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High-dose corticosteroid associated with catheter-related thrombosis after allogeneic hematopoietic stem cell transplantation

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ABSTRACT

Background: Allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients are at an increased risk of thrombotic complications, most of which are catheter-related and present a substantial challenge. The incidence of CRT varies considerably depending on clinical factors. However, the underlying pathogenesis and risk factors remain unclear.

Methods: We performed a retrospective nested case-control study in patients following allo-HSCT. Thrombotic episodes were diagnosed based on the clinical suspicion of the physician (pain, swelling, etc.) with subsequent CVC or PICC thrombosis confirmed via duplex ultrasound. Cases with CRT and controls were matched for time of HSCT, age at HSCT, donor source and type of insertion (CVCs or PICC).

Results: During the 8-year period, catheters were placed in 2896 patients, with a total of 40 patients (1.38%) developed CRT, among which 11 were associated with CVCs and 29 were associated with PICCs. The median duration from catheter insertion to thrombosis was 97 days. Despite reports of an association between thrombosis and infection, central line-associated bloodstream infection was comparable between groups. No significant differences were noted in terms of primary disease, donor type, conditioning regimen or catheter type between the cases and controls. A multivariate regression analysis identified high-dose corticosteroids as independent risk factors for the development of CRT. CRT seems to negatively affect prognosis in allo-HSCT patients.

Conclusion: In conclusion, we demonstrate that the use of high-dose corticosteroids is correlated with the onset of CRT. However, the efficacy and safety of thromboprophylaxis in this population require further investigation.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) provides the best chance for a cure for many diseases [1]. Despite advances in the field, transplantation complications, including graft-versus-host disease, infection and hemorrhagic/thrombotic complications continue to pose great threats to patients undergoing allo-HSCT, thereby affecting their long-term survival and quality of life.

Changes in hemostasis and thrombosis are observed in allo-HSCT recipients, and thrombotic complications indicate an adverse prognosis [2–4]. Allo-HSCT and complications following allo-HSCT as well as treatments contribute to all three components of the Virchow Triad, including hemodynamic changes, vascular endothelial injury and hypercoagulability [5]. HSCT recipients have altered levels of antithrombin and protein C, indicating a hypercoagulable state [6,7]. Heavy tumor load in no remission (NR) or relapsed patients also accelerate thrombogenesis. Endothelial cells play a vital role in thrombotic complications of HSCT. In acute graft-versus host disease (aGVHD), endothelial cell-derived microparticles are substantially elevated, expressing endothelial cell damage [8]. Platelets are strongly and irreversibly activated after conditioning regimen in allo-HSCT recipients, thereby presenting another pathogenesis of thrombosis [9]. In hospitalized patients except for transplantation recipients, amphotericin B has been suggested to increase the risk of developing thrombosis due to low pH or osmolality [10]. The use of corticosteroids and calcineurin inhibitors also impair the normal functioning of endothelial cells [11,12]. Elevated levels of antihemophilic factor in patients treated with prednisone have been elucidated, indicating altered hemostatic functions as well. However, there is no information available on the relationship between medication and catheter-related thrombosis (CRT) in allo-HSCT recipients. The pretransplant prothrombotic risk factors might be another risk factor for the onset of CRT in HSCT patients.

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Patients require long-term stable venous access for the administration of medications, parenteral nutrition and blood products. To achieve this, central venous catheters, primarily subclavian catheters and peripherally inserted central catheter (PICC), are routinely inserted prior to transplantation. However, a central catheter is associated with several complications, including thrombosis, occurring at a rate of 3.6%–31.7% [13–16]. CRT affects the duration of the catheter, increased costs of medical care, and can even lead to lethal pulmonary embolism. Although patients following allo-HSCT are at a high risk of thrombosis, routine systemic prophylactic anticoagulation is not recommended [17–19]. Studies in patients with cancer suggest that thromboprophylaxis does not affect the risk of CRT but does increase the risk of overall bleeding and heparin-induced thrombocytopenia [20–24]. Anticoagulation prophylaxis is limited due to thrombocytopenia in allo-HSCT recipients. Therefore, the benefit of anticoagulation should be weighed against the substantially increased risk of bleeding.

Despite these findings, there is no information available on the incidence of CRT in haploidentical allo-HSCT recipients. Little is known about the role of transplantation complications, immunosuppressants and antimicrobial agents in catheter-related thrombotic events, as well as its impact on patient prognosis [13]. Moreover, several studies indicate a possible relationship between leukemic cell burden and thrombosis. CRT is thus a possible predictor for relapse and outcomes of allo-HSCT recipients.

To analyze the incidence and risk factors of CRT in HSCT recipients, a retrospective, nested case control study was performed. The cumulative incidence of CRT in haploidentical allo-HSCT patients is comparable with that of identical sibling donors. We propose for the first time the possible association between the use of corticosteroid within 30 days and catheter-related thrombotic events in allo-HSCT patients, which can be used to identify patients at a high risk of CRT and provide evidence of anticoagulation prophylaxis and the first to propose that CRT could be a potential indicator of relapse and poor prognosis in HSCT recipients.

2. Materials and methods

2.1. Patients and controls

A nested case-control study design was used. Cases were identified from a cohort of 2897 consecutive patients who underwent allo-HSCT at Peking University People's Hospital from 2006 to 2014, and computerized medical records of all inpatients and outpatients were detailed recorded. All patients received their outpatient follow-up after discharge in the same institute. There were 1 missing data, leaving 2896 eligible patients. Cases were defined as patients with symptomatic CRT during follow up and finally we have got 40 cases in total. Controls consisted of HSCT patients from the cohort who had no clinical evidence of CRT and at risk of developing CRT at the time of case diagnosis. Individual matching was used. For each case, 3–4 controls were randomly selected from the same cohort with the following matching criteria: time of HSCT (±90 days), age at HSCT (±10 years), donor source (identical sibling donors, haplo-identical donors and matched unrelated donors), follow-up time and type of insertion (CVCs or PICC). The characteristics of cases and controls are summarized in Table 1. The study was approved by the ethics committee of Peking University People's Hospital, in accordance with the Declaration of Helsinki.

Table 1
Baseline characteristics of patients with catheter-related thrombosis and control group.

Characteristics	Cases (n = 40)	Controls (n = 143)	p value
Age at HSCT, mean (range), year	31.4 (8–62)	30.1 (4–59)	0.588
Gender (male/female)	21/19	73/70	0.507
Underlying disease			0.335
AML (n)	20	51	
ALL (n)	14	50	
MDS (n)	1	13	
CML (n)	3	20	
Others (n)	2	9	
Status at HSCT			0.509
Standard risk (n)	38	138	
High risk (n)	2	5	
Source of stem cell			0.622
PB	2	8	
PB + BM	38	135	
Donor match			0.998
HLA-identical sibling donor (n)	11	40	
HLA-partially matched related donor (n)	27	96	
Matched unrelated donor (n)	2	7	
Unmatched HLA loci at A, B, DR			0.985
0	13	50	
1–2	9	32	
3	18	61	
Donor-recipient gender			0.103
Identical, n	27	78	
Different, n	13	65	
Pre-HSCT cycles of chemotherapy	4 (0−11)	4 (0–14)	0.400
Conditioning regimen			0.070
BU/CY, n	12	47	
BU/CY + ATG, n	24	93	
Others	4	3	
MNCs ($\times 10^8$/kg, mean ± SD)	7.35 ± 1.70	7.62 ± 1.79	0.269
CD34 ($\times 10^6$/kg, mean ± SD)	3.11 ± 2.17	2.71 ± 1.50	0.300
WBC engraftment	14 (2–24)	14 (10–37)	0.420
PLT engraftment	23 (8–∞)	20 (7–∞)	0.506
Relapse			0.005
Yes, n	10	11	
No, n	30	132	
aGVHD			0.133
0–I, n	31	125	
II–IV, n	9	18	
cGVHD, n	9	18	0.139
History of CMV reactivation, n	21	21	0.000
History of fungal infection, n	12	10	0.001
Follow-up time (months)	40.3 ± 30	48.7 ± 31	0.137

2.2. Catheter insertion and care

A central catheter was routinely implanted prior to the conditioning regimen. In most cases, a CVC at the subclavian vein was used, and in cases of younger children, aplastic anemia and severe thrombocytopenia, a PICC was preferred. Trained doctors insert CVCs and professional vascular nurses insert PICCs at our facility. PICCs were placed under ultrasound guidance. During catheter placement and care, the medical staff routinely employed strict hand hygiene, sterile barriers and Anerdian (LiKang, Shanghai) for skin antisepsis. All catheters were inserted so that their tips terminated in the lower third of the superior vena cava or at the junction of the right atrium and superior vena cava. No catheters were used until the tip position was verified by chest radiography. Routine surveillance imaging for tip malposition or thrombosis was not performed. Catheter assessment and care was performed daily by bedside nurses. All catheter lumens were flushed with 10 mL normal saline followed by 2 mL unfractionated heparin (1000 units/mL), according to routine clinical practice. In the absence of complications, these catheters were used throughout the entire course of HSCT. Catheters were removed in patients who were suspected of catheter-related complications or when discharged after transplantation without further need of a central line.

Thrombotic episodes were diagnosed based on the clinical suspicion of the physician (pain, swelling, etc.) with subsequent CVC or PICC thrombosis confirmed using duplex ultrasound [18]. There was no routing systemic prophylaxis for these patients. When diagnosed with CRT, risk factors, functions and further need of the catheters were carefully evaluated. If catheters were no longer needed or, malpositioned, or there was suspicion of catheter-associated infection, the catheters would be removed after days with or without LMWH, depending on the patient's condition. If catheters were functional and