CASE REPORT Libri Oncol., Vol. 40 (2012), No 1-3, 21 – 25

RECURRENT DEEP VENOUS THROMBOSIS IN A CANCER PATIENT DURING COUMARIN THERAPY – A CASE REPORT

IRENA MIHIĆ LASAN[1], MARIJA SKOKO[1], JELENA CULEJ[1], TIHA VUČEMILO[1], GORANA KRAJAČIĆ KARAS[1] and DEANA ŠTURM[1]

[1]Department for Transfusion Medicine, University Hospital for Tumors, University Hospital Center Sestre milosrdnice, Zagreb, Croatia

Summary

Cancer patients have a four-fold increased risk of developing venous thromboembolism (VTE), relative to the general population. Affecting about 15 % of patients with cancer, it is presenting a great challenge for prophylaxis and treatment. The standard treatment for acute venous thromboembolism consists of initial therapy with low-molecular-weight-heparin (LMWH) followed by long-term therapy with an oral anticoagulant. Despite the use of standard anticoagulant therapy, there is also a three-fold risk of recurrent venous thromboembolism for cancer patients.

In this case report the authors report a case of a 60 year old patient with carcinoma of unknown primary site, who despite standard anticoagulant therapy developed recurrent deep vein thrombosis.

KEY WORDS: *cancer, recurrent venous thromboembolism, anticoagulant therapy, LMWH*

RECIDIV DUBOKE VENSKE TROMBOZE TIJEKOM TERAPIJE KUMARINIMA U BOLESNIKA S KARCINOMOM -PRIKAZ SLUČAJA

Sažetak

Bolesnici s karcinomom imaju četiri puta povećan rizik od razvoja venskog tromboembolizma (VTE), u usporedbi sa zdravom populacijom. Oko 15% bolesnika s karcinomom razvije VTE što predstavlja veliki izazov za profilaksu i liječenje. Standardno liječenje akutnog venskog tromboembolizma počinje sa nisko molekularnim heparinom (LMWH) nakon čega slijedi oralna antikoagulantna terapija. Usprkos terapiji, bolesnici s karcinomom imaju tri puta povećan rizik razvoja recidiva venskog tromboembolizma.

U prikazu slučaja prikazan je 60-godišnji bolesnik s karcinomom nepoznatog sijela, koji je usprkos antikoagulantnoj terapiji imao recidiv duboke venske tromboze.

KLJUČNE RIJEČI: *karcinom, recidiv venskog tromboembolizma, antikoagulantna terapija, niskomolekularni heparin (LMWH)*

INTRODUCTION

The realtionship between cancer and venous thromboembolism (VTE) has been recognized for almost 200 years. Initially, French physician Armand Trousseau was credited for finding an association between thrombosis and cancer in 1865, but it has since been recognised that Bouillard made the first description of deep vein thrombosis in cancer patients 42 years earlier – in 1823. Deep venous thrombosis (DVT) and pulmonary embolism (PE) are commonly known as venous thromboembolism (VTE).

One of the most frequent hematological complications encountered by the practicing oncologist is disordered coagulation, with VTE affecting

approximately 15% of all cancer patients. VTE can even present itself as an early manifestation of cancer. It is the second leading cause of death for cancer patients, although obviously in many of these patients, thromboembolic disease represents only one of many complications of the end-stage patient (1-3).

Cancer patients have a four-fold increased risk of developing venous thromboembolism, relative to the general population. They also have a three-fold risk of recurrent venous thromboembolism (4).

Duplex ultrasound is the preferred investigation for the diagnosis of initial and recurrent deep venous thrombosis. Clinical predictors of recurrence include male gender, increasing age and body mass index, active malignancy and neurological disease with paresis of the extremities. Laboratory abnormalities that predict recurrence include thrombophilias such as antiphospholipid antibodies, deficiency of protein C, S or antithrombin and the Factor V Leiden or prothrombin gene mutations.

D-dimer is a thrombous breakdown product that is almost always detected in the blood of patients with DV (5).

Management of thrombosis in patients with cancer has changed signifcantly in the past decade, but remains firmly dependent on the use of anticoagulants.

The standard treatment for acute venous thromboembolism consists of initial therapy with low-molecular-weight-heparin followed by long-term therapy with an oral anticoagulant (6). This approach is highly effective in most patients, but patients with cancer have a substantial risk of recurrent thromboembolism and hemorrhagic complications (7, 8).

Furthermore, oral anticoagulant therapy is problematic in patients with cancer.

Drug interactions, malnutrition, vomiting and liver dysfunction can lead to unpredictable levels of anticoagulation. Invasive procedures and thrombocytopenia caused by chemotherapy often require interruption of anticoagulant therapy and poor venous access can make laboratory monitoring difficult. These limitations may contribute to the higher risk of recurrent thromboembolism and bleeding in parients with cancer than in patients without cancer (7, 8).

CASE REPORT

A 60 year old male patient with carcinoma of unknown primary site, who despite standard anticoagulant therapy developed recurrent deep vein thrombosis was admitted to our Department of oncology in August 2012.

One year before, this patient, who until then suffered no serious illness, was diagnosed with right-sided pleuropneumonia. Cytological examination found only reactive mesothelial cells, partly multinuclear, with lymphocytes and erythrocytes, which was treated with parenteral antibiotic therapy.

Check-up one month later showed a favorable course of pleuropneumonia and radiological regression of the encapsulated pleura was observed. In January 2012 a follow-up examination showed a complete regression of pleuropneumonia without radiological residues and no functional consequences.

The laboratory result of CYFRA 21-1 tumor marker was 2.39 µg/L (normal <3.3 µg/L).

In March 2012 the patient suffered an ischemic stroke, which was verified by neuroradiology.

One month later he was diagnosed with extensive deep venous thrombosis (DVT) popliteal vein of the right leg. Laboratory results showed d-dimeri 9943 µg/L (normal < 500 µg/L), CEA 4,4µg/L (normal < 2.5 µg/L) and PSA 10.4 µg/L (normal < 4 µg/L). He was then examined by an urologist for a prostate biopsy, which was negative. The patient was then treated with LMWH, following a gradual transition to oral anticoagulant therapy.

A month later he was readmitted with an extensive recurrent DVT of the same leg. He was again treated with LMWH, with a gradual transition to oral anticoagulant therapy.

In June 2012 the patient was again hospitalized due to pericardial and pleural effusion. Pericardiocentesis and pleural puncture were done to obtain cytological results, which both indicated malignant epithelial cells.

Of tumor markers, CYFRA21-1 was now significantly higher (8.75 µg/L), CEA 4.18 µg/L and PSA 11,3 µg/L. The patient underwent an extensive diagnostic evaluation, which did not locate the primary site of the neoplastic processes.

One month later he was diagnosed with thrombophlebitis of the left upper arm, and a pro-

gression of the lower extremity DVT, despite anticoagulant therapy. Thus, a LMWH treatment (fraxiparine 1x 0.8ml sc) through an outpatient clinic was proposed and the patient was referred to our hospital for further treatment and medical care, where he started with his first cycle of chemotherapy on 31.07.2012.

Two weeks later, the patient was admitted to our hospital for recurrent DVT of common femoral vein (VFC), superficial femoral vein (VFS), popliteal vein (VP) and the posterior tibial vein of the right leg and now became a dual therapy (fraxiparine 0.8 ml sc 2x1 and martefarin and 3 mg). The result of d-dimer was 36656 μg/L. The patient started wearing compression stockings during the day.

At a follow-up examination in October, the patient stated that the leg isn't painful nor swollen, and the pain felt while walking or standing for a longer period is negligible. At this moment the patient finished his third chemotherapy cycle.

DISCUSSION

Cancer patients with venous thromboembolism (VTE) are at high risk of recurrent VTE despite standard anticoagulation. To date, very little published literature is available to guide the treatment of cancer patints with recurrent VTE.

Up to 9 % of patients with cancer treated with LMWH and 20 % of those treated with warfarin can develop recurrent VTE. Studies have suggested that the presence of metastasis, younger age, or a short interval between VTE and cancer diagnosis (3 months) are predictors of recurrent thrombosis despite anticoagulation. (10, 11). Whether the risk factors that increased the risk of a first episode of thrombosis also contribute to a higher risk of recurrent thrombosis is unknown. Although randomized controlled trial data are lacking to guide optimal management in oncology patients with recurrent thrombosis, observational data and increasing clinical experience support the use of LMWH in this setting. In patients who develop a recurrence while on warfarin therapy, the recommended practice is to switch these patients to LMWH because it is more efficacious than warfarin .Raising the intensity of warfarin therapy is not recommended because of a potential for increasing bleeding without a benefit in reducing recurrent VTE. Patients with cancer have a high risk of bleeding and a high risk of recurrent thrombosis despite achieving therapeutic and even higher international normalized ratios (INRs).

Dose escalation appears to be effective in the majority of patients who develop a recurrence while on LMWH. In a small cohort study of oncology patients with recurrent thrombosis while on LMWH or warfarin, escalating the dose of LMWH by 20% to 25% or switching to LMWH, respectively, was effective in preventing further thrombotic episodes.(4).

Carrier et al (2008) demonstrate in a retrospective cohort study that recurrent VTE in cancer patients can be effectively and safely managed by escalating the dose of LMWH or switching to LMWH from warfarin. The high rate of response to dose escalation suggests that recurrent VTE in cancer patients might be a consequence of „resistance" to standard doses of LMWH, and the higher doses are needed. This study also shows that the median survival of patients with recurrent VTE, especially following a second recurrent VTE, is very poor in cancer patients (5).

Another study, by Lee et al (2003) shows that the risk of symtomatic, recurrrent thromboembolism among patients with active cancer is significantly lower with dalteparin therapy than with oral anticoagulant therapy (9).

Should the treatment of thromboembolic disease be any different for cancer patients than it is for noncancer patients? One concern is that cancer patients who are anticoagulated might have an increased risk of hemorrhage due to tumor, thrombocytopenia, or concurrent coagulation disorders. Retrospective studies do not provide a clear answer. Some did not find coexistent malignancy to be a risk factor for major hemorrhage during anticoagulation (12, 13) while some did (14). In a prospective cohort study, cancer patients who received warfarin (VKA) for the treatment of DVT and/or PE were no more likely than controls to have hemorrhage (15, 16). A second concern is that compared to patients with nonmalignant disease, cancer patients are more likely to have a recurrence on warfarin or after warfarin is stopped (17-20). Some authors suggest that instead of anticoagulating for 6-24 weeks for a first DVT, cancer patients need to be anticoagulated until there is no evidence of disease. Therefore, in treating a cancer

patient with thromboembolic disease, the oncologist faces a situation where there may be a slightly greater risk of hemorrhage, but also a greater risk of recurrent thrombosis. In most nonmoribund cancer patients, anticoagulation for thromboembolic disease is usually begun unless potential contraindications exist.

Prandoni showed that recurrent VTE in oncology patients was 1.72 times more likely than for patients without cancer. There are no clear clinical data to guide the response to this situation. If a cancer patient has recurrent thromboembolism while on therapeutic doses of warfarin, the oncologist has three choices: A) continue warfarin at a higher target INR; B) switch to continuous intravenous unfractionated heparin or intermittent subcutaneous LWMH, or C) put in an IVC filter (17).

A final issue is whether anticoagulation provides any benefit in treating the underlying malignant disease. In vitro studies show that warfarin, heparin, fibrinolytics, and even antiplatelet agents inhibit tumor growth and metastasis (21).

Still, lots of questions remain concerning the optimal approaches for preventing and treating thrombosis in cancer patients. Primary anticoagulant prophylaxis is recommended in all oncology patients admitted to the hospital for surgical or medical reasons (22).

CONCLUSIONS

Thromboembolic disease is a frustrating and common complication in patients with cancer.

Cancer patients with recurrent VTE have a poor prognosis. The biochemical basis of the thrombophilia of malignancy is poorly understood and studies to unravel its cause and relationship to the underlying malignancy are sorely needed. Current treatment for DVT and PE in cancer patients includes heparin, warfarin, and sometimes IVC filters. The last option is usually reserved for those patients who are not candidates for anticoagulation. Since heparin provides some additional antithrombotic effects that warfarin lacks, it will be important to study whether LMWH may be better than warfarin in the long-term treatment of venous thromboembolism. Furthermore, there is suggestive evidence that warfarin and heparin may actually enhance cancer survival rates; prospective studies are currently underway to address this issue (3).

Risk-Assessment models, targeted prophylaxis, anticoagulant dose escalation for treatment, and ongoing research studying. The interaction of coagulation activation in malignancy may offer improved outcomes for oncology patients (23).

Identifying patients at increased risk for recurrent VTE during anticoagulant therapy, and the time course of recurrence, is clinically relevant for two reasons:

1. this information may help clinicians decide about the frequency of clinical surveillance and ther appropriateness of outpatient treatment of VTE

2. early detection and treatment of recurrent DVT, when the size and occlusiveness of the thrombus are less, may result in improved thrombus regression and a decreased risk of the post-thrombotic syndrome(24).

REFERENCES

1. Green KB, Silverstein RL. Hypercoagulability in cancer. Hematol Oncol Clin North Am 1996;10:499-530.
2. Donati MB. Cancer and thrombosis. Haemostasis 1994;24:128-131.
3. Letai A, Kuter DJ. Cancer, Coagulation and Anticoagulation. The Oncologist 1999; 4:443-449.
4. Carrier M, Le Gal G, Cho R, Tirney S, Rodger M, Lee AY. Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. J Thromb Heamost 2009; 7: 760-5.
5. Gibbs H. The diagnosis of recurrent deep venous thrombosis. Aust Prescr 2007;30:38-40.
6. Hyers TM, Agnelli G, Hull RD, et al. An-tithrombotic therapy for venous thromboembolic disease. Chest 2001;119:Suppl:176S-93S.
7. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancyand achieved international normalized ratio: a retrospective analysis. J Clin Oncol 2000;18:3078-83.
8. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100: 3484-8.
9. Lee AYY, Levine MN, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-15.

10. Trujillo-Santos J, Nieto JA, Tiberio G, et al. Predicting recurrences or major bleeding in cancer patients with venous thromboembolism. Findings from the RIETE Registry. Thromb Haemost. 2008;100:435-439.
11. Lee A Y, Parpia S, Julian J, et al. Risk factors for recurrent Thrombosis and anticoagulant-related bleeding in cancer patients. J Clin Oncol.2009;27(15S):9565.
12. Landefeld CS, Cook EF, Flatley M et al. Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. Am J Med 1987;82:703-713.
13. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am J Med 1989;87:144-152.
14. Gitter MJ, Jaeger TM, Petterson TM et al. Bleeding and thromboembolism during anticoagulant therapy: a population-based study in Rochester, Minnesota. Mayo Clin Proc1995;70:725-733.
15. Bona RD, Sivjee KY, Hickey AD et al. The efficacy and safety of oral anticoagulation in patients with cancer. Thromb Haemost 1995;74:1055-1058.
16. Bona RD, Hickey AD, Wallace DM. Efficacy and safety of oral anticoagulation in patients with cancer. Thromb Haemost 1997;78:137-140.
17. Prandoni P, Lensing AWA, Cogo A et al. The long term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125:1-7.
18. Moore FD, Osteen RT, Karp DD et al. Anticoagulants, venous thomboembolis, and the cancer patient. Arch Surg 1981;116:405-407.
19. Clarke-Pearson DL, Synan IS, Creasman WT. Anticoagulation therapy for venous thromboembolism in patients with gynecologic malignancy. Am J Obstet Gynecol 1983;147:347-369.
20. Martins RG, Colowick AB, Ewenstein BM et al. Anticoagulation in cancer patients with venous thromboembolic disease. Blood 1997;909(suppl 1):297a.
21. Hejna M, Radere M, Zielinski CC. Inhibition of metastases by anticoagulants. J Natl Cancer Inst 1999;91: 22-36.
22. Lyman GH, Khorana AA, Falanga A,et al. American Society Of Clinical Oncology guide line: recommendations for venous Thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol. 2007;25:5490-5505.
23. Lee AYY. Thrombosis in Cancer: an update on prevention, treatment, and survival benefits of anticoagulants. Hematology Am Soc Hematol Educ Program. 2010;2010:144-9.
24. Douketis JD, Foster GA, Crowther MA, Prins MH, Ginsberg JS. Clinical Risk Factors and Timing of Recurrent Venous Thromboembolism During the Initial 3 Months of Anticoagulant Therapy. Arch Intern Med. 2000;160(22):3431-3436.

Author's address: Irena Mihić Lasan, Department for Transfusion Medicine, University Hospital for Tumors, University Hospital Center Sestre milosrdnice, Zagreb, Croatia. E-mail: irenalasan@net.hr