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Prophylaxis of Central Venous Catheter-Related Thrombosis With Minidose Warfarin in Patients Treated With High-Dose Chemotherapy and Peripheral-Blood Stem-Cell Transplantation: Retrospective Analysis of 228 Cancer Patients

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Patients with a central venous catheter (CVC) undergoing high-dose chemotherapy (HDC) followed by peripheral-blood stem-cell transplantation (PBSCT) for malignancies are at high risk of thrombosis, but the use of anti-coagulant prophylaxis remains debatable in this setting of patients. We analyzed the efficacy and the safety of minidose warfarin in 228 patients in whom CVCs had been placed and who had received 292 HDC courses of therapy. The catheters remained in place for a mean of 173 (range 40–298) days. All patients received prophylactic oral warfarin in the fixed dose of 1 mg/day starting on the day of CVC insertion. Prophylaxis was interrupted during aplasia when platelet counts fell below 50,000/dL. There were no toxic deaths related to the prophylaxis. Overall there were 4 thrombotic events. Three occurrences were directly related to the catheter, while the remaining event was a deep saphenous-vein thrombosis. A number of potential predictive factors were analyzed for their impact on thrombotic events without finding any significant correlation. Four episodes of bleeding occurred, with each of these individuals having a normal INR but a platelet count below 50,000/dL. Minidose warfarin is effective and safe to use for preventing thrombotic events in this setting of patients. Am. J. Hematol. 81:1–4, 2006. © 2005 Wiley-Liss, Inc.

Key words: catheter; warfarin; transplant; chemotherapy

INTRODUCTION

Peripheral-blood stem-cell transplantation (PBSCT) requires long-term venous access for adequate cell collection by apheresis and for the administration of medications, blood products, and parenteral hyperalimentation and for blood sampling. Aside from the complications (pneumothorax, hemorrhage) associated with their initial insertion, CVCs are associated with an increased risk of thrombosis in this particular setting of patients [1–3]. In fact, routine venography of asymptomatic patients after autologous or allogeneic bone-marrow transplantation revealed a rate of thrombosis varying between 4% and 42% [4–6], and clinical thrombosis was observed in up to 31% of patients [7]. Despite these incidence figures, the use of anti-coagulant prophylaxis in cancer patients undergoing high-dose chemotherapy to reduce the risk of thrombosis, remains debatable, because many physicians are reluctant to prescribe anti-coagulant prophylaxis because of a perceived high risk of bleeding. On the basis of some

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studies that showed that minidose of warfarin (1 mg/day) reduces catheter-related thrombosis without inducing alterations in the prothrombin time (PT) or activated partial thromboplastin time (aPTT) or causes bleeding [8–11], all patients undergoing high-dose chemotherapy were given prophylaxis with minidose warfarin in our bone-marrow transplantation (BMT) unit.

The aim of this retrospective study was to evaluate the clinical efficacy and the safety of anti-coagulant prophylaxis with minidose warfarin during high-dose chemotherapy (HDT) followed by PBSCT.

PATIENTS AND METHODS

Two hundred twenty-eight patients who underwent HDC treatments followed by autologous PBSCT in our Institute between March 2000 and March 2004 were studied retrospectively. One hundred sixty-four patients received a single autologous transplantation, and 64 had tandem transplantations; the second PBSCT was performed after a median time of 75 days.

The patient characteristics and HDCT regimens used are reported in Tables I and II.

Two types of CVC were used throughout the study period. One hundred seventy-five patients (77%) received a Nutricath-S external catheter (60 cm; Vygon, Ecouen, France), and 53 patients (23%) received an Groshong external catheter (Bard Access System, Salt Lake City, UT). Under local anesthesia, all patients had the CVC positioned by a radiologist in the outpatient angiographic room. All patients received prophylactic oral warfarin at a fixed dose of 1 mg/day starting on the day of CVC insertion. Prophylaxis was interrupted when platelet counts fell below 50,000/dL. The international normalized ratio (INR) was measured 3 times per week. The prothrombin time was measured using Hemoliance RecombiPlasTin (Instrumentation Laboratory Inc., Lexington, MA), the normal value of INR being 0.90–1.18. Patients were clinically monitored for thrombotic complications from the day of line insertion through chemotherapy interruption, CVC dislocation, or patient's death. In patients who developed clinical signs of thrombosis, i.e., swelling and/or redness of the limb or venous engorgement, thrombosis was confirmed with a Doppler ultrasound examination. Patients with a documented thrombosis were treated by heparin intravenously for 5 days followed by oral anti-coagulant therapy for a period of 6 months, if possible.

Statistical analysis was performed using Pearson's method.

TABLE I. Patient Characteristics and Catheters Used

	n	%
Patients	228	
Sex		
Female	117	51
Male	111	49
Disease type[a]		
NHL	75	32
HD	48	21
Breast cancer	38	17
MM	32	14
Sarcomas	15	7
Others	18	9
Catheters used	245	
Vygon	192	78
Groshong	53	22

[a]Abbreviations: NHI; non-Hodgkin lymphoma; HD; Hodgkin disease; MM; multiple myeloma.

TABLE II. Transplant Chemotherapy (*n* = 292)

Regimen[a]	*n*	%
Melphalan	151	52
Thiotepa–melphalan	61	20
BEAM	57	19
Others	23	9

[a]Abbreviations: Melphalan; Melphalan 200 mg/mq IV on day 1; Thiotepa–melphalan; thiotepa 600 mg/mq IV on day 1 and melphalan 140 mg/mq IV on day 3; BEAM; BCNU 300 mg/mq IV on day 1, ARA-C 400 mg/mq on days 2–5, VP-16 200 mg/mq IV on days 2–5, and melphalan 140 mg/mq IV on day 5.

RESULTS

Two hundred forty-five catheters were placed in 228 consecutive patients, resulting in a total of 39,573 days in situ; platelets counts fell below 50,000 for 2,265 days (mean 11.8 days for each patient). Two hundred eleven had one CVC insertion (92%), and the remaining 17 patients had two CVC insertions (8%).

Adequate follow-up was obtained in all cases (mean, 173 days; range 40–598 days), and all patients received the planned therapy and re-infusion of stem cells through the CVC.

No deaths were directly related to the prophylaxis.

The acute complications encountered during or just after insertion were 3 pneumothoraces (1%; drainage was needed in all patients) and 3 hematothoraces (1%). No cases required an early revision of the implant for catheter malfunction, such as narrowing of the lumen or primary dislocation.

We observed 4 thrombotic events, with 3 being directly related to the catheter. Two events were subclavian vein thromboses, one was a subclavian vein thrombosis that extended to the superior vena cava,

and the remaining event was a deep saphenous-vein thrombosis. The median time between line insertion and thrombosis was 89 (range 23–157) days. All had Vygon catheters inserted. The median age was 40 years. Two patients were females, and two were males. Two patients were affected by Hodgkin disease, one by non-Hodgkin lymphoma, and one by breast cancer. They all initially received unfractionated heparin (LMWH) subcutaneously, followed by oral anti-coagulant treatment for a period of 3–6 months.

Four patients developed bleeding, all having thrombocytopenia (platelets < 50,000), but normal INR levels. The median number of platelets in these individuals was 22,000/dL (range 17,000–41,000/dL). Two patients developed menorrhagia, one patient hemorrhaged from esophageal ulcers, and one had acute hemorrhagic conjunctivitis. A number of potential predictive factors, including age, type of neoplasia, chemotherapy regimen, number of previous courses of chemotherapy at the time of presentation, and type of catheter used, were analyzed for their possible predictive value for both thrombosis and bleeding; however, no significant correlations were found.

DISCUSSION

Despite the long duration of severe thrombocytopenia, CVC-associated thrombosis is not a rare event during the harvest of PBSC and HDCT.

Sletnes et al. observed that the plasma levels of markers of activation (prothrombin fragment 1 + 2, thrombin–antithrombin complexes, fibrinopeptide A, and fibrimonomers) increased significantly in association with harvesting, and except for fibrinopeptide A, the indicators of activation were still significantly elevated 24 hr after the procedure [12].

Conlan et al. observed symptomatic thrombosis involving a vessel containing an indwelling CVC in 31% of patients with malignant lymphoma undergoing transplantation in their institution [7].

van Rooden et al. observed a 12% cumulative incidence of clinically manifest thrombosis and another 16% subclinical thrombosis in 105 patients undergoing intensive chemotherapy or stem-cell transplantation [13]. Furthermore, in another study, 33 of 277 (12%) patients receiving an allogeneic bone-marrow transplantation, developed clinical signs of a CVC-associated thrombosis, confirmed by ultrasound [14].

The reasons for this high incidence of thrombotic risk could be the low levels of factor XII and protein C that may develop during the course of high-dose therapy [15]. Furthermore, Timsit et al. [16] demonstrated that the frequency of catheter-related thrombosis is correlated with bacteremia, which was very frequent in this setting of patients.

Thrombosis is a serious complication in such patients because it causes significant morbidity in addition to increasing the risk of pulmonary embolism. The CVC often needs to be removed when the patient is still aplastic and needs parenteral hyperalimentation, intravenous medications, blood products, frequent blood sampling, etc.

Anti-coagulant prophylaxis might be useful to reduce the rate of CVC-related thrombosis. However, it should be noted that the evidence-based data on anti-coagulant prophylaxis in bone-marrow recipients with CVCs is very limited.

In a retrospective study, Lagro et al. found nadroparin to be ineffective in the prevention of CVC-related thrombosis in bone-marrow transplant recipients [17]. The occurrence of thrombosis was 17 out of 221 (8%) in patients taking prophylaxis compared to 10 out of 161 (6%) patients receiving no prophylaxis. The PROTEKT study was a randomized trial of the prevention of CVC-related thrombotic complications with reviparin sodium in children affected by leukemia. This study was prematurely closed because of the slow patient accrual and no benefit observed from the anti-coagulant prophylaxis [18].

On the contrary, minidose warfarin seems to be able to reduce the occurrence of symptomatic catheter-related thrombosis. In one study of 223 patients undergoing standard chemotherapy and high-dose chemotherapy supported by bone-marrow transplantation, a reduction in clinically manifest thrombosis (from 13% to 5%) was reported when 1 mg of warfarin once daily was administered. In this nonrandomized study, a group of historical controls ($n = 115$) without warfarin was used as a reference population [9].

It was clear, however, that clinicians are often reluctant to prescribe anti-coagulant prophylaxis, because of increased risk of bleeding complications in this setting of patients. Although the present study was not randomized, the results suggest that minidose warfarin in patients during high-dose chemotherapy followed by PBSCT is both safe and efficacious.

Only three patients developed a clinical thrombosis in the CVC subclavian vein, and one in the deep saphenous vein. We observed only 4 episodes of bleeding, and all four patients had an INR in the normal range although they did have thrombocytopenia. The low incidence of thrombosis and bleeding meant that potential predictive factors could not be defined. It should be noted, however, that a conservative approach was adopted during the period of aplasia following the stem-cell re-infusion, and warfarin was withdrawn when the platelet count was less

than 50,000/dL. Patients therefore did not receive the warfarin therapy for a short period time (median 11 days) when they were at greatest risk of bleeding. In conclusion, this study in a large cohort of patients and over a long time of observation, suggests that minidose warfarin is both efficacious and safe when used to reduce catheter-related thrombosis in hematological and non-hematological patients undergoing induction therapy, leukapheresis, and high-dose chemotherapy. The results of this study need confirmation in a Phase III study, with more extensive laboratory research included.

REFERENCES

1. Keung YK, Watkins K, Chen SC, Groshen S, Levine AM, Douer D. Increased incidence of central venous catheter-related infections in bone marrow transplant patients. Am J Clin Oncol 1995;18:469–474.
2. Uderzo C, D'Angelo P, Rizzari C, et al. Central venous catheter-related complications after bone marrow transplantation in children with hematological malignancies. Bone Marrow Transplant 1992;17:87–89.
3. Morrison VA, Peterson BA, Bloomfield CD. Nosocomial septicemia in the cancer patient: the influence of central venous access devices, neutropenia, and type of malignancy. Med Pediatr Oncol 1990;18:209–216.
4. Ross A, Griffith C, Anderson J. Thromboembolic complications with silicone elastomer subclavian catheters. JPEN J Parenteral Enteral Nutr 1987;6:61–63.
5. Horne MK 3rd, May DJ, Alexander HR, et al. Venographic surveillance of tunneled venous access device in adult oncology patients. Ann Surg Oncol 1995;2:174–178.
6. Haire WD, Lieberman RP, Edney J, et al. Hickman catheter-induced thoracic vein thrombosis: frequency and long-term sequelae in patients receiving high-dose chemotherapy and marrow transplantation. Cancer 1990;66:900–908.
7. Conlan MG, Haire WD, Kessinger A, Armitage JO. Catheter-related thrombosis in patients with refractory lymphoma undergoing autologous stem cell transplantation. Bone Marrow Transplant 1991;7:235–240.
8. Bern MM, Lokich JJ, Wallach SR, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters. Ann Intern Med 1990;112:423–428.
9. Boraks P, Seale J, Price J, et al. Prevention of central venous catheter associated thrombosis using minidose warfarin in patients with haematological malignancies. Br J Haematol 1998;101: 483–486.
10. Masci G, Magagnoli M, Zucali PA, et al. Minidose warfarin prophylaxis for catheter-associated thrombosis in cancer patients. Can it be safely associated with 5-fluorouracil-based chemotherapy? J Clin Oncol 2003;21:736–739.
11. Magagnoli M, Masci G, Carnaghi C, et al. Minidose warfarin is associated with high incidence of international normalized ratio (INR) elevation during chemotherapy with FOLFOX regimen. Ann Oncol 2003;14:959–960.
12. Sletnes KE, Holte H, Halvorsen S, et al. Activation of coagulation and deep vein thrombosis after bone marrow harvesting and insertion of a Hickman catheter in ABMT patients with malignant lymphoma. Bone Marrow Transplant 1996;17:577–581.
13. van Rooden CJ, Rosendaal FR, Barge RM, 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.
14. Fijnheer R, Paijmans B, Verdonck LF, Nieuwenhuis HK, Roest M, Dekker AW. Factor V Leiden in central venous catheter-associated thrombosis. Br J Haematol 2002;118:267–270.
15. Kaufman PA, Jones RB, Greenberg CS, Peters WP. Autologous bone marrow transplantation and factor XII, factor VII, and protein C deficiencies. Report of a new association and its possible relationship to endothelial cell injury. Cancer 1990; 66:515–521.
16. Timsit JF, Farkas JC, Boyer JM, et al. Central vein catheter-related thrombosis in intensive care patients: incidence, risks factors, and relationship with catheter-related sepsis. Chest 1998; 114:207–213.
17. Lagro SW, Verdonck LF, Borel Rinkes IH, Dekker AW. No effect of nodroparin prophylaxis in the prevention of central venous catheter (CVC)-associated thrombosis in bone marrow transplant recipients. Bone Marrow Transplant 2000;26:1103–1106.
18. Massicotte P, Julian JA, Gent M, et al. An open-label randomized controlled trial of low molecular weight heparin for the prevention of central venous line-related thrombotic complications in children: the PROTEKT trial. Thromb Res 2003;25:101–108.