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Mini Review

Acute Coronary Syndromes in Patients with Thrombocytopenia

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Abstract

Antiplatelet drugs are fully approved in the current guidelines for the treatment of acute coronary syndromes, however they are potentially fatal considering their bleeding effect related to their antiplatelet action. Therefore, the bleeding risk associated with the use of antiplatelet drugs in patients with thrombocytopenia is crucial. Over the next years we will see more patients with thrombocytopenia and appropriate clinical practice guidelines are still required for these patients.

Keywords: Innovative biotechnologies; Personalized medicine; Acute coronary syndromes; Thrombocytopenia; Antiplatelet therapy

Abbreviations

ACS: Acute Coronary Syndromes; AMI: Acute Myocardial Infarction; DAPT: Dual Antiplatelet Therapy; PCI: Percutaneous Coronary Intervention

Introduction

Platelets play a pivotal role in the pathogenesis of Acute Coronary Syndromes (ACS) and thrombocytosis has been demonstrated to be an important risk factor for Acute Myocardial Infarction (AMI); indeed, in patients with essential thrombocythemia the incidence of AMI is about 9.4% [1]. Nevertheless, AMI has been reported also in patients who suffer from thrombocytopenia that could be associated with several conditions [2,3].

Thrombocytopenia is defined as a platelet count of <150 x 10^9/L and it is classified as mild (100-150 x 10^9/L), moderate (50-100 x 10^9/L) or severe (<50 x 10^9/L). Thrombocytopenia is generally expected in 13% of patients, whereas this condition is present in 5% of ACS patients suffering from thrombocytopenia. It is more frequent in several conditions such as older patients, diabetes, renal insufficiency, heart failure and sometimes is considered as a risk factor of AMI, for example in patients with Kawasaki disease [4-6].

As reported in autoptic samples, the pathogenesis of an occlusive thrombus in these patients share similarities with classic atherosclerotic plaque rupture, shedding light on hidden aspects that go beyond platelet count [7]. Indeed, likewise of rodent models, patients with thrombocytopenia may be predisposed to coronary thrombosis because their platelets are larger and more adhesive to the vascular surface [8,9]. Furthermore a higher platelet microparticles activation has been shown in ACS patients with idiopathic thrombocytopenic purpura and middle-aged patients than in control groups [10,11].

The American Heart Association (AHA) and the European Society of Cardiology (ESC) strongly recommend in ACS the Dual Antiplatelet Therapy (DAPT) consisting of aspirin and a P2Y12 receptor antagonist [12,13]. Although DAPT reduces the incidence of stent thrombosis an increased bleeding risk is present. Hence, the management of antiplatelet therapy in ACS patients with thrombocytopenia turn out to be challenging both for the concomitant higher risk of bleeding and ischaemic events in this group [14,15]. In ACS, actual scores such as the PRECISE-DAPT score, might evaluate the usefulness of DAPT duration balancing the ischemic protection and minimizing bleeding risks in the individual patient on the basis of hemoglobin value, white blood cells count, age of the patient, creatinine clearance and a general history of prior bleeding without specific indications (type of bleeding, platelet count, platelet function, secondary predisposing hemorrhagic conditions) [16].

Unfortunately the safety of DAPT and Percutaneous Coronary Intervention (PCI) in patients who have ACS and thrombocytopenia is unknown, and there are no guidelines to suggest a treatment approach in such patients. Indeed, despite representing a substantial proportion of ACS patients, these patients have been under-represented in important clinical trials evaluating antiplatelet strategies [17-20].

Other considerations beyond the platelet count

In addiction, the evaluation of both DAPT and PCI in ACS patients with thrombocytopenia should not only consider the platelet count but also the platelet function and the condition causing thrombocytopenia [21,22].

Older patients or patients with a platelet counts <30 x 10^9/L are associated with an increased risk of bleeding, thus authors have proposed DAPT in ACS patients with a threshold platelet count of > 30 x 10^9/L, choosing a type of stent that allows shortening the therapy duration with the smallest risk of stent thrombosis [23].

An interesting condition that clinicians have to overcome in the future is thrombocytopenia in ACS patients associated with chronic liver disease because of the increased prevalence of metabolic syndrome which can progress to cirrhosis; interestingly, a deficiency of thrombopoietin has been mentioned as a possible cause of the thrombocytopenia of individuals with nonalcoholich fatty liver disease [24]. Nowadays, there are not available recommendations on the most appropriate DAPT in this context and, probably, the perceived bleeding risk in these patients is higher than the real one and

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Table 1: Etiologies of thrombocytopenia.

1. Decreased platelet production
- Congenital macro-thrombocytopenias (Alport syndrome, Bernard-Soulier syndrome, Fanconi anemia, platelet-type or pseudo–von Willebrand disease, Wiskott-Aldrich syndrome)
- Bone marrow failure (aplastic anemia, paroxysmal nocturnal hemoglobinuria, Shwachman-Diamond syndrome)
- Bone marrow suppression (medication, chemotherapy, irradiation)
- Infection (cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, mumps, parvovirus B19, rickettsia, rubella, varicella-zoster virus)
- Chronic alcohol abuse and nutritional deficiencies (vitamin B12 and folate)
- Myelodysplastic syndrome or neoplastic marrow infiltration
2. Increased platelet consumption
- Alloimmune destruction (post-transfusion, neonatal, post-transplantation) or autoimmune syndromes (antiphospholipid syndrome, systemic lupus erythematosus, sarcoidosis, immune thrombocytopenic purpura)
- Disseminated intravascular coagulation/severe sepsis
- Drug-induced thrombocytopenia (Heparin-induced thrombocytopenia)
- Infection (cytomegalovirus, Epstein-Barr virus, hepatitis C virus, HIV, mumps, parvovirus B19,rickettsia, rubella, varicella-zoster virus)
- Mechanical destruction (aortic valve, mechanical valve, extracorporeal bypass, ExtraCorporeal Membrane Oxygenation (ECMO))
- Preeclampsia/ Hemolysis, Elevated Liver enzymes, and Low Platelet count (HELLP) syndrome
- Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
3. Sequestration/other
- Hypersplenism (distributional thrombocytopenia)
- Liver disease (cirrhosis, fibrosis, portal hypertension)
- Pseudothrombocytopenia
- Pulmonary emboli, pulmonary hypertension

lead to less intense antiplatelet therapy, with consequent increased risk of thrombosis. Indeed, the reduction in procoagulant factors is offset by a parallel decrease in anticoagulant factors and an increased concentration of von Willebrand factor which can compensate for the low platelet count and ensure primary hemostasis [25].

Two other common conditions are chemotherapy-related thrombocytopenia and myelodysplastic syndromes. Chemotherapy-related thrombocytopenia is transitory and with a predictable recovery period and a low risk of bleeding in patients with platelet counts >10 x 10^9/L [26].

Thrombocytopenia associated with myelodysplastic syndromes usually has a chronic course and it is associated with a higher bleeding risk than chemotherapy-induced one [27]. Infact in myelodysplastic syndromes, platelets often have abnormally low concentrations of cell surface procoagulant markers or lack intracellular granules, and bleeding is common even with a platelet count >100 x 10^9/L [28].

In the setting of cancer and hematologic malignancies, some small-sized retrospective studies have shown that aspirin may be beneficial in thrombocytopenic ACS patients [29,30].

Outcomes of ACS patients presenting with thrombocytopenia

The presence of thrombocytopenia in ACS patients predicts significantly worse outcomes. Yadav et al. [5] retrospectively examined 10.603 patients who underwent PCI for non-ST-elevation ACS or ST-elevation myocardial infarction and showed that the presence of thrombocytopenia (<150 x 10^9/L) at baseline (607 patients, 5.7%) was an independent predictor of mortality at 1 year (6.7% vs 3.6%; P < 0.0001), ischaemic target lesion revascularization (HR, 1.37; 95% CI, 1.04-1.81; P = 0.03), and major adverse cardiac events (HR, 1.39; 95% CI, 1.09-1.79; P = 0.009). Any association between baseline thrombocytopenia and major or minor bleeding rates at 30 days was found; nevertheless, their cohort of patients included patients with mild thrombocytopenia.

Wang et al. examined 36.182 patients with non-ST-segment elevation ACS [4]. Risks of inpatient mortality and bleeding correlated directly with severity of thrombocytopenia and even mild thrombocytopenia (at least 100-149 x 10^9/L) was associated with increased risks of mortality (adjusted OR, 2.01; 95% CI: 1.69 to 2.38) and bleeding (adjusted OR, 3.76; 95% CI: 3.43 to 4.12). Even mild thrombocytopenia or a platelet count drop >/=50% in the setting of normal baseline values identifies a population of ACS patients at higher risk of mortality and major bleeding.

It hase been suggested that thrombocytopenia in ACS may reflect a greater burden of atherosclerosis or clinically significant thrombosis predisposing platelet consumption; consequently, its presence might be considered a marker of disease severity [31].

The current management of ACS patients presenting with thrombocytopenia

As there are not strong evidence-based recommendations, we might suggest that a proper approach should begin with the identification of the eziology (Table 1) [32] and the correction of any reversible causes of thrombocytopenia or medications such as unfractionated heparin, glycoprotein IIb/IIIa inhibitors, furosemide, NSAIDs and penicillin based antibiotics.

Furthermore, Biino et al. demonstrated the age-, sex- and origin-related variability of platelet count proposing a change of the reference interval 150 x 10^9 platelets/L for all subjects for diagnosing of thrombocytopenia allowing a better bleeding risk stratification and theraphy management of ACS patients [33].

The daily difficulty in clinical practice also lies in choosing the correct antiplatelet strategy in this class of patients. Notably, clopidogrel offers a lower bleeding risk compared with ticagrelor or prasugrel [14,17].

Cangrelor could be advantageous as it has a short plasma half-life and platelet function is restored rapidly after interruption of the infusion. Indeed, in the double-blind placebo-controlled CHAMPION PHOENIX trial, cangrelor significantly reduced the rate of ischaemic events (including stent thrombosis) compared with clopidogrel, without significant increase in severe bleeding. However, patients with a platelet count of <100 x 10^9 /L were excluded [19].

Recently, Claassens et al. investigated the impact of a genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. In this randomized trial, 2488 patients were included and assigned to receive either a P2Y12 inhibitor on the basis of early CYP2C19 genetic testing (genotype-guided group, 1242 patients) or standard treatment with either ticagrelor or prasugrel (standard-treatment group, 1246 patients) for 12 months. In the genotype-guided group, carriers of CYP2C19*2 or CYP2C19*3 loss-of-function alleles received ticagrelor or prasugrel, and noncarriers received clopidogrel. They demonstreted that the genotype–guided strategy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months both in term of thrombotic events (63 patients in the genotype-guided group and in 73 patients in the standard-treatment group; P<0.001) and resulted in a lower incidence of bleeding (122 patients in the genotype-guided group and in 156 patients in the standard-treatment group; P=0.04) [34].

Nowadays, ESC recommendations suggest that clopidogrel in monotherapy should be administered to ACS patients with thrombocytopenia who are not undergoing PCI, if their platelet count is >50 x 10^9/L and in the absence of bleeding.

Clopidogrel is preferred to aspirin monotherapy based on the results of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) [35] randomized controlled trial that demonstrated a statistically significant relative risk reduction in gastrointestinal bleeding with clopidogrel 75 mg as opposed to aspirin 325 mg (P= 0.012).

ESC guidelines do not recommend prasugrel and ticagrelor due to their higher bleeding risk [14].

In patients with a platelet count <50 x 10^9/L or in the setting of active bleeding, all antiplatelet therapy or PCI should be avoided [36].

Patients with ACS and a platelet count >50 x 10^9/L in the absence of bleeding, may need a shorter duration of DAPT based on clopidogrel and low dose of aspirin for one month followed by clopidogrel alone; triple therapy should be avoided if not strictly necessary. In addition, radial approach for PCI should be performed and second generation drug-eluting stents are preferable to bare-metal stents, as demonstrated by two randomized trials: Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug Coated Stent versus the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) [37] and Zotarolimus-eluting Endeavor Sprint Stent in Uncertain DES Candidates (ZEUS) [38].

Conclusion

Antiplatelet drugs are fully approved in the current guidelines for the treatment of ACS, however they are potentially fatal in patients with thrombocytopenia considering both their bleeding effect related to their antiplatelet action and the origin of this condition.

In addition, antiplatelets drugs have been demonstrated to be related to thrombotic thrombocytopenic purpura, potentially life-threatening in patient with platelet disorders [39-41].

Over the next years we are expecting an increasing number of patients suffering from thrombocytopenia who might develop ACS and appropriate clinical practice guidelines are further requested for these patients.

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