

Anticoagulation for breast cancer patients with mechanical heart valve: complications and the novel therapeutic strategy

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Abstract

Oncology patients with mechanical heart valves (MHV) represent a fragile category that needs more attention regarding its management. Patients with MHVs demand lifetime anticoagulant therapy in order to hinder thrombosis of the mechanical valve, a main trouble that can determine serious complications or death. The management of anticoagulant therapy in oncological patients with MHV is challenging due to its great confusion and controversies, being necessary to develop an optimal treatment in order to obtain good hemostasis. We report a clinical case of a 75 year-old woman with breast cancer and mechanical heart valve that developed postoperative bleeding complication with a large hematoma that needed intervention in order to establish an optimal hemostasis. The aim of this case report is to discuss possible effects of anticoagulants and report current data of new direct anticoagulants in cancer associated mechanical heart valves.

Keywords: Mechanical heart valve, breast cancer, hemorrhage, anticoagulant therapy, direct oral anticoagulant

Introduction

Patients with bioprosthetic heart valves (BPHVs) diagnosed with gynecological cancer, represent a challenge when it comes to establish an optimal anticoagulant therapy during perioperative period. Low molecular weight heparins (LMWHs) represent the first choice for long-term administration of oncologic pathologies associated thrombosis [1]. The therapy with LMWH in this fragile category is challenging, and even on therapeutic dosing, there is still a high rate of recurrent bleeding and thrombosis complications compared with non-oncologic patients [2]. The use of Warfarin is also controversial among mechanical heart valves (MHVs) patients. A cohort study, reveals that MHV carriers have a greater risk for developing breast cancer compared with BPHV patients, suggesting that screening for breast cancer should be implemented among female patients who necessitate MHV replacement [3].

The new direct oral anticoagulants (DOACs) are very attractive to be use in oncological area due to their oral administration without the need of monitoring. However, there are various concerns regarding the usage of these therapies in cancer patients because of the complications that can occur and may affect the drug delivery, metabolism, clearance or absorption. In addition, there are worries for the interaction of DOAC and some common chemotherapies and / or hormonal therapies that may determine uncertain pharmacokinetics [1].

Case report

A 75-years-old patient known with MHV (under chronic anticoagulant treatment with Acenocoumarol 4mg/day), was admitted in the Department of Gynecology of Clinical Hospital "Cuza Voda" Iasi, Romania, accusing the appearance of a nodular swelling with 15 mm length situated on the left breast topography, for further investigations. Her pathological history revealed heart failure NYHA class III and atrial fibrillation under treatment.

Physical examination revealed a 15 mm length tumor mass in the upper-inner quadrant of the left mammary gland situated at 2.2 mm depth from the tegument. The tumor was immobile and fixed to adjacent tissues, having a rough consistency. No evidence of breast asymmetry, nipple discharge or skin changes were find, neither the presence of lymphatic nodes in the supraclavicular and axillary regions.

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The breast ultrasound examination revealed in the upper-inner quadrant of the left mammary gland, at 10:00 o'clock, a hypoechoic slightly non-homogeneous tumor mass of 11/9 mm with irregular margins and parenchymal distortion. The Doppler evaluation shown a mainly avascular tumor. Contrariwise, in the left axillary topography, a hypoechoic mass of 66/44.4 mm with slightly non-homogeneous echogenicity and per hilar fat tissue was identified, presenting vascular flow among the peripheral area.

After the cardiology examination performed one week before the surgery, we followed the recommendations and changed the Acenocoumarol treatment to Enoxaparin 6000 IU/0.6 ml twice per day until 12 hours before the surgery. Moreover, we took care that bacterial endocarditis prophylaxis to be done during the surgery. Echocardiography examination was within normal, showing a moderate mitral regurgitation grade II, tricuspid regurgitation grade I, no more than 55% left ventricular ejection fraction, and empty heart cavities without any thrombus. A sentinel lymph node was distinguished during the lymphoscintigraphy after injection of Tc⁹⁹ nanocolloids.

Madden mastectomy surgery was performed in order to treat the breast cancer. During the intraoperative time the tissue probe was sent for extemporaneous examination that confirmed a 15 mm diameter invasive

ductal carcinoma of no special type (NST), within safety oncologic limits. In the axillary region was identified a cluster of 3 lymph nodes of which just one of 5 mm diameter, presented 230 counter radioactivity. Unfortunately, due to its small size of the sentinel lymph node, the pathologist could not work the probe. In the postoperative time, the patient went under Enoxaparin 6000 IU/0.6 ml per 12 hours, Cefotaxime 2g/12 hours and anti-inflammatory drugs. The blood tests were abnormal within WBC= 10.76 10³/uL, NEU= 8.29 10³/uL, Fibrinogen= 405.4 mg/dl, Prothrombin time= 23.1 (sec), Prothrombin index= 58%, and Urea= 72 mg/dl.

Clinical examination on the 5th day after the surgery objectified on the left breast topography, an increased size mass beyond the surgical suture due to a hematoma organization. The blood tests reveal: HGB= 7.8 g/dL, HCT= 22.1%, and PLT= 128 10³/uL, but normal values of the coagulogram parameters. A second surgical intervention had been performed in order to establish good hemostasis and approximately 200 ml of blood and clots were suctioned. After the second intervention, the anticoagulant dose was decreased to 4000 IU/0.4 ml of Enoxaparin and the addition of Gentamicin 80mg x3/day was made. Postoperative evolution was favorable and a week after the second intervention low molecular weight heparin (LMWH) anticoagulant treatment was switched back with Acenocoumarol therapy.



Figure 1. Ultrasound aspects of invasive ductal carcinoma (NST)

Discussions

After we chosen a lower dose of anticoagulant, different than the guidelines recommended, we obtained better results without any further hemorrhages episodes. These disclosures opened new anticoagulant treatment options for patients with MHV, but furthers studies are needed.

According to guidelines, the management of antithrombotic treatment in oncologic patients with MHV should be personalized with the application of some general therapeutic principles. For this category of patients, the intraoperative hemorrhage risk is superior compared with the venous thromboembolism (VTE) risk determined by interrupting the vitamin K antagonist (VKA) therapy within 2-4 days forward the surgery. It is recommended to use ``bridging therapy`` which includes the use of alternative anticoagulation agents that can be stopped and restarted before and immediately after the intervention, normally 12 to 24 hours after. Bridging anticoagulation, using

unfractionated heparins (UFHs) or low-molecular weight heparins (LMWHs), should be initiated when INR levels are

lower than 2.0, normally 2 days anterior to surgery. It should be turned off within 4-6 hours for UFH and 12 hours for LMWH before the procedure [4]. For cancer associated with thromboembolic complications of MHV, the anticoagulant therapy recommended consist of VKA, non-VKA oral treatment and LMWH [5].

In the presented case, the anticoagulant therapy was initially introduced according to guidelines recommendations. Still, the patient suffered postoperative bleeding, being necessary to establish hemostasis in a second intervention and to adjust the LMWH doses. Plaja et al. (2018) reported in a retrospective study the anticoagulation management of thrombotic and bleeding management in patients with cancer and MHV that were treated for long-term period using VKA. In a five year-period of follow up, they found a low incidence of thrombosis compared with a higher incidence of bleeding among the patients who were anticoagulated with VKA.

Moreover, the bleeding incidence was tightly correlated with the surgical treatment [6].

The novel direct oral anticoagulants (DOACs) are nowadays used as the main therapeutic choice in patients with non-valvular atrial fibrillation (AF). Direct oral anticoagulants have shown their efficacy and safety in atrial fibrillation associated with cancers [7].

An observational study of 76 patients who associated AF and malign diseases recorded a decreased global incidence of hemorrhage episodes (3.9%) with a mean annual incidence of 1.4%, encountering minor bleeding in only 9 patients (11.8%). It was proved that presents a good tolerance, with minimum rate of discontinuation [8-10].

Russo et al. conducted a small size multicenter observational study that included 111 patients in order to investigate the safety and efficacy of DOACs in AF patients with bioprosthetic valve (BPV) or before surgical treatment for valve repair. They found DOACs to be a good and valid alternative treatment for AF patients with BPV or prior to surgery. To what regards the use of dabigatran as anticoagulant treatment for patients with AF and MPV is seems to be an inadequate option due to its increased risk of thromboembolism (5% in dabigatran group and 0% in warfarin group) and hemorrhage (4% in dabigatran group and not more than 2 % in the warfarin group) [11]. In the contrast, another study evaluated the effect of rivaroxaban in 7 patients with mechanical mitral prosthesis and found no thromboembolic or bleeding events in 90 days of follow-up [12].

Nowadays, the development in different technological areas improved the adhesion of a thin biomaterial film to a biocompatible surface and brought amazing benefits on mechanical heart valve feasibility, excluding various side effects caused by this [13-17]. The anticoagulation management for varied cardiac-specific conditions such as myocardial infarction or mechanical prosthetic heart valves is changing in dynamic, being necessary to develop new strategies of treatment [18-20]. However, no randomized clinical trials have been organize, regarding anticoagulation management in different types of cancer with mechanical heart valves, and current guidelines are sustained only by reduced retrospective series.

The engineering development have been always considered the foundation of various medical sciences to what consider the treatment techniques such as cardiothoracic surgery, orthopedics, or others [21]. The classic surgery represents an ancient treatment that is rarely used in the developed countries and new devices make the difference when it comes to the postoperative long term prognostic.

Conclusion

Screening for breast cancer should be consider for all the patients that go for MHV replacement, if the association between VKA and MHV will be encounters in their management.

The DOAC therapies are uncertain, regarding pharmacokinetics in oncological patients with MHV and further studies must be conduct. There is a lack in the management of this fragile category of patients and more attention needs to be given for their long-term assessment.

Conflict of Interest

Authors have no conflict of interest to disclose

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