Original Study

A Frontline Approach With Peripherally Inserted Versus Centrally Inserted Central Venous Catheters for Remission Induction Chemotherapy Phase of Acute Myeloid Leukemia: A Randomized Comparison

Marco Picardi,[1] Roberta Della Pepa,[2] Claudio Cerchione,[2] Novella Pugliese,[2] Chiara Mortaruolo,[2] Fabio Trastulli,[2] Claudia Giordano,[2] Francesco Grimaldi,[2] Irene Zacheo,[2] Marta Raimondo,[2] Federico Chiurazzi,[2] Fabrizio Pane[2]

Abstract

Placement of a central venous catheter (CVC) is fundamental for the administration of chemotherapeutic agents and supportive therapy for patients with acute myeloid leukemia (AML). We performed a single-center, randomized trial comparing peripherally inserted central catheter (PICC)-related and centrally inserted central catheter (CICC)-related complications. Among 93 randomized patients, PICC was safer than CICC, with a 36-percentage point reduction in the complication rate, while maintaining effectiveness. We propose PICC as a new frontline central vascular access option for patients with AML.

Background: The incidence of peripherally inserted central catheter (PICC)-related adverse events has been uncertain in the setting of acute myeloid leukemia (AML) compared with the incidence of centrally inserted central catheter (CICC) adverse events. **Patients and Methods:** We conducted a monocentric, randomized trial of patients with previously untreated AML. Of the 93 patients, 46 had received a PICC and 47 had received a CICC as frontline intravascular device. Thereafter, all patients underwent intensive chemotherapy for hematologic remission induction. The primary endpoint was catheter-related (CR)-bloodstream infection (BSI) and venous thrombosis (VT) rate. The secondary endpoints catheter malfunction, catheter removal, and patient overall survival. **Results:** The CR-BSI and CR-VT rate in the PICC and CICC groups was 13% and 49%, respectively, with a difference of 36 percentage points (relative risk for CR-BSI or CR-VT, 0.266; $P = .0003$). The CR-BSI incidence was 1.4 and 7.8 per 1000 catheters daily in the PICC and CICC groups, respectively. Among the CR thromboses, the symptomatic VT rate was 2.1% in the PICC group and 10.6% in the CICC group. In the CICC group, 16 of the 47 patients (34%) had the catheter removed for BSI (n = 5), septic thrombophlebitis (n = 4), VT (n = 2), or malfunction (n = 5) a median of 7 days after insertion. In the PICC group, only 6 of the 46 patients (13%) required catheter removal for VT (n = 2) or malfunction (n = 4). At a median follow-up of 30 days, 6 patients in the CICC group died of CR complications versus none of the patients in the PICC group ($P = .012$). Using PICCs, the reduction in BSI and symptomatic VT decreased mortality from CR infection and venous thromboembolism. In contrast, the CICC approach led to early catheter removal mostly for difficult-to-treat infectious pathogens. **Conclusion:** Our data have confirmed that BSI and symptomatic VT are the major complications affecting frontline central intravascular device-related morbidity in the leukemia setting. The use of a PICC is safer than that of a CICC and maintains the effectiveness for patients with

[1]Department of Advanced Biomedical Sciences
[2]Department of Clinical Medicine and Surgery, Federico II University Medical School, Naples, Italy

Submitted: Oct 30, 2018; Revised: Dec 9, 2018; Accepted: Dec 12, 2018

Address for correspondence: Novella Pugliese, MD, PhD student, Department of Clinical Medicine and Surgery, Federico II University Medical School, Via S. Pansini 5, Naples 80131, Italy
E-mail contact: novypugliese@yahoo.it

2152-2650/$ - see frontmatter
https://doi.org/10.1016/j.clml.2018.12.008

AML undergoing chemotherapy, with an approximate fourfold lower combined risk of infection or thrombosis at 30 days.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■
Keywords: Acute myeloid leukemia, Central venous catheter, CICC, Induction chemotherapy, PICC

Introduction

The outcome for patients with acute myeloid leukemia (AML) has improved greatly during the past 50 years.[1] Despite regional differences, the most commonly used induction regimen has included cytarabine at a daily dose of 100 to 6000 mg/m^2 for 4 to 10 days combined with 3 days of an anthracycline, such as doxorubicin.[1-4] These schedules result in complete remission rates of 60% to 80%, depending on patient age and the cytogenetic and molecular features of the acute leukemia. However, ≤ 60% of patients receiving cytarabine-based treatments will experience grade 3 and 4 hematologic and extrahematologic toxicities, requiring maximal supportive care.[1-4]

Reliable intravascular access is extremely important for the treatment of hematologic malignancies in critically ill patients. An appropriate central venous catheter (CVC) will not only facilitate administration of chemotherapeutic agents but will also provide a route for hydration, blood derivate transfusions, antimicrobial administration, and parenteral hyperalimentation.[5,6] Previously, a centrally inserted central catheter (CICC), implanted in the cervical−thoracic area using a nontunneled or skin-tunneled device for a short (≤30 days) or an intermediate term, respectively, was the conventional venous access used for patients with cancer. Problems have occurred after CICC insertion, especially in the case of acute leukemia. Thromboses and infections are important complications.[7,8] A 10% to 15% incidence of CICC-associated clinically manifest venous thrombosis (VT) and a 30% to 70% incidence of CICC-associated subclinical VT have been reported among patients with AML.[7] The pathogenesis of catheter infection can be secondary to extraluminal or intraluminal contamination.[5-8] The incidence of CICC-associated blood stream infection (BSI) has ranged from 15% to 30% in the setting of patients with acute leukemia with chemotherapy-induced severe neutropenia.[8] The infection of the intravascular device has been most frequently caused by staphylococci,[6,8] which can develop resistance to systemic antibiotics (so-called multidrug-resistance strains) and become difficult to eradicate. In such cases, the risk of septic thrombophlebitis, massive septic pulmonary emboli, and/or septic shock will be increased.[5,6,8]

Peripherally inserted central catheters (PICCs) have increasingly been used for short-term to intermediate-term (<4 months) venous access during the past few years for patients with cancer. This has occurred for several reasons, including the number of uses (eg, drug administration, transfusions, total parenteral nutrition, venous sampling) and the proliferation of nurse led-dedicated teams.[9] The results from systematic reviews and/or meta-analyses have suggested that PICCs might be associated with a greater rate of major adverse events (ie, upper extremity VT and/or BSI) compared with CICCs, especially in the case of acute leukemia.[9-11] Theoretically, these findings were surprising because the use of PICCs might be safer than that of CICCs. First, the insertion of PICCs uses an easier method, with a minor trauma at the implantation site compared with the CICCs.[12,13] Second, the cutaneous area of the middle third of the upper arm (where the PICC is implanted) contains quantitatively fewer microorganisms than the cervical−thoracic cutaneous area (where the CICC is implanted).[12,14,15] Therefore, the burden and risk of complications related to PICCs are uncertain for patients undergoing chemotherapy for acute leukemia and require further investigation. Only a randomized controlled trial of the clinical application, safety, and benefit of using PICCs could resolve this important concern. Thus, in the present open-label, randomized, monocentric, phase IV study, we compared 2 different frontline approaches for CVCs (ie, CICC vs. PICC) in patients with AML receiving intensive chemotherapy for hematologic remission induction.[1-4]

Patients and Methods

Trial Design

The patients were randomized 1:1 to receive a CICC (external, nontunneled heparin-coated Vialon CVC; Becton-Dickinson, Franklin Lakes, NJ) or PICC (open-ended, nonvalved pressure injectable polyurethane PICC with a flexible tip; EU-25541-HP Arrow; Teleflex Medical, Westmeath, Ireland).

The random allocation sequence was performed using a computerized system generated by the statistician's study using the procedure outlined in Supplemental Material 1 (available in the online version).[16] All patients were hospitalized in the Hematology Unit of Federico II University (Naples, Italy). All CVCs were implanted before chemotherapy began.

Implantation Procedures

External nontunneled CVCs (CICCs) were inserted by 3 of us (intensive care medicine: N.P., M.R., F.C.), using the Seldinger technique into the internal jugular or subclavian vein, according to the clinical guidelines on central venous catheterization used in our institution.[17,18] These 3 physicians had had specific training in central venous catheterization. All CICCs had been consistently implanted using a strict antiseptic regimen with maximal barrier precautions. Ultrasound (US) scanning was always used before implantation to assess the anatomy of the target vein and adjacent anatomic structures. When possible, US guidance was used. A chest radiograph and echocardiography were routinely performed after CICC application to confirm the tip location.

All PICCs were inserted by medical hematology staff who had been specifically trained in vascular access (M.P., R.D.P., F.T., C.M., C.G., I.Z.), with strict adoption of the GAVeCeLT (Gli Accessi Venosi Centrali a Lungo Termine [Long-Term Central Venous Access]) protocol for the safe insertion of PICCs (so-called SIP protocol).[12]

All CVCs were secured with a sutureless device (Grip-Lok CVC 3601 Securement Device; TIDI Products, Neenah, WI). The nurses strictly used the CVC policies in our hospital for dressing changes, changes of the needle-free connector, flushing the lumen with a 0.9% sterile NaCl solution, and locking the lumen.

Antimicrobial prophylaxis with levofloxacin and posaconazole was performed before chemotherapy until neutrophil recovery.[8] No patient received prophylaxis with heparin. Patients with platelet counts < 10,000/μL received concentrated platelet infusions before catheter insertion.

Oversight

The present study was designed and planned in accordance with the Declaration of Helsinki, October 2008 (59th World Medical Association General Assembly, Seoul, Korea). All competent ethics committees provided ethical approval, and all the patients provided written informed consent. The present study was registered in the ClinicalTrials.gov database (ClinicalTrials.gov identifier, NCT02405728).

Patients

The included patients were aged ≥18 years and had newly diagnosed AML according to the World Health Organization classification system.[19] Patients who had not previously received systemic chemotherapy and/or radiotherapy were eligible. The patients were required to have the following clinical indications: receipt of a cytotoxic agent regimen with an expected duration of chemotherapy-induced aplasia of ≥ 7 days (for hematologic remission induction)[1-4] and an implanted CVC with an expected use of ≥ 30 days.[5,6] Patients with a suspected or confirmed bacterial/fungal infection or thrombosis affecting the veins in the arms, neck, or mediastinum were ineligible. In addition, patients with acute promyelocytic leukemia, a diagnosis of other forms of cancer within 12 months before AML onset, or any evidence of clinical conditions indicating an inability to receive intent-to-cure chemotherapy, and those who did not provide written informed consent were excluded from the present study.

Endpoints

The main endpoint was the cumulative incidence of catheter-related (CR)-BSI and CR-VT, occurring from catheter insertion until 30 days later. This composite endpoint was chosen specifically to evaluate the safety of the primary implanted CVC and encompassed 2 possible outcomes. Each represented an early problem in the induction chemotherapy phase to cure AML.[7,8]

The diagnosis of CR-BSI required either a differential time to positivity of > 2 hours in a pair of central and peripheral blood cultures (ie, the growth of microbes from a blood sample taken from a central catheter hub ≥ 2 hours before microbial growth was detected in a blood sample obtained from a peripheral vein) or the detection of the same pathogen in a blood culture and at the catheter tip. Either of these methods could be used as the diagnostic criterion for the diagnosis of CR-BSI (Supplemental Material 2; available in the online version).[14]

The diagnosis of CR-VT used objective criteria from US scans (noncompressibility, absence of respiratory variation, and/or visualization of a clear pericatheter thrombus [ie, a ≥ 0.5-cm echogenic intravascular mass extending from the CVC to the vessel wall]) and clinical signs and symptoms (symptomatic thrombotic complication).[7,8] Alternatively, CR-VT was detected only by systematic screening with ultrasonography (using the objective US diagnostic criteria listed) in the absence of clinical signs and symptoms (asymptomatic thrombotic complication). Only cases of mural thrombus on the vessel wall adjacent to the CVC that had partially or completely occluded the vein in which the catheter resided were included in the present study. The fibroblastic sleeve was specifically excluded.[20] Additional data for the definition of CR-VT are provided in Supplemental Material 3 (available in the online version). We have provided the rates of symptomatic thrombotic events separately. Only these latter events and the CR-BSIs were considered clinically relevant CR major complications.[18]

The secondary endpoints were complications associated with catheter positioning (serious bleeding, arterial puncture, and/or pneumothorax), catheter malfunction (dislocation, occlusion, and/or rupture), catheter removal, and overall mortality (Supplemental Material 4; available in the online version).

Assessments

The patients were monitored for CR complications using the same diagnostic evaluations for both groups. For BSI events, in the case of neutropenic fever, 3 blood cultures obtained from both the peripheral vein and the CVC were evaluated, along with conventional clinical and laboratory assessments (Supplemental Material 5; available in the online version).[21] For thrombotic events, the veins of the arm and cervical−thoracic areas were clinically assessed daily by expert physicians (F.G., F.P.). In addition, the veins in the ipsilateral side of catheter insertion routinely underwent US scanning by 2 members of the catheter implantation staff (M.P. and N.P., with > 10 years' experience with color Doppler US) to rule out subclinical VT, as previously reported (Supplemental Material 6; available in the online version).[8]

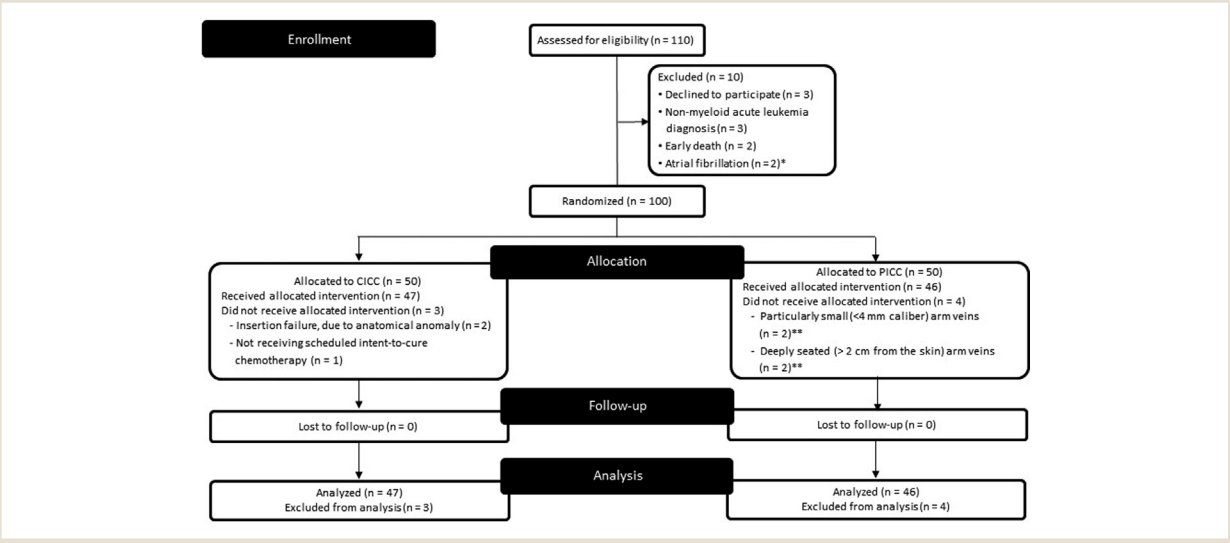
Treatment of CR-BSI and CR-VT

Cases of CR-BSI and/or CR-VT were managed in both groups in accordance with international clinical guidelines.[5,6,14] Antimicrobial therapy and/or antithrombotic-specific therapy were given as previously reported.[7,8] In the case of staphylococcus coagulase-negative infection, we attempted to salvage the catheter with systemic antibiotic therapy. For all other pathogens associated with CR-BSI, the device was promptly removed on microbiologic detection. Low-molecular-weight heparin was introduced only for patients with a platelet count of ≥ 20,000/μL.

Statistical Analysis

A power analysis was performed, with the assumption that BSI and VT associated with CICCs would be detected in ∼50% of patients with acute leukemia.[7,8] In the case of PICC, the assumption was that such complications would occur in ∼15% of patients with acute leukemia.[22] Superiority was predefined as a difference in the 30-day CR-BSI and CR-VT rate between the CICC and PICC groups of ≥ 35 percentage points. Thus, a minimum sample of 44 patients in each group would be required to demonstrate superiority at a 2-sided significance level of 5% with 90% statistical power (α error of 0.05 and β error of 0.9), corresponding to a relative risk

Figure 1 Flowchart Showing Patient Inclusion and Exclusion. *Atrial Fibrillation did not Allow Use Intracavitary Electrocardiographic Guidance for Accurate Positioning of the Peripherally Inserted Central Catheter (PICC) tip; **Both Conditions, Detected by Ultrasound Scans, Were Considered Contraindications to Implantation of ≥4 Fr PICC



Abbreviation: CICC = centrally inserted central catheter.

(RR) of 0.3. Because we assumed that 10% of patients would not be included in the efficacy analysis, we set an enrollment goal of ≥ 50 patients in each group (for 100 patients).

Continuous variables were compared using the Student *t* test for normally distributed variables or the Mann-Whitney *U* test for non-normally distributed variables. Categorical variables were evaluated using the χ^2 or 2-tailed Fisher exact test. The RR and 95% confidence intervals (CIs) were calculated. The results are presented as the median and range for the continuous variables or as percentages of the group from which they were derived for the categorical variables. Two-tailed *t* tests were used to determine statistical significance and $P < .05$ was considered statistically significant. The SPSS Statistics, version 22, program (IBM Corp., Armonk, NY) was used.

Results

Patients

From April 1, 2015 through October 31, 2017, 100 adult patients with untreated AML who had been referred to the hematology department (Federico II University, Naples, Italy) were randomly assigned to receive a CICC (standard group, n = 50) or a PICC (PICC group; n = 50). All randomized patients received the allocated intervention, with the exception of 4 patients in the PICC group and 3 patients in the CICC group (standard group). No other patient was lost to follow-up, nor did any patient withdraw consent to participate in the present study during the follow-up period. Thus, the data from 93 patients (CICC group, n = 47; PICC group, n = 46) were analyzed for the primary endpoint. Ten patients (9%) did not meet the screening criteria. A flowchart of the present study is shown in Figure 1. The baseline characteristics of the analyzed patients were well balanced between the 2 groups (Table 1).

CVC Positioning and Use

The characteristics and use of the catheters in both groups are summarized in Table 2. In the CICC (standard) group, central intravascular access was obtained through the subclavian vein in ~75% of patients. The most frequent catheter implanted was a 7Fr device with a triple lumen. In the PICC group, central intravascular access was obtained through the basilic vein in 89% of cases and the most frequent catheter implanted was a 5 Fr device with a double lumen. The first insertion attempt success rates were similar in both groups, showing the same expertise for both teams in CVC implantation. The catheter tips were positioned between the lower third of the superior vena cava and cava–atrial junction in 100% of patients.

Chemotherapy infusions were administered through the CVC in all the patients. No significant differences were observed between the 2 groups with regard to the cytarabine-containing induction chemotherapeutic regimens. The median percentage of the received dose intensity of the cytotoxic agents was 93% in the CICC group and 94% in the PICC group. The durations of chemotherapy-induced severe neutropenia (median, 15 days for the CICC group; median, 16 days for the PICC group) and thrombocytopenia (median, 10 days for the CICC group; median, 10 days for the PICC group) were similar between the 2 groups.

Safety

After a median follow-up period of 30 days (range, 7-30 days), CR-BSI and CR-VT complications, the primary endpoint, had developed in 13% of patients in the PICC group and 49% of those in the CICC group (6 of 46 vs. 23 of 47; RR, 0.266; 95% CI, 0.119-0.594; absolute difference in risk, 0.359, 95% CI, 0.170-0.547; $P = .0003$).

CR-BSI occurred in 2 patients in the PICC group and 11 in the CICC group (4.3% vs. 23.4%; $P = .014$). The incidence rate was

Table 1 Baseline Characteristics of Analyzed Patients

Characteristic	All Patients	CICC Group	PICC Group	*P* Value
Total patients	93	47	46	
Sex				.46
Male	47 (50.5)	22 (46.8)	25 (54.3)	
Female	46 (49.5)	25 (53.2)	21 (45.7)	
Age, years				.64
Median	53.8	53	54.5	
Range	18-80	18-74	24-80	
Prothrombotic risk factors				
BMI $\geq$ 25 kg/m^2	12 (12.9)	7 (14.8)	5 (10.8)	.20
Smoker	27 (29)	15 (31.9)	12 (26)	.14
Hypertension	39 (41.9)	19 (40.4)	20 (43.4)	.15
Diabetes	12 (12.9)	7 (14.8)	5 (10.8)	.56
AML subtype[a]				
AML with maturation	53 (56.9)	25 (53.2)	28 (60.8)	.45
AML without maturation	16 (17.2)	10 (21.2)	6 (13)	.29
AML with minimal differentiation	9 (9.6)	5 (10.6)	4 (8.7)	.75
Acute myelomonocytic leukemia	6 (6.4)	3 (6.3)	3 (6.5)	.98
Acute monoblastic/monocytic leukemia	5 (5.3)	2 (4.1)	3 (6.5)	.63
Pure erythroid leukemia	2 (2.3)	1 (2.3)	1 (2.25)	.98
Acute megakaryoblastic leukemia	2 (2.3)	1 (2.3)	1 (2.25)	.98
Blood cell count				
White blood cells, $\times 10^3$/mm^3				.18
Median	3.4	3.2	3.9	
Range	0.97-147	0.97-96	1.0-147	
Hemoglobin, g/dL				
Median	9.5	9.7	9.5	
Range	5.9-12.6	5.9-12.1	6.6-12.6	
Platelets, $\times 10^3$/mm^3				
Median	41	36	42.5	
Range	3.0-275	3.0-275	9.0-232	

Data presented as n (%) or median and range.
Abbreviations: AML = acute myeloid leukemia; BMI = body mass index; CICC = centrally inserted central catheter; PICC = peripherally inserted central catheter.
[a]According to the 2016 World Health Organization classification of myeloid neoplasms and acute leukemia.[14]

1.4 and 7.8/1000 catheters/d in the PICC and CICC groups, respectively. The median interval between catheter insertion and BSI episodes was 15 days (range, 8-23 days) for the PICC group and 7 days (range, 7-22 days) for the CICC group. The distribution of causative pathogens is presented in Table 3. Coagulase-negative staphylococci were the most frequently isolated pathogens.

CR-VT occurred in 4 patients in the PICC group and 12 patients in the CICC group (8.7% vs. 25%; $P = .03$). The incidence rate was 2.9 and 8.5/1000 catheters/d in the PICC and CICC groups, respectively. The median interval between catheter insertion and thrombotic episodes was 10 days (range, 7-10 days) for the PICC group and 7 days (range, 7-15 days) for the CICC group. Overall, 10 of 16 patients (60%) experienced CR asymptomatic thrombotic events detected only by systematic US scans. The remaining patients experienced CR symptomatic thrombotic complications (Table 3). Thus, the rate of symptomatic VT was 2.1% in the PICC group and 10.6% in the CICC group.

During follow-up of the 13 patients with CR-BSI, 4 of the 11 patients (36%) in the CICC group developed septic thrombophlebitis, ipsilateral to the catheter insertion site. The septic thrombophlebitis was characterized by VT (confirmed by US scanning) with clinical features of inflammation (ie, pain, induration, erythema, exudates, and/or asymmetric venous distension). For these 4 patients, the organisms responsible for infection were multidrug-resistance strains and included *Escherichia coli*-producing extended-spectrum β-lactamases (n = 2), *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (n = 1), and azole-resistant *Candida parapsilosis* (n = 1). In contrast, neither of the 2 patients with CR-BSI in the PICC group developed septic thrombophlebitis.

Secondary Endpoints

Early mechanical complications associated with catheter positioning occurred in 13 patients (27.6%) in the CICC group (serious

Table 2 Characteristics of Implanted Central Venous Catheters and Their Use

Characteristic	All Patients	CICC Group	PICC Group
Total patients	93 (100)	47 (100)	46 (100)
Device insertion site			
Basilic vein	41 (44)	NA	41 (89.1)
Brachial vein	5 (5.4)	NA	5 (10.9)
Subclavian vein	35 (37.6)	35 (74.5)	NA
Internal jugular vein	12 (12.9)	12 (25.5)	NA
Right side	70 (75.3)	37 (78.7)	33 (71.7)
Left side	23 (24.7)	10 (21.3)	13 (28.3)
Device type			
Untunneled	93 (100)	47 (100)	46 (100)
4 Fr	14 (15)	NA	14 (30.4)
5 Fr	29 (31.2)	NA	29 (63)
6 Fr	3 (3.2)	NA	3 (6.6)
7 Fr	35 (37.7)	35 (74.4)	NA
8 Fr	12 (12.9)	12 (25.6)	NA
Single lumen	14 (15)	-	14 (30.4)
Double lumen	49 (52.6)	20 (42.5)	29 (63)
Triple lumen	30 (32.4)	27 (57.5)	3 (6.6)
Attempts at venipuncture, n			
Median	1	1	1
Range	1-3	1-3	1-2
Tip location[a]			
Lower third of superior vena cava	23 (24.7)	13 (27.7)	10 (21.7)
Cavo—atrial junction	70 (75.3)	34 (72.3)	36 (78.3)
Reason for CVC			
Sampling	83 (89.2)	42 (89.4)	41 (89.1)
Transfusion	75 (80.6)	35 (74.5)	40 (87.0)
Total parenteral nutrition	40 (43.0)	20 (42.6)	20 (43.5)
Antimicrobial agent	81 (87.1)	41 (87.2)	40 (87.0)
Chemotherapy	93 (100)	47 (100)	46 (100)
Induction course of EORTC-GIMEMA AML-10 regimen[b]	41(44.1)	21 (44.6)	20 (43.4)
Induction course of HOVON-SAKK regimen[c]	18 (19.4)	10 (21.3)	8 (17.4)
Induction course of FLAG-Ida regimen[d]	24 (25.8)	11 (23.4)	13 (28.3)
Induction course of GIMEMA AML-12 regimen[e]	10 (10.7)	5 (10.7)	5 (10.9)
Interval from CVC implantation to chemotherapy start, d			
Median	1.5	1	1
Range	1-3	1-3	1-3
Chemotherapy-induced side effect			
Severe neutropenia[f]	93 (100)	47 (100)	46 (100)
Severe thrombocytopenia[g]	93 (100)	47 (100)	46 (100)

Data presented as n (%) or median and range.

Abbreviations: AML = acute myeloid leukemia; CICC = centrally inserted central catheter; CVC = central venous catheter; EORTC = European Organization for Research and Treatment of Cancer; FLAG = fludarabine, cytarabine, granulocyte colony-stimulating factor; GIMEMA = Gruppo Italiano Malattie Ematologiche dell' Adulto; HOVON = Hemato-Oncologie voor Valwassenen Nederland; Ida = idarubicin; NA = not applicable; PICC = peripherally inserted central catheter; SAKK = Swiss Group Clinical Cancer Research.

[a]Tip location was assessed by postprocedural chest radiograph and echocardiography in the CICC group and intraprocedural electrocardiography in the PICC group; the correct tip location was between the lower third of the superior vena cava and the cavo—atrial junction.

[b]EORTC-GIMEMA AML-10 protocol: the schedule for the induction course was continuous intravenous infusion of cytarabine 100 mg/m^2 daily for 10 days plus etoposide 100 mg/m^2 daily by 1-hour intravenous infusion on days 1-5 plus daunorubicin 50 mg/m^2 daily as a 5-minute intravenous infusion (31 patients) or idarubicin 10 mg/m^2 as a 5-minute intravenous infusion (5 patients) or mitoxantrone 12 mg/m^2 as a 30-minute intravenous infusion (5 patients) on days 1, 3, and 5.[2]

[c]HOVON-SAKK protocol: the schedule for the induction course was continuous intravenous infusion of cytarabine 200 mg/m^2 daily for 7 days plus idarubicin 12 mg/m^2 daily as a 3-hour intravenous infusion on days 5-7.[1]

[d]FLAG-Ida protocol: the schedule for the induction course was cytarabine 2000 mg/m^2 daily as a 3-hour intravenous infusion for 4 days plus fludarabine 30 mg/m^2 daily as a 30-min intravenous infusion for 4 days plus idarubicin 12 mg/ m^2 daily as a 1-hour intravenous infusion on days 2-4.[3]

[e]EORTC-GIMEMA AML-12 protocol: the schedule for the induction course was cytarabine 3000 mg/m^2 every 12 hours as a 3-hour intravenous infusion on days 1, 3, 5, and 7 plus daunorubicin 50 mg/m^2 daily as a 5-minute intravenous infusion on days 1, 3, and 5 plus etoposide 50 mg/m^2 daily as a 1-hour intravenous infusion on days 1-5.[4]

[f]Defined as neutrophil count $< 500/mm^3$ with a duration of ≥ 7 days.

[g]Defined as platelet count $< 10{,}000/mm^3$ with a duration of ≥ 7 days.

Table 3 Characteristics of Catheter-related Deep VTs and BSIs

Characteristic	CICC Group (n = 47)	PICC Group (n = 46)
Catheter-related deep VTs		
Events, n	12	4
Thrombosis symptoms/clinical signs		
No	7	3
Yes	5	1
Ultrasound examinations[a]		
Baseline	47	46
+3 days	46	46
+7 days	42	46
+15 days	35	44
+23 days	29	40
+30 days	21	36
Thrombolysed catheter size, Fr		
5	0	4
7	7	0
8	5	0
Thrombus site		
Basilic vein	0	3
Brachial vein	0	1
Axillary vein	6	2
Subclavian vein	7	0
Internal jugular vein	7	0
Brachiocephalic vein	6	0
Thrombosis in multiple sites	7	2
Thrombus size, mm		
Median	20	20
Range	5-80	5-50
Platelet count,[b] $\times 10^3/mm^3$		
Median	40	35
Range	5-80	4-90
Prophylactic concentrated platelet infusion		
Yes	15	13
No	32	33
Antithrombotic-specific therapy[c]		
Yes	8	2
No	4	2
Catheter-related BSIs		
Events, n	11	2
Causative pathogens		
Gram-positive	6	2
Staphylococcus haemolyticus	2	2
Staphylococcus epidermidis	2	-
Staphylococcus aureus	1	-
Enterococcus spp.	1	-
MDR gram-positive bacteria[d]	4	1
Gram-negative	4	0
Escherichia coli	3	0
Klebsiella pneumoniae	1	0
MDR gram-negative bacteria[e]	3	0
Candida parapsilosis[f]	1	0
WBC count,[b] $\times 10^3/mm^3$		
Median	0.2	0.1
Range	0.1-1	0.1-1
Antimicrobial prophylaxis		
Levofloxacin (oral 500 mg/d)	47	46
Posaconazole (oral 200 mg 3×/d)	47	46

Data presented as number of patients or median and range.
Abbreviations: BSIs = blood stream infections; CICC = centrally inserted central catheter; MDR = multidrug resistance; PICC = peripherally inserted central catheter; VTs = venous thromboses; WBC = white blood cell.
[a]Patients who had undergone follow-up ultrasound scans at the scheduled time points.
[b]Defined as platelet or WBC count at the thrombotic or infectious event, respectively.
[c]Low-molecular-weight heparin was introduced only for patients with a platelet count $\geq 20 \times 10^3/mm^3$.
[d]Among the 8 patients with gram-positive infection, 5 had MDR bacteria (ie, methicillin-resistant *Staphylococcus* spp. [4 cases in the CICC group and 1 in the PICC group]).
[e]Among the 4 patients with gram-negative infection, 3 had MDR bacteria (ie, *Escherichia coli*-producing extended-spectrum β-lactamases in 2 and *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* in 1, all in the CICC group).
[f]Azole-resistant *Candida parapsilosis*.

bleeding in 7, arterial puncture in 5, and pneumothorax in 1) compared with 2 patients (4%) in the PICC group (serious bleeding in 1 and arterial puncture in 1; $P = .002$).

Catheter malfunction occurred in 5 patients (10%) in the CICC group (dislocation in 2, occlusion in 2, and rupture in 1) compared with 4 patients (8.6%) in the PICC group (occlusion in 2, dislocation in 1, and rupture in 1; $P = .7$).

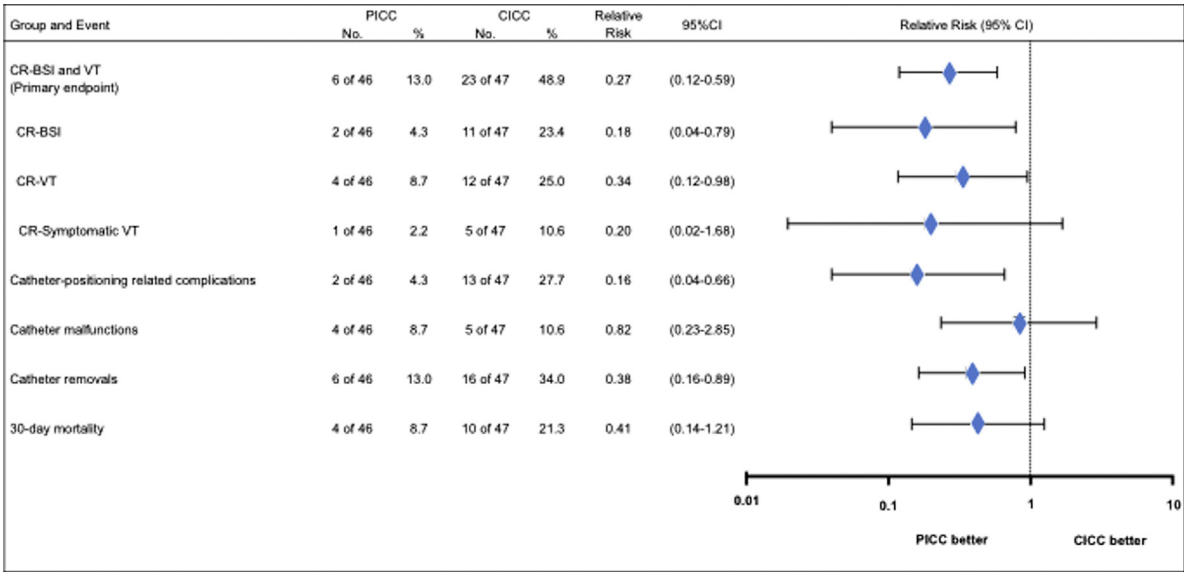
Sixteen patients (34%) in the CICC group required removal of the device (median, 7 days after insertion). Removal was required because of BSI in 5 patients (methicillin-resistant *Staphylococcus haemolyticus* in 2, methicillin-resistant *S. epidermidis* in 1, *S. aureus* in 1, and *E. coli* in 1), septic thrombophlebitis in 4 patients, VT in 2, and malfunction in 5 patients. In contrast, 6 patients (13%) in the PICC group required catheter removal (median, 10 days after insertion). The reason for removal was VT in 2 patients and malfunction in 4 ($P = .017$).

The 30-day overall mortality was 21% (10 of 47 patients) in the CICC group. Death was from venous thromboembolism associated with CICC in 4 patients and leukemia progression in 3, septic shock associated with CICC in 2 patients (*S. aureus* in 1 and methicillin-resistant *S. haemolyticus* in 1), and cerebral hemorrhage in 1 patient. In contrast, the 30-day overall mortality was 8.6% (4 of 46 patients) in the PICC group. Death was from leukemia progression in 2 patients, cerebral hemorrhage in 1 patient, and pulmonary aspergillosis in 1 patient ($P = .09$).

Discussion

The choice of central venous access for frontline therapy in patients with acute leukemia has been controversial.[1-6] The American Society of Clinical Oncology and European Society for Medical Oncology clinical practice guidelines have generally left the decision of which device to use to the discretion of the treating physician.[5,6]

Figure 2 Rates and Relative Risk of Primary and Secondary Endpoints



Abbreviations: BSI = bloodstream infection; CI = confidence interval; CICC = centrally inserted central catheter; CR = catheter-related; PICC = peripherally inserted central catheter; VT = venous thrombosis.

However, often the risk of adverse events related to a CVC has not been considered but should be accurately discussed with the patient.[14] BSI and/or VT associated with intravascular devices are very critical complications that can increase patient morbidity and mortality during the initial phase of antileukemic treatment.[7-11,14]

To the best of our knowledge, the present study is the first comparative controlled randomized trial with an adequate sample size providing clear evidence of the significant benefits of a PICC-driven strategy compared with a CICC-driven strategy in the specific setting of patients with AML undergoing cytarabine-based induction chemotherapy.[1-4] The study objective of showing the superiority of PICC versus CICC in terms of safety was achieved. The rates of infection and thrombotic adverse events with a frontline central venous approach using PICCs were significantly lower (36 percentage points less) than those using CICCs.

First, the CICC group had a 34% risk of CR-BSI and symptomatic CR-VT compared with a 6.5% risk in the PICC group (16 of 47 vs. 3 of 46; RR, 0.197; 95% CI, 0.056-0.614; absolute difference in risk, 0.275; 95% CI, 0.113-0.424; $P = .0015$). Thus, PICC insertion corresponded to an approximately fivefold reduction in risk of CR major complications compared with CICC insertion during the first 30-day catheter in situ follow-up period, confirming the benefits of a PICC-driven strategy. Second, approximately one third of the CICCs required early removal mostly due to difficult-to-treat infections. In contrast, approximately one tenth of the PICCs required removal and none was for device infection. Thus, our PICC-driven strategy allowed an approximately one quarter reduction in premature CVC removal compared with the CICC-driven strategy. Third, the difference in 30-day overall mortality between the 2 groups was not statistically significant. However, when we considered only the deaths from CR complications, the difference became statistically significant. None of the 4 deaths in the PICC group were associated with catheter-related adverse events. In contrast, 6 of the 10 deaths (60%) in the CICC group were associated with catheter-related adverse events. These included venous thromboembolism as a complication of septic thrombophlebitis in 4 patients and septic shock as a complication of BSI in 2 patients. In all these patients, multidrug-resistance pathogens were involved ($P = .012$). Finally, for one half of the secondary endpoints in the present trial, the comparison showed significant disadvantages for CICCs (Figure 2).

In our randomized study, we examined 2 different frontline approaches for central venous access, one using CICCs and one using PICCs, in patients receiving induction chemotherapy for AML.[1-4] We arbitrarily chose a composite primary endpoint of CR-BSI and CR-VT because of the remarkable effect of these events on daily clinical practice for patients with AML.[7-11] The CICC was selected as the standard approach for the present study and was inserted in the hematology unit by a team of intensive care medicine physicians especially trained in strict antiseptic regimens (with maximal barrier precautions), US evaluations, and tip location assessment, as described in the international guidelines.[17,18] All CICCs were secured with a sutureless device. Within our hospital, the policy was to implant external nontunneled CICCs, preferably in the subclavian vein, for first-line short- to intermediate-term use, especially for patients with newly diagnosed AML who required urgent treatment.[23] Skin-tunneled CICCs were reserved for those patients scheduled to subsequently undergo stem cell rescue. Central venous access using PICCs was selected as the experimental group. We have highlighted the written procedures (collected and reviewed before the start of enrollment) that defined the PICC insertion protocol.[12,13,24] The protocol included bilateral US scans

of all veins of the arm and neck before the procedure. In addition, the appropriate vein at the upper mid-arm ("the green zone of the zone insertion method") chosen was the vein with a diameter in millimeters on the US scan that was at least that of the catheter diameter in French. Also, a clear identification on the US scan of the median nerve and brachial artery was required before venipuncture, which was performed with US guidance. We also strictly performed hand washing, an aseptic technique, and maximal barrier protection. An US scan of the internal jugular vein was also performed during introduction of the catheter. Finally, we used an intracavitary electrocardiographic method to assess the tip position and secured the PICC with a sutureless device.[12,13,22,24]

When examining the reported studies, the data available from cases of acute leukemia have suggested that PICCs confer an increased risk of upper extremity VT and/or infection compared with CICCs.[7,9-11] However, all studies on this issue were retrospective, included patients at different phases of antileukemic treatment (eg, consolidation or salvage treatment, transplantation and, thus, undergoing second- or third-line central venous access), and did not test the role of specific procedures (protocol) followed by the implantation teams during and after catheter insertion.[7,9-11] In the present trial, our protocol (detailed in the previous paragraph) was strictly followed during the study period, which might have contributed to the relatively low incidence of major adverse events in the PICC-assisted patients. In contrast, in patients treated with cytarabine-containing intensive regimens, a severe immunocompromised status, a profound tendency to hemostasis dysfunctions, and poor wound-healing ability could represent factors that negatively affect patients' ability to tolerate a CICC.[1-4] In such cases, infection and thrombosis should not be considered separate entities, given their bidirectional relationship.[8,25] The mechanical trauma intrinsically associated with subclavian catheter insertion means the procedure is more invasive. Vein wall endothelial damage and/or inflammatory mediator release contribute to thrombosis, creating a more prothrombotic environment.[8,12,14] Moreover, the skin of the cervical–thoracic area will have been colonized by a diverse collection of microorganisms, especially gram-positive bacteria.[15] It has been reported that 50 to 100 colony-forming units/10 cm^2 will be present on the skin of the middle third upper arm compared with 1000 to 10,000 colony-forming units/10 cm^2 at the cervical–thoracic area.[13-15] We believe these findings might explain the greater incidence amount and severity of CICC-associated infectious and thrombotic events compared with those associated with PICCs.

Our study had several limitations. First, it was a single-center study with a small number of events, which limited the statistical results. Hence, our findings should be validated in a prospective large trial. Second, the clinical relevance of asymptomatic CR thrombosis continues to be debate, and routine screening with objective testing has not generally been recommended.[7] In the present study, the difference in the symptomatic CR-VT rates between the 2 groups (5 of 47 [10.6%] in the CICC group vs. 1 of 46 [2.1%] in the PICC group) was not statistically significant ($P = .09$). However, our decision to also study asymptomatic events was determined by the consideration that therapy with low-molecular-weight heparin is more effective in the presence of early thrombosis.[26] Third, skin-tunneled CICCs have been reported to have significantly lower rates of VT and BSI compared with external nontunneled CICCs.[5,6,11,14] Fourth, for the clavicular vein approach, US guidance will often not be feasible, increasing the mechanical trauma intrinsically associated with CICC insertion. Fifth, the choice of using heparin-coated CICCs might have facilitated staphylococcus infections,[27] and the absence of an intraprocedural tip location method in the CICC group might have increased the risk of VT. Finally, we restricted our investigation to pressure-injectable polyurethane PICCs. However, the latest-generation polyurethane power-injectable PICCs have been associated with a minor rate of adverse events, as previously reported by others.[28]

Conclusion

The presented data have shown that the PICC is an easy-to-use device that enables safe and effective central intravascular access for patients receiving intensive chemotherapy for hematologic remission induction of AML.[1-4] In contrast, BSI and septic thrombophlebitis emerged as life-threatening complications for neutropenic patients with external nontunneled CICCs in situ.[8] Our findings highlight the importance of a team experienced in PICC positioning and care, with a well-written protocol to optimize the catheter insertion procedures and subsequent management.[12,13,24] With optimal conditions and experienced physicians, we propose the use of PICC as a new frontline option for CVC[29] in patients with acute leukemia undergoing intensive chemotherapy.[1-4]

Clinical Practice Points

- PICCs provided superior safety compared with CICCs and maintained effectiveness as primary central venous access for patients undergoing chemotherapy for remission induction of AML.
- We suggest this minimally invasive device as a new option for frontline CVC in patients with acute leukemia.

Supplemental Data

The supplemental data accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2018.12.008.

References

1. Lowenberg B, Pabst T, Vellenga E, et al. Cytarabine dose for acute myeloid leukemia. *N Engl J Med* 2011; 364:1027-36.
2. Mandelli F, Vignetti M, Suciu S, et al. Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: the EORTC and GIMEMA Groups study AML-10. *J Clin Oncol* 2009; 27:5397-403.
3. Fleischhack G, Hasan C, Graf N, Mann G, Bode U. IDA-FLAG (idarubicin, fludarabine, cytarabine, G-CSF), an effective remission-induction therapy for poor-prognosis AML of childhood prior to allogeneic or autologous bone marrow transplantation: experiences of a phase II trial. *Br J Haematol* 1998; 102:647-55.
4. Willemze R, Suciu S, Meloni G, et al. High-dose cytarabine in induction treatment improves the outcome of adult patients younger than age 46 years with acute myeloid leukemia: results of the EORTC-GIMEMA AML-12 trial. *J Clin Oncol* 2014; 32:219-28.
5. Schiffer CA, Mangu PB, Wade JC, et al. Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2013; 31:1357-70.
6. Sousa B, Furlanetto J, Hutka M, et al. Central venous access in oncology: ESMO clinical practice guidelines. *Ann Oncol* 2015; 26(suppl 5):v152-68.
7. Cortelezzi A, Moia M, Falanga A, et al. Incidence of thrombotic complications in patients with haematological malignancies with central venous catheters: a prospective multicentre study. *Br J Haematol* 2005; 129:811-7.

8. Picardi M, Pagliuca S, Chiurazzi F, et al. Early ultrasonographic finding of septic thrombophlebitis is the main indicator of central venous catheter removal to reduce infection-related mortality in neutropenic patients with bloodstream infection. *Ann Oncol* 2012; 23:2122-8.
9. Chopra V, Anand S, Hickner A, et al. Risk of venous thromboembolism associated with peripherally inserted central catheters: a systematic review and meta-analysis. *Lancet* 2013; 382:311-25.
10. Refaei M, Fernandes B, Brandwein J, Goodyear MD, Pokhrel A, Wu C. Incidence of catheter-related thrombosis in acute leukemia patients: a comparative, retrospective study of the safety of peripherally inserted vs. centrally inserted central venous catheters. *Ann Hematol* 2016; 95:2057-64.
11. Sriskandarajah P, Webb K, Chisholm D, et al. Retrospective cohort analysis comparing the incidence of deep vein thromboses between peripherally-inserted and long-term skin tunneled venous catheters in hemato-oncology patients. *Thromb J* 2015; 13:21.
12. Scoppettuolo G, Pittiruti M. Ultrasound guided placement of peripherally inserted central venous catheters. In: Lumb P, Karakitsos D, eds. *Critical Care Ultrasound*. Philadelphia: Elsevier-Saunders; 2014:89-94.
13. Dawson RB. PICC zone insertion method™ (ZIM™): a systematic approach to determine the ideal insertion site for PICCs in the upper arm. *J Assoc Vasc Access* 2011; 16:156-65.
14. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 49:1-45.
15. Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol* 2011; 9:244-53.
16. Begg CB, Iglewicz B. A treatment allocation procedure for sequential clinical trials. *Biometrics* 1980; 36:81-90.
17. Frykyolm P, Pikawer A, Hammarskjöld F, et al. Clinical guidelines on central venous catheterisation. *Acta Anaesthesiol Scand* 2014; 58:508-24.
18. Rupp SM, Apfelbaum JL, Blitt C, et al. Practice guidelines for central venous access: a report by the American Society of Anesthesiologists Task Force on Central Venous Access. *Anesthesiology* 2012; 116:539-73.
19. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016; 127:2391-405.
20. Fabiani A, Pittiruti M, Russo S, Sanson G. Early-onset thrombosis of internal jugular vein associated with introducer catheter for heart catheterization in cardiac surgery. *Vasc Access* 2015; 16:57-63.
21. Pugliese N, Salvatore P, Iula DV, et al. Ultrasonography-driven combination antibiotic therapy with tigecycline significantly increases survival among patients with neutropenic enterocolitis following cytarabine-containing chemotherapy for the remission induction of acute myeloid leukemia. *Cancer Med* 2017; 6:1500-11.
22. Morano SG, Latagliata R, Girmenia C, et al. Catheter-associated bloodstream infections and thrombotic risk in hematologic patients with peripherally inserted central catheters (PICC). *Support Care Cancer* 2015; 23:3289-95.
23. Camera A, Villa MR, Pezzullo L, et al. Central venous catheter insertion: a bedside procedure for haematological patients. *Eur J Haematol* 1996; 56:93-4.
24. Lamperti M, Bodenham AR, Pittiruti M, et al. International evidence-based recommendations on ultrasound-guided vascular access. *Intensive Care Med* 2012; 38:1105-17.
25. Del Principe MI, Buccisano F, Maurillo L, et al. Infections increase the risk of central venous catheter-related thrombosis in adult acute myeloid leukemia. *Thromb Res* 2013; 132:511-4.
26. Debourdeau P, Farge D, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. *J Thromb Haemost* 2013; 11:71-80.
27. Shanks RM, Donegan NP, Graber ML, et al. Heparin stimulates *Staphylococcus aureus* biofilm formation. *Infect Immun* 2005; 73:4596-606.
28. Pittiruti M, Emoli A, Porta P, Marche B, DeAngelis R, Scoppettuolo G. A prospective, randomized comparison of three different types of valved and non-valved peripherally inserted central catheters. *J Vasc Access* 2014; 15:519-23.
29. Cerchione C, Di Perna M, Della Pepa R, Pugliese N, Pane F, Picardi M. Frontline vascular access devices in acute leukemias—peripherally inserted central catheter (PICC) versus traditional central venous catheter (CVC): a phase IV randomized trial (NCT02405728). Haematologica; Congress of the European Hematology Association Madrid, Spain, June 22-25, 2017:1-882. *Clin Lymph Myeloma Leuk* 2017; 17(suppl 2):S396-7.

Supplemental Data

Supplemental Material 1

The random allocation sequence used a minimization method,[16] in which the patients were assigned to 2 study groups using a computerized system and ensuring equal distribution on the basis of sex, age, body mass index, smoking history, hypertension, diabetes, acute myeloid leukemia subtype, blood cell count at baseline, and scheduled induction chemotherapy regimen.[1-4]

Supplemental Material 2

CR-BSIs were defined using the Infectious Diseases Society of America guidelines.[14] Definite CR-BSI required either a differential time to positivity > 2 hours in a pair of peripheral and central blood cultures (ie, growth of microbes from a blood sample taken from a central catheter hub ≥ 2 hours before microbial growth was detected in a blood sample obtained from a peripheral vein) or the detection of the same pathogen with the same susceptibility pattern in a blood culture and at the catheter tip. We used either of these methods as the diagnostic criterion for CR-BSI.

Supplemental Material 3

CR-VT was defined as thrombus occurring acutely in the ipsilateral side of device insertion and involving the deep veins of the upper arm or cervical−thoracic area (ie, basilica, brachial, axillary, subclavian, internal jugular, and/or brachiocephalic veins; all seated ipsilateral to the catheter site).[7,8] Ultrasound-detected thrombotic episodes associated with CVC in the absence of specific clinical signs and/or symptoms were considered events in our study. Thrombosis was detected clinically (physical examination findings of pain, induration, erythema, exudates, and/or asymmetric venous distension) and/or radiologically (US findings: noncompressibility, absence of respiratory variation, and/or visualization of a clear intraluminal thrombus [ie, a ≥ 0.5-cm echogenic pericatheter intravascular mass]).[7,8] Thrombotic events included mural thrombosis (the presence of a blood clot adhering to the vessel wall and that could occlude the tip of the catheter but did not completely occlude the vein in which the catheter was positioned; blood flow present on color Doppler; the thrombus was directly visualized, and/or the vein was incompressible) and complete thrombosis (the presence of a blood clot around the catheter that adhered to the vessel wall and completely occluded the vein; the thrombus was directly visualized, and/or the vein was incompressible; with no blood flow present on color Doppler).[20] The presence of a fibroblastic sleeve (ie, a cylinder image with well-defined margins that originated at the site of catheter insertion and fluctuated within the vessel lumen without creating an obstruction [fully compressible vessel, with blood flow present throughout the vascular section]) was not considered as thrombotic event.[20]

Supplemental Material 4

Complications associated with catheter positioning were defined as serious bleeding (blood transfusion requirement), arterial puncture, and/or pneumothorax (ie, the entry of air into the pleural space as detected by chest radiography) during implantation of the central intravascular device.[7] Catheter malfunction was defined as dislocation (>4 cm), occlusion (no infusion, no withdrawal), and/or rupture of the catheter during the 30-day study period.[7] Overall mortality included death from any cause, from catheter insertion until 30 days later. All deaths were reviewed by an independent adjudication committee, which evaluated the possibility of a relationship with the central venous catheter. In particular, the following catheter-related fatal events were evaluated: septic shock (systemic inflammatory response and ≥ 1 organ dysfunction)[14] and pulmonary embolism (confirmed by the presence of a thrombus in a segmental or more proximal pulmonary artery on computed tomography pulmonary angiography or ventilation-perfusion scan).[7,9]

Supplemental Material 5

For blood cultures, 10 mL of blood was analyzed (Sygnal System, Oxoid, Hants, United Kingdom). The Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France) was used for blood stream isolate identification and antimicrobial susceptibility testing. Minimum inhibitory concentrations were evaluated using E-test strips (BioMerieux) and classified in accordance with the European Committee on Antimicrobial Susceptibility Testing guidelines. Blood isolates of multidrug-resistant *Enterobacteriaceae* spp., such as *Escherichia coli*-producing extended-spectrum β-lactamases and *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*, or methicillin-resistant *Staphylococcus* spp. were confirmed using adjunct microbiological tests.[21]

Supplemental Material 6

All randomized patients were scheduled to undergo US scans (including compression, B-mode imaging with the addition of color- and pulsed-wave Doppler) before and 3, 7, 15, 23, and 30 days after CVC insertion, using an US scanner (iU22; Philips Healthcare, Bothell, WA) equipped with 9-3 and 12-5 MHz broadband linear probes.[8] The following US parameters were recorded on both sides of the basilica, brachial, axillary, subclavian, internal jugular, and/or brachiocephalic veins: venous vessel patency, presence or absence of vein compressibility, echogenicity within the vein lumen, characteristics of venous flow, including the presence or absence of cardiac pulsatility transmitted, and the response to respiratory maneuvers.[8] The US investigations were performed directly at the patient's bedside.