Immune Thrombocytopenia Patients Requiring Anticoagulation—Maneuvering Between Scylla and Charybdis

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Immune thrombocytopenia (ITP) is no longer a disorder of young people. Half of the patients are older than 50 and comorbidities become more common with age. Anticoagulation has to be discussed when an ITP patient develops atrial fibrillation, venous or arterial thromboembolism, myocardial infarction, or stroke. At the same time low platelet counts often prohibit therapeutic anticoagulation. Guidelines do not give guidance for these situations. This article summarizes experiences from case reports and small series and suggests an approach to ITP patients with thrombocytopenia and an indication for anticoagulation.
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Immune thrombocytopenia (ITP) is a rare disorder with a yearly incidence rate between 2–4:100,000 adults. The prevalence has been estimated at ~20:100,000.[1–5] ITP affects both old and young patients with a median age of ~50 years.[1,3]

Older ITP patients are more likely to develop comorbidities. The incidence of atrial fibrillation (AFib), coronary artery disease (CAD) with acute myocardial infarction (AMI), cerebrovascular disease (CVD) with stroke and transient ischemic attacks (TIAs), and of venous thromboembolism (VTE) increases with age. The incidence of AFib in the non-ITP population is estimated at 1%, and in those >60 years even at 6%.[6,7] The prevalence of stroke is 2%–3% and of CAD 6%.[7–9] From age 30 to 75, the risk of VTE increases steadily and exponentially by a factor of 10.[10] Anticoagulation poses a clinical challenge in ITP patients because it is usually contraindicated with thrombocytopenia <50,000–75,000/μL.[11] ITP patients requiring anticoagulation have been excluded from all pivotal studies on newer therapeutic agents and clinical data are scarce.[12,13] This article summarizes experiences from case reports and small series and suggests an approach to the ITP patient with thrombocytopenia.

ITP AND THROMBOEMBOLIC COMORBIDITIES

Thrombocytopenia does not protect ITP patients against thromboembolic disease. Myocardial infarction, stroke, and VTE occur in ITP patients as they occur in the normal population[14–17] and even with platelet counts <30,000/μL.[17,18] One study even found the risk of VTE in ITP to be as high as in cancer patients.[19] The risk of AFib, AMI, and stroke might even be higher in ITP patients than in age-matched controls.[20] Another study describes a transient ischemia-like syndrome in ITP with recurring dizzy spells, memory loss, and cognitive impairment progressing to dementia. This syndrome is more common after splenectomy.[21]

The pathophysiology of venous and arterial thromboembolic events in ITP remains elusive. Paradoxically, the risk seems to be higher with lower platelet counts.[15] This suggests a causal relationship. Hyperreactive young platelets[22] and antiphospholipid antibodies have been discussed. Hospitalization and immobilization for bleedings and side effects of ITP treatments pose additional risks. Intravenous immunoglobulin (IVIg)[23] and corticosteroids (eg, dexamethasone, tranexamic acid)[24–26] are documented prothrombogenic agents. Splenectomy

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carries a particularly high VTE risk.[27,28] For the new thrombopoietin receptor agonists (TRAs) initially an increased risk had been discussed. Recent studies find that this is only true when TRAs are given in non-ITP indications.[29,30] In ITP patients with TRAs the risk seems not to be higher than in ITP patients without TRAs.[31–33] Nevertheless and interestingly, platelet counts >150,000 (German Fachinformation) or >200,000 (US food and Drug Administration prescribing information) should be avoided with TRAs.

ITP AND ATRIAL FIBRILLATION

A Medline search for the terms ''immune thrombocytopenia'' and ''atrial fibrillation'' found no publications on anticoagulation in patients with ITP. Only one recent article describes the case of a 91-year-old man with AFib who was started on romiplostim to raise his platelet counts so he could safely be anticoagulated with an oral vitamin K antagonist.[34]

ITP AND ACUTE MYOCARDIAL INFARCTION

Several case reports describe ITP patients with AMI.[35–39] Thrombocytopenia did not protect against coronary thrombosis. The authors discuss that steroids or IVIg could have precipitated the acute events but the patients were also elderly and had coronary risk factors. AMI has been reported in conjunction with the use of the new thrombopoietic agents.[31,32] These articles do not comment on post-AMI anticoagulation.

ITP AND CARDIOVASCULAR SURGERY

In the 1980s, open-heart operations were successfully performed together with simultaneous splenectomy.[40,41] In the 1990s and 2000s, perioperative management, such as high-dose immunoglobulins and platelet transfusions, allowed safe surgical treatment without splenectomy.[42–49] These publications focus on the perioperative management and do not give recommendations for postoperative anticoagulation.

ITP AND PTCA

Some more recent reports describe successful percutaneous transluminal coronary angioplasty (PTCA) in ITP patients. Patients were placed on acetylsalicylic acid (ASS) and thienopyridines as post-stenting therapy.[50–54] Long-term efficacy and safety were not reported.

ITP AND STROKE

Few articles describe CVAs or a TIA-like syndrome in ITP.[18,21,55] Because of low platelet counts, anticoagulation was not started in one case.[56] Other authors tried to raise platelet counts to safe levels before starting anticoagulation.[55,57]

ITP AND VENOUS THROMBOEMBOLISM

ITP patients have a substantial risk of VTE,[17] particularly after splenectomy.[28,58] VTE has been reported with the new thrombopoietic agents but without further details on anticoagulant efficacy and safety.[12,30,59]

ANTICOAGULATION ASSOCIATED WITH OTHER TYPES OF THROMBOCYTOPENIA AND THROMBOPATHY

Thrombotic thrombocytopenic purpura (Moschcowitz syndrome, TTP), heparin-induced thrombocytopenia type II (HIT II), antiphospholipid antibody syndrome (APS), and disseminated intravascular coagulation (DIC) are thromboembolic syndromes with thrombocytopenia and important differential diagnoses of ITP. The underlying pathophysiologies differ and so do the therapeutic approaches. VTE is common in HIT and patients are treated with therapeutic doses of alternative, non-heparin anticoagulants.[60] ASS and plasmapheresis are given in TTP.[61] APS patients have a high risk of VTE. When they are thrombocytopenic at the same time then management is like maneuvering between a rock and a hard place because of a high risk of bleeding and re-thrombosis.[62] Heparin has been historically used as a treatment for DIC with varying outcomes in different clinical situations.[63]

As far as congenital platelets disorders are concerned, thrombotic events have been described in Glanzmann thrombasthenia[64–68] and in Bernard–Soulier syndrome.[69–71] Recommendations for ITP patients cannot be derived from these few cases.

PROPHYLAXIS AND TREATMENT

In 1996 the American Society of Hematology published its first ITP Guideline to provide guidance to non-experts of this rare disorder.[72] This is still the most cited article in the field. Several updates and newer guidelines have been published since then.[73–76] None comments on the management of ITP patients with a need for anticoagulation. This is due to the scarcity of clinical data. However, the absence of data should not justify the absence of opinion.[77]

Prophylactic anticoagulation is usually offered to immobilized medical patients or to postoperative surgical patients. These patients may have a high risk of thromboembolism (eg, total hip or knee replacement, etc). This risk has to be weighed against the risk of bleeding in thrombocytopenia. Since patients do not actually have thromboembolism there is less

pressure to start anticoagulation right away compared to patients with established thromboembolism. Anglo-American cancer guidelines recommend thromboprophylaxis as long as the platelet count does not fall to <50,000/μL.[78,79] The Austrian/German/Swiss guideline on anticoagulation in cancer patients is more liberal and allows prophylaxis to a threshold of 30,000/μL.[80] With lower counts, mechanical prophylaxis (compression stockings, pneumatic devices) should be considered.

For therapeutic-dose anticoagulation in ITP patients with severe thrombocytopenia the authors recommend:

- Give corticosteroids and IVIg to raise platelet counts rapidly to a safe level (ie, >30,000–50,000/μL).
- Start TRAs to maintain platelet counts in a safe range when corticosteroids are tapered and the effect of IVIg starts to wear off.
- Do not give anticoagulation, no matter what the platelet count, in patients with life-threatening bleeding or bleeding requiring transfusion (World Health Organization [WHO] grade III/IV). Consider a vena cava filter in DVT patients.
- In all other ITP patients (no bleeding, petechiae, hematomas, stable hemoglobin = WHO grade 0/I/II), consider anticoagulation.
  - With platelet counts ≥ 50,000/μL start standard-dose therapeutic anticoagulation.
  - With lower counts, <50,000/μL, give half-standard doses and increase to full doses when platelets rise to ≥50,000/μL.
- Further adapt intensity of anticoagulation to bleeding symptoms and platelet count as outlined in Figure 1.

The treatment algorithm has been derived from cancer patients with both thromboembolism and a very high bleeding risk at the same time.[81,82] In these high-risk patients one usually starts with unfractionated heparin (UFH) instead of low-molecular-weight heparins (LMWH). UFH has a shorter half-life and can be stopped, monitored, and potentially better reversed immediately when severe bleeding occurs (at the expense of the necessary IV line, difficult monitoring and dose adjustments.) When patients remain without bleeding after 48 hours, one may switch to LMWH.

This algorithm should be regarded as a starting point for the necessary discussion on how to anticoagulate ITP patients with arterial or venous thrombotic events. Future guidelines will have to address this issue. Our patients will ask for it.

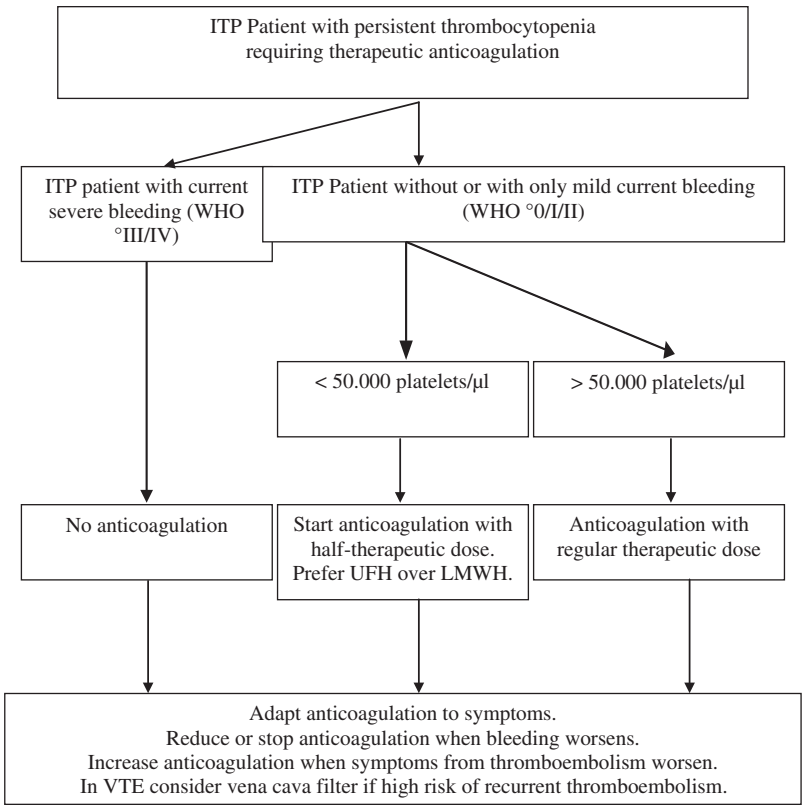

Figure 1. Treatment algorithm.

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