Management of essential thrombocytopenia

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Essential thrombocytopenia: Clumping of platelets in blood (M. Podolak-Dawidziak)
Differential diagnosis of thrombocytosis
PLT > 450 G/L (× 10⁹/L)

Primary thrombocytosis ~ 12%
- Essential thrombocythemia (< 10%)
- Polycythemia vera
- Chronic myeloid leukemia
- Idiopathic myelofibrosis
- MDS: 5 q- syndrome
- Hereditary or familial thrombocytosis

Reactive thrombocytosis (RT) (majority)
- Malignant conditions: metastatic cancer (Ca lung, Ca breast), lymphoma
- Non-malignant haematologic conditions: acute blood loss, acute haemolytic anaemia, Fe deficiency anaemia, rebound effect after ethanol-induced thrombocytopenia
- Inflammatory disease (RA, ulcerative colitis)
- Tissue damage: burns, severe trauma, postsplenectomy
Haematopoietic stem cells

CFU-MK → MGKs

Platelet pool
2/3 – circulating in blood
1/3 – in spleen

PLT count: 150-450 G/L
PLT survival time: 7-10 days
Essential thrombocythemia (ET)

- a stem cell disorder, but involving a clonal proliferation of megakaryocyte cell line

- persistent thrombocytosis is found that is neither reactive nor due to another myeloproliferative neoplasm (MPN) or myelodysplastic disorder - a diagnosis by exclusion

- life expectancy for ET patients is normal, but without disease related complications!!
Megakaryocyte colony cultured in methylcellulose: translucent cells
(M. Podolak-Dawidziak)
History of ET

1934 – Epstein E and Goedel A: first described „hemorrhagic thrombocytopenia”

1951 – Dameshek W: introduced term „myeloproliferative disorders, MPD”

**WHO classification**

2001 – „chronic myeloproliferative diseases CMPD”

2008 – „myeloproliferative neoplasms, MPN”
ET characteristic

- True incidence is unknown, but probably up to 3 per 100,000 (Johansson P: J Intern Med. 2004; 256:161-165)

- Gender: slight excess in 1.5-2 ♀ : 1 ♂

- Age at diagnosis:
  - median age ~ 60 years
  - in some cases < 40 years
  - very rare < 20 years
Pathogenesis of ET

- **Etiology** – unknown
- **No association** with viral infection, drugs, chemicals or radiation
- **Pathogenetically heterogenous**
- **JAK2V617F mutation** in ~ 55% ET patients, but very rarely this mutation in homozygous (*Baxter E: Lancet 2005;365: 1054-1061*)
Gene mutations in ET
(Kralovics R: Expert Meeting Hermagor 2014)
Gene mutations in ET and patients outcome

**JAK 2 (+)**

- In some of these patients there are an evidence of clonality, including a mutation of the TPO receptor ~ 1%
- may have a higher frequency of thrombotic complications and their clinical course can be more similar to PV


**CALR (+)**

- patients experience better survival and lesser thrombotic risk than those with JAK2 or MPL mutation

*(Kralovics R: Expert Meeting Hermagor 2014)*
Clinical features

- 50% of patients are asymptomatic at presentation (often an incidental finding)
- Others may present with:
  - vasomotoric symptoms in ~ 40% of patients
  - thrombosis (more often) and/or haemorrhage
- Splenomegaly occurs with different frequency (less common and less marked than in other MPN; in some patients splenic atrophy from microinfarcts)
- Recurrent miscarriages and fetal growth retardation
- Constitutional symptoms: fatigue, weakness, itching, sweating; low-grade fevers in advanced cases
Vasomotoric symptoms

- in 40% of cases

- visual disturbances, headache, dizziness, light-headedness, slurred speech and other signs of inadequate flow of blood to the brain called “transient ischemic attacks” (TIAs)

- palpitations, atypical chest pain, livedo reticularis, and paresthesiae

- erythromelalgia: erythema and burning discomfort in hands or feet due to digital microcirculation occlusion
Laboratory investigations

- **Full blood count**: PLT > 450 G/L, Hb usually N, WBC ↔, caution: giant PLT can be counted as RBC!

- **Blood film**: PLT anisocytosis, giant platelets and PLT clumps

- **Peripheral blood mutation screening** for JAK2 (can be false + or -) and other new mutations (CALR)

- **Other blood tests**: uric acid ↑ in 25%, pseudohypokalemia in 25% (potassium released from PLT), ESR and CRP ↔ normal in ET and raised in RT

- **TPO serum concentration** does not help to differentiate ET from RT
Blood film in ET

- **PLT**: thrombocytosis, platelet anisocytosis, giant platelets, platelet clumps, megakaryocyte fragments

- **RBC**: hypochromic and microcytic (in Fe deficiency); Howell-Jolly bodies (basophilic clusters of DNA: hypo- or asplenia, postsplenectomy

- Platelet-leukocyte aggregates
Essential thrombocythemia: megakaryocyte fragments and platelets in blood film (M. Podolak-Dawidziak)
Bone marrow (BM) aspirate

- Megakaryocyte hyperplasia:
  - ↑ large megakaryocytes with hyperlobed nuclei and often atypical forms,
  - ↑ platelet clumps

- No granulocytic or erythroid hyperplasia

- Fe stores in 40-70%
Megakaryocyte in bone marrow aspirate (M. Podolak-Dawidziak)
Mature hypersegmented megakaryocyte in bone marrow aspirate
(M. Podolak-Dawidziak)
Bone marrow trephine biopsy in ET

- Megakaryocyte lineage: proliferation and clustering pleomorphic megakaryocytes
- Granulopoiesis or erythropoiesis: no proliferation or immaturity
- No or only borderline increase in reticulin
- No dysplastic features

BM examination confirms diagnosis and help to exclude other clonal diseases as MPNs, MDS q- or RT
Cytogenetics in ET

- Abnormal in 5%
- No specific diagnostic abnormalities
- Most frequent: 20q-, +1, +8, +9 or der (1;7)
- Ph-negative
Diagnostic criteria for WHO – ET (2008)

1. Persistent elevation of PLT count \( \geq 450 \) G/L
2. Megakaryocyte proliferation with large and mature megakaryocytes; no sign (or little) granulocyte or erythroid proliferation
3. Not meeting WHO criteria for CML, PV, PMF, MDS, or other MPN
4. Demonstration of \( JAK2 - V617F \) or other clonal marker or in the absence of a clonal marker, no evidence of RT

All 4 criteria are required for diagnosis of ET

Essential thrombocythaemia: Megakaryocytes in trophine biopsy (Sandoz Atlas Clinical Haematology 1994)
## Laboratory ad clinical characteristics of essentials thrombocythaemia and reactive thrombocytosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Essential thrombocythaemia</th>
<th>Reactive thrombocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis or haemorrhage</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Occasionally present</td>
<td>Often present</td>
</tr>
<tr>
<td>Abnormal platelet morphology and platelet aggregates on peripheral blood smear</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Suboptimal platelet aggregation responses in <em>in-vitro</em>/spontaneous platelet aggregation</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Clusters of dysplastic megakaryocytes in bone marrow</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Bone marrow reticulum/fibrosis</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Spontaneous megakaryocyte colony formation in <em>in vitro</em> cell cultures</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Abnormal cytogenetics</td>
<td>Occasionally present</td>
<td>Absent</td>
</tr>
<tr>
<td>JAK2 mutation</td>
<td>Present in 50% of cases</td>
<td>Absent</td>
</tr>
<tr>
<td>CALR mutation</td>
<td>Present in about 25% of cases</td>
<td>Absent</td>
</tr>
</tbody>
</table>
Reactive thrombocytosis (RT)

- Is generally transient and not associated with ↑ risk or thrombosis and no specific treatment is required.
- For marked thrombocytosis - such as occurring immediate after splenectomy: short term anticoagulant or ASA.
- Treat the underlying disease.
- If secondary to Fe deficiency PLT normalizes after Fe therapy.
- If impossible to define cause of thrombocytosis a watch-and-wait policy.
- If MPN is suspected start diagnostic procedure.
Natural history of ET

- Life expectancy of individuals with ET have been difficult to ascertain as most studies have been retrospective with limited follow-up times.

- A retrospective analysis of 322 patients with ET followed for a median of longer than 13 years (Wolansky AP et al. Mayo Clin Proc 2006; 81:159-166).

- In this study, a median age was 54 years (82.9% treated with cytoreductive therapy, 62.4% treated with ASA), median survival time was 18.9 years, and survival during 1st decade was similar to that of normal population.

- But, at 20 years after diagnosis of ET, median survival was ~50% compared with 70% for controls.
A risk factors for survival in ET patients

- Arterial and venous thrombotic events
- Risk of leukemic transformation is low in 1st decade after diagnosis, but increases with each subsequent decade
- In ET patients 10 years survival rate is 89% and 15 years survival years 80%; leukemia transformation rate at 10 years 0.7% and at 15 years 2.1%
- Evolution to myelofibrosis rate at 10 years 0.8% and at 15 years 9.3%

Primary Thrombocythemia

Peripheral gangrene acrocyanosis

Atypical TIAs

Coronary artery disease

Transient or occlusive platelet thrombi in arterioles

Activated platelets

Secretion, aggregation

Platelet derived growth factor

Smooth muscle cell proliferation
Fibromuscular intimal proliferation of arterioles

Prostaglandin endoperoxides but not thromboxane A₂

Nonspecific inflammation and congestion

(From Michiels JJ, van Genderen PJJ, Lindemans J, Van Vliet HHDM: Erythromelalgia, thrombotic and hemorrhagic manifestations of 50 cases of thrombocythemia. Leuk Lymphoma 28[suppl]:47, 1996, with permission.)

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Large pulmonary embolus
(Howard MR, Hamilton PJ: Haematology 1997)
Risk factors of thrombosis in ET

- age > 60 years
- history of thrombosis
- cardiovascular risk factors (smoking, hypercholesterolemia, hypertension, diabetes)
- hereditary thrombophilia (FVLeiden, prothrombin gene mutation), reduction of natural anticoagulants (AT, PC, PS) and APCR
- clonality
- WBC >11 G/L
- \textit{JAK2V617F} mutation (especially homozygocity) as predictor of arterial thrombosis
- male gender as a predictor of venous thrombosis

Thrombophilia

**Acquired**
- Immobilization
- Surgery/trauma
- Malignancy
- Oral contraceptives
- HRT
- Pregnancy
- LA
- MPN
- PNH
- TTP, HIT
- Nephrotic syndrome
- Anticardiolipin antibodies
- Drugs (thalidomide, L-ASPA)
- Age, obesity
- Congestive heart failure

**Inherited**
- FVL mutation
- Prothrombin G20210A mutation
- ↑ homocysteine
- P C deficiency
- PS deficiency
- AT deficiency
- ↑ F VIII activity

**Mixed/unknown**
- F VIII
- F IX
- F XI
- F I
- TAFI
- PAI
- Homocysteine
- APCR
- ↓ TFPI
Thrombosis in ET

- At presentation - in 15-20% of cases, and during the course of the disease in 10-20%, but major thrombosis < 10%

- Death from thrombosis in 11-25%; arterial thrombosis 60-70% of vascular events (Vannucchi AM and Barbui T. Hematology 2007; 143: 363-370)

- Incidence did not correlate significantly with gender, PLT count at diagnosis or at the time of thrombotic event during follow-up or disease duration, but it did correlate with age and prior history of cardiovascular disease and/or thromboembolic events (Radaeli F. et al. Hematol. Oncol 2007; 25: 115-120)
Arterial thrombosis in ET

- Arterial thrombotic vs venous events (ratio, 3.1:1) 
  \textit{(Bazzan M at al. Ann Hematol 1999; 78: 539-543)}

- Arterial thrombosis accounts for about 60-70\% of all cardiovascular events

- Myocardial infarction, ischemic stroke, peripheral arterial occlusion

- ASA 75 mg/d (rapid response in TIA and erythromelalgia) if there are no contraindications (history of bleeding episodes)

- HU to normalize PLT count

- Plateletpheresis in life threatening situations, e.g. very high platelet count at delivery
Model of altered ASA pharmacodynamics in ET

Sites of action of currently available antiplatelet agents

Anticoagulation in ET

- **ASA:** once daily, but in some high risk patients twice daily

- **New antiplatelet drugs:** are they effective in ET? are they safe in ET?

- **New oral anticoagulants:** are they effective in ET? are they safe in ET?
  For bleeding reversion aPCC or VIIa?
Venous thrombosis in ET

- Less common than in polycythemia vera (PV)
- Lower extremity deep venous thrombosis (DVT), pulmonary embolism, and splenchnic vein thromboses (SVT, which includes portal vein thrombosis, mesenteric thrombosis, and thrombosis in the heptic veins causing Budd-Chiari syndrome)
- Treatment: Heparin (LMWH) followed by oral anticoagulant therapy (INR 2-3)
- HU to reduce the risk of recurrence
- Monitor PLT count and INR
Megakaryocyte and platelets in ET (M. Podolak-Dawidziak)
Bleeding in ET

- High thrombocytosis (> 1500 G/L) – bleeding may occur in 25%, but major bleeding < 5%
- Qualitative and quantitative platelet disorders
- Acquired von Willebrand disease (AVWD)
- Drugs: cytoreductive therapy, anti-aggregant or nonstroidal anti-inflammatory agents
- Symptoms: easy bruising, mucosal or GI bleeding; rarely prolonged bleeding after trauma or surgery

Acquired von Willebrand syndrome (AVWS) in ET

- **Symptoms:** easy bruising, mucosal or gastrointestinal bleeding (GI); rarely prolonged bleeding after trauma or surgery

- **Laboratory findings:** prolonged APTT + bleeding time (PFA-100)

- ↓ in ristocetin cofactor activity (vWF:RCo), but vWF:Ag and FVIII:C can be normal + ↓ in ability to bind vWF to collagen (vWF:CB)+ the loss of large vWF multimers (due to increased binding of vWF to PLT receptors (GPIb, GPIIbIIIa), and all these changes significantly correlated with extremely increased PLT count

- Low - dose ASA can be used if ristocetin cofactor activity (vWF:RCo) level is > 50%
Acquired von Willebrand disease

- ET treatment

- Minor bleeding: DDAVP

- Major bleeding or prior to surgery: FVIII + vWF; there is fast elimination though repeated transfusions or bolus is required

- Prednison and IVIg (IgG)

- In some cases with very high PLT count – plateletpheresis
### European LeukemiaNet-definition of clinic-hematological response in ET


<table>
<thead>
<tr>
<th>Response grade</th>
<th>Definition</th>
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| Complete response | 1. Platelet count $\leq 400$ G/L and  
2. no disease related symptoms*, and  
3. normal spleen size on imaging, and  
4. white blood cell count $\leq 10$ G/L |
| Partial response | In patients who do not fulfill the criteria for complete response: platelet count $\leq 600$ G/L or decrease greater than 50% from baseline |
| No response | Any response that does not satisfy partial response |

Disease related symptoms: microvascular disturbances, pruritis, headache*
**Essential thrombocythemia risk stratification and treatment algorithm**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Risk factors</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Age &lt; 60 years; without history of thrombosis and cardiovascular risk factors</td>
<td>Observation or low-dose aspirin (ASA)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Neither low nor high risk</td>
<td>Individualized therapy</td>
</tr>
<tr>
<td>High</td>
<td>Age &gt; 60 years, history of thrombosis, cardiovascular risk factors</td>
<td>Low-dose ASA + cytoreductive therapy</td>
</tr>
</tbody>
</table>
All patients with ET patients

- Advice healthy life style: low fat diet, exercises, stop alcohol, and smoking cessation as in multivariant analysis smoking was associated with a significant risk of arterial thrombotic events (Marchioli R et al: J Clin Oncol 2005; 23: 2224-2232)

- Patients > 60 years are at high risk!!

- Treat hypertension and hypercholesterolema

- Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) and standard dose of ASA due to risk of haemorrhage

- Low-dose ASA when PLT count is high, but vWF: RCo > 50%
Low risk ET patients

- No ↑ risk of thrombosis or haemorrhage
- No added risk with pregnancy or surgery
- „Watch and wait policy”

- Microvascular symptoms (erythromelalgia) → indication for low-dose ASA (start with 300-500/d followed by 75-100mg maintenance) (McCarthy L et al. Transfusion 2002; 42:1245)
Intermediate risk ET patients

- Individualize therapy
- Observation
- Try to relief symptoms caused by thrombocytosis e.g. erythromelalgia (low-dose ASA) or bleeding
High risk ET patients

- **ASA:** for patients with previous thrombotic events or at high risk of thrombosis

- **Cytoreductive therapy:**
  - 1st line: Hydroxyurea (HU; Hydoxycarbamide,HC)
  - 2nd line: Anagrelide an imidazo (2-1-b) quinazolin-2-1 compound, and eventually Busulfan (an alkylating agent) in some patients >75 years

- **Interferon-α (IFN-α):** in younger patients intolerant to anagrelide and in women in childbearing not using birth control or in older patients intolerant to HU
Hydroxyurea (1)

- Antimetabolite that prevents DNA synthesis
- Consider HU in patients > 60-65 years and in some younger at high risk of thrombosis or haemorrhage, and with massive splenomegaly; not use in women in childbearing age
- Starting dose of HU is 15-20 mg/kg/day orally until response is obtained; the maintenance dose should be administered to keep the response without reducing leukocyte counts below $2.5 \times 10^9/L$
- Laboratory control: complete hemogram every 2 weeks during the first months, then every month, and in steady state in responding patients every 3 months
Hydroxyurea (2)

- **Advantages:** convenience, efficacy, effective in reducing the incidence of thrombotic complications in high risk ET patients

- **HU toxicity:** major short term adverse effects include reversible bone marrow suppression manifested as neutropenia and macrocytic anaemia
  
  → gastrointestinal side effects (nausea, vomiting, diarrhea), skin changes (including severe painful ankle ulcerations), rarely fever

- **Possible acceleration of ET transformation into AML:** leukemia free survival was reduced in patients given busulfan prior to HU

- **The incidence of transformation to AML:** ~ 3.5% at median follow-up of 8.2 years when HU is used alone, but 14% when HU + pipobroman (*Sterkers Y et al. Blood 1998; 91: 616-522*)
Anagrelide

- An imidazo (2-1-b) quinazolin-2-1 compound

- **Mode of action:** interfere with platelet maturation and has an antiaggregating effect on platelets (inhibits cyclic nucleotide phosphodiesterase and the release of arachidonic acid from phospholipase)

- **The elimination half-life:** 76 hours, and ~ 75% is administered dose is excreted by urine over 6 days. Dose adjustment is necessary if renal failure occurs
Anagrelide

- As 2nd line treatment, but often as 1st line in younger high risk high risk patients (leukemogenic effect of HU)

- The recommended initial dose of anagrelide is 0.5 mg orally two times (1 mg) or four times daily (2 mgs)

- Initial dose should be increased by a maximum of 0.5 mg per day every 5 to 7 days until the desired reduction of PLT count is achieved.

- The median time to maximal response is ~ 11 days and the dose needed to achieve a response ranged from 0.5 to 9.0 mg/day, but 95% of patients responded to a dose of 4 mg per day or less (Anagrelide Study Group. Am J Med 1992; 92: 69-76)

- The maximum dose should not exceed 10 mg per day or 3 mg per dose (Spencer CM, Brogden RN. Drugs 1994; 47: 809-822)

- In some patients: both, HU and anagrelide are used in lower doses
Possible adverse effects of Anagrelide

- **Cardiovascular**: palpitations and tachycardia (36%) – dose related and coffee intake, fluid retention or edema (24%), congestive heart failure (2.5%)

- **Neurologic**: headache (30%) – „vascular” and „migraine-like”, dizziness (8%)

- **Gastrointestinal**: nausea (19%), diarrhea (15%)

- **Others**: little or no immediate effect on myelopoiesis, but in long term use can reduce Hb (not deeply) and cause granulocytopenia; rash and hyperpigmentation, liver function abnormalities

- **Not use in pregnancy**: crosses placenta
The Primary Thrombocythemia – 1 (PT-1) randomized trial

- Included 809 ET patients diagnosed according to PVSG criteria, there were patients with and without cytotoxic therapy.
- Design of the trial: Anagrelide + ASA has been compared head to head to HU + ASA.
- Results: patients in anagrelide arm showed an increase rate of arterial thrombosis and myelofibrotic transformation, but a decreased incidence of venous thrombosis compared to HU. Transformation to AML was comparable between the two arms (4 anagrelide vs 6 HU).
- Responses to treatment in the PT-1 trial were influenced by JAK2 status.
- PT-1 study was made according to the PVSG classification and it remains questionable if it can be applied to a WHO classification.
Anahydrété trial

- A randomized single blind international multicenter phase III
- Designed to evaluate the non-inferiority of anagrelide vs HU in 259 previously untreated high risk ET patients diagnosed according to the 2008 WHO diagnostic criteria
- Confirmatory proof of non-inferiority of anagrelide was achieved after 6 months, and further confirmed after an observation time of 12 and 36 months
- Results: there was no significant difference between the anagrelide and HU group regarding incidences of major arterial (7 vs 8) and venous (2 vs 6) thrombosis, severe bleeding events (5 vs 2), and minor arterial (24 vs 20) and venous (3 vs 3) thrombosis
Anahydret trial

- ET transformation into myelofibrosis or secondary leukaemia was not reported.

- Anagrelide, a selective platelet lowering agent, is not inferior to HU in preventing thrombotic complications in patients with WHO-ET.

- Main side effects: fluid retention, headache, palpitations, congestive heart failure.

- Anagrelide should be avoided in patients with cardiovascular comorbidities.
Interferon-α (IFN-α)

- **Action:** Suppresses the proliferation of hematopoietic progenitors, directly inhibits marrow fibroblast progenitors, and antagonize action of cytokines, which may be involved in to the development of myelofibrosis.

- In about 90% of ET patients reduces PLT count < 600 G/L after about 3 months of treatment with an average dose of 3 million IU daily [analysis of several cohort studies Lengfelder E et al Leuk Lymphoma 1996; 22 (suppl.1): 135-142]

- IFN-α is not known to be teratogenic, and does not cross the placenta, though it can be used throughout pregnancy.

- **Side effects:** fever and flu-like, signs of chronic toxicity as weakness, myalgia, weight and hair loss, and depression.
Busulfan

- Cell cycle non-specific alkylating agent of the class of alkyl sulfonates

- at low doses (usually, 2-4 mg daily) it can produce prolonged control of hematologic parameters

- ELN recommends busulfan to the elderly (> 75 years) whose comorbidities make them intolerant to other therapies (Barbui T et al: J Clin Oncol 2011; 29: 761-770)

- Leukemogenic risk associated with low dose of busulfan is probably small, but the sequential use of busulfan and HU resulted in significant increase in the risk of 2nd malignancies, including leukemia (Finazzi G et al Br J Haematol 2000; 110: 577-583, Finazzi G et al Blood 2005; 105: 2664-2670)
Comparisons of HU, IFN-α and Anagrelide

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HU</th>
<th>IFN-α</th>
<th>Anagrelide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Orally</td>
<td>SC</td>
<td>Orally</td>
</tr>
<tr>
<td>Selectivity of platelet reduction</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Leukemogenicity</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hematologic side effects</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Very good/good</td>
<td>Fair/poor</td>
<td>Good/fair</td>
</tr>
<tr>
<td>Possibility to induce remission</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Use in pregnancy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Regression of splenomegaly</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Surgery in ET patients

- Normalize PLT count before surgery

- But, thrombosis in 8% of surgical patients with ET though median PLT count was 477 G/L, Ht 43% and prophylaxis with heparin in 56%, ASA in 74% and warfin in 6% was used (Masa RA et al Cancer 2006; 107: 361-370)

- Major surgery: majority of patients: LMWH (dosage > 3000 anti-Xa U) or UH (2 daily or 3 × daily), starting before intervention and continued until 7-15 after surgery, and some of them (more often PV) had antiplatelet therapy at the same time

- Minor surgery: no prophylaxis in 41% of patients or LMWH
Fetus and newborn: the live birth is about 60% due to an overall incidence of 1st trimester miscarriage of 31-36%, and ↑ risk of intrauterine growth retardation, intrauterine death and stillbirth (8%)

Major maternal complications in ~ 8%

JAK2 gene mutation increase risk of pregnancy complications

ET treatment in pregnant women

- About 3-6 month prior to conception HU and anagrelide should be gradually withdrawn
- IFN -α a drug of choice during pregnancy
- ASA in all pregnant women: 75 mg throughout pregnancy, and about 2 weeks before delivery ASA is substituted by LWMH, which is given 6 weeks after delivery
- LMWH should be given during whole pregnancy if the mother or fetus is at high risk of thrombotic complication
- Breast feeding is safe with heparin.
  Doses: deltaperin 5000 U or enoxaparin 40 mg daily
## Treatment for ET

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Age &lt; 60 years</th>
<th>Age ≥ 60 years</th>
<th>Women of childbearing age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>? Low-dose ASA*</td>
<td>Not aplicable</td>
<td>? Low-dose ASA*</td>
</tr>
<tr>
<td>Intermediate risk**</td>
<td>Low-dose ASA*</td>
<td>Not aplicable</td>
<td>Low-dose ASA*</td>
</tr>
<tr>
<td>High risk</td>
<td>HU/IFN-α/Anagrelide*** + low-dose ASA</td>
<td>HU + low -dose ASA</td>
<td>IFN-α + low-dose ASA</td>
</tr>
</tbody>
</table>

* In the absence of contraindication (including a vWF: RiCo< 50%)

** Decision to use a cytoreductive agents should individualized

***The Nordic MPD Group Guidelines recommend IFN-α and anagrelide as 1st and 2nd choice for pts < 60 years with HU 3rd line unless leukocyte reduction or constitutional symptom control is required when it is 2nd line to IFN-α
Tefferi A and Barbui T: Leukemia 2013; 27: 1617-1620
Possibilities in Dubrovnik

(M. Podolak-Dawidziak)
Physiological pathways in blood coagulation

(Howard MR, Hamilton PJ: Haematology 2008)