive marker to monitor total body iron stores but may be increased in inflammatory states such as infection and active cancer.[26] It may decline when a long-term cancer remission state has been achieved. Our data support existing recommendations advocating lower thresholds for screening of multitransfused patients with cancer with a lifetime transfusion burden of ≥ 10 RBC units starting from serum ferritin levels of > 500 µg/L during follow-up.[7-10,27]

The levels of hepatic iron overload found in our population of cancer survivors have previously been reported to correspond with progressive liver fibrosis and development of cardiomyopathy in 6.7% of patient.[28,29] Even though LIC is a good surrogate marker for total body iron, the heart and other iron-sensitive organs have different mechanisms of iron uptake and clearance.[30,31] Serum ferritin and LIC do not correlate well with cardiac iron deposition, and despite observed improvement of LIC after chelation therapy, cardiac iron overload may persist.[32-34] As organ toxicity gradually increases with each RBC unit transfused and iron is cleared more slowly from the heart than the liver,[28,29,35,36] early assessment and timely treatment of iron overload is of essence. Noninvasive measurement of tissue iron by MRI is helpful to identify presymptomatic patients at risk.

However, early detection of cardiac iron overload may be challenging because normal myocardial iron concentrations are as low as 0.29 – 0.47 mg Fe/g dw, and many factors influence MR T2* values.[20,21,32,37-39] In addition, noninvasive cardiac iron measurements using MR T2* parameters were not validated in live humans but extrapolated from a rodent model and postmortem studies of 12 human hearts with cardiac iron content in high ranges (i.e., > 2.17 mg Fe/g dw, T2* values < 12 ms).[20,21,38] Because cardiac iron deposition was previously reported to be found at autopsy in 11% and 28% of patients receiving 26 – 50 and 51 – 75 RBC units, respectively,[2] challenges in the detection of

cardiac iron depositions in the low range may explain the normal MRI T2* findings in our population of long-term survivors.

Pancreas MR R2* values may predict cardiac iron loading.[40,41] Quantification may be challenging in older patients, in contrast to children and young adults, because of pancreatic fatty infiltration.[42] Measurements are often not routinely done. None of our long-term multitransfused survivors had signs of beta-cell dysfunction (i.e., normal fasting glucose and HbA1c; data not shown) in agreement with findings in sickle cell disease that pancreatic iron overload only occurred in patients with a LIC of > 10 mg Fe/g.[43]

Until now, literature about the occurrence of hepatic and cardiac iron overload in adult patients with solid malignancies was lacking. Most reports concerned older retrospective studies with a relatively short follow-up of 12 months without details on lifetime transfusion burden or iron overload.[44,45] More recently, a population-based cohort study from Denmark (1998 – 2003) demonstrated that within 120 days after diagnosis, 40% of 1,782 newly diagnosed patients with hematopoietic and solid cancer with chemotherapy-related anemia were transfused,[46] which is lower than the 49.5% we observed in newly diagnosed patients. As the incidence of anemia increases with each chemotherapy cycle and with each line of therapy,[47] the considerably longer observation period since cancer diagnosis in our study may well explain the higher percentage of transfused patients compared with historical data only reporting RBC transfusions during a limited time period. The Danish study reported that a median of 2 RBC units was transfused the first time, indicating that most oncologists in Denmark also adhered to a double unit transfusion strategy. Patients treated with subsequent transfusions received a median of 5.0 RBC units, but pediatric and adult solid cancers were lumped together with hematological malignancies. Separate information about the 4-month transfusion burden of newly diagnosed adult patients with solid malignancies only was not provided, and lifetime transfusion burden in this patient population is unknown.

Strategies to reduce RBC transfusion burden include single unit transfusion and a restrictive transfusion policy defined by use of a hemoglobin transfusion trigger of 7.0 – 8.0 g/dL.[48,49] Gross *et al.* observed a significant reduction of the mean number of RBC transfusions per patient after implementation of a patient blood management program in their cancer center (U.S.) despite marked decline in ESA use because of warnings issued by the Food and Drug Administration and regulatory restrictions.[50] Excluding patients with leukemia, 198 patients received a mean of 5.3 RBC units during a 5-year period from January 2008 to July 2013. Data on lifetime transfusion burden or long-term cancer survivorship were not provided. The mean pretransfusion hemoglobin level decreased from 6.83 to 6.55 g/dL without significant change of in-hospital mortality rates (6.6% vs. 6.7%). An earlier study by Vadhan-Raj et al. reported that with a mean pretransfusion hemoglobin of 8.4 g/dL, the amount of RBC transfusions did not increase significantly in their cancer center despite a 26% – 61% decrease in ESA use in 2007 – 2008 compared with 2006.[51] Mortality rates were not addressed in this study.

Although restrictive transfusion policies are deemed safe in the surgical oncology setting and inpatient intensive chemotherapy treatment setting of hematological malignancies, where patients typically remain hospitalized until bone marrow recovery,[49,52] the only randomized-controlled study in patients with solid cancer compared a "restrictive" transfusion policy (hemoglobin trigger < 10.0 g/dL) with a liberal transfusion policy (hemoglobin trigger < 12.0 g/dL) in patients with advanced gastric cancer receiving first-line chemotherapy.[53]

Whether and to what extent these data can be extrapolated to ambulant patients with cancer receiving curative intensive chemotherapy when treatment delay and dose reduction are not desirable has not been assessed.[54] Moreover, a restrictive transfusion policy (hemoglobin trigger < 7.0 g/dL) had a negative impact on survival of elderly patients aged more than 65 years, who form a large proportion of adult patients with cancer, and critically ill patients with cancer with septic shock when compared with a more liberal transfusion policy (hemoglobin trigger < 9.0 g/dL).[55,56] Recently, the scientific committee of the 2018 International Consensus Conference on Patient Blood Management concluded that insufficient data exist to guide clinical practice with regard

to transfusion thresholds in patients with solid tumors and advocated that future research in this field should prioritized.[57] Use of a treatment intensity rating system for solid cancers may facilitate future cross-study comparison,[58] although its development may be challenging because of the wide range of cancers and diversity of treatment schedules applied in adult oncology patients.

Anemia management may also include erythrocyte-stimulating agents and administration of intravenous iron. However, the risks and benefits of each treatment modality should be carefully weighed by physicians.[59,60] Importantly, as cancer cells have high iron requirements to support their growth,[61,62] iron administration may negatively impact patient outcome.

Measurement of serum hepcidin prior to initiation of intravenous iron and erythrocyte-stimulating agents may assist clinical decision making, as it may predict response to treatment.[63,64] Alternatively, timely initiation of chelation therapy may counteract iron toxicity, although different chelators carry risks and side effects of their own. For long-term survivors without anemia, phlebotomy may be the safest option.

Conclusion

As shown by real-world data collected from an academic hospital-based cancer registry, a considerable proportion of patients with diverse solid malignancies become multitransfused even when adhering to restrictive RBC transfusion policies. Multitransfused long-term survivors may demonstrate hepatic iron overload and be at risk for undetected progressive organ dysfunction and decreased quality of life. With the improved cancer survivorship achieved in recent decades, it becomes increasingly important to raise awareness among oncologists of the occurrence of TRIO. Implementation of a hemovigilance program to electronically capture lifetime transfusion burden in individual patients may be essential to ensure optimal care for patients with cancer and long-term survivors.

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The authors declare that they have no competing interests relevant to this article.

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