Critical Reviews in Oncology / Hematology 132 (2018) 76–88

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Antithrombotic medication in cancer-associated thrombocytopenia: Current evidence and knowledge gaps

A. Leader[a,b,c,*], H. ten Cate[a,d], G. Spectre[b,c], E.A.M. Beckers[e], A. Falanga[f]

[a] Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, the Netherlands
[b] Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel
[c] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[d] Thrombosis Expert Center, Maastricht University Medical Center, Maastricht, the Netherlands
[e] Department of Hematology, Maastricht University Medical Center, Maastricht, the Netherlands
[f] Immunohematology and Transfusion Medicine Department, Hospital Papa Giovanni XXIII, Bergamo, Italy

ARTICLE INFO

Keywords:
Anticoagulants
Arterial thrombosis
Bleeding
Neoplasms
Platelet aggregation inhibitors
Platelet transfusion
Thrombocytopenia
Venous thromboembolism

ABSTRACT

In cancer patients, antithrombotic medications (i.e. anticoagulation or antiplatelet therapy) are frequently prescribed for prior or new indications such as venous thromboembolism or stoke prevention in atrial fibrillation. Balancing the risks of bleeding and thrombosis during periods of thrombocytopenia represents a significant challenge. Management is informed mainly by expert opinion and several recent retrospective studies on venous thromboembolism. The main management options include no change, temporarily withholding antithrombotic therapy, reducing dose, changing the regimen, and increasing the platelet transfusion threshold. Important recent advances in knowledge include the prognostic importance and apparent safety of aspirin in acute myocardial infarction and thrombocytopenia and data suggesting a low risk of recurrent venous thromboembolism in autologous stem cell transplantation patients who had anticoagulation withheld. This paper will review the literature on antithrombotic medication in thrombocytopenic patients with cancer. The significant knowledge gaps will be summarized and considerations for practice and research will be provided.

1. Introduction

Cancer is associated with an increased risk of venous (Heit et al., 2000; Walker et al., 2013) and arterial thrombosis (Navi et al., 2017). Contemporary cancer care allows for treatment of older patients with comorbidities such as ischemic heart disease (IHD) and atrial fibrillation (AF). Thus, a significant proportion of cancer patients may have new indications for antithrombotic medication (i.e. anticoagulation or antiplatelet therapy [APT]), in addition to pre-cancer indications. These patients also have varying incidence, depth and duration of thrombocytopenia, depending on cancer type, anticancer treatment, bone marrow involvement and comorbidities (Liebman, 2014). Accordingly, antithrombotic medication, for a variety of indications, is not uncommon in cancer patients with thrombocytopenia (Leader et al., 2018a; Vinholt et al., 2016). Indications for antithrombotic therapy include prior venous thromboembolism (VTE), AF, ischemic stroke or IHD, among others.

Management of antithrombotic therapy with concomitant thrombocytopenia is complex and informed mainly by expert opinion (Saccullo et al., 2013), descriptive case series (Ibrahim et al., 2016) and retrospective studies on VTE, since clinical trials of antithrombotic medication exclude patients with thrombocytopenia ($< 50–75 \times 10^9$/L) (Lee et al., 2003, 2015; Raskob et al., 2017). Fig. 1 depicts the flow of the main management options. Some management choices are linked; for example, an increase in platelet transfusion target is more likely when anticoagulation is continued (Chalayer et al., 2017; Samuelson et al., 2016).

This paper will review the literature on APT and anticoagulation, prescribed for arterial or venous thrombosis-related indications, in adult cancer patients with hypoproliferative thrombocytopenia ($< 100 \times 10^9$/L). We performed a non-systematic literature review of the pubmed database using the following MeSH major topics: [*neoplasms* OR *thrombocytopenia*] AND [*platelet aggregation inhibitors* OR *anticoagulants*]. This search yielded 3437 items and was narrowed down to 1607 by adding the term *thrombocytopenia* in the title or abstract (13 August 2018). We screened the title and abstract of the 685 articles from the last ten years. The reference lists of the relevant articles were screened for additional papers.

* Corresponding author at: Institute of Hematology, Rabin Medical Centre, 39 Jabotinsky, Petah Tikva, 4941492, Israel.
E-mail address: avileader@yahoo.com (A. Leader).

https://doi.org/10.1016/j.critrevonc.2018.09.014
Received 19 April 2018; Received in revised form 17 August 2018; Accepted 25 September 2018
1040-8428/ © 2018 Elsevier B.V. All rights reserved.

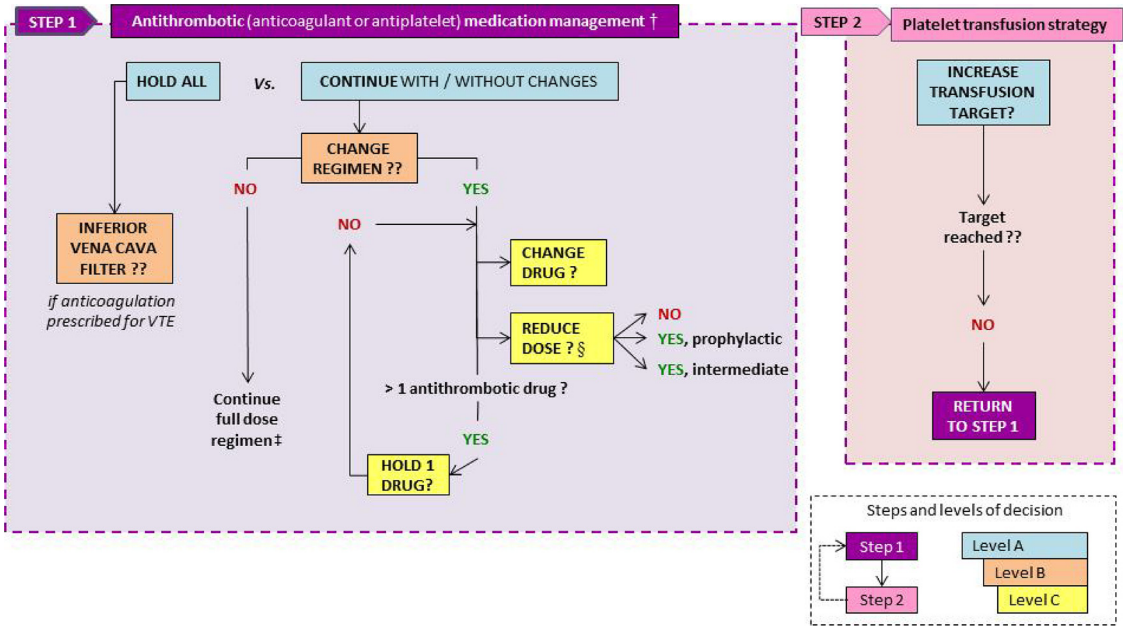

Fig. 1. This figure depicts a stepwise framework for documenting management in patients with thrombocytopenia and antithrombotic medication.
† Changes are described relative to the chronic treatment or indicated regimen (if new indication)
‡" Full dose" may be prophylactic, intermediate or therapeutic doses, depending on the indication
§ Dose reductions are primarily relevant for anticoagulants
VTE, venous thromboembolism

The literature focuses mainly on patients with hematological malignancy who have a high incidence of thrombocytopenia and bleeding (Liebman, 2014; Stanworth et al., 2013), and accordingly this review focuses primarily, but not exclusively, on this population. The general risks of bleeding in thrombocytopenia patients will be discussed, but a special focus will be placed on the thrombosis risk, since it is the uncertainty of balancing up specific additional therapy for thrombosis on a background of thrombocytopenia that requires management.

2. Thrombosis and bleeding in cancer

2.1. Thrombosis risk

The mechanisms contributing to the elevated thrombosis risk in cancer patients are shown in Fig. 2, along with possible effects of antithrombotic medication.

2.1.1. Venous thrombosis

Cancer is associated with a 4 to 6.5-fold higher VTE risk compared to patients without (Heit et al., 2000; Walker et al., 2013). As reviewed recently (Falanga et al., 2017), the pathophysiology is complex (Fig. 2) and multiple patient, tumor and treatment-related factors affect the VTE risk. Risk assessment models are used to stratify VTE risk which ranges from 1.5% in low risk patients at 6 months to 17.7% in those with the highest risk (Ay et al., 2010). Even with full anticoagulation the VTE recurrence rates in cancer are high, ranging between 7% and 17% (Lee et al., 2003, 2015), especially during the first month of therapy (Prandoni et al., 2002).

2.1.2. Arterial thrombosis

In an ageing population both ischemic cardiovascular diseases (myocardial infarction [MI], ischemic stroke) and cancer are increasingly prevalent (Bhatnagar et al., 2015; Torre et al., 2012). Patients with incident cancer face an increased short-term risk of atherothrombotic events (hazard ratio [HR] 2.2, 95% CI: 2.1–2.3) as well as adverse outcomes, compared to patients without cancer (Navi et al., 2017; Velders et al., 2013). This holds true for both myocardial infarction and ischemic stroke, and varies according to the type of cancer across solid and hematological malignancies (Navi et al., 2017; Del Prete et al., 2018). For instance, arterial thrombosis occurred at a cumulative incidence of 4.7% (95% CI: 4.6–4.8%) at 6 months and was associated with mortality in a recent population-based cohort study of mixed cancer types (Navi et al., 2017). Therefore, APT, prescribed as secondary prevention for cardiovascular events, is frequently encountered in cancer patients (Vinholt et al., 2016).

2.1.3. Atrial fibrillation

2.1.3.1. AF is common in cancer. AF occurs in approximately 1.5%–2% of the general population(Fitzpatrick et al., 2017), increases with age and is associated with an elevated risk of stroke and thromboembolism (Wolf et al., 1991). As reviewed recently, although data is limited, cancer patients appear to have a higher risk of AF than controls (Fitzpatrick et al., 2017; Farmakis et al., 2014), particularly in the 90 days after diagnosis (Guzzetti et al., 2008; Erichsen et al., 2012; Saliba et al., 2018), and adjacent to hematopoietic stem cell transplantation (HSCT; 7–27%) (Mathur et al., 2016). This may be related to multiple factors (Farmakis et al., 2014; Mathur et al., 2016). Moreover up to 1 in 4 patients with AF have a history of cancer (Melloni et al., 2017).

2.1.3.2. CHA_2DS_2-VASc score is useful for predicting thrombosis and cancer may not add to embolic risk. Since there is an increased risk of arterial thrombosis in cancer (Navi et al., 2017), patients with AF and cancer may theoretically have an increased risk of thromboembolism compared to non-cancer patients. This, however, was not demonstrated in a recent analysis of the ORBIT-AF registry and remains to be proven (Melloni et al., 2017). Risk stratification (e.g. CHA_2DS_2-VASc score) allows for the selection of AF patients who warrant anticoagulation to reduce the risk of embolic events (Kirchhof et al., 2016). Individuals with a CHA_2DS_2-VASc score ≥ 2 generally have an annual ischemic stroke risk of > 2% and are indicated anticoagulation. Limited evidence suggests that these prediction scores still perform well in segregating high and low risk individuals in cancer populations with AF (Elbadawi et al., 2017; Patell et al., 2017). Studies are yet to show that a prior or current diagnosis of cancer improves the predictive value of the

Download English Version:

https://daneshyari.com/en/article/11025453

Download Persian Version:

https://daneshyari.com/article/11025453

Daneshyari.com