انجمن هماتولوژی و انکولوژی ایران
Iranian Society of Medical Oncology and Hematology

NOVARTIS

Disclaimer :

- The opinions expressed in this presentation and on the following slides are those of the presenter and not necessarily those of Novartis.
- The content of this slide deck is accurate to the best of the presenter’s knowledge at the time of production




Dr Alireza Rezvani MD
Medical oncologist and hematologist
Shiraz university of medical science

انجمن هماتولوژی و انکولوژی ایران
Iranian Society of Medical Oncology and Hematology

NOVARTIS

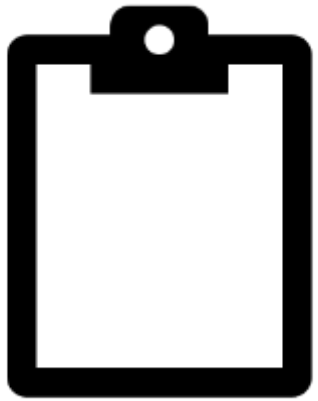
- A 78-year-old woman was referred because of an abnormal complete blood count found during a routine check-up:
- Platelet count 12 x103/mL (215 x 103/mL 6 months earlier)
- hemoglobin 12.8 g/dL
- WBC:5300
- Blood smear remarkable only for the decrease number of platelets.
- She had **hypertension, diabetes, and osteoporosis and was taking aspirin**.
- She had bruises on her hands.

- What is your initial evaluation 

Table II. Investigations in suspected immune thrombocytopenia

Investigations in patients with thrombocytopenia
Full blood count, reticulocytes, platelet volume and blood film
Renal, liver and bone profile
Immunoglobulins
Lymphocyte subsets
Dilute Russell venom viper test
Anti cardiolipin antibody
ANA ± ds DNA and ENA
Thyroid function tests
Hepatitis B
Hepatitis C
Human immunodeficiency virus
Helicobacter pylori antigen test
Ultrasound scan abdomen (liver disease, splenomegaly)
Investigations which may be helpful in patients with persistent or chronic disease, atypical disease or refractory disease
Bone marrow examination
Antiplatelet antibodies
Cytomegalovirus PCR (blood and urine)
Epstein-Barr virus PCR
Genetic screen for causes of thrombocytopenia
Thrombopoietin levels

- When you recommend BMA?
- Is a bone marrow examination necessary in ITP?



I recommend bone marrow examination in:

- Patients **over 65 years of age**
- Patients with atypical features
- Abnormalities on blood film or any other full blood count (FBC)
- Presence of lymphadenopathy/splenomegaly
- Patients who do not respond appropriately to IVIG and steroids.
- Also recommend bone marrow examination before using TPO-RAs and in most patients with persistent ITP

Nichola Cooper

Hammersmith Hospital, Imperial College, London, UK

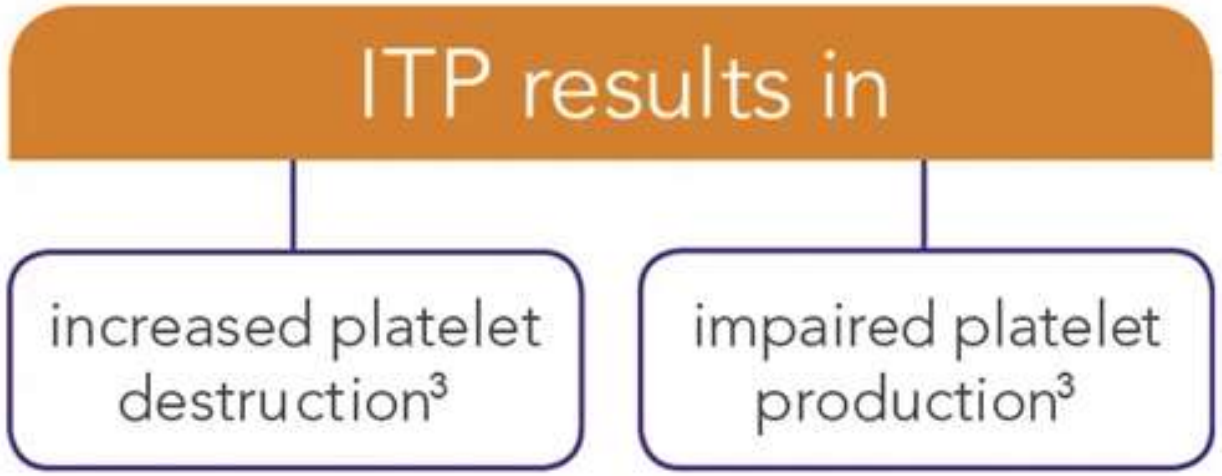
Does the measurement of anti-platelet antibodies (APA)have a role in the management of ITP?

- Measurement of APAs is not recommended in either consensus document of ASH guidelines. However, although APAs are not sensitive for ITP (up to 40% of patients have no detectable

  Antibodies, glycoprotein-specific assays are **highly specific for ITP**
- and in patients with **refractory** disease, a strongly positive test helps to reassure that the disease is antibody mediated.
- Furthermore, the type of APA may predict the responses to steroids or IVIG and may predict chronic disease and bleeding

Indications for platelet antibody testing (only helpful when positive)
Minimal or no response to corticosteroids or i.v. immunoglobulins
Differential diagnosis ITP vs. drug-induced or toxic bone marrow damage (e.g. chronic alcohol abuse)
Differential diagnosis ITP vs. hereditary thrombocytopenia
Confirm the diagnosis of ITP in patients with concomitant liver diseases, splenomegaly

What is the value of thrombopoietin testing?



- Patients with ITP have normal or only slightly higher than normal thrombopoietin levels.

- In contrast, patients with other causes of thrombocytopenia, in particular aplastic anemia, have very raised levels of thrombopoietin Although not routinely available, this may become an important tool in the diagnosis of ITP, although it is not recommended in the current ASH guidelines

- When you decided to treat??
- What is your initial treatment??

Table III. Treatment triggers

Treatment triggers
Blood blisters in mouth
Organ bleeding (Intracranial haemorrhage, gastrointestinal)
Haematuria
Anaemia and microcytosis caused by bleeding
Menorrhagia
Impact on life
Loss of work or school activities
Potential treatment triggers
Persistent severe thrombocytopenia
Significant bruises and petechial
Depression
Fatigue
Anxiety
Risk activity (skiing)
Stage of life related to considered risk
Co morbidity
Inability to review case regularly or to access emergency treatment (off shore working)

Table 2 - Observation vs. Treatment (Newly Diagnosed ITP)

Platelet count ≥30 x 10^9/l and asymptomatic or minor mucocutaneous bleeding	Management with observation[1] ✓
Platelet count <30 x 10^9/l and asymptomatic or minor mucocutaneous bleeding	Treatment with corticosteroids[2] C

[1] *For patients with a platelet count at the lower end of this threshold, for those with additional comorbidities, anticoagulant or antiplatelet medications, or upcoming procedures, and for elderly patients (>60 years old), treatment with corticosteroids may be appropriate.*

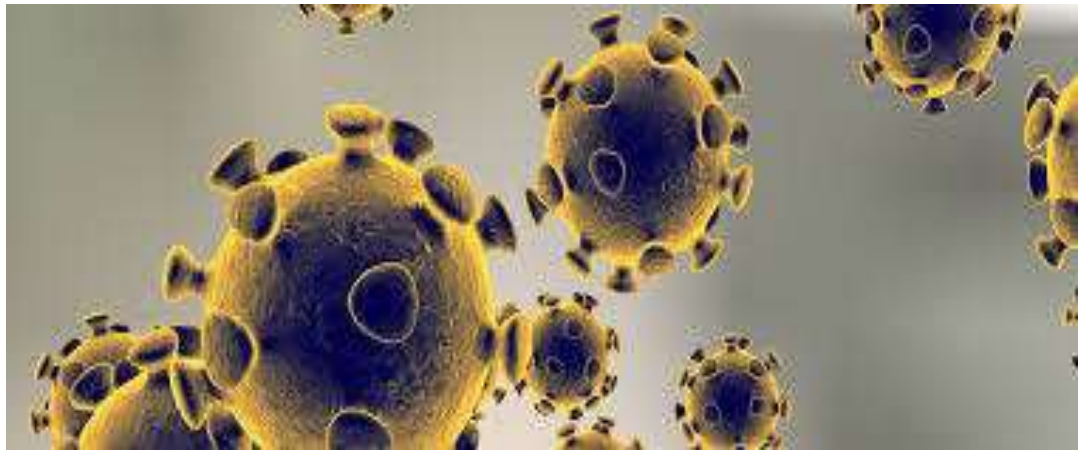
[2] *This should include consideration of the severity of thrombocytopenia, additional comorbidities, use of anticoagulant or antiplatelet medications, need for upcoming procedures, and age of the patient.*

- Our aim is to use high dose steroids for as short a period as possible As long as bleeding has stopped and the platelet count has stabilized (but not necessarily normalized), we use prednisolone 1 mg/kg for only 4 days and then reduce to 40 mg once a day (OD) for 2 weeks, 20 mg OD for 2 weeks,10 mg OD for 2 weeks, 5 mg OD for 2 weeks then stop

post

Era??

- In patients who are **negative for COVID-19**, TPO-RAs
- may be preferred as first-line treatment in order to avoid corticosteroids, which may increase risk of COVID-19 infection during the pandemic.
- In patients who are **positive for COVID-19**, TPO-Ras may potentially
- increase the thrombotic complications, and identifying eltrombopag hepatotoxicity may be difficult.



- Thus, whilst further evidence is awaited, **steroids** may be the better option for COVID-19 positive patients presenting with new or relapsed ITP

A **starting dose of 20 mg daily** may be considered in non-bleeding patients, with increase to 1 mg/kg after 3–5 days if there has been no response

- Aspirin was discontinued, and prednisone was initiated at 1 mg/kg per day.
- Platelet count increased to 62 x103/mL after 2 weeks.
- Prednisone was gradually tapered by 5 to 10 mg/d weekly, but the platelet count fell to pretreatment levels at 10 mg/d

  Her blood sugar became persistently elevated requiring addition of another antidiabetic agent.
- **What is you next step??**

strongly recommend limiting corticosteroid treatment for 6 to 8 weeks maximum and quickly switching to other therapy if unresponsive or corticosteroid dependent

Prompting a return of prednisone dose to 30 mg/d.

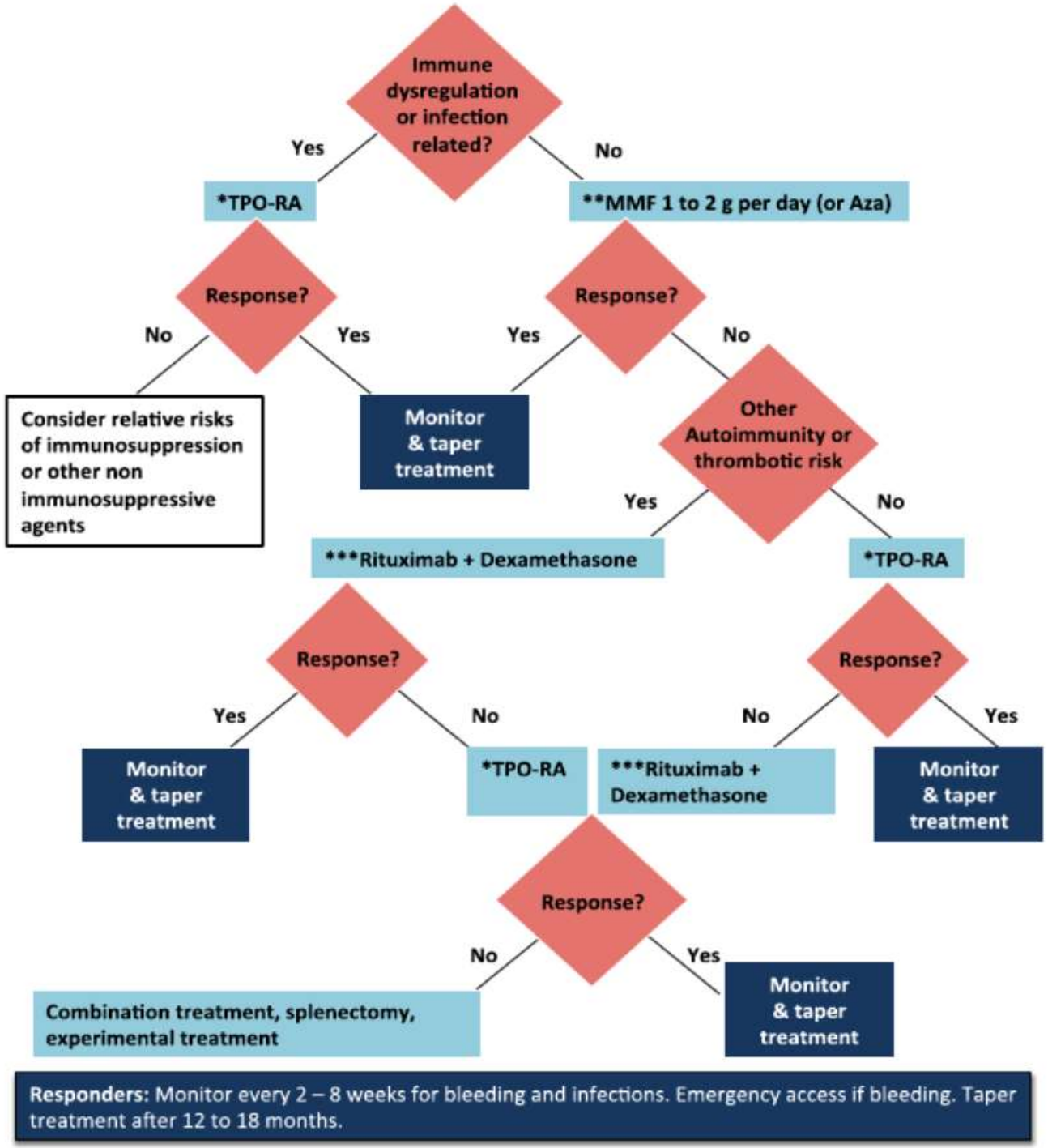
- At a follow-up visit 12 weeks after diagnosis, she was still receiving prednisone 20 mg/d with a platelet count of 34 x 103/mL

- **What is you next step??**

Therapy	Route of administration	Mechanism of action	Dosage	Response rate	Adverse effects
Romiplostim	Subcutaneous injections	TPO-RA	1-10 μg/kg once weekly	Overall response of 75%; durable response at 6 mo is 65%; 10% to 30% may achieve treatment remission	Headache, muscle aches, venous and arterial thromboembolism, possible increase in bone marrow reticulin, and collagen fibrosis
Eltrombopag	Oral (restricted diet)	TPO-RA	25-75 mg once daily		Headache, venous and arterial thromboembolism, elevated liver enzymes, possible increase in bone marrow reticulin, and collagen fibrosis
Avatrombopag	Oral	TPO-RA	20-40 mg once daily	65% at day 8*	Headaches, arthralgia, and venous and arterial thromboembolism
Rituximab	Intravenous administration	Immunosuppressive; anti-CD20	Infusions of 375 mg/m^2 each week for 4 weeks or 1000 mg every other week, for 2 weeks†	Initial response rate 60%; durable response rate at 6-12 mo is ~40% and at 5 y is ~20% to 30%	Infusion-related side effects (chills, upper respiratory discomfort, and bronchospasm), neutropenia, hypogammaglobulinemia, serum sickness, increased risks of infection and progressive multifocal leukoencephalopathy (very rare).
Fostamatinib	Oral	Immunosuppressive; splenic tyrosine kinase inhibitor	100-150 mg twice daily	Overall response 43%‡; stable response 18%§	Hypertension, diarrhea, nausea, and transaminitis

- I also use rituximab in patients who have a thrombotic risk, and in those who require a more sustained increase in the platelet count
- may require antiplatelet agents and may not be able to tolerate the fluctuating platelet counts seen with TPO-RA)

Nichola Cooper



انجمن هماتولوژی و انکولوژی ایران
Iranian Society of Medical Oncology and Hematology

NOVARTIS

- Choosing among the 3 medical therapies based on their durable
- response rates (at 6 months) favored a TPO-RA (;65%) over rituximab (;40%) and fostamatinib (18%).9,44 A possible increased
- thromboembolism risk with TPO-RAs should be considered.

waleed ghanima

If patient not respond to Eltrombopag??

- Reduced response, or experienced side effects, switching to another TPO-RA may have been effective, as studies have shown

②

- A 69-year-old man presented with platelets of 10 x103/mL generalized mucocutaneous bleeding, and recurrent epistaxis.
- Hb 12.2 g/dL, WBC 3.1 3 103/mL, normal blood smear.
- He had atrial fibrillation and hypertension and took apixaban 5 mg twice daily in addition to antihypertensive medication.
- Apart from thrombocytopenia, a diagnostic work-up revealed only ITP
- along with mild iron deficiency.
- Apixaban was immediately discontinued.

- Prednisolone ***vs*** Dexamethasone

Standard prednisone treatment with a subsequent taper has been associated with greater platelet stability than has treatment with dexamethasone pulses

High-dose dexamethasone may be more likely to precipitate acute psychotic complications in the elderly or those with a history of psychiatric disease, however, and this should be considered upon agent selection

- high dose dexamethasone, compared with prednisone 1 mg/kg for 4 weeks with taper, showed a platelet count response (79% vs 58%) at 14 days, but there was no difference in overall platelet response at 6 months (54% vs 53%) or rates of sustained response.

Two weeks later, his platelet count was still 10 x103/mL, but he had no bleeding.

Although usually not needed, because of his failure to respond to corticosteroids and his anemia, a bone marrow examination was performed that excluded other causes of thrombocytopenia. In general, we recommend that patients who fail to respond to any initial therapy (corticosteroids, IVIG, and anti-D) be assessed for other causes of thrombocytopenia (eg, myelodysplastic syndrome, congenital thrombocytopenia

Definition of refractory ITP?

- TPO-RA

vs

- Rituximab

- A rapidly acting second-line therapy such as a TPO-RA or fostamatinib would be preferable to rituximab.

Because of the desire for a rapid elevation in platelet count and a higher durable response rate, a TPO-RA was preferred over fostamatinib

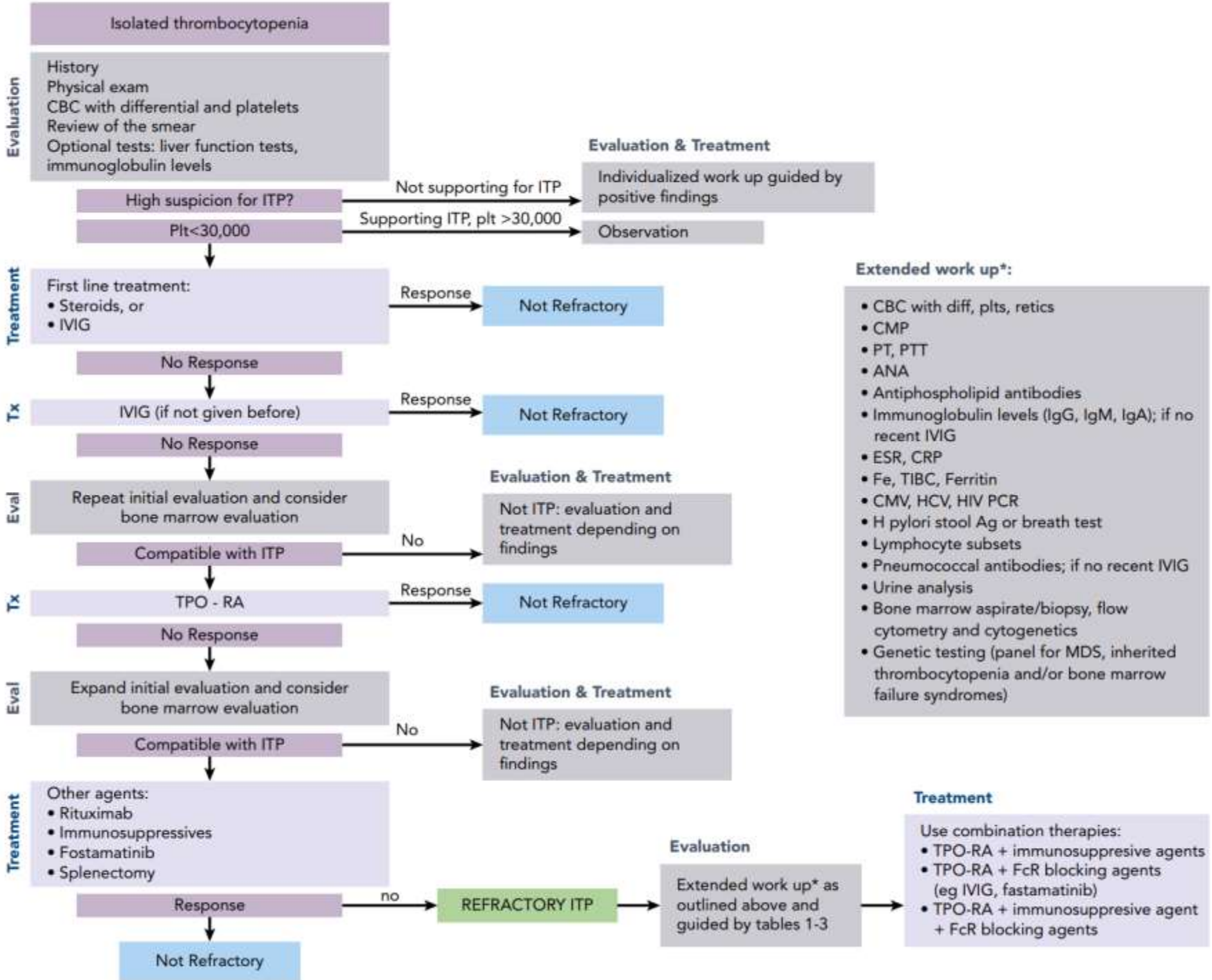
- As supported by clinical trials data, we usually start at 3 mg/kg (and even higher initial doses when there is bleeding) and increase by 2 mg/kg per week. At week 4, the platelet count reached 64 3 103/mL, and apixaban was reinitiated

- After 6 month patients admitted due to hematuria with PLT: 20,000

What is your next ste

- Description of “refractory” for patients whose platelet counts do not respond to >2 treatments, there is no single medication to which they respond, and their platelet counts are very low and accompanied by bleeding


LAST
CHANCE



- An otherwise healthy 46-year-old airline pilot presented with easy bruising, petechiae, and a platelet count of 12 x 103/ml. Three years ago, he had had a platelet count of 62x 103/mL and hematuria and had been treated with prednisone 60 mg/d with his platelet count rising to 181x103/ml. Corticosteroids were tapered over 9 months, and his platelet count remained at 105 3 103 to 135 3 x103/ml.
- He was frustrated by the recurrence of ITP because he had been told the corticosteroids had “cured” his disease. He was fearful that he would lose his certification as a commercial pilot.

- He was encouraged to consider medical therapy first with either a TPO-RA or rituximab, which had durable response rates of 65% and 40%, respectively but treatment-free remission rates with either is substantially lower than with splenectomy

- Anticoagulation Prophylaxis?

- Thromboprophylaxis was given for 2 weeks after surgery

- Unfortunately, over the next 4 months, his platelet count returned to 12 x103/mL

Next step?

- TPO-RA

- Rituximab

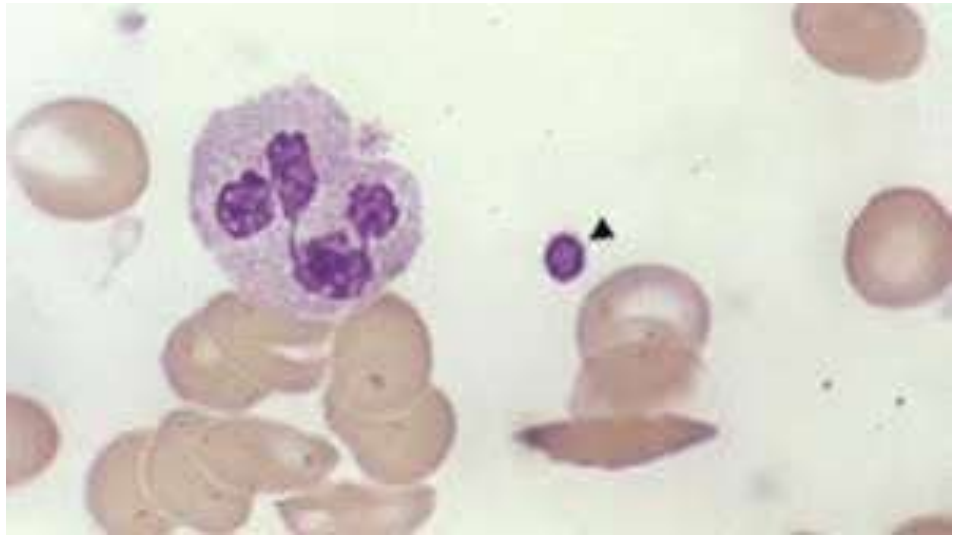
- How long do you wait for a TPO-RA response?

- Clinicians would wait for no more than 3–6 weeks at the maximum dose of TPO-RA

- How do you manage wide fluctuations in platelet counts?

- There was consensus that the first step was to make smaller and less frequent dose changes. This was achieved through less frequent FBC checks in asymptomatic patients or reacting to out of range counts only if persistent on several occasions.
- Five cited bleeding symptoms as an indication to increase dose and one would interrupt therapy if the platelet count was above the normal range, especially in those with risk factors for cardiovascular disease.
- One respondent would manage wide fluctuation by reducing TPO-RA dose and introducing a second agent.
- Three reported that they would switch to Eltrombopag if wide swings were persistent and one only used Eltrombopag for this reason

After 8 month….



انجمن هماتولوژی و انکولوژی ایران
Iranian Society of Medical Oncology and Hematology

NOVARTIS

Would you add in a second agent to facilitate responses?

- Ten would consider adding mycophenolate
- Eight would consider a low dose of steroid and one IVIg