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ORIGINAL ARTICLE

Catheter-associated bloodstream infections and thrombotic risk in hematologic patients with peripherally inserted central catheters (PICC)

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Abstract
Purpose The use of peripherally inserted central catheters (PICC) as an alternative to other central venous access devices (CVAD) is becoming very frequent in cancer patients. To evaluate the impact of complications associated to these devices in patients with hematologic malignancies, we revised the catheter-related bloodstream infections (CRBSI) and the catheter-related thrombotic complications (CRTC) observed at our institute between January 2009 and December 2012.
Methods A total of 612 PICCs were inserted into 483 patients at diagnosis or in subsequent phases of their hematologic disease. PICCs were successfully inserted in all cases. The median duration of in situ PICC placement was 101 days (interquartile range, 48–184 days).
Results A CRBSI occurred in 47 cases (7.7 %), with a rate of 0.59 per 1000 PICC days. A CRTC was recorded in 16 cases (2.6 %), with a rate of 0.20 per 1000 PICC days. No serious complication was associated to these events. Cox regression analyses of variables associated to CRBSIs and to CRTCs showed that only the type of disease (acute leukemia compared to other diseases) was significantly associated to a higher incidence of CRBSIs, while no feature was predictive for a higher risk of CRTCs.
Conclusions PICCs represent a useful and safe alternative to conventional CVAD for the management of patients with hematologic malignancies.

Keywords PICC · Hematologic malignancies · Infections · Thrombosis

Introduction

Central venous access devices (CVAD) are essential for the management of cancer patients. In view of the limited availability of peripheral veins [1], a safe and easy to manage intravenous line is required for the administration of chemotherapy, autologous and allogeneic stem cell transplantation procedures, blood and platelet transfusions, parenteral nutrition, and other supportive therapy. However, a number of side effects, such as insertion-related and long-term complications including infections and thrombosis, have been associated to the use of CVAD [2]. In this context, the use of peripherally inserted central catheters (PICCs) for intermediate-term access has been increasingly adopted during the last few years, since they are easier to insert, and associated to a lower rate of early and late complications compared to conventional percutaneously inserted CVAD. Furthermore, PICCs are also easy to remove and less expensive than other CVAD. The high degree of satisfaction reported in 97 % of patients appears very encouraging [3].

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In the setting of hematologic malignancies, there is limited information on the usefulness and safety of PICCs in the various clinical settings [4]. The aim of the present retrospective study was to assess the feasibility and safety of the use of PICCs in the management of a large and representative cohort of patients affected by hematologic malignancies in various phases of the disease and undergoing different treatment modalities. In particular, we focused on the incidence of catheter-related bloodstream infections (CRBSI) and catheter-related thrombotic complications (CRTC).

Materials and methods

Central venous devices management and patient population

This study was performed at the Hematology Center, Policlinico Umberto I, Sapienza University of Rome, a referral hematologic institution in Italy. At our center, a dedicated team for the insertion and management of CVADs, which includes specifically trained physicians and nurses, was constituted in 2005. All PICCs, whether as an elective or urgent procedure, were inserted in a dedicated interventional surgical facility within the Hematology Center using aseptic techniques and only occasionally at the patient's bedside. Several types of catheters—PICC Groshong 4 Fr Bard, PICC per-q-cath 5 Fr Bard, and Power PICC 5 Fr Bard (Bard Access Systems, Salt Lake City, UT)—were used in relation to the type and duration of the planned treatment.

Before PICC insertion, all patients were screened with complete peripheral blood counts and standard coagulative tests. Patients with platelet (PLT) counts lower than 10×10^9/l received concentrated PLT infusions prior to the PICC insertion. Peripheral venous accesses were obtained through the basilica, brachial, or cephalic vein. A local anesthetic (carbocaine 2 %) was injected into the subcutaneous tissue close to the anterior vein wall. A 21(e)-22 gauge needle was systematically inserted under ultrasound guidance until the anterior vein wall was reached and crossed. The needle was introduced into the vessel until a blood return was observed. A metallic 0.018-inch guide wire was then introduced into the vein under fluoroscopic guidance. The puncture site was then enlarged slightly with a scalpel blade, and the micro-introducer assembly was introduced over the guide wire. The catheter was inserted into the micro-introducer sheath, and fluoroscopy was routinely performed in all patients to verify a correct location of the tip (close to the cavo-atrial junction). None of the PICCs was sutured; they were held in place with StatLock adhesive dressings (StatLock; Bard, Murray Hill, NJ). The position of the punctured vein was systematically recorded. Hospitalized patients received routine PICC medications in the hematologic ward; outpatients received routine PICC medications in a surgical room from the dedicated "CVADs team." All patients were followed at a weekly interval by the clinicians or nursing staff in order to verify the occurrence of PICC-related complications (insertion site infection, hematoma, blockage and leakage, thrombotic complications) until removal of the catheter or until death of the patient. All PICCs were removed by the CVADs team at our center. The major criteria for PICC removal due to a complication were the persistence of bacteremia despite appropriate antibiotic therapy and catheter obstruction or malfunction or dislocation. In patients with CRTC, low-molecular-weight heparins were employed and PICC was eventually removed only after echo-Dopller evidence of vessel recanalization.

We retrospectively reviewed the data regarding all 612 consecutive PICCs inserted between January 2009 and December 2012 in 483 patients with hematologic malignancies, submitted to chemotherapy, autologous stem cell transplant, and other supportive therapy (no allogeneic stem cell transplant patient was included). When an individual patient had more than one PICC inserted during the study period, each was regarded as a separate event. All patients were informed about the procedure and its potential complications and gave a written informed consent for the insertion of the catheter and for the use of the data for scientific purposes.

Definition of PICC-related complications

CRBSIs were defined according to modified criteria of the National Nosocomial Infections Surveillance System of the CDC of Atlanta, USA [4]. In particular, for the definition of a CRBSI, all the following conditions were required: (a) a bacterial or fungal pathogen isolated from one or more blood cultures (for common skin commensal—e.g., diphteroids, coagulase-negative staphylococci, *Micrococcus* spp., *Propionibacterium* spp., *Bacillus* spp.—two or more positive blood cultures were required); (b) the presence of at least one clinical sign and symptom of systemic infection (fever >38 °C, chills, rigors, hypotension) within 24 h of a positive blood culture being collected; (c) PICC placed within 48 h before the event and the isolated organism not related to an infection at another site; and (d) the same organism isolated from the blood isolated also from the tip of the PICC (roll tip culture method) when removed or the organism isolated from a blood sample drawn from the PICC not isolated from blood samples obtained concomitantly from a peripheral vein. The criteria of a different time to positivity between blood cultures drawn from the central venous line and from a peripheral vein [5] was not used for the definition of CRBSI due to the lack of a semiautomatic blood culture system at our microbiology laboratory where a manual blood culture method (Oxoid Signal System, Oxoid, USA) was used.

A CRTC was defined as a thrombotic episode assessed by ultrasonographic diagnostic imaging upon overt symptoms

and signs, such as pain or tenderness, warmth, swelling, or edema. The criteria of non-compressibility (compression ultrasound) and the direct visualization of thrombotic material in the venous lumen were used to establish the presence or absence of thrombosis. In addition, a Doppler technique was used to obtain qualitative and quantitative information of the blood flow. Ultrasonographic examinations were not performed to monitor the venous flow in asymptomatic patients; thus, thrombotic episodes associated to the PICC in the absence of specific symptoms and signs were not considered in our study.

Data analysis

The clinical data were prospectively recorded for all patients in a database managed by the CVADs team, and an informed consent for the use of the data for scientific purposes was requested from each patient. The study was approved by the institutional review board of the center. This was a non-interventional cohort study, and the collection and storage of data were performed by the investigators directly involved in the patients' care using current techniques of confidentiality.

The unit of analysis was a PICC within a patient, and the primary outcome was the number of line days until the occurrence of a CRBSI or CRTC. The incidence of CRBSIs and CRTCs per number of PICCs and the number of CRBSIs and CRTCs per 1000 catheter days were calculated. In addition, the cumulative incidence of CRBSIs and CRTCs was calculated accounting for the competing risks of infection-free death and PICC removal due to complications other than infection, and for thrombosis-free death and PICC removal due to complications other than thrombosis, respectively. The cumulative incidence was assessed using the cmprsk package in R, version 2.15.

Additionally, independent risk factors for CRBSIs and CRTCs were identified using a Cox proportional hazards regression model, constructed using the SPSS software for Windows, version 17.0. Initially, each variable was tested using the univariate Cox regression model and only those variables with $P<0.2$ were retained. A backward elimination method was then used to remove variables from a multivariable Cox regression model, with variables excluded sequentially on the basis of Wald's P value, until all remaining variables had a $P<0.05$.

Results

On the whole, 612 PICCs were inserted into 483 patients. The demographic characteristics, underlying hematologic diseases and different phases of the disease at the moment of the PICC insertion are listed in Table 1.

Table 1 Patient characteristics

No. of patients	483
Sex (female/male)	251/232
Age (years)	Median 54.7 Interquartile range 36.2–67.1
Type of disease	
Non-Hodgkin lymphoma	157 (32.5 %)
Acute myeloid leukemia	104 (21.5 %)
Hodgkin lymphoma	94 (19.5 %)
Myelodysplastic/myeloproliferative syndromes	39 (8.1 %)
Acute lymphoid leukemia	34 (7 %)
Multiple myeloma	30 (6.2 %)
Severe aplasia anemia	13 (2.7 %)
Hemophilia	12 (2.5 %)
Phase of disease at PICC insertion[a]	
Onset	242 (39.5 %)
Complete remission	38 (6.2 %)
Pre-autologous stem cell transplantation	75 (12.3 %)
Relapse	85 (13.9 %)
Chronic phase	98 (16.0 %)
Advanced/terminal phase	74 (12.1 %)

[a] 612 PICCs were inserted into 483 patients. Overall, 1, 2, and 3 PICCs were inserted in 387, 71, and 25 patients, respectively

A peripheral venous access was obtained through the basilic vein in 475 cases (77.6 %), the brachial vein in 134 (21.9 %), and the cephalic vein in 3 (0.5 %). A PICC Groshong 4 Fr was used in 531 cases (86.8 %), a PICC per-q-cath 5 Fr in 63 (10.3 %), and a Power PICC 5 Fr in 18 cases (2.9 %). A PICC placement was achieved in all patients at the first puncture. No accidental puncture of the brachial artery occurred. More than one PICC insertion was carried out in 96 patients.

The median duration of in situ PICC placement was 101 days [interquartile range (IR) 48–184, with a total number of 79,040 in situ days]. The reasons for PICC removal was a mechanical complication or malfunction in 107 (17.5 %) cases, a CRBSI in 47 (7.7 %) cases, the completion of treatment in 331 (54 %) cases, while it remained inserted until death in the remaining 127 cases (20.8 %).

Overall, a CRBSI occurred in 47 of 612 cases (7.7 %) prior to having any competing risk, with a rate of 0.59 per 1000 PICC days. The median interval between PICC insertion and the onset of an infective complication was 33 days (range 4–299; IR 14–83). The cumulative incidence of a CRBSI was 6.0, 8.4, and 9.4 % at 100, 200, and 300 days from catheter insertion, respectively. After day +300 from PICC insertion, no new infective episode was recorded. One competitive risk was present in 232 cases (37.9 %). When infection was documented, the absolute number of absolute neuthophil count

(ANC) was $<0.5\times10^9$/l in 18 cases (38 %), it was between 0.5 and 1.0×10^9/l in 7 cases (15 %), while in the remaining 22 cases (47 %), it was $>1.0\times10^9$/l. The number of patients who developed a CRBSI and the incidence according to the different diseases are described in Table 2.

The different pathogens associated to CRBSI are reported in Table 3. In patients who died with an in situ PICC, the CRBSI never represented the primary cause of death.

A CRTC was recorded in 16 cases (2.6 %) prior to having a competitive risk, with a rate of 0.20 per 1000 PICC days. The median interval between PICC insertion and thrombotic episode was 17 days (range 3–96; IR 6–41). The cumulative incidence of CRTCs was 1.7, 2.5, and 3.1 % at 20, 50, and 100 days from catheter insertion, respectively. After day +96 from the PICC insertion, no new thrombotic episode was recorded. One competitive risk was present in 276 cases (45.1 %). When the thrombosis occurred, PLTS were $<50\times10^9$/l in six cases (37.5 %). The number of patients who developed a CRTC and the incidence according to the different diseases are described in Table 4.

None of the catheters was removed early due to thrombotic episodes. After the thrombotic episode, all patients were treated with low-molecular-weight heparin (LMWH) while the catheter remained in place; in case of PLTs $<50\times10^9$/l low dose LMWH were used. No fatal event related to the CRTC was observed.

Cox regression analyses of variables associated to CRBSIs and to CRTCs are shown in Table 5. Only the type of disease (acute leukemia compared to other diseases) resulted significantly associated to a higher incidence of CRBSIs at multivariate analysis, while no feature was predictive for a higher risk of CRTCs.

Discussion

The use of CVADs in onco-hematologic patients has improved clinical management, allowing an easier administration of chemotherapy and of a series of supportive care treatments. However, the use CVADs continues to be associated to early (hemo/pneumothorax, hemorrhages, arterial punctures, malpositions) and delayed (CRBSI, CRTC, occlusions) complications. PICC lines provide a reliable central venous access for different categories of patients, in particular due to the easiness of the insertion technique with a possible bedside placement and a low risk of complications. In the last years, due to the security of the PICC's profile, the number of devices inserted has significantly increased in hematologic patients, a population who very often presents neutropenia and thrombocytopenia with a consequent exposure to severe and frequent infective and hemorrhagic risks [6, 7]. Maki et al. [8] reviewed the risk of CVAD-related infections in 200 prospective studies in several categories of patients. This review reported that the incidence of CRBSIs in patients carrying PICC lines was 2.1 per 1000 PICC days [8]. More recently, other studies have reported an incidence of CRBSIs between 1.5 and 6.6 per 1000 PICC days [2, 9].

Few studies focusing on the use of PICCs in hematologic patients have been reported in the literature (Table 6) [4, 6, 10–12]. These studies showed a variable and broad rate of CRBSIs, probably related to the technique of PICC insertion used (blind vs eco-guided), to the different criteria for the definition and detection of these complications, to the collection of data which was generally retrospective and to the

Table 3 Microbial isolates of catheter-related bloodstream infections

Pathogens	Number (% of CRBSIs)
Coagulase-negative staphylococci	13 (27.6)
Staphylococcus aureus	6 (12.8)
Enterococcus faecalis	8 (17.0)
Escherichia coli	8 (17.0)
Klebsiella pneumoniae	1 (2.1)
Enterobacter species	2 (4.3)
Pseudomonas aeruginosa	2 (4.3)
Stenotrophomonas maltophylia	3 (6.4)
Alcaligenes faecalis	1 (2.1)
Achromobacter xylosoxidans	1 (2.1)
Candida albicans	2 (4.3)

Table 2 Number and rate of catheter-related bloodstream infections (CRBSI) in different diseases

Underlying disease	No. of events/no. of patients (%)	Cases×1000 gg PICC
Hodgkin's lymphoma	5/94 (5.3)	0.41
Non-Hodgkin's lymphoma	12/157 (7.6)	0.44
Acute myeloid leukemia	17/104 (16.3)	1.07
Acute lymphoid leukemia	8/34 (23.5)	1.40
Multiple myeloma	2/30 (6.6)	0.41
Severe aplastic anemia	2/13 (15.3)	0.32
Myelodisplastic syndrome	1/39 (2.5)	0.15

Table 4 Number and rate of catheter-related thrombotic complications (CRTC) in different diseases

Underlying disease	No. of events/no. of patients (%)	Cases×1000 gg PICC
Hodgkin's lymphoma	6/94 (6.3)	0.50
Non-Hodgkin's lymphoma	4/157 (2.5)	0.15
Acute myeloid leukemia	3/104 (2.8)	0.38
Acute lymphoid leukemia	2/34 (8.8)	0.35
Multiple myeloma	1/30 (3.3)	0.20
Severe aplastic anemia	0/13	0
Myelodisplastic syndrome	0/39	0

Table 5 Cox regression analysis of variables associated to catheter-related bloodstream infections (CRBSI) and catheter-related thrombotic complications (CRTC)

Variables	CRBSI				CRTC	
	Univariate		Multivariate		Univariate	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*	HR (95 % CI)	*P*
Male vs female	1.05 (0.59–1.86)	0.87			1.12 (0.42–2.98)	0.82
Age, ≤60 years vs >60 years	1.19 (0.65–2.17)	0.58			1.08 (0.58–5.61)	0.30
Underlying disease, no acute leukemia vs acute leukemia	0.33 (0.19–0.59)	<0.0001	0.33 (0.19–0.59)	<0.0001	0.87 (0.30–2.51)	0.80
Disease risk, standard vs high	0.61 (0.34–1.08)	0.09			0.54 (0.20–1.43)	0.21
Site of PICC insertion , basilic vein vs brachial vein	0.74 (0.38–1.43)	0.37			4.1 (0.55–31.4)	0.17
Type of PICC tip, closed vs open	0.71 (0.53–1.71)	0.37			0.43 (0.14–1.34)	0.15
No. of neutrophils at the time of PICC insertion, ≤500/cmm vs >500/cmm	0.48 (0.22–1.03)	0.06			0.75 (0.17–3.32)	0.71
No. of platelets at the time of PICC insertion, ≤20.000 vs >20.000	1.51 (0.71–3.24)	0.29			0.4 (.0001–27.89)	0.34

Table 6 Catheter-related bloodstream infections (CRBSI) and catheter-related thrombotic complications (CRTC) in PICC studies in hematologic patients

Author, year of publication (reference)	Type of study	No. of PICCs	Technique	Duration	Catheter-related bloodstream infections	Catheter-related thrombotic complications
Strahilevitz, 2001 [10]	Retrospective	52	Blind	Range 3–441 days Median 63 days	38.4 %, 0.47×1000 PICC days	3.8 %, 0.05 per 1000 PICC days
Worth, 2009 [4]	Prospective	75	Blind	Range 1–114 days Median 22.6 days	6.6×1000 PICC days	18.7 %, 7.7 per 1000 PICC days
Kabsy, 2010 [11]	Prospective	52	Eco-guided	Range 2–291 days Median 26 days	1.9 %	1.9 %
Mollee, 2011 [12]	Prospective	332	Eco-guided	Range 1–936 days Median 29 days	3.7×1000 PICC days	Not reported
Bellesi, 2013 [6]	Prospective	60	Eco-guided	Range 6–124 days Median 19 days	3.3 %, 1.5×1000 PICC days	5 %, 2.3 per 1000 PICC days

limited number of cases. The largest experience in cancer patients was reported by Mollet et al. [12]. In this study, the incidence of CRBSI was 3.7 per 1000 PICC days (the CRTC were not considered) in the 332 PICCs inserted into patients with hematologic malignancies. The rate of CRBSIs in hematologic patients was significantly higher (more than double) compared to other cancer patients. However, the use of a PICC in hematologic patients was associated to a lower CRBSI rate compared to other CVADs (7.3 and 17.3 per 1000 catheter days in tunneled and non-tunneled CVADs, respectively).

In our experience, the rate of CRBSIs was very low (0.59 CRBSIs per 1000 PICC days) compared to what reported in the literature. The rate of infections in patients with indwelling PICC was lower than that previously observed by our group in patients with other CVADs (Groshong tunneled catheters Fr 7) where the incidence of CRBSIs was 1.3 per 1000 catheter days [13]. The management of the catheters during the whole insertion period by a dedicated CVADs team probably explains this favorable epidemiologic finding. Infections in patients with a PICCs indwelling were distributed along a prolonged period, but half of the cases occurred within the first month after the insertion. In the Cox regression analysis, only an underlying acute leukemia represented a variable associated to an increased risk for CRBSIs. The high infectious risk associated to a compromised host immune status, intensive chemotherapy treatments and frequent use of the venous access for the administration of intensive support measures justify the high rate of CRBSIs observed in acute leukemia patients.

With regard to CRTCs, in the past years, different reviews have reported a variable but relatively high incidence of such complications (4–36 %) in patients with a PICCs indwelling [11, 13–16]. In the last 10 years, after the introduction of ultrasonographic techniques to monitor PICCs' insertion, the rate of thrombosis has decreased significantly and has been reported to occur in about 2–5 % of patients [6, 17, 18]. A systematic review and meta-analysis of the literature aimed at comparing the frequency of venous thromboembolisms in PICCs and other CVADs has recently been published [18]. This study concluded that PICCs are associated with an increased risk of deep vein thrombosis when compared to tunnelized CVADs, but not of pulmonary embolism [18]. There was a high variation of reported CRTCs rates in hematologic populations (Table 6). However, it was only investigated in small materials and with different detection criteria. In line with previous observations, we reported a rate of CRTCs of 2.6 % (0.2 per 1000 PICC days). The vast majority of episodes was recorded early within the first weeks after the catheter insertion and no case was documented after day 100. Furthermore, the type of PICC did not impact on the risk of CRCTs. It is worth noting that the vast majority of data in the literature derives from oncologic patients and that the setting of hematologic diseases may be characterized by a different risk of thrombotic complications. In particular, thrombocytopenia, which occurs frequently in hematologic patients, has been considered a protective factor for thrombotic complications. However, in our experience, thrombocytopenia was present only in six patients who developed thrombosis, indicating that a low PLT count is not sufficiently protective in the presence of a catheter, which represents per se a major local thrombotic risk factor. The time distribution of thrombotic events and the lack of clear predisposing factors seem to suggest that local factors of the catheterized vein, more than the underlying disease or other conditions, are determinant for the risk of CRTCs in patients with hematologic diseases carrying a PICCs indwelling.

The favorably low rate of infectious and thrombotic complications associated to the use of PICCs in our study may be justified by the expertise in the management of CVADs at our institution. The presence of a CVADs team with dedicated doctors and nurses which follow standardized procedures for the overall management of PICCs, from the insertion to weekly monitoring and follow-up, could have contributed to this finding [19, 20]. In conclusion, PICCs are a safe and feasible alternative option to other CVADs in the clinical management of patients with hematologic malignancies undergoing intensive and prolonged treatments. These devices are easy to place and manage, and the related complications have a limited incidence and severity. Even in the absence of an adequate comparison with other venous accesses, our favorable experience with PICCs prompted us to extend the use of this CVAD to other clinical settings, including allogeneic stem cell transplant. A continuous prospective collection of data is ongoing at our center in order to confirm these very encouraging results.

Conflict of interest There is no conflict of interest to report for any author of the manuscript entitled "Catheter-Associated Bloodstream Infections and Thrombosis Risk in Hematologic Patients with Peripherally Inserted Central Catheters (PICC)" submitted for publication in the Journal of Supportive Care in Cancer.

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