Annals of Oncology 23: 2122–2128, 2012
doi:10.1093/annonc/mdr588
Published online 6 January 2012

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

M. Picardi[1], S. Pagliuca[1], F. Chiurazzi[1], D. Iula[2], M. Catania[2], F. Rossano[2] & F. Pane[1]*

[1]*Departments of Biochemistry and Medical Biotechnology;* [2]*Cellular and Molecular Biology and Pathology, Federico II University Medical School, Naples, Italy*

Received 24 September 2011; revised 17 November 2011; accepted 21 November 2011

Background: Septic thrombophlebitis increases patient morbidity and mortality following metastatic infections, pulmonary emboli, and/or septic shock. Central venous catheter (CVC) removal for occult septic thrombophlebitis challenges current strategy in neutropenic patients.

Patients and methods: We prospectively evaluated infection-related mortality in 100 acute leukemia patients, with CVC-related bloodstream infection (CRBSI) after chemotherapy, who systematically underwent ultrasonography to identify the need for catheter removal. Their infection-related mortality was compared with that of a historical cohort of 100 acute leukemia patients, with CRBSI after chemotherapy, managed with a clinically driven strategy. Appropriate antimicrobial therapy was administered in all patients analyzed.

Results: In the prospective series, 30/100 patients required catheter removal for ultrasonography-detected septic thrombophlebitis after 1 median day from BSI onset; 70/100 patients without septic thrombophlebitis retained their CVC. In the historical cohort, 60/100 patients removed the catheter (persistent fever, 40 patients; persistent BSI, 10 patients; or clinically manifest septic thrombophlebitis, 10 patients) after 8 median days from BSI onset; 40/100 patients retained the CVC because they had not clinical findings of complicated infection. At 30 days median follow-up, one patient died for infection in the ultrasonography-assisted group versus 17 patients in the historical cohort ($P < 0.01$). With the ultrasonography-driven strategy, early septic thrombophlebitis detection and prompt CVC removal decrease infection-related mortality, whereas clinically driven strategy leads to inappropriate number, reasons, and timeliness of CVC removal.

Conclusion: Ultrasonography is an easy imaging diagnostic tool enabling effective and safe management of patients with acute leukemia and CRBSI.

Key words: bloodstream infections, central venous catheter, septic thrombophlebitis, ultrasonography scans

introduction

Long-term central venous catheter (CVC) insertion has improved the management of patients with acute leukemia by facilitating administration of cytotoxic drugs, antimicrobials, blood products, and parenteral hyperalimentation [1]. Many types of problems are reported following the CVC insertion [1]. Bloodstream infection (BSI) and thrombosis are the most important long-term complications [1, 2]. Catheter-related infection and thrombosis should not be seen as separate entities, given their bidirectional relationship [1, 2]. A number of bacteria and fungi bind to fibronectin and other serum components that coat catheters by means of specialized adhesive matrix molecules [1, 2]. In the biofilm created by the protein sheath, the pathogens may exceed a critical amount with release of microorganisms in the blood and, consequently, BSI [1–3]. In such instances, thrombosis should be assumed to be infected, establishing the inflammatory entity of septic thrombophlebitis [1, 3]. Metastatic infections, massive septic pulmonary emboli, and/or septic shock may complicate this condition, thus increasing patient morbidity and mortality [3, 4].

A 10%–15% incidence of CVC-associated clinically manifest venous thrombosis and a 30%–70% incidence of CVC-associated subclinical venous thrombosis are reported among

Correspondence to: Prof. F. Pane, Hematology Division, Department of Biochemistry and Medical Biotechnology, University of Naples Federico II School of Medicine, Via S. Pansini 5, 80131 Naples, Italy. Tel. +390817462068; Fax +390817462165; E-mail: fabpane@unina.it

cancer patients with neutropenic fever [1–7]. Consequently, a number of such patients could have no physical examination findings suggesting catheter-related septic thrombophlebitis [5–7] This condition requires specific management, which includes prolonged antimicrobial administration, anticoagulants, and, especially, catheter removal. Few data exist regarding the impact of strict imaging surveillance, of CVC sites, on the identification of the most appropriate time for removing complicated catheters, and/or the subpopulation of patients who would benefit most from such intervention [1–7].

In view of the wide use of ultrasonography to detect thrombosis [8, 9], we conducted a prospective study in acute leukemia patients with CVC-related BSI, undergone systematically ultrasonography to identify the need for catheter removal. We then compared 30-day mortality in these patients with that of a historical cohort of patients with acute leukemia, in whom CVC-related BSIs were conventionally managed (the decision for catheter removal was based on clinical criteria) [1]. We tested the hypothesis that treatment strategy, planned on the basis of an ultrasonography-driven approach, resulted in a better outcome than a clinically driven approach, for the early detection of septic thrombophlebitis by ultrasonography and, consequently, the prompt removal of CVC, contributing to infected thrombus rapid dissolution thereby avoiding septic thrombophlebitis lethal complications [1, 3, 4, 9].

patients and methods

study design

Four hundred consecutive patients with newly diagnosed acute leukemia [10], referred to our institution between January 2004 and December 2009, were screened for enrollment. Inclusion criteria were (i) age <75 years, (ii) World Health Organization performance score 0–3, (iii) a long-term CVC *in situ* (expected permanence ≥2 weeks), (iv) administration of chemotherapy inducing neutropenia, and (v) CVC-related BSI. Patients for whom appropriate data were not available, patients not receiving at least 60 h of effective antimicrobial treatment on the basis of *in vitro* susceptibility (without delay or reduction), or patients not receiving heparin at standard dosage [1, 9, 11] in case of venous thrombosis (if the platelet count was < 30 000/μl, anticoagulant was not administered) were excluded. In this group, all patients systematically underwent ultrasonography screening for CVC-related septic thrombophlebitis. Ultrasonography findings of septic thrombophlebitis prompted the immediate CVC removal.

A historical cohort of 400 patients with newly diagnosed acute leukemia [10], and referred to our institution between January 1997 and December 2003, was considered for the comparison. This control group was retrospectively collected. Inclusion and exclusion criteria were the same as for the ultrasonography-assisted group, except that catheter site ultrasonography was not routinely carried out. In this cohort, CVC was removed for (i) clinical findings of septic thrombophlebitis, (ii) persistent/recurrent bacteremia or fungemia, and/or (iii) persistent/recurrent fever [1, 11].

The study took place at the Hematology Division of the University of Naples 'Federico II' (Italy), after institutional review board approval. Patients were informed of the study aim. Informed consent was obtained from all patients studied, according to the Helsinki declaration.

All patients were hospitalized from the start of chemotherapy and received antimicrobial prophylaxis. An untunneled heparin-coated Vialon catheter (Becton-Dickinson) was inserted in the internal jugular or subclavian vein by the same specialized medical staff, using the Seldinger technique, before chemotherapy administration [12]. In the event of neutropenic fever, all patients underwent detailed history and physical examination, complete blood study, and paired blood samples drawn from CVC and a peripheral vein for cultures (10 ml of blood per bottle; signal system, Oxoid, Hants, UK) repeated every 72 h until fever disappearance. In both the groups of patients, CVC-related BSI was defined as isolation of the same phenotypic microorganism from at least one catheter sample and one peripheral venous sample, with no other identifiable source of infection [1, 11]. Additional assessments included blood samples for cultures every 72 h until infection eradication, and further evaluations if clinically indicated.

Thus, all patients included in the study had positive blood culture results. In the historical cohort, septic thrombophlebitis was defined as being present if pain, induration, erythema, exudates and/or asymmetric venous distension involving the catheter insertion site, and/or ipsilateral arm and/or chest were detected by physical examination [1, 7, 11]. In the prospective series, septic thrombophlebitis was considered present if a clear intraluminal thrombus, i.e. a ≥0.5 cm echogenic intravascular mass, was visualized at gray-scale ultrasonography of CVC area [3–8].

ultrasonography procedures

In the prospective series, a hematologist (MP) [13] carried out ultrasonography scans of the bilateral internal jugular, subclavian, and axillary veins, within 24 h of BSI onset, using a scanner (iU22; Philips Healthcare, Bothell, WA) equipped with a 9-3 MHz broadband linear probe. The ultrasonography investigations were carried out directly at the patient's bedside and were repeated every 3 days until infection resolution. Each vessel was scanned in real-time B-mode and color Doppler, according to a standardized protocol [5–8]. Patients with uninterpretable ultrasonography images because of insufficient views or poor image quality were excluded [1, 3–9].

statistical analysis

Our hypothesis was that in cohorts of at least 98 patients each, statistical significance could be achieved if an absolute difference of 15% in overall survival between the ultrasonography-driven and the clinically driven approaches was reached, with an 80% statistical power and a 5% significance level (α error = 0.05, β error = 0.20).

The time-related dependent variable used in the trial was overall survival. Death from any cause was considered an event. Overall survival was calculated from the date of BSI onset to the date of the event or last follow-up visit 30 days after BSI onset; overall survival was estimated by the Kaplan–Meier method. For the statistical evaluations, the log-rank test, χ^2 test, and *t*-test were carried out. *P* values <0.05 were deemed statistically significant.

results

patient enrollment

From 2004 to 2009, 110/400 (27%) consecutive patients with acute leukemia received a diagnosis of CVC-related BSI after induction chemotherapy; 10 of them were excluded. In the historical cohort, 108 patients with acute leukemia had a diagnosis of CVC-related BSI after induction chemotherapy; 8 of them were excluded. The remaining 100 patients of the ultrasonography-assisted group and the 100 patients of the historical cohort constituted the study population (Figure 1).

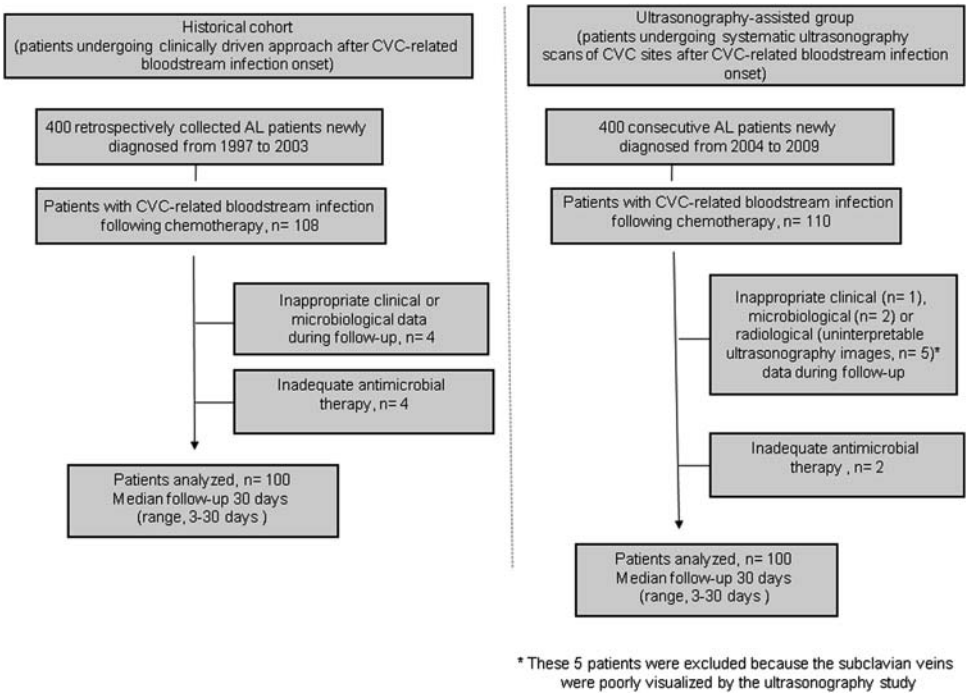

Figure 1. Flow-chart of the study. AL, acute leukemia; CVC, central venous catheter.

patient demographics and characteristics

The two series were comparable with respect to baseline prognostic variables (acute myeloid leukemia treated with cytarabine-based regimens, 80% of patients; acute lymphoblastic leukemia treated with anthracycline-based regimens, the patient remainder). Median time with neutrophil count < 500/μl and platelet count < 10 000/μl was 11 days and 10 days, respectively (Table 1). The organisms responsible for BSI differed between the two groups: 60 patients with Gram-positive bacteremia, 35 patients with Gram-negative bacteremia, and 5 patients with fungemia in the historical cohort versus 50 patients with Gram-positive bacteremia, 41 patients with Gram-negative bacteremia, and 9 patients with fungemia in the ultrasonography-assisted group. The rates of antibiotic-resistant Gram-positive bacteria and of Gram-negative bacteria producing extended-spectrum β-lactamases are shown in Table S1 (available as supplementary data in *Annals of Oncology* online). Overall, median time between CVC insertion and BSI onset was 18 days.

treatment of CVC-related BSI

Overall, 168 patients received antibiotic therapy, 14 patients antifungal therapy, and 25 patients heparin therapy. Daptomycin, linezolid, tigecycline, and caspofungin were administered only in patients in the prospective series. Despite a similar median number of days of i.v. antibiotics (supplemental Table S2, available at *Annals of Oncology* online), there was significant difference between the two groups with regard to the duration of antibiotic treatments, owing to more early events in the historical cohort compared with the prospective series (see below). There was no significant difference between the two groups in terms of duration of antifungal and heparin treatment.

Among patients surviving at 30 days follow-up, median time to achieve complete clinical and microbiological response was 10 days (range, 4–15 days) in the historical cohort and 9 days (range, 3–10 days) in the ultrasonography-assisted group.

removal of CVC

The number of CVCs removed differed significantly between the two groups. Sixty patients (Gram-positive bacteremia, 35 patients; Gram-negative bacteremia, 20 patients; and fungemia, 5 patients) in the historical cohort versus 30 patients (Gram-negative bacteremia, 15 patients; Gram-positive bacteremia, 10 patients; and fungemia, 5 patients) in the ultrasonography-assisted group required catheter removal ($P < 0.01$).

The time to CVC removal since BSI onset differed significantly between the two groups. CVCs were removed after a median of 8 days (range, 4–9 days) inthe historical cohort versus 1 day (range, 1–3 days) in the ultrasonography-assisted group ($P < 0.01$). Median time from BSI onset to CVC removal for the specific pathogens isolated in the two series is shown in Table 2.

The reasons for removing the CVCs differed significantly between the two groups. The reason for removing CVCs in the prospective series was ultrasonography-detected septic thrombophlebitis (30/30, 100%). In the historical cohort, CVCs were removed following persistent or recurrent fever (40/60, 67%), persistent or recurrent bacteremia or fungemia (10/60, 16%), or clinically manifest septic thrombophlebitis (10/60, 16%).

Thus, in the historical cohort, the cumulative incidence of clinically manifest septic thrombophlebitis was 10%.

Table 1. Baseline characteristics of the population analyzed

Variable	Ultrasonography-assisted group	Historical cohort	*P*
No. of patients	100	100	NS
Median age, years (range)	51 (18–74)	53 (18–74)	NS
Male/female	45/55	47/53	NS
Hematological disease			NS
Acute myeloid leukemia	82	80	
Acute lymphoblastic leukemia	18	20	
FAB subtypes			NS
M0–M2	40	40	
M3	2	3	
M4–M7	40	37	
L1–L2	13	15	
L3	5	5	
WHO status			NS
0–1	75	75	
2–3	25	25	
Chemotherapy treatment			NS
Cytarabine-based regimen	82	80	
Anthracycline-based regimen	18	20	
Central venous catheter type			NS
Untunneled	100	100	
Double lumen	45	40	
Tri lumen	55	60	
Central venous catheter site			NS
Jugular vein	40	35	
Subclavian vein	60	65	
Post-chemotherapy aplasia			NS
Neutropenia <500/μl	100	100	
Prolonged neutropenia, days (range)	11 (7–28)	11 (7–28)	
Thrombocytopenia <10 000/μl	100	100	
Prolonged thrombocytopenia, days (range)	10 (7–20)	10 (7–20)	

Unless otherwise indicated, data refer to the number of patients.
FAB, French–American–British revised criteria; NS, not significant; WHO, World Health Organization.

Table 2. Removal of central venous catheters in the patients analyzed

Variable	Ultrasonography-assisted group	Historical cohort	*P*
No. of CVC removed	30	60	<0.01
Causative pathogens of bloodstream infections in patients removing CVC			NS*
Gram-positive	10	35	–
Gram-negative	15	20	–
Fungus	5	5	–
Time to CVC removal since bloodstream infection onset Median, days (range)	1 (1–3)	8 (4–9)	<0.01
Time to CVC removal since bloodstream infection onset, for the specific pathogens isolated			<0.01
Gram-positive Median, days (range)	3 (2–3)	8 (4–9)	–
Gram-negative Median, days (range)	1 (1–3)	7 (5–8)	–
Fungus Median, days (range)	1 (1–3)	6 (5–6)	–
Reasons for removing CVC			<0.01
Persistent/recurrent fever	0	40	–
Persistent/recurrent bacteremia or fungemia	0	10	–
Septic thrombophlebitis	30	10	–

NB. Unless otherwise indicated, data refer to the number of patients.
CVC, central venous catheter.
*P value = 0.07.

ultrasonography scanning results

In the prospective series, all patients received the scheduled imaging surveillance. A median of four ultrasonography examinations was carried out per patient (range, 3–6), each complete examination requiring 30 min on average (range, 20–40 min). Septic thrombophlebitis was detected by systematic ultrasonographic scans of the jugular, subclavian, and/or axillary veins in 30/100 patients. The locations of the thrombi were to the subclavian vein in 10 patients, to the internal jugular vein in 10 patients, and to two or more veins in 10 patients (Figure S1, available in *Annals of Oncology* online). None of the patients receiving diagnosis of septic thrombophlebitis showed clinical signs or symptoms of thrombophlebitis.

In the patients of both the series with a diagnosis of septic thrombophlebitis, blood cultures yielded *Staphylococcus* spp. (19 cases), *Enterobacteriaceae* spp. (16 cases), and *Candida* spp. (5 cases). The distribution of the pathogens of patients with a diagnosis of septic thrombophlebitis in the two series is illustrated in supplemental Figure S2 (available at *Annals of Oncology* online). A similar number of patients with septic thrombophlebitis related to *Staphylococcus* spp. was observed in the two series. In contrast, ultrasonography identified more patients with septic thrombophlebitis related to *Enterobacteriaceae* spp. and *Candida* spp. than the physical examination. In particular, 15 cases of septic thrombophlebitis related to *Escherichia coli* and 5 to *Candida parapsilosis* were detected in the ultrasonography-assisted group versus 1 case related to *E. coli* and no septic thrombophlebitis related to *Candida* spp. in the historical cohort.

In the prospective series, the median time between BSI onset and ultrasonography-detected septic thrombophlebitis was 1 day (range, 1–3 days). In the historical cohort, the median time between BSI onset and physical examination-detected septic thrombophlebitis was 8 days (range, 7–10 days). This difference reflected the very early removal of CVCs in the prospective series compared with removal time in the historical cohort (Figure 2).

overall survival of patients analyzed

The median observation time was 30 days (range, 3–30 days) in both the groups. At a 30-day follow-up, the overall survival of the entire population was 87%: 25 of the 200 patients analyzed had died. The 25 events observed were not evenly

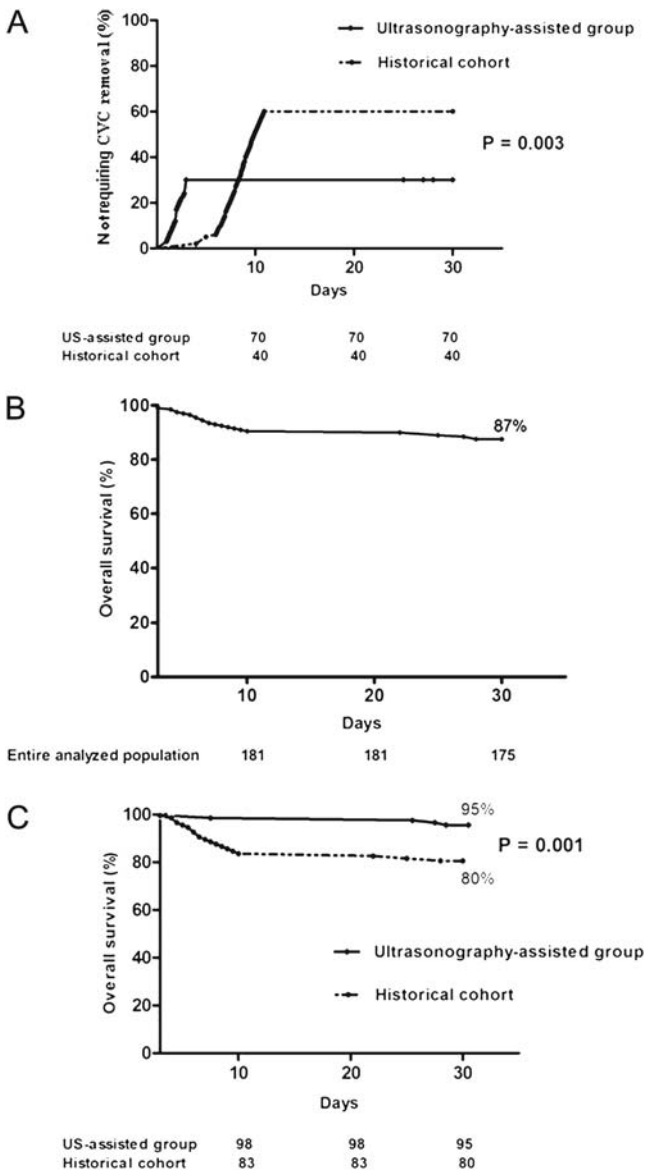

Figure 2. Probability of removing the central venous catheter in patients with bloodstream infection after chemotherapy for acute leukemia, in the historical cohort and in the ultrasonography-assisted group (A). Overall survival of the entire population analyzed (B), and of patients in the historical cohort (n = 100) and the ultrasonography-assisted group (n = 100) (C). Days, days from bloodstream infection onset; US, ultrasonography. The number of patients without events at each time point is given beneath the graph.

distributed in the two series. Death occurred in 5 of the 100 patients in the prospective series. Thus, patients in the ultrasonography-assisted group achieved a 95% overall survival. In contrast, 20 of the 100 patients in the historical cohort died. Consequently, overall survival was 80% in the historical cohort ($P < 0.01$; Figure 2). The causes of death were cerebral hemorrhage ($n = 1$), underlying malignancy progression ($n = 2$), and BSI ($n = 17$) in the historical cohort and cerebral hemorrhage ($n = 2$), underlying malignancy progression ($n = 2$), and BSI ($n = 1$) in the ultrasonography-assisted group. Mortality rate was 34% (12/35) for Gram-negative bacteremia (*E. coli*, nine patients; *Acinetobacter baumannii*, one patient; *Stenotrophomonas maltophilia*, one patient; *Klebsiella pneumoniae*, one patient), 3% (2/60) for Gram-positive bacteremia (*Corynebacterium jeikeium*, one patient; *Staphylococcus haemolyticus*, one patient), and 60% (3/5) for fungemia (*Candida parapsilosis*, three patients) in the historical cohort compared with 2% (1/50) for Gram-positive bacteremia (*S. haemoliticus*) in the ultrasonography-assisted group. Thus, infection-related mortality was 17% in the historical cohort versus 1% in the ultrasonography-assisted group ($P < 0.01$).

discussion

CVC removal in neutropenic patients with BSI is controversial [1, 4, 11, 14]. The clinically driven strategy—a standard approach—leaves to the attending physician the decision to remove the CVC on the basis of clinical findings suggestive of complicated infection [1, 4, 11].

The present experience is the first example so far reported of ultrasonography-driven strategy in neutropenic patients with a long-term CVC *in situ* and BSI [5–7]. This is a prospective interventional trial based on the early identification of the settings of patients requiring CVC removal. At BSI onset, in addition to the administration of adequate antimicrobial therapy [1, 4, 11], a strict and prolonged surveillance of CVC sites was carried out by using ultrasonography. Patients with ultrasonography-detected septic thrombophlebitis [3–8] underwent prompt CVC removal [4, 9]. Patients without septic thrombophlebitis continued to undergo diagnostic work-up that spared CVC removal.

Our ultrasonography-driven strategy seems to offer advantages over a clinically driven strategy adopted in a historical cohort of patients with CVC-related BSI, balanced for clinical features to the patient prospective series. First, early ultrasonographic identification of septic thrombophlebitis together with the prompt removal of complicated catheter enabled an effective control of BSI. At 30 days follow-up, overall survival rate was significantly higher in patients in the ultrasonography-assisted group than in patients of the historical cohort. Patients not protected by ultrasonographic surveillance had a 17% risk of infection-related mortality, with the majority of events occurring relatively early. By contrast, the infection-related mortality risk was 16% points lower in patients in the ultrasonography-assisted group. Probably, the timeliness of CVC removal represented the factor that influenced the outcome in our study. Among patients with Gram-negative bacteremias and candidemias in the prospective series, CVCs were removed after 1 median day from the BSI onset, which is significantly different from the 7 median days for Gram-negative bacteremias and the 6 median days for candidemias in the historical cohort Table 2. Second, ultrasonography was significantly more effective in identifying septic thrombophlebitis than physical examination. We reported 30% of ultrasonography-detected septic thrombophlebitis versus 10% of physical examination-detected septic thrombophlebitis, with an interval between onset of BSI and diagnoses of septic thrombophlebites of 1 median day in the ultrasonography-

assisted group versus 8 median days in the historical cohort ($P < 0.01$). Physical examination is poorly able to detect patients with such complication and it entails an extent of false-negative results [5–7]. In our prospective series, *Candida non-albicans* (5/9, 55%) and *Enterobacteriaceae* spp. (15/37, 40%) were potent inductors of septic thrombophlebitis compared with *Staphylococcus* spp. (10/38, 26%). It is reasonable to assert that in the historical cohort, occult septic thrombophlebitis was present at the time of the first days of BSI, and the nonremoval of CVC together with the persistently infected intravascular thrombus were the cause of the rapid clinical worsening. Finally, we would like to underline the appropriateness of criteria used for CVC removal in the prospective series, i.e. ultrasonography-detected septic thrombophlebitis, compared with criteria taken on clinical grounds [14]. Our ultrasonography-driven strategy permitted a 50% reduction in CVC removal, i.e. more salvages of CVCs, compared with the clinically driven approach. The ability to predict BSI unlike to be complicated by septic thrombophlebitis permitted us to safely leave the CVC *in situ*. In the prospective series of the 70 patients who did not remove the CVC because the ultrasonography screening was negative, only one died for BSI. On the contrary, the clinically driven approach led to late and/or unnecessary CVC removal, as reflected by a substantial increase in the number of patients who died for infection in the historical cohort despite the large number of CVCs removed.

Our study has several limitations. First, it is a single-center nonrandomized study (comparison with retrospective series) with a small number of events, which limits the statistical results; hence, our findings need to be validated in a prospective large trial. Second, the general improvement of the management including the availability of new and effective antimicrobial drugs [4] and the particular attention to CVC removal for the existence of prospective trial by itself may have substantially influenced the outcome of patients in the prospective series. In the historical cohort, a too conservative approach was used for CVC removal, likely accounting for the deaths reported. Third, in this study, CVC-related BSIs were diagnosed without knowing the differential time to positivity between the blood samples [1, 4]. Fourth, the septic thrombophlebitis high rate in the ultrasonography-assisted group could be due to a selection of aggressive pathogens over the 13-year study period [4, 11]. Fifth, anticoagulation therapy role is not clear [1, 9] since several patients did not undergo anticoagulants for severe thrombocytopenia. Sixth, none of our patients who died underwent autopsy, which limits the knowledge of the definitive cause of the event. Finally, a number of patients were excluded from the ultrasonographic study for poorly visualized vessels within the thorax [1, 9]. Others imaging tools could be used for diagnosing septic thrombophlebitis [1, 9, 15].

In conclusion, septic thrombophlebitis is a hidden threat for neutropenic patients with CVC *in situ* and BSI [1, 4, 9, 14]. Our study underlines the importance of including an imaging modality in the frame of the diagnostic work-up to optimize the treatment of these patients [5–7]. We propose ultrasonography as new standard to scan CVC sites [1, 5–7, 9] because it provides an early diagnosis of septic thrombophlebitis. The ultrasonography is able to identify a subset of patients who need prompt CVC removal to reduce the risk of infection-related mortality [16, 17], and similarly important, it is able to salvage CVCs in a relevant number of patients.

acknowledgements

This article is dedicated to the late Bruno Rotoli for his leadership and guidance during this project. We thank Rosanna Scala for text editing.

funding

Associazione Italiana contro le Leucemie (Napoli section).

disclosure

The authors declare no conflicts of interest.

references

1. Boersma RS, Jie G, Verbon A et al. Thrombotic and infectious complications of central venous catheters in patients with hematological malignancies. Ann Oncol 2008; 19: 433–442.
2. van Rooden Cornelis J, Schippers Emile F, Barge Renée MY et al. Infectious complications of central venous catheters increase the risk of catheter-related thrombosis in hematology patients: a prospective study. J Clin Oncol 2005; 23: 2655–2660.
3. Chirinos JA, Garcia J, Alcaide ML et al. Septic thrombophlebitis: diagnosis and management. Am J Cardiovasc Drugs 2006; 6: 9–14.
4. Mermel A, 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.
5. van Rooden Cornelis J, Rosendaal Frits R, Barge Renèe MY et al. Central venous catheter related thrombosis in haematology patients and prediction of risk by screening with Doppler-ultrasound. Br J Haematol 2003; 123: 507–512.
6. Lordick F, Hentrich M, Decker T et al. Ultrasound screening for internal jugular vein thrombosis aids the detection of central venous catheter-related infections in patients with haemato-oncological diseases: a prospective observational study. Br J Haematol 2003; 120: 1073–1078.
7. Crowley AL, Peterson Gail E, Benjamin DK, Jr et al. Venous thrombosis in patients with short- and long-term central venous catheter-associated *Staphylococcus aureus* bacteremia. Crit Care Med 2008; 36: 385–390.
8. Baarslag H, van Beek EJ, Koopman MM et al. Prospective study of color duplex ultrasonography compared with contrast venography in patients suspected of having deep venous thrombosis of the upper extremities. Ann Intern Med 2002; 136: 865–872.
9. Baskin JL, Pui CH, Reiss U et al. Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. Lancet 2009; 374: 159–182.
10. Bennet JM, Catovsky D, Daniel MT et al. Proposed revised criteria for the classification of acute myeloid leukemia. Ann Intern Med 1985; 103: 626–629.
11. Leonard A, Barry M, Sherertz RJ et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 2001; 32: 1249–1272.
12. Camera A, Villa MR, Pezzullo L et al. Central venous catheter insertion: a bedside procedure for haematological patients. Eur J Haematol 1996; 56: 93–94.
13. Picardi M, Gennarelli N, Ciancia R et al. Randomized comparison of power Doppler ultrasound-directed excisional biopsy with standard excisional biopsy for the characterization of lymphadenopathies in patients with suspected lymphoma. J Clin Oncol 2004; 22: 3733–3740.

14. O'Grady NP, Alexander M, Burns LA et al. Guidelines for the prevention of intravascular catheter-related Infections. Clin Infect Dis 2011; 52: 162–193.
15. Miceli M, Atoui R, Walker R et al. Diagnosis of deep septic thrombophlebitis in cancer patients by fluorine-18 fluorodeoxyglucose positron emission tomography scanning: a preliminary report. J Clin Oncol 2004; 22: 1949–1956.
16. Jones MA, Lee DY, Segall JA et al. Characterizing resolution of catheter-associated upper extremity deep venous thrombosis. J Vasc Surg 2010; 51: 108–113.
17. Slavin MA, Sorrell TC, Marriott D et al. Candidaemia in adult cancer patients: risks for fluconazole-resistant isolates and death. J Antimicrob Chemother 2010; 65: 1042–1051.

Annals of Oncology 23: 2128–2137, 2012
doi:10.1093/annonc/mdr578
Published online 11 January 2012

Racial disparities in Hodgkin's lymphoma: a comprehensive population-based analysis

A. M. Evens[1*], M. Antillón[2], B. Aschebrook-Kilfoy[2] & B. C.-H. Chiu[2,3]

[1]Division of Hematology/Oncology, The University of Massachusetts Medical School and the UMass Memorial Cancer Center, Worcester; [2]Department of Health Studies, The University of Chicago, Chicago; [3]The University of Chicago Comprehensive Cancer Center, Chicago, USA

Received 23 August 2011; revised 9 November 2011; accepted 15 November 2011

Background: Racial disparity has been investigated in a number of cancers; however, there remains a comparative paucity of data in Hodgkin's lymphoma (HL).
Patients and methods: We examined time-, age-, and gender-specific incidence, disease characteristics, and survival across and within races for adolescent/adult HL (age 10–79 years) diagnosed during 1992–2007 in the SEER 13 registries.
Results: A total of 15 662 HL cases were identified [11 211 non-Hispanic whites, 2067 Hispanics, 1662 blacks, and 722 Asian/Pacific Islanders (A/PI)]. Similar to whites, A/PIs had bimodal age-specific incidence, while blacks and Hispanics did not. Further, HL was significantly more common in Hispanics versus whites age >65 years ($7.0/1 \times 10^6$ versus $4.5/1 \times 10^6$, respectively, P <0.01). By place of birth, US-born Hispanics and A/PIs age 20–39 years had higher incidence of HL versus their foreign-born counterparts (P <0.05), however, rates converged age >40 years. Interestingly, from 1992–1997 to 2003–2007, A/PI incidence rates increased >50% (P <0.001). Moreover, this increase was restricted to US-born A/PI. We also identified a number of disease-related differences based on race. Finally, 5-, 10-, and 15-year overall survival rates were inferior for blacks and Hispanics compared with whites (P <0.005 and P <0.001, respectively) and A/PI (P <0.018 and P <0.001, respectively). These differences persisted on multivariate analysis.
Conclusion: Collectively, we identified multiple racial disparities, including survival, in adolescent/adult HL.
Key words: cancer, epidemiology, ethnicity, Hodgkin lymphoma, prognosis, race

introduction

Racial disparity has been investigated in a number of cancers [1–10]. Many studies have noted significant differences in incidence rates, patient and disease-related characteristics, and/or survival based on race. However, population-based survival analyses of racial disparities have been reported mostly in solid tumors (e.g. breast, colon, prostate, and lung) with recent reports in non-Hodgkin's lymphoma (HL) [6] and multiple myeloma [10]. A comparative paucity of data are available in adult HL.

In pediatric HL, Metzger et al. [11] found that disease-related features and clinical characteristics did not differ between races (white and black children). Furthermore, black children with HL had lower event-free survival (EFS) compared with white children, while both populations had similar 5-year overall survival (OS). Studies examining racial disparities in adult HL including age-specific HL incidence patterns have been reported, however they have been smaller scope (statewide), did not encompass all races (i.e. including Hispanics and Asian/Pacific Islanders (A/PI)), and/or did not include analyses by place of birth [12, 13].

The overall incidence of HL varies greatly throughout the world. Pathogenesis of this geographic discrepancy of HL incidence is not known; however, environmental and lifestyle factors have been theorized as potential factors [14]. A British

*Correspondence to: A. M. Evens, Division of Hematology/Oncology, Lymphoma Program, UMass Memorial Cancer Center, The University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA. Tel: +1-774-443-7433; Fax: +1-774-443-2298; E-mail: andrew.evens@umassmed.edu