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Infections increase the risk of central venous catheter-related thrombosis in adult acute myeloid leukemia

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ABSTRACT

Introduction: Central venous catheters (CVC) related thrombosis (CRT) represents a well known complication in patients with acute myeloid leukemia (AML) receiving intensive chemotherapy but the efficacy of antithrombotic prophylaxis still remains controversial.
Patients and Methods: We analyzed 71 consecutive AML patients whose CVC was inserted before each chemotherapy cycle for an overall number of 106 CVC placements. In 47/106 insertions, a prophylaxis with 100 **IU**/kg/day low molecular weight heparin (LMWH) was administered for 7 days after CVC insertion and additional 7 after CVC removal. This unconventional dose of LMWH, although higher than usual, appeared adequate for a short-course approach. LMWH was delivered regardless of the platelet (PLT) count once provided that it should have been maintained above $20x10^9$/L by transfusions.
Results: Of 106 insertions, we observed 19 (18%) episodes of CRT, 58 (54%) of sepsis and 50 (47%) infections of CVC-exit site with no difference between LMWH and no-LMWH group. Occurrence of CRT was significantly associated with CVC-exit site infections (14/19, $p = 0.01$) and sepsis (16/19, $p = 0.005$) with no difference between LMWH and no-LMWH group. In multivariate analysis, both CVC-exit site infections and sepsis were confirmed to be independent risk factors for CRT development.
Conclusion: Our retrospective study, although based on a small sample size, suggests that the occurrence of CVC-exit site infections and neutropenic sepsis following chemotherapy significantly increases the risk of CRT in AML, independently from the use of LMWH prophylaxis.

Introduction

Venous manifestations of cancer-associated thrombosis include deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as visceral or splanchnic vein thrombosis, all together known as venous thromboembolism (VTE). VTE risk is 4- to 5-fold higher in cancer patients as compared to the general population and occurs in up to 20% of the cases [1,2] with 15% of the patients with unprovoked VTE being diagnosed with cancer in the subsequent 12 months [3,4]. The rate of VTE in patients with hematologic malignancies is comparable to the one of patients with "high-risk" solid tumors, such as colon, pancreatic and ovarian cancers [5,6] and the use of central venous catheters (CVC) amplifies such a risk. In fact, the major complications related to CVC insertion are infections and thrombosis. The incidence of symptomatic CVC-related thrombosis (CRT) in cancer patients ranges from 0,3 to 28% [7]. The role of antithrombotic prophylaxis in these patients remains controversial [1] and few data are available in patients affected with acute myeloid leukemia (AML). To this aim, we analyzed retrospectively 71 consecutive AML patients receiving intensive chemotherapy and who were treated or not with prophylactic low-molecular-weight-heparin (LMWH). The aims of our study were to determine: 1) the risk factors associated with CRT and their frequency in a homogeneous population of patients with AML; 2) the impact of an antithrombotic prophylaxis using LMWH on CRT occurrence.

Patients and Methods

We analyzed retrospectively a series of 71 consecutive AML patients who, from December 2008 to March 2012, underwent CVC positioning, being candidates to chemotherapy programs; these patients form the basis for the present study. The series encompasses two cohorts of patients, those who received LMWH for CRT prophylaxis and those who did not (no-LMWH). Decision to introduce LMWH prophylaxis was made in the attempt to minimize incidence of CRT which was 8%

Abbreviations: CVC, Central venous catheters; CRT, Central venous catheters related thrombosis; AML, acute myeloid leukemia; LMWH, low molecular weight heparin; PLT, platelet; PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism; SVC, non-tunneled subclavian venous catheter; PICC, peripherally inserted central-venous catheter; WBC, white blood cell; MTHFR, methylentetrahydrofolatereductase; TF, tissue factor; G-CSF, granulocyte cell stimulating factors; PN, parenteral nutrition.

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in the no-LMWH group. Approval for this study was obtained from the institutional review board. Forty-seven patients with previously untreated, non-M3 AML were treated according to cytarabine-based induction and consolidation regimens [8,9]. Eighteen patients with non-M3 relapsed AML received fludarabine and cytarabine-based salvage regimens [10–12]. Six M3 AML patients were treated according to national reference protocols [13]. CVCs were implanted after obtaining informed consent in accordance with local regulations. CVCs were categorized as non-tunneled subclavian venous catheter (SVC) and peripherally inserted central-venous catheter (PICC). Catheters were indwelt by a team of experts composed of physicians and nurses operating in an aseptic, surgical condition and under guidance of ultrasound ecography. Double or triple-lumen non-tunneled SVCs were implanted in subclavian vein. Four French single-lumen PICCs were inserted through the antecubital, basilic, brachial or cephalic vein. The decision to insert a PICC was made once the results of ultrasound ecography examination were available; in fact, in cases where the explored veins had an adequate diameter (>4 mm) PICC was chosen due to the lower occurrence of complications as compared to SVC. After CVC insertion, all patients underwent a chest X-ray examination to confirm the correct placement of CVC and to rule out any complication. To the purpose of the present study, each CVC positioning was considered as a single event, so that a patient who had completed the scheduled observation period was registered as a new case for the study if another CVC was inserted. CVC indwelling duration was calculated from the day of insertion to date of removal. Neutropenic patients received antibiotic prophylaxis with ciprofloxacin, and those reporting a positive family history of unprovoked recurrent thrombosis or premature VTE or women undergoing hormone therapy were tested for heritable thrombophilia [14]. LMWH (enoxaparin) was administered at dosage of 100 IU/kg once a day, for 7 days after CVC insertion and other 7 after CVC removal, regardless of the platelet (PLT) count. LMWH therapy was initiated after obtaining informed consent in accordance with local regulations. The choice of an unconventional prophylaxis in terms of dose and schedule was based on the assumption that CVC insertion and removal are the phases where the risk for CRTs is the highest. Therefore, a dose of 100 IU/kg/day, although higher than usual, appeared adequate for a short-course approach. Thrombocytopenic patients received platelets transfusion in no-LMWH group according to the ASCO guidelines [15] whereas those belonging to the LMWH group received regular transfusions to maintain a PLT count $\geq 20x10^9$/L. The occurrence of the following events was recorded and analyzed: CRT, CVC exit-site infections, sepsis and major bleeding. Swelling, pain, redness, discoloration and cyanosis were symptoms suggestive of CRT, diagnosis of which was made by compression ultrasonography in presence of thrombosis of the vein in which CVC was placed or occlusion of a CVC lumen [16]. CVC exit-site infection was diagnosed and graded based on the presence of erythema, induration and/or tenderness within 2 cm of catheter exit area [17]. Sepsis was defined according to international standard criteria as an infection, documented or suspected, with one or more of the following: general inflammatory variables, hemodynamic variables, organ dysfunction variables and tissue perfusion variables [18]. Considering the type of disease and the frequent need of transfusion in our patients, major bleeding was defined as the one causing prolongation of hospital stay, life-threatening or fatal.

Statistical Analysis

Descriptive statistical analysis was performed to compare the different subgroups. Either Pearson chi-squared (for categorical data) or Mann-Whitney U test (for continuous data) were used to test for differences in clinical data. P values <0.05 were considered significant. The Cox proportional hazard model was used for multivariate analysis of CRT. The variables for which univariate analysis had shown a significant association were challenged in the multivariate model.

Results

During the study period, in the 71 patients under evaluation a total of 106 CVC insertions were carried and for 47 of them a prophylaxis with LMWH was instituted, whereas for 59 it was not. The characteristics of patients are shown in Table 1. The median time of CVC indwelling was 62 days (range 10-300), this time length was comparable in LMWH versus no-LMWH group. PICCs were kept in place longer than SCV (median 101 versus 26 days, range 16-300 versus 10-90). No significant difference was recorded between no-LMWH group and LMWH group with regards the age, gender, type of CVC, chemotherapy phase, PLT count, white blood cell (WBC) count, body mass index, hormonal therapy, granulocyte cell stimulating factors (G-CSF) therapy, parenteral nutrition (PN) and bulky disease. Overall, nineteen episodes (18%) of CRT were observed: 4 (20%) were symptomatic and 2 (10%) occurred in patients with AML-M3. No significant correlation was found between CRT and demographic variables, obesity or treatment associated risk factors as shown in Table 2. Seventeen (89%) of 19 episodes of CRT occurred during the induction/salvage phase (Table 2). Of 106 insertions, 58 (54%) episodes of sepsis and 50 (47%) infections of the CVC exit site were recorded. Fifteen (26%) episodes of sepsis were pneumonia-associated and 43 (74%) bloodstream infection-associated. Twenty-six episodes of CVC exit site infections were associated with bloodstream infections, mainly due to Gram positive organisms. There was no significant difference in CRT rate between non-tunneled SVC vs PICC (Table 2). Moreover, a significant correlation was found between CVC-exit site infections and SCV (37/50, $p = 0.0008$) while sepsis was not associated with either SCV or PICC. In univariate analysis, a significant correlation was found between CRT and a higher median PLT count ($p = 0.04$), CVC exit site infection ($p = 0.01$) and sepsis ($p = 0.005$, Table 2). Forty-eight patients were tested for heritable thrombophilia and 19 were found to carry mutations: heterozygosis of *F2*G20210A in 5, heterozygosis of *F5*G1691A-Factor V Leiden in 4, Protein C or Protein S deficits in

Table 1
Patients Characteristics.

Characteristic	Patients°	no-LMWH group	LMWH group*
Total patients	106	59	47
Age (median years)	58	58	57
Range	(18-75)	(17-71)	(21-75)
<60 years, n(%)	60(57)	31(52)	29(62)
>60 years, n(%)	46(43)	28(48)	18(38)
Type of CVC,			
SCV, n(%)	60(57)	31(53)	29(61)
PICC, n(%)	46(43)	28(47)	18(38)
Gender,			
Male, n(%)	63(59)	34(58)	29(62)
Female, n(%)	43(41)	25(42)	18(38)
Chemotherapy phase,			
Induction, n(%)	66(63)	32(54)	34(72)
Consolidation, n(%)	22(20)	14(24)	8(17)
Salvage, n(%)	18(17)	13(22)	5(11)
PLT count (median)	$75.5x10^9$/L	$81x10^9$/L	$65x10^9$/L
Range	($6-645x10^9$/L)	($6-645x10^9$/L)	($8-360x10^9$/L)
<50 $x10^9$/L,n(%)	46(43)	33(56)	20(43)
<20 $x10^9$/L,n(%)	20(19)	12(20)	8(17)
WBC count (median)	$13x10^3$/L	$10x10^3$/L	$13x10^3$/L
Range	($1.2-200x10^3$/L)	($1.8-180x10^3$/L)	($1.2-200x10^3$/L)
Body mass index >30, n(%)	20(19)	10(17)	10(22)
Hormonal therapy, n(%)	15(21)	9(15)	6(13)
G-CSF, n(%)	10(9)	6(10)	4(8)
Bulky disease, n(%)	2(3)	1(1)	1(2)

LMWH, low molecular weight heparin; CVC, central venous catheters; PICC, peripherally inserted central-venous catheter; SCV, non-tunneled subclavian venous catheter; PLT, platelet; WBC, white blood cell count; G-CSF, granulocyte cell stimulating factor.
°defined as a single CVC placement.
*All p values were not significant.