How to manage antithrombotic treatments in thrombocytopenic patients with cancer. Comments on the European Haematology Association guidelines

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BACKGROUND

With ageing of the population, both the risks of cardiovascular disease (CVD) and cancer are increasing worldwide, and the risk factors (*e.g.* obesity, diabetes) are often shared between the two conditions. Thus, more subjects will also develop the two illnesses concurrently.[1]

The continuous improvement and refinement of anticancer therapy, outcomes and survival of cancer leaves more persons exposed to CV risk factors (*e.g.* hypertension) and diseases (*e.g.* atrial fibrillation). Subjects with cancer may also develop acute thrombosis while on chemotherapy, since some drugs increase the thrombotic risk. Moreover, it is well established that cancer patients are also at increased risk of venous and arterial thrombosis and of cardioembolic complications, independently of other factors.[2-4] Hence, patients with cancer are increasingly likely to be on antithrombotic medication for prophylaxis, acute treatment or secondary prevention of thromboembolism.

Subjects with cancer requiring antithrombotic medications often develop intercurrent episodes of thrombocytopenia (TP) associated with cancer or, more often, with chemotherapy. TP can significantly and independently increase the risk of major bleeding, on the other hand cancer- or chemotherapy-related transient TP does not protect against thrombosis. Thus, when TP occurs, physicians need to decide on the complex management of antithrombotic medications, including the transient drug interruption or de-escalation strategies. These decisions are not only based on the degree of TP, since cancer is independently associated with thrombotic risk as well. Thus, a careful and complex decision making with regard to antithrombotic medication(s) is needed, taking into account multiple factors, from the thrombosis, cancer and chemotherapy perspectives.

Since trials on antithrombotic drugs typically exclude patients with cancer as well as patients at highest risk for bleeding, including those with TP, there is hardly any

high-quality evidence to guide the management of patients with cancer and TP with an indication of antithrombotic medication(s), thus there is a relevant, albeit growing, unmet therapeutic need.

It is for this growing population that the Scientific Working Group on Bleeding and Thrombosis of the European Haematology Association (EHA) has developed Guidelines to provide practice guidance to help clinicians in the management of patients with cancer and TP in need of antithrombotic medication.[5] A task force was assembled based on the selection of representatives from the EHA in collaboration with the European Society of Cardiology, to obtain a broad and relevant representation for the hematology, oncology, cardiology and clinical pharmacology fields.

This task force undertook a comprehensive review of the relevant available literature for antiplatelet and anticoagulant agents, or their combination, different reperfusion techniques, including assessment of the risk-benefit ratio in the conditions of TP and cancer. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to the Oxford Centre for Evidence-Based Medicine (available at: https://www.cebm.ox.ac.uk/resources/levels-of-evidence). Each recommendation underwent a Delphi consensus among the Experts. The outcome of this process was recently published as a consensus based open access guideline.[5] Here, we highlight several points and refer to the original document for all details.[5]

GENERAL CONSIDERATIONS

Thrombocytopenia is a broad term and first the Task Force defined a clinically relevant range of platelet counts based on the National Cancer Institute Common Terminology Criteria for Adverse Events with an upper limit of 100×10^9/L further segregated in four strata, with a lower platelet count $<25\times10^9$/L as the stratum with the highest risk of major bleeding in cancer patients, in absence of antithrombotic medication.

As for the general management of patients with an absolute indication for antithrombotic therapy and TP, both the risks of thrombosis and bleeding should be carefully weighed (see tables 3 and 4 of Falanga *et al.*).[5] This should also include reassessment of the indication for antithrombotic therapy in addition to traditional bleeding and thrombosis risk factors. The duration of TP should be estimated, and a clear antithrombotic therapy plan should be formulated on an individual patient basis, and this should be frequently re-assessed. Once the TP has raised above a certain threshold, specific for each condition, resuming antithrombotic therapy in case it had been stopped, should be put in place without delays. In addition, a number of general pharmacological strategies to prevent bleeding (*i.e.* gastroprotection, avoidance of non-steroidal anti-inflammatory drugs as analgesics) is recommended, summarized in the paragraph below.

General recommendations for all antithrombotic regimens in cancer patients with thrombocytopenia (Falanga *et al.*)[5]

- In all patients on single or combined antithrombotic drugs, we advise against the use of traditional NSAIDs and high doses of aspirin (≥300 mg) as analgesic or antipyretic drugs. *Level 1, grade A*
- In all patients on single or combined antithrombotic drugs, we recommend using proton pump inhibitors to prevent gastrointestinal bleeding. *Level 1, grade A*
- Among patients receiving clopidogrel, omeprazole and esomeprazole are not recommended, and pantoprazole must be considered instead. *Level 1, grade A*
- Clinically relevant drug-drug interactions should be always considered, especially for clopidogrel, ticagrelor, warfarin, and dabigatran. *Level 1, grade D*
- In all patients at high/very-high CV risk, we advise to always optimize the treatment of modifiable CV or cardioembolic risk factors including hypertension and hypercholesterolemia. *Level 5, grade D*
- Platelet function monitoring is not recommended to guide single or dual antiplatelet therapy (APT). *Level 1, grade A*

In patients in whom antithrombotic therapy is continued, TP should be regularly verified, depending on stage of chemotherapy and platelet count, see table 2 of the original document.[5] Coxibs can be a valuable option for analgesia given their gastrointestinal and hemostatic safety.

In general, the task force recommended against platelet transfusion to correct the platelet count except for critical situations characterized by a very high thrombotic risk or acute thrombosis and severe, grade 4 TP. In such exceptional cases thrombopoietin administration may also be considered on an individual basis taking into account the likely duration of the TP and the delayed effect of the thrombopoietic agents.

ANTITHROMBOTIC MANAGEMENT AND THROMBOCYTOPENIA

Anticoagulation

The use of anticoagulant therapy for the main indications of atrial fibrillation (AF), venous thromboembolism and mechanical heart valve is indicated in Figure 1 in the source document[5] depicting continued use of therapeutic doses of anticoagulation in patients with TP grades 1-2 and reduced or arrested doses in grades 3-4.

In case of cessation of anticoagulation, alternative options with devices like inferior vena caval filters or intermittent pneumatic compression (prophylaxis), and central venous catheter removal and, in case of AF, left atrial appendage occlusion, may be considered on an individual basis.

Antiplatelet therapy

Single antiplatelet therapy (APT, mostly low-dose aspirin) for secondary prevention can usually be continued in those with grade 1, and grade 2 TP, in absence of major bleeding risk factors, while it should be halted in grade 3, unless there are major thrombotic risk factors, and stopped in grade 4 TP, as shown in Figure 1. The advice is similar for aspirin and clopidogrel, although for clopidogrel drug-drug-interactions should be considered since clopidogrel safety/efficacy profile is modified by several CYP450-interacting drugs and may, in turn, affect also some chemotherapeutic agents based on the same mechanism (supplementary table in Falanga *et al.*).[5] Primary prevention with low-dose aspirin, can only be continued in grade 1 TP, but is not recommended for >1 grades TP.

Dual APT should be tailored, depending on the severity of TP, but in general should preferably comprise of aspirin and clopidogrel, while prasugrel and ticagrelor should be avoided based on their higher bleeding risk as compared with clopidogrel, as shown in Figure 2. For acute coronary interventions in acute coronary syndrome (ACS) the risks and benefits should be carefully weighed in the individual patient (table 7 in Falanga *et al.*).[5] Dual APT with aspirin and clopidogrel can be used for transient ischemic attack or acute ischemic stroke for 21 days in grade 1 and 2 TP, provided there are no additional bleeding risk factors; for grades 3-4 either low-dose aspirin monotherapy or no APT is recommended, until recovery of platelet count, as shown in Figure 2. For acute symptomatic intracranial artery stenosis, the same restrictions apply but the duration of dual APT, if applicable, differs from above.

Combinations of anticoagulants and APT should preferably be avoided unless the risk of arterial thrombosis is very high, as in the ACS, and TP is within the grade 1-2 range.

The use of thrombolytic therapy for acute ischemic stroke should be avoided given the high bleeding risk and alternative options including mechanical thrombectomy are preferred. For acute and life- threatening pulmonary embolism, the use of thrombolysis or surgical clot removal should be considered only in experienced centers and on a case-by-case basis, after having measured the degree of TP.

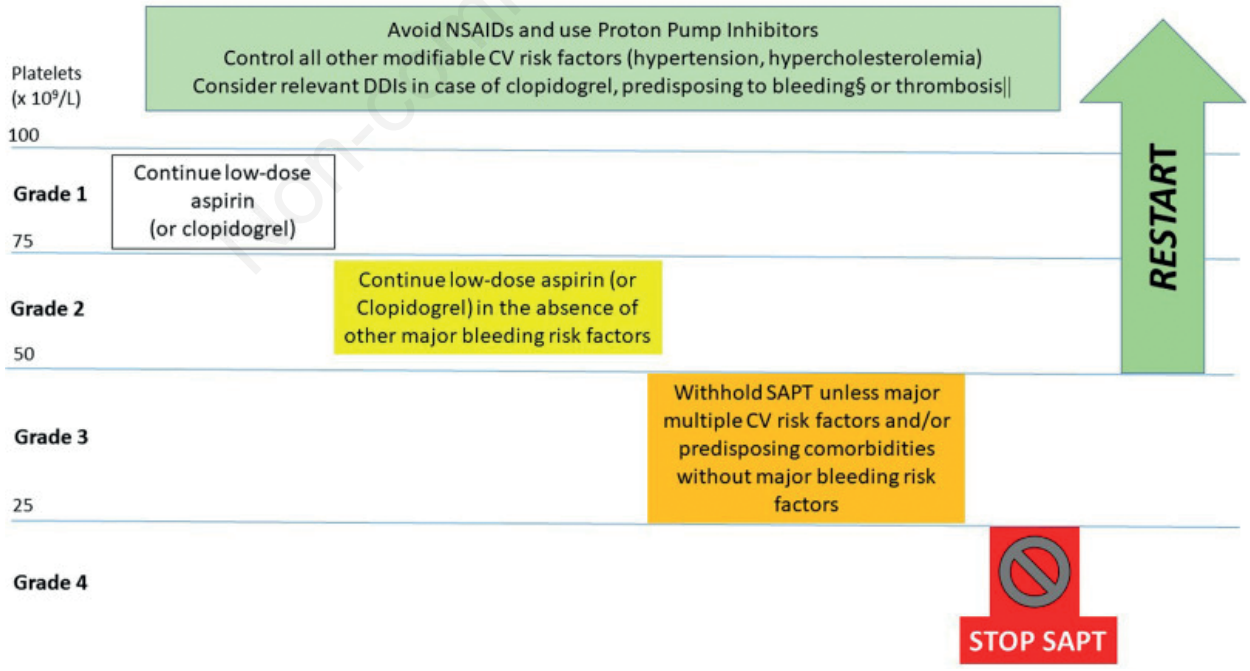

Figure 1. Management of SAPT for secondary prevention in cancer patients with TP. The flow chart depicts the recommendations for patients with a clear indication of single antiplatelet drug in the setting of secondary prevention of serious vascular events. CV = cardiovascular; DDI = drug-drug interaction; NSAID = nonsteroidal anti-inflammatory drugs; SAPT = single antiplatelet therapy; TP = thrombocytopenia. Reproduced from reference 5, with permission.

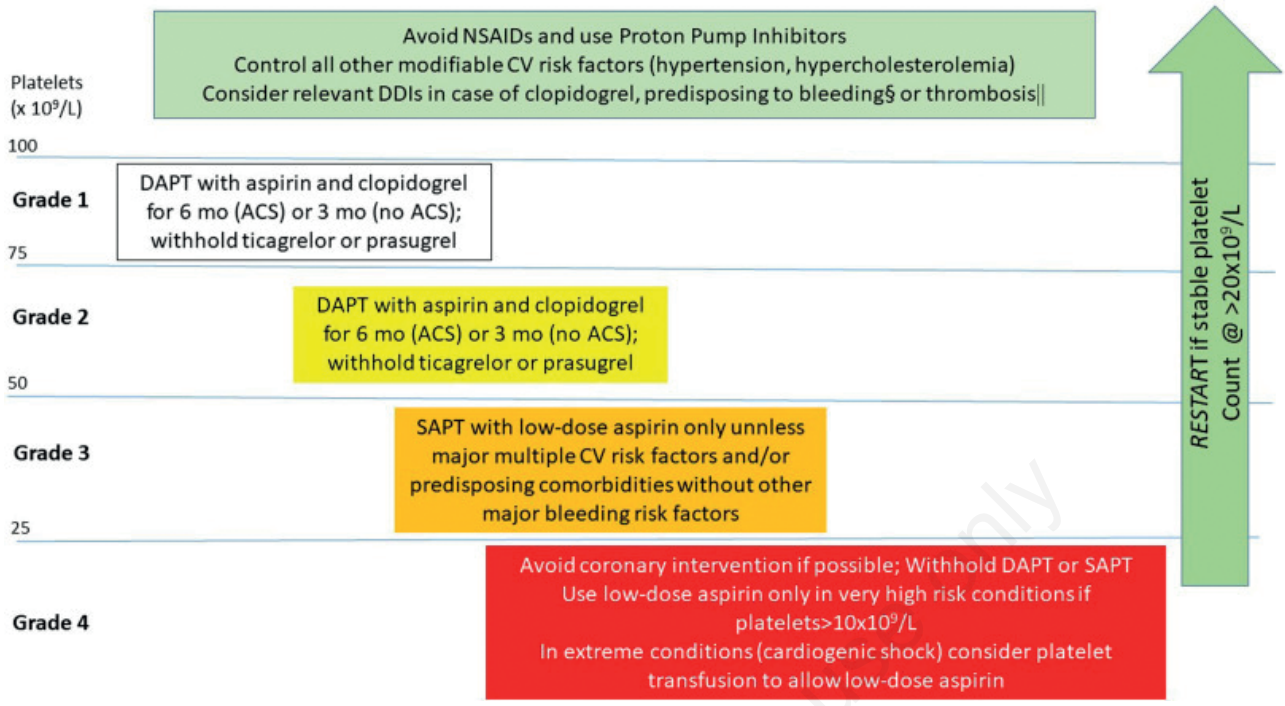

Figure 2. Management of APT in patients with ACS and POST-PCI. The flow chart depicts the recommendations for patients with a clear indication for dual antiplatelet drug in the setting of acute coronary syndromes (ACS) or after percutaneous coronary revascularization (PCI). CV = cardiovascular; DDI = drug-drug interaction; DAPT = dual antiplatelet therapy; NSAID = nonsteroidal anti-inflammatory drugs; SAPT = single antiplatelet therapy; TP = thrombocytopenia. Reproduced from reference 5, with permission.

CONCLUSIONS

How to treat thrombocytopenic cancer patients with acute or chronic thromboembolic diseases remains an unmet clinical need and a challenge for the future. Well-designed randomized clinical studies are needed. However, for the time being, this guideline based on current available evidence, can be an aid for clinicians for complex decision making at the patient side.

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