PIASTRINOPENIA E TRATTAMENTI ANTICOAGULANTI: LUCI ED OMBRE

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CLASSIFICAZIONE DELLE PIASTRINOPENIE

Cause più comuni di piastrinopenia

1. PREVALENTE DIFETTO DI PRODUZIONE

- Leucemie, mielodisplasie, linfomi, infiltrazione midollare da altre neoplasie
- Aplasia midollare
- Piastrinopenia amegacariocitaria
- Secondarietà ad infezioni, chemioterapia, radiazioni, insetticidi, sostanze chimiche, farmaci vari
- EPN
- Forme ereditarie (malattia di Fanconi, discheratosi congenita, piastrinopenia ciclica, disordini correlati a MYH9, sindrome di Wiskott-Aldrich)
- Anemie megaloblastiche

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Cause più comuni di piastrinopenia

2. PREVALENTE ACCELERATA DISTRUZIONE

- Piastrinopenia immune primaria (ITP)
- Piastrinopenia indotta da eparina (HIT)
- Piastrinopenia da farmaci
- Porpora post-trasfusionale
- Piastrinopenia alloimmune (isoimune) neonatale
- TTP
- HUS
- CID
- Emangioma cavernoso
- Infezioni acute
- Piastrinopenia gestazionale

CLASSIFICAZIONE DELLE PIASTRINOPENIE

Cause più comuni di piastrinopenia

3. PREVALENTE ALTERATA DISTRIBUZIONE

- Patologie associate a splenomegalia (ipertensione portale, malattia di Gaucher ecc.)

Target platelet count during surgery and procedures with bleeding risk

Consensus-based recommendation for target platelet counts during surgery in adults (Evidence level IV)

Dental prophylaxis (descaling, deep cleaning) **≥20–30 × 10^9/L**

Simple extractions **≥30 × 10^9/L**

Complex extractions **≥50 × 10^9/L**

Regional dental block **≥30 × 10^9/L**

Minor surgery **≥50 × 10^9/L**

Major surgery **≥80 × 10^9/L**

Major neurosurgery **≥100 × 10^9/L**

Provan D, Blood 2010

‘Sailing in troubled waters’: a review of the use of anticoagulation in adult cancer patients with thrombocytopenia *Ibrahim RB et al. Blood Coagul Fibrinolysis, 2016*

Simply providing anticoagulation therapy is not as straightforward of **a solution in cancer patients who have concurrent thrombocytopenia** owing to the increased **risk of bleeding complications**. Currently, few guidelines are in place to assist clinicians in safely managing thrombocytopenic cancer patients on anticoagulation

‘Sailing in troubled waters’: a review of the use of anticoagulation in adult cancer patients with trombocitopenia

Ibrahim RB et al. Blood Coagul Fibrinolysis, 2016

UFH LMWH

Table 1 Reports of unfractionated heparin and LMWH use in adults with cancer-related thrombocytopenia

Reference	Publication type	Indication for anticoagulation	Anticoagulation	Results
Bearman *et al.* [13] 1990	Prospective cohort study with historical controls ($n=28$ each arm)	Autologous and allogeneic HSCT patients; VOD prevention	UFH (started on the day of preparative chemotherapy until 10 days post-HSCT): Dose level I: 50 units/kg then 10–15 units/kg per h (1.5–2 × baseline PTT) Dose level II: 5000 units then 10 units/kg per h (1.5–2 × baseline PTT) Dose level III: 3000 units, then 10 units/kg per h (1.2–1.6 × baseline PTT) Dose level IV:1000 units, then 150 units/kg per day (<1.2 × baseline PTT)	Platelet count ranged between 28 and 76 × 10^9/l at UFH discontinuation in one patient Twenty-seven patients experienced bleeding; 25 minor bleed and two patients develop major nonfatal gastrointestinal bleeding. Dose level I/II ($n=16$): two major/13 minor bleeds Dose level III ($n=2$): two minor bleeds Dose level IV ($n=10$): 10 minor bleeds
Attal *et al.* [16] 1992	Prospective randomized placebo controlled ($n=81$ UFH vs. $n=80$ placebo)	Autologous and allogeneic HSCT patients; VOD prevention	UFH 100 units/kg per day continuous infusion; started on the day of preparative chemotherapy until discharge/30 days post-HSCT	Mean duration of thrombocytopenia (<25 × 10^9/l): 18.2 days No major bleed UFH discontinued in three patients because of poor response after platelet transfusion given for minor gastrointestinal bleeding
Drakos *et al.* [20] 1992	Case series ($n=5$)	Autologous HSCT patients; CR-DVT treatment	Enoxaparin 40 mg bid × 14 days, then 40 mg daily × 60 days; anti-Xa levels range: 0.17–0.4 units/ml	Baseline platelet count: 19–126 × 10^9/l No bleeding complications were noted
Or *et al.* [21] 1996	Double-blind placebo-controlled feasibility and safety ($n=28$ intervention vs. 33 placebo)	Autologous HSCT patients; VOD prevention	Enoxaparin 40 mg daily prior to high-dose chemotherapy and continued for 40 days post-HSCT	Mean duration of severe thrombocytopenia less than 20 × 10^9/l = 8.7 ± 6.9 days vs. 13 ± 10 in the LMWHs and control group, respectively 5/28 in the LMWH arm vs. 6/33 in the control arm had bleed (gastrointestinal, subdural, mucocutaneous); no further details provided
Schimmer *et al.* [24] 1998	Retrospective case–control ($n=10$ intervention vs. 20 control)	Autologous HSCT patients; *Intervention*: CR-DVT ($n=8$), PE ($n=1$), atrial fibrillation with arterial leg thrombosis ($n=1$); *Control*: CR-DVT prevention	Intervention: IV UFH 5000 units followed by 1000 units/h (goal PTT = 50–70 s) then warfarin; Control: warfarin 1 mg daily	Median platelet count: 68 × 10^9/l (range: 16–188 × 10^9/l) Intervention: three of 10 (30%) with hematemesis and hematuria; median PTT = 75 s (range: 66.7–83.1 s); Control: two of 20 (10%) with hematuria hematochezia
Simon *et al.* [12] 2001	Retrospective cohort study	Autologous/allogeneic HSCT patients; VOD prevention; four groups: (i) enoxaparin ($n=106$) (ii) UFH ($n=104$) (iii) UFH + prostaglandin ($n=110$) (iv) No prophylaxis ($n=142$)	UFH 5 units/kg per h (goal PTT ≤ 50 s) or enoxaparin 30 mg q12h within 24 h of high-dose chemotherapy; both continued either until day of discharge or day 28–30 post-HSCT	Median time to platelets more than 20 × 10^9/l = 20 days in the enoxaparin arm Median time to platelets more than 20 × 10^9/l = ~28 days in both of UFH arms No difference in the rate of fatal hemorrhagic events between the four groups
Park *et al.* [19] 2002	Prospective trial between UFH + ursodiol ($n=82$) vs. UFH ($n=83$)	autologous/allogeneic HSCT patients; VOD prevention	UFH 5 units/kg per h; titrated down by 50 units/day to goal PTT 50 s or less; started on 12–24 h prior to preparative chemotherapy until discharge/30 days post-HSCT	Seventeen patients discontinued UFH due to bleeding or sustained PTT more than 50 s Twenty-six patients experienced various grades of bleeding with one fatality
Forrest *et al.* [25] 2003	Prospective single-arm phase II ($n=40$)	Allogeneic HSCT patients; VOD prevention	Dalteparin 2500 units on the day before high-dose chemotherapy and continued until day of discharge or day 30 post-HSCT	Median time to sustained platelets more than 20 × 10^9/l = 13 days (range 6–45) Three major bleeds; 24 patients developed minor bleed
Cortelezzi *et al.* [11] 2003	Case series ($n=126$; catheters = 207)	Patients with hematological malignancies; thromboprophylaxis for CR-DVT	UFH (catheters = 169)[a]: 2500 units/day; intravenous nadroparin (catheters = 21): 3800 IU/day	Median platelet count = 76 × 10^9/l (range:1–672 × 10^9/l) No major bleeding observed

‘Sailing in troubled waters’: a review of the use of anticoagulation in adult cancer patients with trombocitopenia

Ibrahim RB et al. Blood Coagul Fibrinolysis, 2016

UFH LMWH

Table 1 (*continued*)

Reference	Publication type	Indication for anticoagulation	Anticoagulation	Results
Herishanu *et al.* [26] 2004	Case series ($n=10$)	HSCT patients ($n=9$);[b] thromboprophylaxis ($n=5$) and CR-DVT treatment ($n=5$)	Thromboprophylaxis: enoxaparin 0.25–1 mg/kg (anti-Xa level 0.2–0.5 IU/ml in two patients);CR-DVT: enoxaparin 0.5–2 mg/kg (anti-Xa level ranged between 0.32 and 1.65 IU/ml in three patients)	Lowest platelet count (range): $1-18\times10^9$/l (thromboprophylaxis group) and $14-22\times10^9$/l (CR-DVT group) No major bleeding observed
Imberti *et al.* [27] 2004	Small case series ($n=4$)	Patients with acute leukemia; diagnosed with VTE (all lower extremity VTEs; one patient with concomitant PE)	Enoxaparin 100 IU/kg twice daily × 1 month, then 150 IU/kg once daily × at least 5 months; when platelet count is less than 20×10^9/l: 50% dose reduction	Baseline platelet count for each patient: 12, 17, 46, 121×10^9/l No major bleeding observed
Monreal *et al.* [23] 2004	Prospective cohort study ($n=203$)	Patients with metastatic cancer and VTEs	Dalteparin: Platelet count more than 50×10^9/l = 10 000–12 500 IU/day; platelet count less than 50×10^9/l = 5000 IU/day; platelet count less than 10×10^9/l = 2500 IU/day	55 patients (27%) developed transient thrombocytopenia (platelet count less than 100×10^9/l); 33 patients with a platelet count less than 50×10^9/l Only seven bleeds (all minor) observed during thrombocytopenia
Ibrahim *et al.* [29] 2005	Observational case series ($n=26$)	HSCT patients; mainly for VTE treatment	Enoxaparin: ~ 0.5 mg/kg per day (range: 0.34–0.75 mg/kg per day) during thrombocytopenia; anti-Xa level ranged between 0.04 and 0.4 IU/ml in five patients)	Median platelet count days less than 55×10^9/l = 10 days (range: 1–72 days) Median platelet count days less than 20×10^9/l = 2 days (range: 0–20 days); 53% of patient did not have a platelet count less than 20×10^9/l 7% major bleeding – 14% minor bleeding Mean platelet transfusions: 4 (range: 0–32)
Politi *et al.* [32] 2012	Case series ($n=12$; 19 apheresis sessions)	Mostly patients with hematological malignancies; thromboprophylaxis prior to apheresis in high-VTE risk HSCT patients	Enoxaparin, 20–40 mg, 10–12 h before the procedure as a single dose	Mean platelet count = 37×10^9/l (range:$19-50\times10^9$/l) No major or minor bleeding observed
Saccullo *et al.* [33] 2012	Prospective cohort study ($n=49$ with thrombocytopenia due to chemotherapy)	Cancer patients at risk for VTE	LMWHs (enoxaparin or nadroparin) at ~ 4000 IU once/twice daily); started after stopping warfarin (~ 5 days before chemotherapy) and stopped when platelet count is less than 30×10^9/l	Median platelet nadir = 35×10^9/l (range: $9-94\times10^9$/l) Major bleeding: 4.1%
Babilonia *et al.* [41] 2014	Retrospective review of hospitalized patients ($n=93$)	Cancer patients with VTEs	Patients with platelet between 20 and 50×10^9/l: dalteparin 100 units/kg per day ($n=35$); patients with platelet more than 50×10^9/l ($n=58$): 200 units/kg per day	8.6% of patients in the platelet less than 20×10^9/l arm had bleeding of any severity vs. 9.4% in the platelet more than 50×10^9/l arm ($P=0.607$)

Unless otherwise indicated, doses are subcutaneous. CR-DVT, catheter-related deep venous thrombosis; HSCT, hematopoietic stem cell transplantation; LMWH, low molecular weight heparin; PE, pulmonary embolism; PTT, partial thromboplastin time; UFH, unfractionated heparin; VOD, venoocclusive disease; VTE, venous thrombotic event, that is, deep venous thrombus in the lower extremity or pulmonary embolism. [a] One patient received warfarin and 16 received no prophylaxis. [b] The 10th patient received chemotherapy for mantle cell lymphoma.

Fixed-dose low-molecular-weight heparin for secondary prevention of venous thromboembolism in patients with disseminated cancer: a prospective cohort study *Monreal M et al. JTH , 2004*

- **Effectiveness and safety of long-term subcutaneous dalteparin** in a series of consecutive patients with symptomatic VTE and metastatic cancer. 203 patients, aged 36–96 years
- Initial treatment: a 7-day course of subcutaneous dalteparin according to body weight.
- Then, a fixed dose of 10 000 IU dalteparin once daily for at least 3 months.
- In patients developing transient thrombocytopenia (55) the dose was reduced to 5000 IU daily while the platelet count remained <50 000/μl; and to 2500 IU daily while it remained <10 000/μl.
- Eleven patients (5.4%) developed major bleeding complications (6 fatal) during the 3-month study period, and 18 patients (8.9%) developed VTE recurrences (2 patients died).
- **Seven minor bleeds during thrombocytopenia.**

The dose adjustment for patients with thrombocytopenia, surgery or invasive procedures was safe

Safety and efficacy of enoxaparin treatment in venous thromboembolic disease during acute leukemia

Imberti et al. Tumori, 2004

- Four patients with acute leukemia developed VTE complications (mean age 55.7 y)
- All were treated with **enoxaparin 100 IU/kg subcutaneously twice daily for one month, followed by 150 IU/kg once daily for at least five months**. When the platelet count was below 20,000 x 10^9/L, the dose was reduced by 50%.
- During antithrombotic treatment neither VTE recurrences nor hemorrhagic complications or HIT occurred.
- **Mean platelet count at the beginning of enoxaparin was 55,750 x 10^9/L**; range, 12,000-121,000 x 10^9/L) and treatment did not affect platelet recovery.
- Enoxaparin proved to be efficacious and safe in the management of VTE in patients affected by acute leukemia.

Enoxaparin cured acute venous thrombosis, prevented recurrences and did not cause any hemorrhagic complications despite prolonged severe thrombocytopenia

Cancer patients requiring interruption of long-term warfarin because of surgery or chemotherapy induced thrombocytopenia: the use of fixed sub-therapeutic doses of low-molecular weight heparin *Saccullo G et al. Am J Hematol, 2012*

- **The efficacy and safety of fixed doses of LMWH was tested in substitution of VKA because of invasive procedures or chemotherapy induced thrombocytopenia.**
- In cancer patients on VKA, therapy was discontinued 5 ± 1 days before surgery or chemotherapy.
- **LMWH was given at prophylactic dosage in patients at low risk and at fixed subtherapeutic doses (3,800 or 4,000 UI anti-FXa, b.i.d.) in those at high-risk for thrombosis**. It was reinitiated 12 hr after surgery and VKA the day after.
- In patients receiving chemotherapy, **LMWH** was reinitiated 12/24 hr after obtaining a stable platelet count **30,000 mmc3** and **VKA** after a stable platelet count **50,000 mmc3**.
- **156** patients (**49 with thrombocytopenia**), 56.4% at low risk and 43.5% at high risk for thrombosis, were enrolled.
- In the **group of patients who experienced chemotherapy induced thrombocytopenia**, the **rate of thrombosis and major bleeding was 2.0% and 4.1%, respectively**; **median nadir** platelet count was **35,000 mmc3** (range, 9,000–94,000 mmc3). **LMWH was stopped when platelets <30,000 mmc3.**

In conclusion, the use of fixed doses of LMWH as a bridging regimen in cancer patients on long-term VKA is feasible and appears to be safe, because it is associated with a relatively low risk of recurrent thrombosis and major bleeding.

Antithrombotic therapy in patients with thrombocytopenic cancer: outcomes associated with reduced-dose, low-molecular-weight heparin during hospitalization

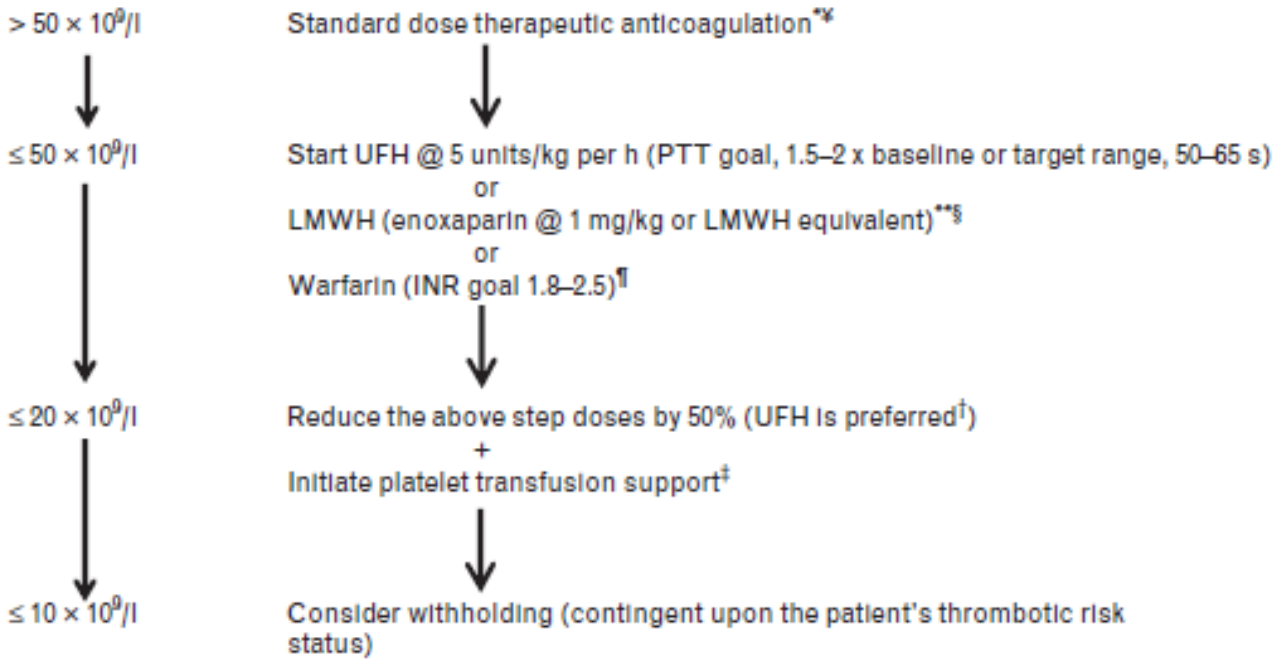
Babilonia KM et al. Clin Appl Thromb Hemost 2014

- **Hospitalized adults with cancer-associated thrombosis (CAT) and platelets ≤50 × 10⁹/L** were managed with dalteparin 100 units/kg sc once daily. Comparator patients with CAT and platelets >50 × 10⁹ /L were managed with dalteparin 200 units/kg/d.
- **35 patients with thrombocytopenia** (mean plt count **26 ± 8.3×10⁹ /L**) and **58 comparator patients** (mean plt count **155 ± 75 × 10⁹/L**)
- Incidence of **bleeding in patients with thrombocytopenia (8.6%)** was **similar to that in comparator patients (9.4%)** (risk ratio 0.94, 95% CI 0.37-2.39, P = .607)
- **In hospitalized patients having thrombocytopenia with CAT, reduced-dose low-molecular-weight heparin was generally efficacious, without significant new–onset VTE vs comparator group**

‘Sailing in troubled waters’: a review of the use of anticoagulation in adult cancer patients with trombocitopenia

Ibrahim RB et al. Blood Coagul Fibrinolysis, 2016

Fig. 1

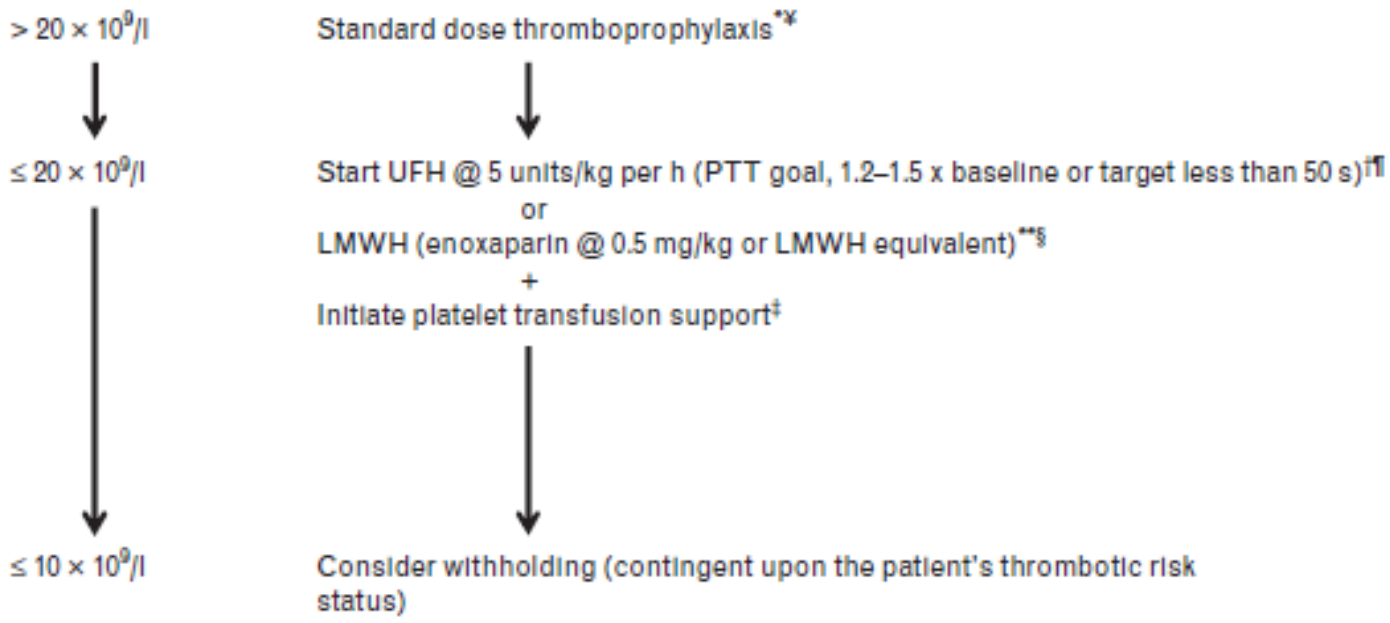


Algorithm for full-dose anticoagulation dosing in thrombocytopenic adult cancer patients. *Consider preemptive dose reduction if the platelet count is anticipated to drop further in the ensuing 24–48 h. ¥A recent consensus document supported no anticoagulation dose reduction for platelet count between 50 and 100 × 10^9/l [96]. **Among LMWHs, enoxaparin has the most safety data regarding LMWH use in thrombocytopenic cancer patients. §A target anti-Xa level between 0.4 and 0.8 IU/ml is a consideration. ¶On the basis of clinical experience. †Owing to its rapid anticoagulant effect reversal and the availability of a full antidote in protamine – should severe bleeding occur. Conversely, because of opposing reasons (i.e., prolonged anticoagulant effect); warfarin is *not* recommended at this stage. ‡Barring adequate and timely support in the outpatient setting, the implementation of platelet transfusion support entails an inpatient hospital admission, especially if UFH is given. The algorithm assumes that no bleeding risk factors (recent surgery or bleeding episode, renal failure, etc.), other than thrombocytopenia and being on an anticoagulant, are present. As stated in the text, these recommendations are solely based on the available ‘safety’ evidence. In our opinion, efficacy at the above-recommended doses cannot be determined with the current state of evidence.

‘Sailing in troubled waters’: a review of the use of anticoagulation in adult cancer patients with trombocitopenia

Ibrahim RB et al. Blood Coagul Fibrinolysis, 2016

Fig. 2



Algorithm for low-dose anticoagulation dosing in thrombocytopenic adult cancer patients. *Consider preemptive dose reduction if the platelet count is anticipated to drop further in the ensuing 24–48 h. ¥A recent consensus document supported no anticoagulation dose reduction for platelet count between 50 and 100 × 10^9/l [96]. †UFH is preferred owing to its rapid anticoagulant effect reversal and the availability of a full antidote in protamine – should severe bleeding occur. ¶Due to the conflicting evidence of the fixed dose regimen (i.e., 1 mg/day) in this setting, and the lack of appropriate evidence of other dosing schemes (i.e., adjusted-dose for an INR target between 1.5 and 1.9), warfarin thromboprophylaxis is *not* recommended. **Among LMWHs, enoxaparin has the most safety data regarding LMWH use in thrombocytopenic cancer patients. §A target anti-Xa level between 0.1 and 0.4 IU/ml is a consideration. ‡Barring adequate and timely support in the outpatient setting, the implementation of platelet transfusion support entails an inpatient hospital admission, especially if UFH is given. The algorithm assumes that no bleeding risk factors (recent surgery or bleeding episode, renal failure, etc.), other than thrombocytopenia and being on an anticoagulant, are present. As stated in the text, these recommendations are solely based on the available ‘safety’ evidence. In our opinion, efficacy at the above-recommended doses cannot be determined with the current state of evidence.

‘Sailing in troubled waters’: a review of the use of anticoagulation in adult cancer patients with thrombocytopenia *Ibrahim RB et al. Blood Coagul Fibrinolysis, 2016*

- **LMWH (most notably enoxaparin**), and to a lesser extent UFH, represent the class of anticoagulants with the most data as far as anticoagulant use in thrombocytopenic cancer patients is concerned.
- The evidence would suggest that these anticoagulants could be given at a reduced dose in face of different degrees of thrombocytopenia.
- A cautionary note is in order: the evidence consists mostly of observational reports.
- **This leaves many questions unanswered, such as, what is the lowest platelet count at which a reduced dose of LMWH/UFH can be safely administered**.

‘Sailing in troubled waters’: a review of the use of anticoagulation in adult cancer patients with thrombocytopenia

Ibrahim RB et al. Blood Coagul Fibrinolysis, 2016

Oral anticoagulants Vitamin K antagonists

- It is difficult to draw firm conclusions about the safety of low-dose warfarin (warfarin or acenocoumarine 1–2 mg/day with a goal PT INR of 1.5) in thrombocytopenic cancer patients given the above said shortcomings of the existing literature.
- The lack of efficacy may also be the reason for the observed low rate of major bleeding as a whole with the low-dose warfarin modality: no clinically important impairment of hemostasis is achievable with it in most patients.
- Adjusted dose warfarin, that is, INR= 1.5–1.9, tended to cause more bleeding than a fixed-dose strategy.

“In our clinical experience, we have safely given therapeutic warfarin doses, following parenteral anticoagulation, in VTE-afflicted cancer patients with thrombocytopenia with stable platelet count ranging between 30 and 50x10^9/L”

‘Sailing in troubled waters’: a review of the use of anticoagulation in adult cancer patients with thrombocytopenia

Ibrahim RB et al. Blood Coagul Fibrinolysis, 2016

- **Novel oral anticoagulants (NOAC)**
- At this time, the evidence to inform the dosing of NOAC in thrombocytopenic cancer is lacking.

- **When compared with extended LMWH therapy, dose titration of the NOAC in cancer patients with thrombocytopenia is likely to be more complicated**

Yeh CH et al. Blood 2014

Management of challenging cases of patients with cancer associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH *Carrier M et al. JTH, 2013*

Management of CAT* in patients with thrombocytopenia

1) **We recommend giving full therapeutic doses of anticoagulation**** without platelet transfusion in patients with CAT and a **platelet count of ≥ 50 x 10^9 /L**

2) For acute CAT and thrombocytopenia (< 50x 10^9/ L)

i. **We recommend full therapeutic doses** of anticoagulation with **platelet transfusion** to maintain a platelet count ≥ 50 x 10^9/L

ii. If platelet transfusion is not possible or is contraindicated, **we suggest insertion of a retrievable filter** and removal of the filter when the platelet count recovers and anticoagulation can be resumed.

*CAT= cancer-associated thrombosis ** LMWH

Management of challenging cases of patients with cancer associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH *Carrier M et al. JTH, 2013*

Management of CAT in patients with thrombocytopenia

3) **For subacute or chronic CAT and thrombocytopenia (<50x10⁹/L)**

i. **We suggest reducing the dose of LMWH to 50%** of the therapeutic dose **or using a prophylactic dose of LMWH in patients with a platelet count of 25–50x10⁹/L**

ii. **We suggest discontinuing anticoagulation in patients with a platelet count of < 25x10⁹/L**

Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: treatment *Easaw JC et al. Curr Oncol, 2015*

Recommendations - Patients with low platelet counts

1.Should cancer patients with persistent or severe thrombocytopenia receive anticoagulation therapy for established VTE?

- **Patients with persistent or severe thrombocytopenia should be referred to a hematologist or thrombosis expert where possible.** 5D (after discussion)
- **In patients with significant thrombocytopenia, LMWH or UFH is preferred over vitamin K agonist if anticoagulation is necessary.** 5D (after discussion)

Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: treatment *Easaw JC et al. Curr Oncol, 2015*

2.Should cancer patients with a platelet count below 20,000/µL receive anticoagulation for established VTE?

- For **acute clot (<1 month) in patients with platelet counts below 20,000/µL, hold anticoagulation** unless platelet transfusion support is available to maintain a **platelet count of at least 50,000/µL.** 5D (after discussion)
- For **chronic or subacute VTE (≥1 month)** in patients with **platelet counts below 20,000/µL, hold anticoagulation.** 5D (after discussion)

Canadian consensus recommendations on the management of venous thromboembolism in patients with cancer. Part 2: treatment *Easaw JC et al. Curr Oncol, 2015*

3. Should cancer patients with a platelet count of 20,000–50,000/µL receive anticoagulation for established VTE?

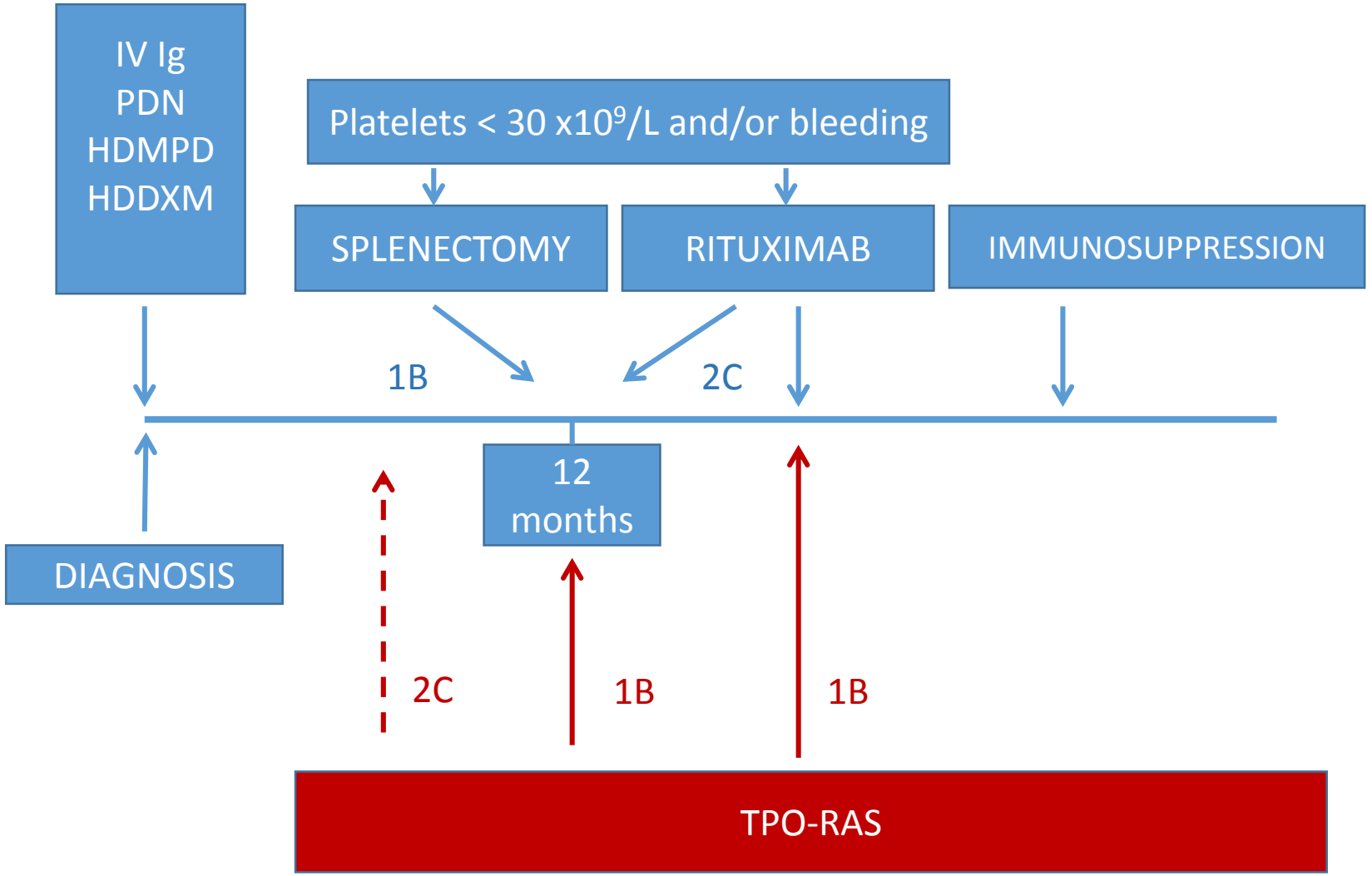
- For **acute clot (<1 month)** in patients with platelet counts of **20,000–50,000/µL**, consider **full-dose anticoagulation** if the patient can be supported with **platelet transfusions.** 5D (after discussion)
- For **chronic or subacute VTE (≥1 month)** in patients with platelet counts of **20,000– 50,000/µL, use dose-reduced LMWH.** 5D (after discussion)

4. Should cancer patients with a platelet count of 50,000–100,000/µL receive anticoagulation for established VTE?

- Patients with a **platelet count of 50,000–100,000/µL can receive anticoagulation without the need for dose reductions** unless the risk of bleeding is high. 5D (after discussion)

Anticoagulazione in ITP primaria o secondaria

- In piastrinopenie immuni, specie primarie, è possibile incrementare i livelli piastrinici con agenti terapeutici ad hoc nei pazienti che necessitino di trattamento, anche in particolari contingenze
- **Ia Linea: corticosteroidi, IVIG**
- **IIa Linea: splenectomia, Rituximab, mimetici della trombopoietina (TPO-RAs)**
- **IIIa Linea: Rituximab, TPO-RAs, altri immunosoppressori**


IV Ig
PDN
HDMPD
HDDXM
Platelets < 30 x10^9/L and/or bleeding
SPLENECTOMY
RITUXIMAB
IMMUNOSUPPRESSION
1B
2C
12 months
DIAGNOSIS
2C
1B
1B
TPO-RAS

Immune thrombocytopenia and anticoagulation: the role of romiplostim in the early treatment

Cantoni N et al. BJH, 2012

91-year-old man with newly diagnosed ITP- plt count 4x10^9/L-not responsive to corticosteroids and IVIG and on oral anticoagulation for chronic atrial fibrillation-> Romiplostim was early started with success-> after stabilization of the **plt count at >100x 10^9/L during romiplostim (dose 3µg/kg/week), the anticoagulation was restarted.**

Long-term follow-up of concomitant treatment with romiplostim and warfarin in a patient with immune thrombocytopenia and severe cardiac comorbidities

Baldini S et al. Platelets, 2013

68-year-old man with chronic ITP not responsive to corticosteroids and IVIG and with severe cardiac comorbidities has achieved a 1-year follow-up of combined treatment with romiplostim and warfarin. He had stopped warfarin for plt count 21x0^9/L. After romiplostim start, anticoagulation was restarted as platelet count overcame the threshold of 100x10^9/L achieving a target INR between 2.5 and 3.0 during all 52 weeks.
Concluding, the combination of warfarin and romiplostim was feasible and effective for up to 1 year in a patient with chronic ITP and severe comorbidities.

Feasible concomitant treatment with eltrombopag and oral anticoagulation in a patient with chronic immune thrombocytopenia and severe cardiac comorbidities *Sanchez-Gonzalez B et al. Platelets, 2014*

84-year-old man with chronic ITP. He was taking a vitamin K antagonist, acenocoumarol, due to a metallic cardiac valve and chronic atrial fibrillation.

Severe thrombocytopenia occurred (plt count platelet count 15x10^9/L) and diagnosis of ITP was made. Anticoagulation was stopped: corticosteroids and IVIG were the first line treatments for ITP, but the increase of plt count was not sufficient to allow a restart of acenocoumarol.

In this setting, a TPO-RA was started: due to patient's preference, eltrombopag was chosen. Platelet counts increased and remained stable with an actual mean value of 100x10^9/L, allowing the restart of oral anticoagulation. A stable INR was also maintained.

Donna di 73 anni

- **Nel 1974 (31 anni) diagnosi di cardiopatia reumatica mitro-aortica con successivo intervento di sostituzione valvola con protesi biologica aortica**

Aprile 1986 (43aa), diagnosi di ITP presso Ematologia-Sapienza Roma

- **Emocromo: piastrine 60.000/mmc**, in assenza di sintomatologia emorragica -> **watch&wait**

  -Agoaspirato midollare: serie eritro-granuloblastica normo-maturanti, megacariociti presenti in fase attiva

  -PIE negative

  - Test di Dixon positivo

  -Autoimmunità: debole positività degli ANA

Giugno 1986

- **Emocromo: piastrine 30.000/mmc -> inizia terapia con deflazacort** 30 mg/die-> piastrine max 58.000/mmc

  Dopo circa 4 mesi reazione allergica cutanea di probabile natura farmacologica con ricovero in ambiente ospedaliero-> sospesa terapia steroidea

Febbraio 1989

- **Terapia di mantenimento con prednisone**

Aprile 1991

- **Emocromo: piastrine 54.000/mmc**; ACA assenti; ANA debolmente positivi

Dicembre 1994

- **Per steno-insufficienza mitralica ed aortica, intervento di sostituzione valvolare aortica, mitralica e tricuspidale con protesi meccanica (piastrine 56.000)-> inizio terapia con AVK (warfarin); piastrine 37.000-92.000/mmc, nessuna complicanza emorragica**

Gennaio 2007

- Urea breath test positivo-> terapia eradicante

Gennaio 2008

- Impianto di pace-maker

Persa al follow-up da giugno 2011 a febbraio 2014

Luglio 2014

- **Per estesi ematomi (piastrine 32.000/mmc) sospende TAO ed inizia terapia con EBPM* che sospende a novembre per scarsa compliance-> reinserimento TAO (piastrine 41.000/mmc)**

* Nadroparina calcica 0,6, 11400 UI /die

Ottobre 2015

- Nuova sintomatologia emorragica con estesi ematomi(piastrine 30.000/mmc) per cui fu sospesa terapia con AVK ed iniziata nuovamente terapia con EBPM

SCARSA COMPLIANCE ALLA TERAPIA EPARINICA
SINTOMATOLOGIA EMORRAGICA IN RELAZIONE ALLA TERAPIA CON AVK

↓

Novembre 2015

INIZIO TERAPIA CON ELTROMBOPAG
(dosaggio 50mg/die)

ANA, ENA positivi
Ab anti Cardiolipina ed antibeta2GP1 negativi
SCT e DRVVT negativi

RISPOSTA ALLA TERAPIA CON ELTROMBOPAG

Inizio terapia → piastrine 30.000/mmc

I settimana → piastrine 56.000/mmc

II settimana → piastrine 67.000/mmc

III settimana → piastrine 69.000/mmc

IV settimana → piastrine 85.000/mmc → **RIPRESA TAO**

ELTROMBOPAG 50 mg/die

Da dicembre 2015 a novembre 2016, media piastrine pari a 107.000/mmc (89.000-134.000/mmc)

Eltrombopag progressivamente ridotto fino a 250 mg/settimana (~ 36 mg/die)

PT INR sempre in range terapeutico (2,5-3,5)

Nessun effetto collaterale, nessuna tossicità