International Heart and Vascular Disease Journal • Volume 6, № 19, September 2018

Journal of the Cardioprogress Foundation

LEADING ARTICLE

Cardiovascular Management in Cancer Patients With Thrombocytopenia

Tonusri Nag[1], Cynthia Taub[2], Mohammad Hassan Khan[1], Wilbert S. Aronow[1]*

[1]Department of Medicine, Cardiology Division, Westchester Medical Center and New York Medical College, Valhalla, NY, USA

[2] Department of Medicine, Albert Einstein Medical College, Bronx NY, USA

Authors

Tonusri Nag, DO, Resident.

Cynthia C Taub, MD, Professor of Medicine and Director of Noninvasive Cardiology

Mohammad Hasan, MD, Cardiology Fellow.

Aronow Wilbert, MD, Professor of Medicine and Director of Cardiology Research Westchester Medical Center and New York Medical College.

Abstract

Cardiovascular disease and cancer are two of the leading causes of death worldwide. Although these disease processes are separate, they share a number of common risk factors. With millions of cancer survivors, the prevalence of coronary artery disease in cancer patients will continue to increase. Chemotherapy/radiation therapies carry a risk of cardiotoxicity and accelerated atherosclerosis. Hence, management of acute coronary syndrome (ACS) in this subset of cancer patients is challenging. There are limited established management strategies to address the management of ACS in cancer patients.

Thrombocytopenia in cancer patients presenting with ACS complicates the management of ACS requiring intervention, dual antiplatelet therapy, and stent placement. Randomized trials are lacking in these patients. The complexity of managing patient with malignancy who is concurrently suffering from ACS and thrombocytopenia requires attention to management of these patients. This review article intends to highlight the pathophysiology of cancer- related thrombocytopenia and management of these patients with coronary artery disease.

Keywords: *acute coronary sy14ndrome, Cancer, Thrombocytopenia, Chemotherapy.*

Conflict of interest: None declared.

Received: 01.08.2018
Accepted: 07.08.2018

* Corresponding author. Tel.: (914) 493-5311. E-mail: wsaronow@aol.com

Introduction

Cardiovascular disease and cancer are two of the most common causes of mortality in the United States (1). Common risk factors for cardiovascular disease are also established predisposing factors for developing cancer including hypertension, hyperlipidemia, smoking, and family history, placing a large portion of the population at risk for these two major causes of morbidity and mortality [1]. Often overlooked are the short- and long-term effects of cancer treatment on cardiovascular disease. Cancer-related thrombocytopenia, either acute or chronic, poses a challenge in the management of coronary artery disease (CAD). Despite advances in the management of acute coronary syndromes (ACS) and chronic CAD including drug-eluting stents and dual antiplatelet therapy (DAPT), altered physiology and limited data in cancer patients lead to management dilemmas, especially with respect to thrombocytopenia. Thrombocytopenia not only increases the risk of bleeding, but also changes the hemodynamic milieu to promote a prothrombotic state due to the properties of platelets in thrombocytopenia. With the aging population and rising prevalence of cancer patients and survivors, the implications of chemotherapy and radiation therapy-induced thrombocytopenia on cardiovascular disease need to be understood. This review will discuss the pathophysiology of CAD in cancer patients with thrombocytopenia, the identification of cancer patients at risk for thrombocytopenia and CAD, and management strategies for ACS and CAD in cancer patients with thrombocytopenia.

Molecular Mechanisms of Ischemia in Cancer Patients with Thrombocytopenia

Platelets are the first responders to any acute injuries. They play a major role in pathogenesis of thrombosis and ischemic events through activation, aggregation, and degranulation. The activation sequence starts as circulating platelets come in contact with exposed collagen fibers of injured endothelium or extracellular matrix of tumor cells [2]. Once activated, degranulation of platelets releases adhesion molecules, coagulation factors, fibrinolytic factors, growth factors, and pro-inflammatory factors [2]. Factors such as thromboxane A_2, thrombin, and adenosine diphosphate recruit additional platelets and lead to formation of thrombus as surface receptors of the platelets form bonds and aggregates. Cancer cells regulate these mechanisms in a similar way by releasing prothrombotic factors like thrombin, tissue factors, and prostaglandin E_2. Hence, the risk of thrombosis in cancer patients is even greater.

Thrombocytopenia and prothrombotic states in cancer are well known. Most malignant cells disseminate hyperactive reticulated platelets [3], tissue factor, and procoagulant factors [4, 5] which regulate the formation of thrombus (Figure 1). The incidence of arterial thromboembolism is higher within the first six month of diagnosis of cancer [6]. The pathophysiologic mechanism of thrombus formation due to active malignancy is known, but the formation of thrombosis in the setting of acquired thrombocytopenia in cancer patients remains a poorly understood topic. Evidence of accumulated tissue factors within fibrin-platelet thrombi [7, 8] and activation of the extrinsic

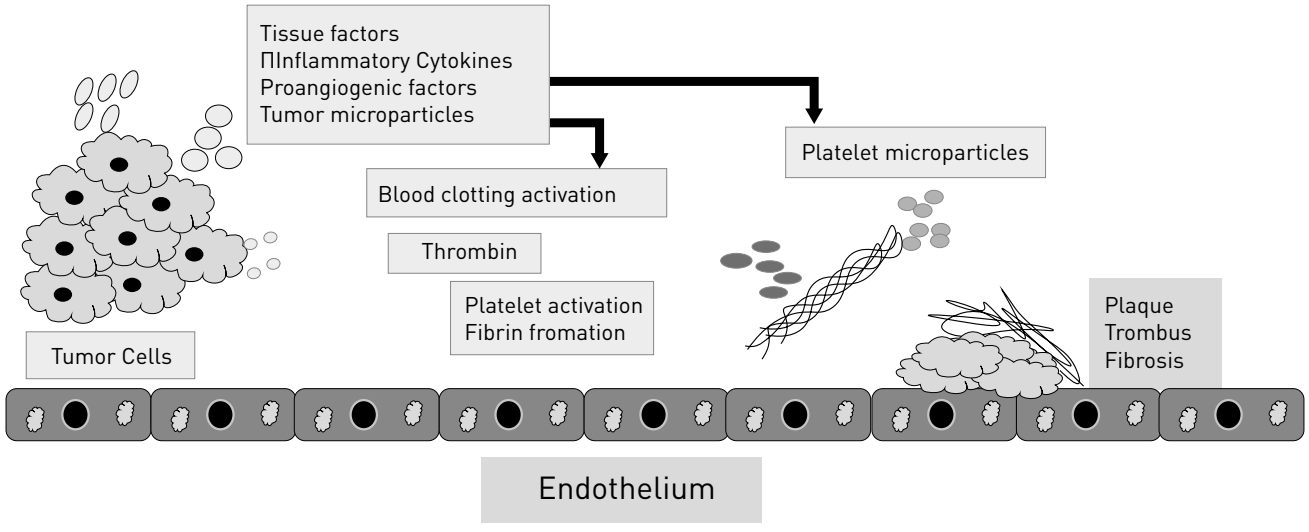

Figure 1. Tumor cells release various pro-coagulopathic particles, which enhance the extrinsic and intrinsic pathways, eventually increasing the risk of thrombus formation. This can occur both in the local vicinity and in the systemic circulation.

pathway via granules of malignant promyelocytes [8] in patients with acute promyelocytic leukemia support that severely thrombocytopenic patients are also susceptible to hypercoagulability.

Thrombocytopenia by definition is a reduced platelet count which does not protect against forming thrombus. The microvascular hemostasis and the properties of platelets are vastly affected in thrombocytopenia. It can be stated that the vulnerability of thrombus formation is due to the hypercoagulability microparticles of malignancy and the altered properties of platelets in acquired thrombocytopenia. Arterial thrombus is largely platelet rich, and hence understanding the properties of platelet in cancer state is important [9]. Chronic thrombocytopenia increases the amount of megakaryocyte production, and results in larger platelets [10]. These large platelets tend to have higher thrombotic potential and may predispose to acute cardiac events [11, 12]. In the event of a ruptured atherosclerotic plaque, these platelets are subject to high shear forces, thereby promoting adhesion and thrombus formation [13]. Furthermore, prothrombin, fibrinogen, factor V, and factor VII, all of which participate in the coagulation cascade [2], are noted to be elevated in patients with ACS and thrombocytopenia [14, 15]. Hence, platelet function rather than the absolute platelet count is a driving factor in the development of ACS in cancer patients with thrombocytopenia.

Mechanisms of Chemotherapy and Radiation-Induced Ischemic Heart Disease

Many chemotherapeutic agents have been identified in developing ischemia and arterial thrombosis. Chemotherapy alters cardiovascular infrastructure through remodeling of the microvasculature architecture by direct vascular toxicity and cellular damage, which can result in CAD, ACS, stroke, heart failure, and arrhythmias. Angiogenesis inhibitors, alkylating agents, antimetabolites, and antimicrotubules are known to cause cardiovascular toxicities through endothelial dysfunction, platelet aggregation, reduced levels of nitrous oxide, elevated levels of reactive oxygen species, and vasospasm [16].

One of the many unwanted side effects of chemotherapy is acquired thrombocytopenia which also contributes to myocardial ischemia. Thrombocytopenia predisposes patients with CAD to ischemic events within 30 days [17, 18]. Table 1 lists some of the common chemotherapeutic agents known to cause myocardial ischemia and thrombocytopenia.

Table I. **Chemotherapeutic agents associated with myocardial ischemia and thrombocytopenia**

Chemotherapeutic Agent	Uses
Cisplatin [19-21]	Squamous cell of head and neck, bladder, cervical, ovarian, testicular, mesothelioma.
Sunitinib [22, 23]	Renal cell, gastrointestinal stromal tumor, pancreas tumor
Pozapanib [24, 25]	Renal cell, soft tissue sarcoma
Nilotinib [26-28]	Chronic Myeloid Leukemia
Ponatinib [29, 30]	Chronic Myeloid Leukemia
Capecitabine [31, 32]	Colorectal, breast cancer
5-Flourouracil and Sorafenib [33, 34]	Colorectal, pancreas, gastric, breast, squamous cell cancer of head and neck

Radiation therapy is used in approximately 50% of cancer patients [35]. The site and doses of radiation are significantly linked to developing cardiac disease. For example, childhood cancer survivors who received high doses of radiation are at high risk of developing heart disease [36]. Increased cardiac mortality has been associated with left- sided breast cancer radiation as opposed to right-sided breast cancer [37, 38]. The most common manifestations of radiation-induced heart disease include accelerated atherosclerosis, and adverse myocardial remodeling. The onset of these complications is usually observed more than a decade after therapy. However, some of these changes can be noted within days of radiation exposure [39, 40]. Ionizing radiation helps in cancer eradication by inflicting cellular injury and distorting numerous molecular processes (Figure 2). The cellular membrane disruption leads to an unopposed release of various intracellular factors including procoagulants and tissue factors with often wide spread complications including progression of cholesterol plaques, inflammation, thrombocytopenia, thrombosis, and fibrosis [35].

Management of Stable CAD in Cancer Patients

The onset of CAD is multifactorial in cancer patients. In addition to the heightened risk of CAD in cancer patients' due to a systemic biochemical imbalance of hemostasis, chemotherapy and radiation therapy themselves can both cause and worsen ischemia. Vasospasm, endothelium damage, and oxidative stress in cancer patients undergoing therapy are the culprit factors of developing CAD [16]. Coronary events have been reported to occur two years prior to the time of cancer diagnosis [41] and within a few months of diagnosis [42].

The goal in treating patients with CAD and cancer is to improve survival and quality of life. Identifying

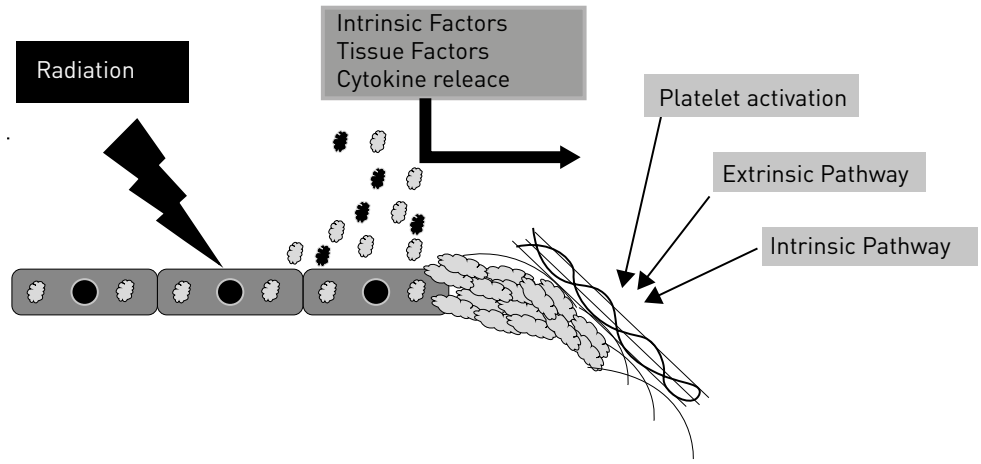

Figure 2. Radiation causes thickening of the arterial lining, eventually provoking atherosclerosis. The cellular damage by ionizing radiation also alters major biochemical pathways and releases micro-granules which have propensity to active coagulation pathways.

patients with increased risk of developing CAD is the crucial part of early detection and management of stable CAD. For example, adult survivors of childhood malignancies, breast cancer survivors are associated with late presentation of heart disease [35, 43]. These high-risk patients should be screened annually. Further screening with electrocardiography, echocardiography, or stress testing should be utilized based on expert consensus [44]. A collaborative team including a cardiologist and oncologist would provide an individualized approach in managing these patients.

In addition, other cardiovascular risk factors such as hypertension, obesity, and smoking should be identified and promptly treated. Bevacizumab, sorafenib, and sunitnib cause iatrogenic systemic hypertension [45]. Angiotensin-converting enzyme inhibitors (ACE-I) have been shown to improve overall survival in renal cell carcinoma patients being treated with sunitinib [46]. Beta blockers have been shown to improve mortality in patients receiving radiation for non-small-cell lung cancer [47]. In another retrospective study, beta blockers and aspirin improved survival of patients with myocardial infarction (MI) and cancer [48]. The treatment options for these patients are largely based on studies performed in non-cancer patients. Prophylactic cardioprotective treatment with beta-blockers, statins, and ACE-I have been recommended by several society guidelines [35, 48-54]. Randomized controlled trials studying the efficacy of using such cardioprotective regimens in cancer patients are lacking. It has also been recommended to stratify patients based on risk factors in order to initiate or continue cardio protective medication [35, 44, 55] (Figure 3).

Managing ACS in Cancer Patients with Thrombocytopenia

ACS is the result of a complex interplay between the vulnerable atherosclerotic plaque and hematopoietic system dysfunction, both of which are prevalent in oncology patients. The indication to take a non-cancer patient for early revascularization [57], and subsequent stenting is dictated by standardized, evidence-driven protocols. Malignancy- driven hypercoagulability and weakening of mucosal barriers due to chemotherapy expose vessels to an increased risk of thrombosis and bleeding [58]. The management of cancer patients in an acute setting has more limited evidence, and becomes cumbersome with concurrent thrombocytopenia which may defer potential clinical benefits of coronary intervention which requires antiplatelet therapy. Low platelet count, coagulation abnormalities, and bleeding are major roadblocks in the effective management of ACS in these patients. The conglomeration of these pathologies makes management difficult.

The benefit of reperfusion therapy for ACS is well established. Thrombolytic or percutaneous coronary intervention (PCI) both reduces the mortality and morbidity during the initial onset of symptoms [59]. There is no absolute contraindication to use thrombolytic agents in patients with ACS and thrombocytopenia. However, profound thrombocytopenia has been associated with intracranial bleeding. The American Heart Association guidelines recommend that platelet counts less than 100,000 is an absolute contraindication to administer thrombolytic in the setting of acute stroke to avoid fatal complications [60]. There is no absolute contraindication to use fibrinolytics

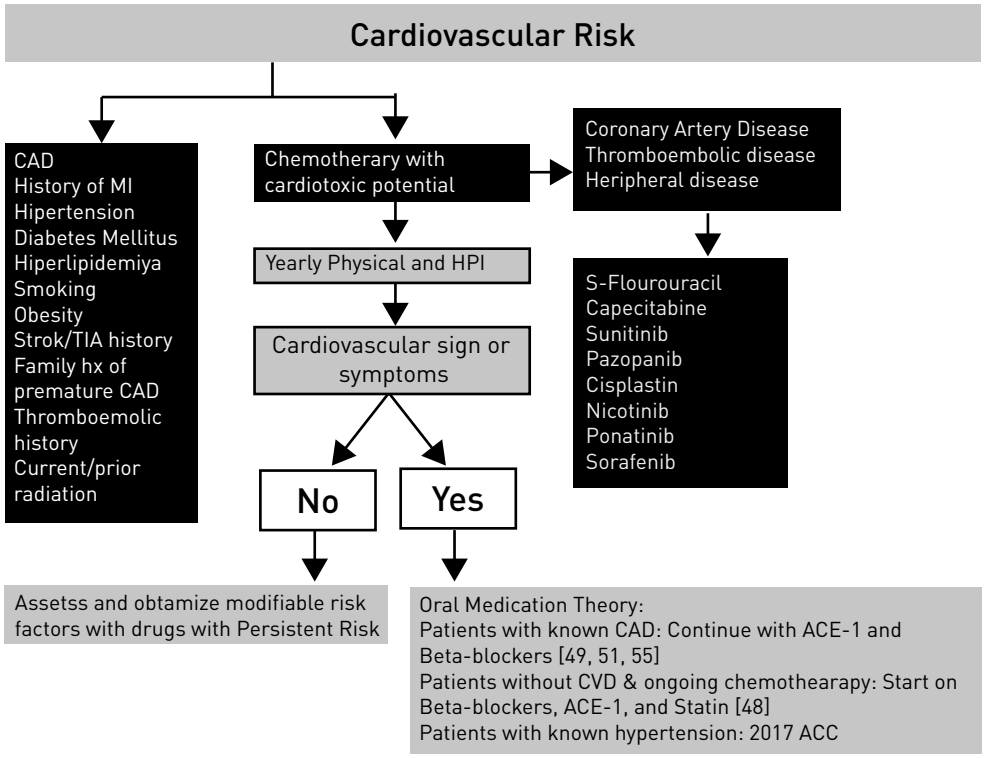

Figure 3. Patients should be risk stratified with cardiovascular risk factors. Patients with known coronary artery disease (CAD) might provide additional cardio protection by adding beta blockers or angiotensin-converting enzyme inhibitors (ACE-I) [42, 49, 53]. New onset of hypertension or established hypertension should be treated according to recent proposed hypertension guideline even though cancer as a subset group of patient population was not discussed [56]. Beta-blockers, statins, or ACE-I can be used prophylactically for patients on chemotherapy and with no cardiovascular disease (CVD) [48].

in thrombocytopenic patient for ACS. The increased risk of bleeding diathesis limits its use [59].

The role of DAPT poses another hurdle when a thrombocytopenic patient presents with ACS and requires coronary intervention. Although the overall risk of death is higher in the cancer population [61] than in the general population, cancer and non-cancer patients have no significant difference in cardiac death over the 1-year period following MI. In general, patients with leukemia and lymphoma have worse outcomes, but a potential contributor is a physician's bias of avoiding medical therapy or PCI because of the underlying comorbidities and perception of enhanced adverse effects [48]. Despite less definitive clinical pathways, patients with hematologic malignancies routinely undergo invasive cardiac procedures with acceptable outcomes [13, 62, 63], and neither leukemia nor thrombocytopenia are absolute contraindications to primary PCI. The following concerns are major dilemmas in cancer patients with ACS and thrombocytopenia.

1. Safe platelet count thresholds to carry out coronary interventions

2. Stenting in thrombocytopenia can complicate management of DAPT

3. Non-elective, cancer-related surgical interventions in the setting of DAPT

Quality versus Quantity of Platelets in Thrombocytopenia

There is no minimum platelet level that is an absolute contraindication for PCI (64). Normally, a heparin bolus of 50-70 U/kg is given during the procedure for patients with platelet counts greater than 50,000/mm^3, with additional heparin administered to maintain the activated clotting time (ACT) of about 250 seconds. A heparin dose of 30-50U/kg is administered in patients with platelet counts less than 50,000/mm^3 [13, 35]. Platelet counts as low as 40,000-50,000/mm^3 is typically sufficient to perform major interventional procedures in the absence of coagulation abnormalities [64, 65]. In patients with platelet counts <10,000/mm^3, the risks of bleeding must be balanced against the risk of not intervening [55]. Patients with platelet counts as low as 10,000/mm^3 have underwent successful cardiac interventions [13]. However, in clinical practice, most interventionists feel uncomfortable performing PCI in the setting of profound thrombocytopenia. Despite these challenges, standardized guidelines for blood transfusion for coronary inter-

ventions are lacking. The standard recommendation for prophylactic transfusion is for platelet counts less than 10,000/mm^3 in chronic thrombocytopenia and less than 20,000/mm^3 in higher risk patients [64]. One may argue in favor of transfusion when the platelet count rather than the platelet function is the concern. In these cases, it is advised to use ABO-compatible platelets as it decreases the rate of refractory platelet transfusion [66].

PCI should be the standard for oncology patients presenting with ACS irrespective of the presence of thrombocytopenia in the absence of active bleeding. Patients with malignancy, and thrombocytopenia presenting with ACS have the same constricted time for any acute coronary intervention. Thus, alternative approaches to assess the platelet function besides the platelet count may offer a better management approach. For example, modalities such as thromboelastography (TEG) can evaluate platelet and coagulation function, which can guide the need for transfusion. TEG analyzes the elastic property of whole blood and provides an assessment of hemostatic function. Transfusion based on abnormal TEG has been utilized by few cardiovascular and liver transplant teams [67, 68] and reported to have overall successful outcomes. Even though reports of TEG- guided transfusion in thrombocytopenia are limited, it may be an alternate way of assessing thrombocytopenic patients requiring cardiac interventions.

Access and Stenting

In general, cancer patients are at high risk of bleeding diathesis and are vulnerable to infection. It is important to minimize these stumbling blocks by using extra precautions in maintaining a sterile setting along with frequent catheter and sheath flushing (35). Ultrasound -guided access and use of micropuncture technique can offer to further mitigate the risk of bleeding [69-71]. A femoral access allows more flexibility during intervention, but a radial access is associated with a reduced risk of bleeding [72] and should be the preferred approach in thrombocytopenic patients [73, 74].

The onset of ACS in cancer patients is increased by chemotherapy infusion or vulnerability of platelet aggregation. Depending on the etiology, the patient may or may not require invasive intervention. Whether the coronary intervention is emergent or elective, intraprocedural evaluation of the coronary anatomy is the initial crucial step. Fractional flow reserve (FFR) has been demonstrated to be an accurate way to evaluate the functional severity of coronary lesions and to determine the next step [75]. In the absence of a culprit lesion or ischemic biomarkers, FFR may allow patients to continue on medical therapy with a favorable outcome [76]. Most cancer surgeries are not elective, and stent placement can postpone necessary interventions. Cancer therapy can complicate post stenting DAPT management. The clinical outcome of cancer patients with thrombocytopenia overlaps with numerous decision making. In non-emergent cases, noninvasive ischemic evaluation with stress tests, and assessment of myocardial structure and function with echocardiography can be helpful in assessing patients and should be undertaken prior to catheterization. Nevertheless, liberal use of FFR during the acute setting can defer stenting in patients with hemodynamically insignificant disease. The clinical outcome of medical therapy in deferred revascularization for FFR <0.8 and >0.75 had no significant difference [77]. Use of FFR can also allocate time for completing cancer therapy.

Theoretically, antineoplastic therapy can prolong the time period required for stent endothelialization [78]. Acute thrombosis within twenty minutes after stent placement has been reported in cancer patients [79]. Therefore, coronary stenting in patients with ongoing radiation not only raises the concern of interrupted endothelialization, but also increases the risk of thrombosis and may prolong the need for antiplatelet therapy. The main determinants of stent thrombosis in the early phase of implantation are stent underexpansion and stent dissection at the edges [18]. If stenting is inevitable, intravascular ultrasound (IVUS) or optical coherence tomography (OCT) should be utilized to guide stent sizing and deployment in order to avoid overlapping stenting which increases the risk of re-occlusion.

OCT can visualize abrupt thrombosis, aid adequate stent deployment, and detect malposition and stent dissection at stent edges [80], all of which are major pitfalls to avoid. OCT-guided PCI has been proven to have improved outcomes [81], and could ameliorate adverse outcomes in cancer patients. IVUS offers better plaque burden penetration [82] and can alternatively be used in patients with cancer or in those who underwent chemo-radiation as their anatomy is typically associated with greater fibrotic changes. Routine use of IVUS and OCT in every patient may result in less stent thrombosis complications in cancer patients with thrombocytopenia even if DAPT has to be stopped.

The Role of Antiplatelet Therapy

The duration of antiplatelet therapy depends on the indication of PCI versus medical management of ACS, stent generation and type, and individualized bleeding risk assessment. DAPT therapy is crucial to minimize the risk of stent thrombosis after PCI. Due to the complexity of malignancy, chemotherapy, and concurrent thrombocytopenia, randomized clinical trials evaluating the safety use of DAPT are lacking. The strategies to manage these distinct pathophysiological presentations are based on anecdotal experiences.

The choice of stents is usually guided by how long the DAPT can be safely continued. Bare- metal stents (BMS) take about four weeks to endothelialize with DAPT. Some new drug-eluting stents (DES) have been shown to endothelialize with three months of DAPT. However, cancer patients were not included in these studies [83]. Studies to determine the safety of DAPT therapies in the setting of thrombocytopenia are lacking. Therefore management of these patients needs to be individualized. A conservative approach including balloon angioplasty with a provisional BMS has been previously suggested [84, 85]. However, balloon angioplasty alone is associated with a higher risk of recurrent coronary events [86] and is less favorable in routine practice.

The shorter duration of use of DAPT with BMS is helpful for anticipated thrombocytopenia in the setting of ongoing cancer therapy. The use of DAPT in patients with thrombocytopenia has been reported in a few case reports in patients with acute myeloid leukemia [87, 88]. According to an expert clinical consensus, DAPT with aspirin and clopidogrel can be given when the platelet count is >30,000/mm^3, and aspirin alone can be given when the platelet count is >10,000/mm^3 [55]. Aspirin and clopidogrel are associated with less bleeding complications than are prasugrel and ticagrelor. . Prasugrel and ticagrelor are associated with thrombocytopenia and should routinely be avoided in these patients [35]. In the event noncardiac surgery is needed, it is advised to continue clopidogrel or aspirin or administer an intravenous short acting IIb/IIIa receptor blocker until shortly before surgery [35]. After surgery, the oral antiplatelet therapy should be restarted [78].

Aspirin as a single agent has been shown to be safe in patients with ACS and thrombocytopenia in a retrospective study [89]. Premedication with aspirin before PCI has shown a protective benefit [90], while withholding aspirin in cancer patients with ACS and thrombocytopenia has been harmful [89]. Aspirin alone does not increase the risk of bleeding [89]. Even in post coronary artery bypass graft patients with thrombocytopenia, continuing aspirin was associated with a longer vein graft patency with platelet counts of 10,000-20,000/mm3 in the absence of active bleeding [91]. Aspirin has been shown to increase the platelet count in patients with antiphospholipid syndrome -induced thrombocytopenia [92] and to decrease thrombus formation in patients with moderate thrombocytopenia [93]. This supports that the notion of platelet function rather than quality is the driving factor of hypercoagulability. A proposed management algorithm for thrombocytopenic patients with ACS is shown in Figure 4.

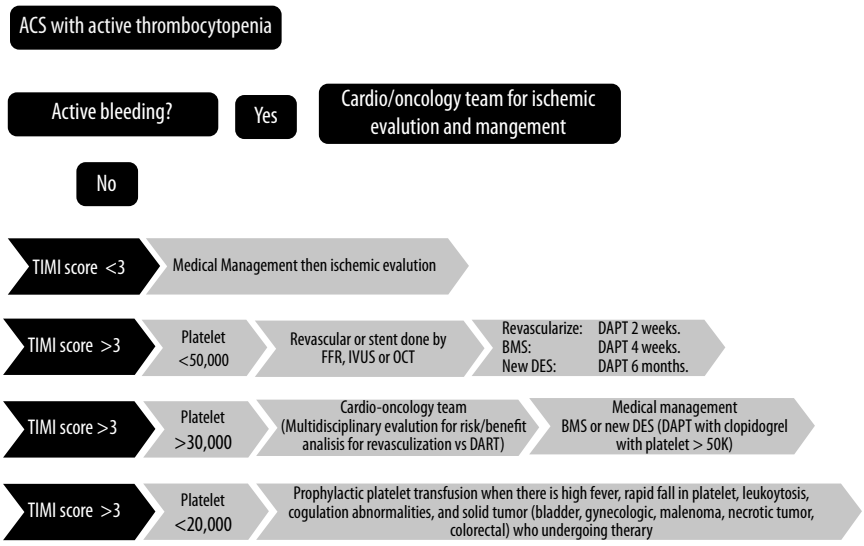

Figure 4. No minimum platelet count has been defined to be cut off criteria. A general proposal of patients with cancer and thrombocytopenia presenting with acute coronary syndrome. Each case should be individually evaluated. The proposed outline is a combination of criteria from an expert consensus [35]. ACS = acute coronary syndrome; TIMI = thrombolysis in acute myocardial infarction.; DAPT = dual antiplatelet therapy

Summary

As the growing awareness of the vascular and metabolic mechanisms of oncologic therapy continues to increase, cardio-oncology as a subspecialty requires research and educational initiatives. Many of these drugs have proven to be effective in improving cancer prognosis, but their possible cardiovascular effects have to be carefully monitored and treated. Upcoming large-scale trials including Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-Day Intensive Dual Antiplatelet Therapy in All-Comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family DrugEluting Stent Use (GLOBAL-LEADERS) and Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) will give us important information on the safety of using shorter courses of DAPT.

Conflicts of interest: None declared.

References

1. Koene RJ, Prizment AE, Blaes A, et al. Shared Risk Factors in Cardiovascular Disease and Cancer. Circulation 2016;133:1104-14.
2. Menter DG, Tucker SC, Kopetz S, et al. Platelets and cancer: a casual or causal relationship: revisited. Cancer Metastasis reviews 2014;33:231-69.
3. Macchi I, Chamlian V, Sadoun A, et al. Comparison of reticulated platelet count and mean platelet volume determination in the evaluation of bone marrow recovery after aplastic chemotherapy. Eur J Haematol 2002;69:152-7
4. De Cicco M. The prothrombotic state in cancer: pathogenic mechanisms. Critical Reviews in Oncology/Hematology 2004;50:187-96.
5. Gouin-Thibault I, Achkar A, Samama MM. The thrombophilic state in cancer patients. Acta haematologica 2001;106:33-42.
6. Navi BB, Reiner AS, Kamel H, et al. Risk of Arterial Thromboembolism in Patients With Cancer. J Am Coll Cardiol 2017;70:926-38.
7. Altwegg SC, Altwegg LA, Maier W. Intracoronary thrombus with tissue factor expression heralding acute promyelocytic leukaemia. Eur Heart J 2007;28:2731.
8. Solomons HD, Stanley A, King PC, et al. Acute promyelocytic leukaemia associated with acute myocardial infarction. A case report. South African Medical Journal 1986;70:117-8
9. Reitsma PH, Versteeg HH, Middeldorp S. Mechanistic view of risk factors for venous thromboembolism. Arteriosclerosis, thrombosis, and Vascular Biology 2012;32:563-8.
10. Corash L, Chen HY, Levin J, et al. Regulation of thrombopoiesis: effects of the degree of thrombocytopenia on megakaryocyte ploidy and platelet volume. Blood 1987;70:177-85
11. Chesnutt JK, Han HC. Platelet size and density affect shear-induced thrombus formation in tortuous arterioles. Physical Biology 2013;10:056003.
12. Van der Loo B, Martin JF. A role for changes in platelet production in the cause of acute coronary syndromes. Arteriosclerosis, Thrombosis, and Vascular Biology 1999;19:672-9
13. Iliescu C, Durand JB, Kroll M. Cardiovascular interventions in thrombocytopenic cancer patients. Tex Heart Inst J 2011;38:259-60
14. Ozner MD, Ahn YS, Horstman LL, et al. Chronic Platelet Activation and Acute Coronary Syndromes in 13 Middle-Aged Patients. Clinical and Applied Thrombosis/Hemostasis 1997;3:46-53.
15. Jy W, Horstman LL, Arce M, Ahn YS. Clinical significance of platelet microparticles in autoimmune thrombocytopenias. The Journal of Laboratory and Clinical Medicine 1992;119:334-45
16. Hassan SA, Palaskas N, Kim P, et al. Chemotherapeutic Agents and the Risk of Ischemia and Arterial Thrombosis. Current Atherosclerosis Reports 2018; 20: 10.doi:10.1007/s11936-018-0625-z
17. Hakim DA, Dangas GD, Caixeta A, et al. Impact of baseline thrombocytopenia on the early and late outcomes after ST-elevation myocardial infarction treated with primary angioplasty: analysis from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. American Heart Journal 2011;161:391-6.
18. McClure MW, Berkowitz SD, Sparapani R, et al. Clinical significance of thrombocytopenia during a non-ST-elevation acute coronary syndrome. The platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy (PURSUIT) trial experience. Circulation 1999;99:2892-900
19. Hitron A, Steinke D, Sutphin S, et al. Incidence and risk factors of clinically significant chemotherapy-induced thrombocytopenia in patients with solid tumors. Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners 2011;17:312-9.
20. Karabay KO, Yildiz O, Aytekin V. Multiple coronary thrombi with cisplatin. Journal of Invasive Cardiology 2014;26:E18-20
21. Stefenelli T, Kuzmits R, Ulrich W, et al. Acute vascular toxicity after combination chemotherapy with cisplatin, vinblastine, and bleomycin for testicular cancer. European Heart Journal 1988;9:552-6
22. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma. N Engl J Med 2013;369:722-31.

23. Shekarriz R, Koulaeinejad N, Nosrati A, et al. Sunitinib Induced Immune Thrombocytopenia. Iranian Journal of Pharmaceutical Research 2015;14:1295-97
24. Lim WT, Ng QS, Ivy P, et al. A Phase II study of pazopanib in Asian patients with recurrent/metastatic nasopharyngeal carcinoma. American Association for Cancer Research 2011;17:5481-9.
25. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a Multikinase Angiogenesis Inhibitor, in Patients With Relapsed or Refractory Advanced Soft Tissue Sarcoma: A Phase II Study From the European Organisation for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group (EORTC Study 62043). Journal of Clinical Oncology 2009;27:3126-32.
26. Aichberger KJ, Herndlhofer S, Schernthaner GH, et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. Am J Hamatol 2011;86:533-9.
27. Barak AF, Bonstein L, Lauterbach R, et al. Tyrosine kinase inhibitors induced immune thrombocytopenia in chronic myeloid leukemia? Hematology Reports 2011;3:95-97.
28. Tefferi A, Letendre L. Nilotinib treatment-associated peripheral artery disease and sudden death: yet another reason to stick to imatinib as front-line therapy for chronic myelogenous leukemia. Am J Hamatol 2011;86:610-1.
29. Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in Refractory Philadelphia Chromosome–Positive Leukemias. N Engl J Med 2012;367:2075-88.
30. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A Phase 2 Trial of Ponatinib in Philadelphia Chromosome–Positive Leukemias. N Engl J Med 2013;369:1783-96.
31. Pierga JY, Fumoleau P, Brewer Y, et al. Efficacy and safety of single agent capecitabine in pretreated metastatic breast cancer patients from the French compassionate use program. Breast Cancer Research and Treatment 2004;88:117-29.
32. Polk A, Vaage-Nilsen M, Vistisen K, et al. Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: a systematic review of incidence, manifestations and predisposing factors. Cancer Treatment Reviews 2013;39:974-84.
33. Sho T, Nakanishi M, Morikawa K, et al. A Phase I Study of Combination Therapy with Sorafenib and 5-Fluorouracil in Patients with Advanced Hepatocellular Carcinoma. Drugs in R&D 2017;17:381-8
34. Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. Oncology 2015;29:282-94
35. Iliescu CA, Grines CL, Herrmann J, et al. SCAI Expert consensus statement: Evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (endorsed by the cardiological society of india, and sociedad Latino Americana de Cardiologia intervencionista). Catheterization and Cardiovascular Interventions 2016;87:895-9.
36. Haddy N, Diallo S, El-Fayech C, et al. Cardiac Diseases Following Childhood Cancer Treatment: Cohort Study. Circulation 2016;133:31-8.
37. Taylor CW, Nisbet A, McGale P, et al. Cardiac doses from Swedish breast cancer radiotherapy since the 1950s. Radiotherapy and oncology : Journal of the European Society for Therapeutic Radiology and Oncology 2009;90:127-35.
38. Taylor CW, Povall JM, McGale P, et al. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. International Journal of Radiation Oncology, Biology, Physics 2008;72:501-7.
39. Stewart FA, Heeneman S, Te Poele J, et al. Ionizing radiation accelerates the development of atherosclerotic lesions in ApoE-/- mice and predisposes to an inflammatory plaque phenotype prone to hemorrhage. American Journal of Pathololgy 2006;168:649-58.
40. Lee MS, Finch W, Mahmud E. Cardiovascular complications of radiotherapy. Am J Cardio 2013;112:1688-96.
41. Naschitz JE, Yeshurun D, Abrahamson J, et al. Ischemic heart disease precipitated by occult cancer. Cancer 1992;69:2712-20
42. Zoller B, Ji J, Sundquist J, Sundquist K. Risk of coronary heart disease in patients with cancer: a nationwide follow-up study from Sweden. European Journal of Cancer 2012;48:121-8.
43. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572-82.
44. Chang HM, Okwuosa TM, Scarabelli T, et al. Cardiovascular Complications of Cancer Therapy: Best Practices in Diagnosis, Prevention, and Management: Part 2. J Am Coll Cardiol 2017;70:2552-65.
45. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. Journal of the National Cancer Institute 2010;102:596-604.
46. Izzedine H, Derosa L, Le Teuff G, et al. Hypertension and angiotensin system inhibitors: impact on outcome in sunitinib-treated patients for metastatic renal cell carcinoma. Annals of Oncology 2015;26:1128-33.
47. Wang HM, Liao ZX, Komaki R, et al. Improved survival outcomes with the incidental use of beta-blockers among patients with non-small-cell lung cancer treated with definitive radiation therapy. Annals of Oncology 2013;24:1312-9.
48. Yusuf SW, Daraban N, Abbasi N, et al. Treatment and outcomes of acute coronary syndrome in the cancer population. Clinical Cardiology 2012;35:443-50.
49. Bosch X, Rovira M, Sitges M, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive

ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol 2013;61:2355-62.

50. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 2006;114:2474-81.
51. Elitok A, Oz F, Cizgici AY, et al. Effect of carvedilol on silent anthracycline-induced cardiotoxicity assessed by strain imaging: A prospective randomized controlled study with six-month follow-up. Cardiology Journal 2014;21:509-15.
52. Kaya MG, Ozkan M, Gunebakmaz O, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. International Journal of Cardiology 2013;167:2306-10.
53. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.
54. Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiotoxicity: challenges and opportunities. J Am Coll Cardiol 2014;64:938-45.
55. Chang HM, Moudgil R, Scarabelli T, et al. Cardiovascular Complications of Cancer Therapy: Best Practices in Diagnosis, Prevention, and Management: Part 1. J Am Coll Cardiol 2017;70:2536-51.
56. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. J Am Coll Cardiol 2017; Nov 7: published online.
57. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360:2165-75.
58. Mohanty BD, Mohanty S, Hussain Y, et al. Management of ischemic coronary disease in patients receiving chemotherapy: an uncharted clinical challenge. Future cardiology 2017;13:247-57.
59. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. J Am Coll Cardiol 2013;61:78-140.
60. Edward C. Jauch BC, Opeolu Adeoye, William Meurer, et al. Adult Stroke, 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122:S818-S828 October 17, 2010;122:657-664.
61. Kurisu S, Iwasaki T, Ishibashi K, et al. Comparison of treatment and outcome of acute myocardial infarction between cancer patients and non-cancer patients. International Journal of Cardiology 2013;167:2335-7.
62. Fecher AM, Birdas TJ, Haybron D, et al. Cardiac operations in patients with hematologic malignancies. Eur J Cardiothorac Surg 2004;25:537-40.
63. Potapov EV, Zurbrugg HR, Herzke C, et al. Impact of cardiac surgery using cardiopulmonary bypass on course of chronic lymphatic leukemia: a case-control study. The Annals of Thoracic Surgery 2002;74:384-9
64. Schiffer CA, Anderson KC, Bennett CL, et al. Platelet transfusion for patients with cancer. Journal of Clinical Oncology 2001;19:1519-38.
65. Norfolk DR, Ancliffe PJ, Contreras M, et al. Consensus Conference on Platelet Transfusion. Br J Haematol 1998;101:609-17
66. Nahirniak S, Slichter SJ, Tanael S, et al. Guidance on platelet transfusion for patients with hypoproliferative thrombocytopenia. Transfusion Medicine Reviews 2015;29:1-13.
67. Kwak YL, Kim JC, Choi YS, et al. Clopidogrel responsiveness regardless of the discontinuation date predicts increased blood loss and transfusion requirement after off-pump coronary artery bypass graft surgery. J Am Coll Cardiol 2010;56:1994-2002.
68. Mahla E, Suarez TA, Bliden KP, et al. Platelet function measurement-based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET-CABG) study. Circulation: Cardiovascal Intervention 2012;5:261-9.
69. Abdelaal E, Rimac G, Plourde G, et al. 4Fr in 5Fr sheathless technique with standard catheters for transradial coronary interventions: technical challenges and persisting issues. Catheterization and Cardiovascular Interventions 2015;85:809-15.
70. Ben-Dor I, Maluenda G, Mahmoudi M, et al. A novel, minimally invasive access technique versus standard 18-gauge needle set for femoral access. Catheterization and Cardiovascular Interventions 2012;79:1180-5.
71. Rao SV, Tremmel JA, Gilchrist IC, et al. Best practices for transradial angiography and intervention: a consensus statement from the society for cardiovascular angiography and intervention's transradial working group. Catheterization and Cardiovascular Interventions 2014;83:228-36.
72. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. J Am Coll Cardiol 2012;60:2481-9.
73. Hamon M, Rasmussen LH, Manoukian SV, et al. Choice of arterial access site and outcomes in patients with acute coronary syndromes managed with an early invasive strategy: the ACUITY trial. EuroIntervention 2009;5:115-20
74. Jao GT, Knovich MA, Savage RW, Sane DC. ST-elevation myocardial infarction and myelodysplastic syndrome with acute myeloid leukemia transformation. Tex Heart Inst J 2014;41:234-7.

75. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention. N Engl J Med 2009;360:213-24.
76. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991-1001.
77. Kang DY, Ahn JM, Lee CH, et al. Deferred vs. performed revascularization for coronary stenosis with grey-zone fractional flow reserve values: data from the IRIS-FFR registry. Eur Heart J 2018; Feb 24: Published online
78. Krone RJ. Managing coronary artery disease in the cancer patient. Progress in Cardiovascular Diseases 2010;53:149-56.
79. Lee JM, Yoon CH. Acute coronary stent thrombosis in cancer patients: a case series report. Korean Circulation Journal 2012;42:487-91.
80. Prati F, Kodama T, Romagnoli E, et al. Suboptimal stent deployment is associated with subacute stent thrombosis: optical coherence tomography insights from a multicenter matched study. From the CLI Foundation investigators: the CLI-THRO study. American Heart Journal 2015;169:249-56.
81. Prati F, Romagnoli E, Burzotta F, et al. Clinical Impact of OCT Findings During PCI: The CLI-OPCI II Study. J Am Coll Cardiol 2015;8:1297-305.
82. Zeng Y, Tateishi H, Cavalcante R, et al. Serial Assessment of Tissue Precursors and Progression of Coronary Calcification Analyzed by Fusion of IVUS and OCT: 5-Year Follow-Up of Scaffolded and Nonscaffolded Arteries. J Am Coll Cardiol 2017;10:1151-61.
83. Feres F, Costa RA, Abizaid A, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: The optimize randomized trial. JAMA 2013;310:2510-22.
84. Jao GT, Knovich MA, Savage RW, Sane DC. ST-Elevation Myocardial Infarction and Myelodysplastic Syndrome with Acute Myeloid Leukemia Transformation. Tex Heart Inst J 2014;41:234-37.
85. Velders MA, Boden H, Hofma SH, et al. Outcome after ST elevation myocardial infarction in patients with cancer treated with primary percutaneous coronary intervention. Am J Cardiol 2013;112:1867-72.
86. Zhu MM, Feit A, Chadow H, et al. Primary stent implantation compared with primary balloon angioplasty for acute myocardial infarction: a meta-analysis of randomized clinical trials. Am J Cardiol 2001;88:297-301
87. Jachmann-Jahn U, Cornely OA, Laufs U, et al. Acute anterior myocardial infarction as first manifestation of acute myeloid leukemia. Annals of hematology 2001;80:677-81
88. Lou Y, Mai W, Jin J. Simultaneous presentation of acute myocardial infarction and acute promyelocytic leukemia. Annals of hematology 2006;85:409-10.
89. Sarkiss MG, Yusuf SW, Warneke CL, et al. Impact of aspirin therapy in cancer patients with thrombocytopenia and acute coronary syndromes. Cancer 2007;109:621-7.
90. Nikolsky E, Sadeghi HM, Effron MB, et al. Impact of in-hospital acquired thrombocytopenia in patients undergoing primary angioplasty for acute myocardial infarction. Am J Cardiol 2005;96:474-81.
91. Faraday N. PRO: Should aspirin be continued post-cardiac surgery in the setting of thrombocytopenia? Journal of Cardiothoracic and Vascular Anesthesia 2006;20:112-13.
92. Alarcon-Segovia D, Sanchez-Guerrero J. Correction of thrombocytopenia with small dose aspirin in the primary antiphospholipid syndrome. Journal of Rheumatology 1989;16:1359-61
93. Bobbio-Pallavicini E, Gugliotta L, Centurioni R, et al. Antiplatelet agents in thrombotic thrombocytopenic purpura (TTP). Results of a randomized multicenter trial by the Italian Cooperative Group for TTP. Haematologica 1997;82:429-35