OPTIMAL MANAGEMENT OF MPN IN AUSTRALIA

Dr Cecily Forsyth

MPN Management: Goals

- Reduce risk of vascular and thrombotic events
  - Cytoreductive agents
  - Antiplatelet/anticoagulant therapy
  - Cardiovascular risk factors
- Recognise, acknowledge and manage symptom burden
  - MPN10
  - Landmark study
  - Pt support – MPNAA, LF
- Reduce progression and transformation of disease

Harrison Ann Hematol 2017;96:1653-1665

Thrombotic and Haemorrhagic Events

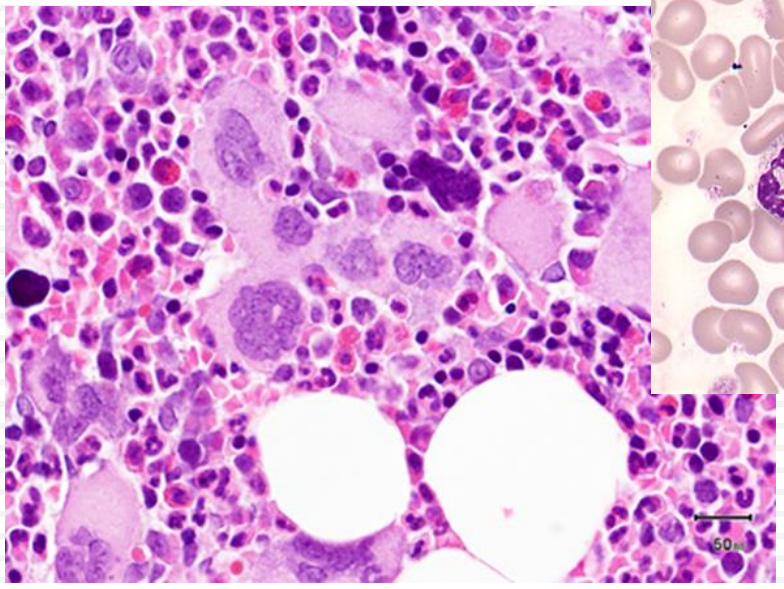
	All Pts *n=438*	PV *n=139*	ET *n=132*	PMF *n=109*	Post-PV/ET MF or MPN-U *n=58*
Thrombosis	33.6%	38.9%	25%	31.2%	45%
Bleeding	8.2%	9.4%	3.8%	9.3%	14%

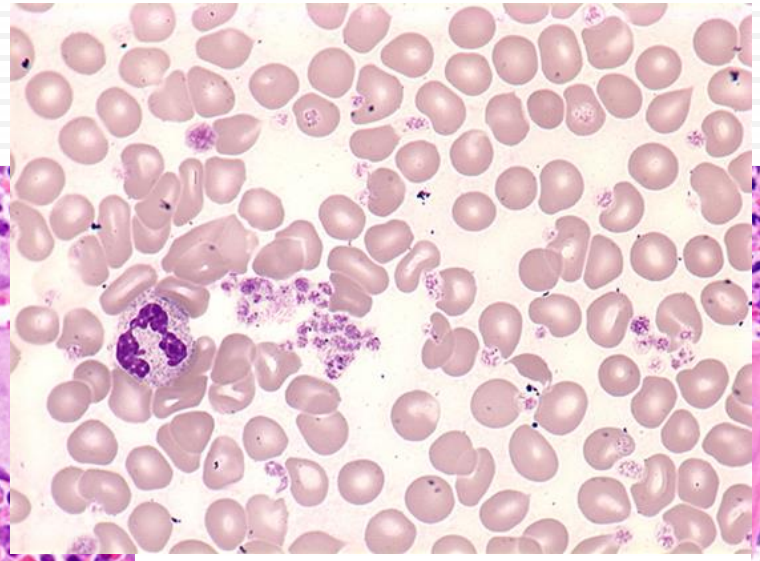
Bleeding, thrombosis, and anticoagulation in myeloproliferative neoplasms (MPN): analysis from the German SAL-MPN-registry. Kaife. J Hematol Oncol 2016; 9:18

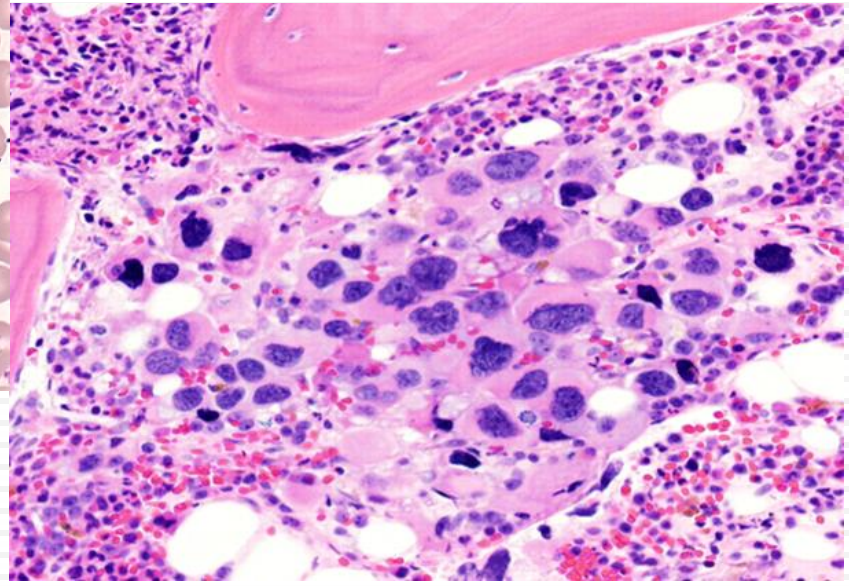
MPN Therapy

- Reducing vascular and thrombotic risk
  - Thrombotic risk
    - Increased in pts >60 yrs
    - Arterial and venous thrombosis
    - Reduced by cytoreductive therapy
    - ET: Doesn't correlate with platelets but some correlation with white cells
    - PV: Increased risk if Hct >0.45
  - Bleeding risk increased with:
    - High platelets (>1500 x 10^9/L)
      - Reduction in platelets corrects defect and reduces bleeding

Essential Thrombocythaemia







ET Management

- Indications for aspirin
  - Age ≥60 yrs
  - Cardiovascular risk factors
  - JAK2V617F mutation
- Once daily aspirin may be inadequate
  - ARES study (ET) underway to compare different dose regimens
- Contraindications for aspirin therapy
  - Extreme thrombocytosis
  - Acquired von Willebrand syndrome (avWs – coagulopathy)
  - Low-risk CALR-positive ET

De Stefano Blood Cancer J 2018;8:49

ET Management

- PT-1 study
  - 382 pts with ET, aged 40 to 59 yrs, no high-risk features
    - Randomised to aspirin alone or HC plus aspirin
    - Median follow-up 73 mths
    - No significant difference b/w arms
      - Vascular events
      - Myelofibrotic transformation
      - Leukaemic transformation
    - Pts aged 40 to 59 years without other clinical indications for treatment and a platelet count $<1500 \times 10^9/L$ should not receive cytoreductive therapy

Godrey J Clin Oncol 2018 (Epub)

ET: Therapy

- Indications for cytoreduction
  - High-risk pts
    - Age ≥60 yrs
    - Major thrombotic event
  - Additional indications
    - Platelets >1500 x 10^9/L
    - Uncontrolled myeloproliferation (e.g. symptomatic splenomegaly)
    - Uncontrolled ET-related systemic symptoms
- First-line cytoreduction
  - Hydroxycarbamide (HC)
  - Interferon (rIFNα)
- Second-line cytoreduction
  - HC
  - Anagrelide
  - rIFNα
  - Busulfan

Barbui Leukaemia 2018;32:1057-1069

Hydroxycarbamide (HC)

- Previously the “gold standard” of therapy
- Reduces
  - Thrombosis (esp in JAK2+ pts)
    - Target platelets $<400 \times 10^9/L$
  - Bleeding events
- A randomised study in ET demonstrated
  - Thrombosis risk
    - 24% on no treatment
    - 4% on hydroxyurea (platelets decreased to $<600 \times 10^9/L$)

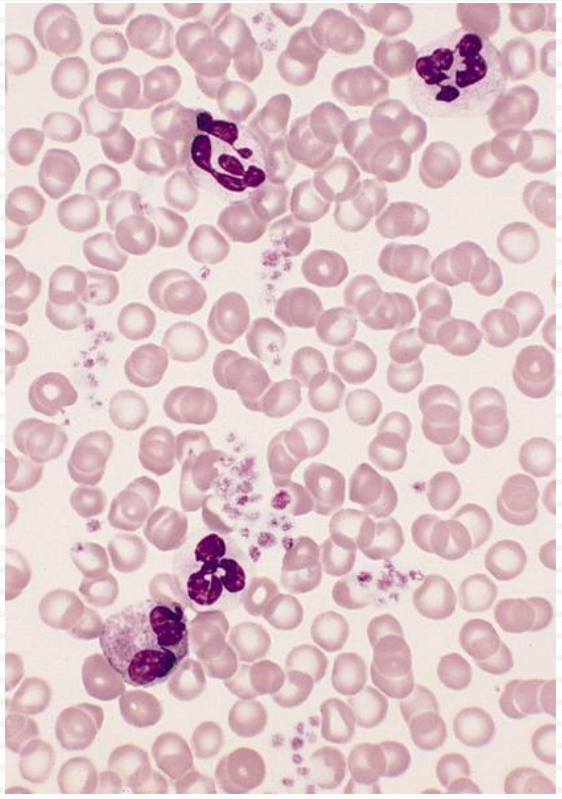
Hydroxycarbamide

- Most commonly used myelosuppressive (cytoreductive) agent for MPNs
  - Reduces blood cells production by slowing cell division
  - Commence 500 mg BD and titrate dose according to FBC
  - Side effects
    - Myelosuppression – low blood counts
    - Macrocytosis – large red cells
    - Leg ulcers
    - Rare drug fever, hepatitis, skin cancers
  - Recent studies suggest HC doesn't increase risk of leukaemia
    - Risk may be increased if combination therapy

Anagrelide

- FBC effects:
  - Controls thrombocytosis in most pts
  - Reduces clotting and bleeding but less well than HC
  - Does not affect WCC
  - Anaemia common and often progressive
- Used
  - Second-line therapy for HC refractory or intolerant
  - Combination therapy with HC
- Does not
  - Reduce MF transformation
  - Increase risk of leukaemia
- Side effects in up to 1/3rd of pts limits tolerability
  - Vasodilatory effects: headaches, fluid retention, headaches
  - Positive inotropic actions: palpitations, arrhythmias (care in pts with cardiac disease)
  - Diarrhoea

Polycythaemia vera



PV Complications

- Thrombotic complications
  - More common than bleeding complications
  - Hyperviscosity
    - Headache, blurred vision, and plethora
  - Thrombosis in larger vessels
    - Arterial: heart attack, stroke
    - Venous: DVT, pulmonary emboli, splanchnic (gut)
  - Thrombosis in small blood vessels
    - Cyanosis
    - Erythromelalgia (painful red extremities)
    - Ulceration or gangrene in fingers/toes
- Bleeding (2-10%)
  - Epistaxis, bruising, GIT and gum bleeding
  - Severe bleeding episodes are unusual

PV Therapy

- All pts
  - Aspirin
    - Consider BD in pts with arterial events
  - Phlebotomy
    - Target Hct <0.45
    - CYTO-PV study
      - 2.7% pts with Hct <45% had vascular events
      - 9.8% pts with Hct 45-50% had vascular events
      - Reinforced previous empiric recommendation of Hct <0.45
  - Management of cardiovascular risk factor
    - Smoking, DM, HTN, lipids

Marchioli N Engl J Med 2013;368:22-33

PV Therapy

- Indications for cytoreduction
  - High-risk pts
    - Age ≥60 yrs, or
    - Previous thrombotic event
  - Additional indications
    - Poor tolerance of phlebotomy
    - Platelets >1500 x 10^9/L
    - WCC >15 × 10^9/L
    - Uncontrolled myeloproliferation (e.g. increasing splenomegaly)
    - Uncontrolled PV-related systemic symptoms
- First-line cytoreduction
  - HC (hydroxycarbamide)
  - rIFNα (interferon)
- Second-line cytoreduction
  - HC
  - rIFNα
  - Busulfan
    - Intermittent therapy in very elderly
  - Ruxolitinib
    - Not available in Aust for PV

Barbui Leukaemia 2018;32:1057-1069

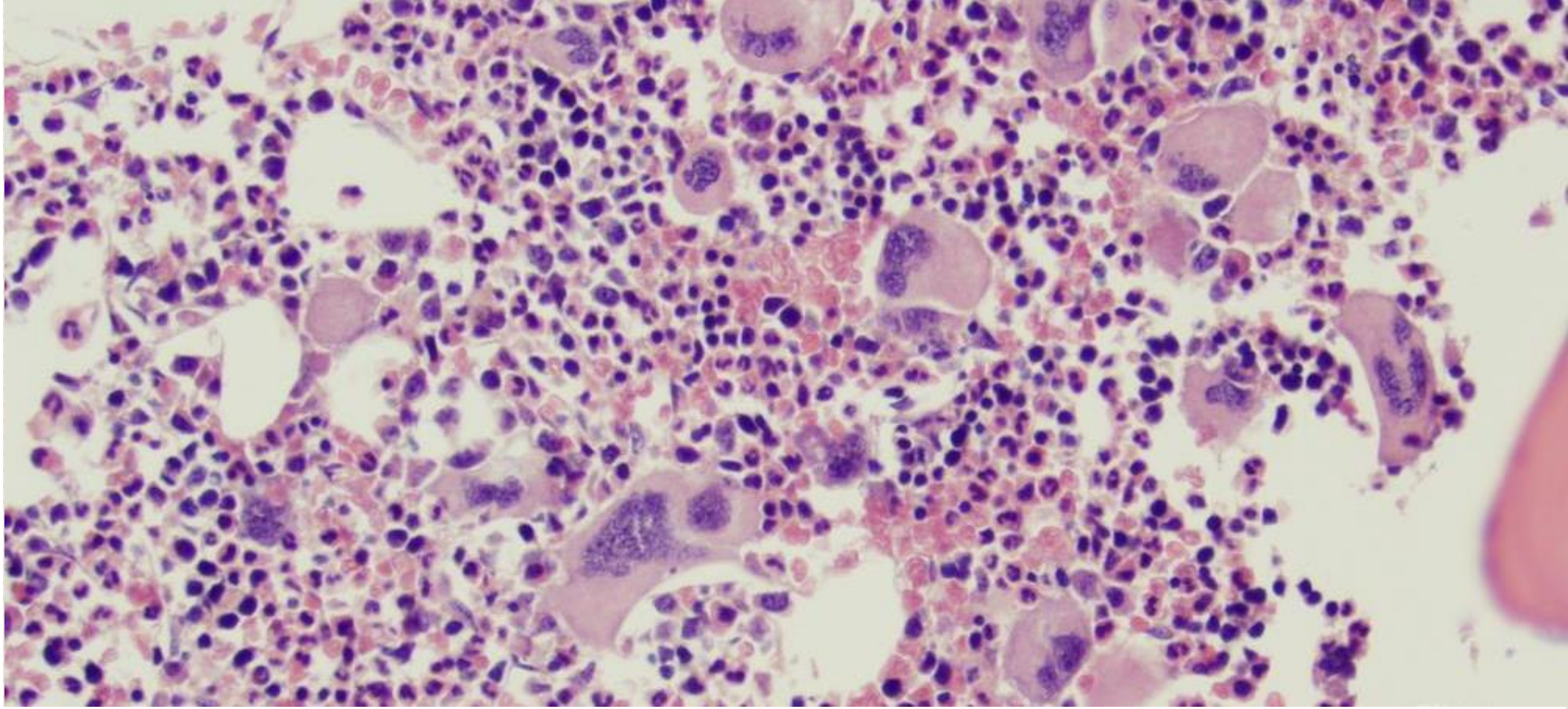
PV Therapy

- Busulfan
  - Older, high-risk pts
  - Prolonged myelosuppression can occur
  - Particularly effective for control of leukocytosis
  - 2-4 mg day, reduce promptly once target reached
    - Maintenance dose (2-4 mg/wk), or
    - Cessation once counts controlled

PV Therapy: Ruxolitinib

- RESPONSE study: Ruxolitinib (JAK inhibitor) in PV
  - HC refractory pts randomised ruxolitinib or BAT
  - Ruxolitinib superior
    - Hct control at 32 wks: 60% on R, 19.6% on BAT (89% maintained at 80 wks)
    - SV reduction at 32 wks: 38.2% on R, 0.9% on BAT (all maintained at 80 wks)
    - Improved symptom control (pruritus)
    - Reduced thrombosis
  - At 208 wks 37% of pts randomised to Rux remained on therapy

Kiladjian. 2017 ASH Abstract 322



Interferon

PEG-IFN in PV and ET

- Studies of PEG-IFN in >400 pts with PV and ET
  - 80% objective haematological responses
  - 60% freedom from phlebotomy in PV pts
  - Reduces thrombosis
  - Improved pruritus
  - Molecular responses
    - Reduction in JAK2 V617F/CALR up to 65%
    - CMR up to 24% at 3 yrs
  - Not curative
    - Relapse can rapidly occur after rIFNα discontinuation

Kiladjian Leukemia 2016; 30: 776-781

PEG-IFN: Practical issues

- Dosing
  - 45 µg/wk
  - Gradual escalation
  - >180 µg/wk poorly tolerated
- Flu-like side effects (fever, myalgia, chills)
  - Almost universal
  - Paracetamol and nocte administration
  - Settle with repeated dosing
  - Recur with dose increase
- https://www.mpnallianceaustralia.org.au
  - Information on PEG-IFN administration

MPD-RC 112

- MPD-RC 112 phase 3 trial
  - Treatment-naïve pts with high-risk PV or ET
  - Randomised to PEG-IFN or HC
  - Interim analysis
    - 75 pts, 12-months of therapy
    - No difference in haematological or molecular response
    - Grade 3 AEs more common with PEG-IFN
      - PEG-IFN:16/36, 44%
      - HC: 5/36, 14%
    - Symptom burden improvement
      - Greater with PEG-IFN than HC in first 6 mths
      - Pt-reported toxicities of PEG-IFN increased over time
  - Longer follow up essential

Mascarenhas Blood 2016;128:479
Mesa Blood 2016; 128:4271

MPD-RC 112: Adverse events

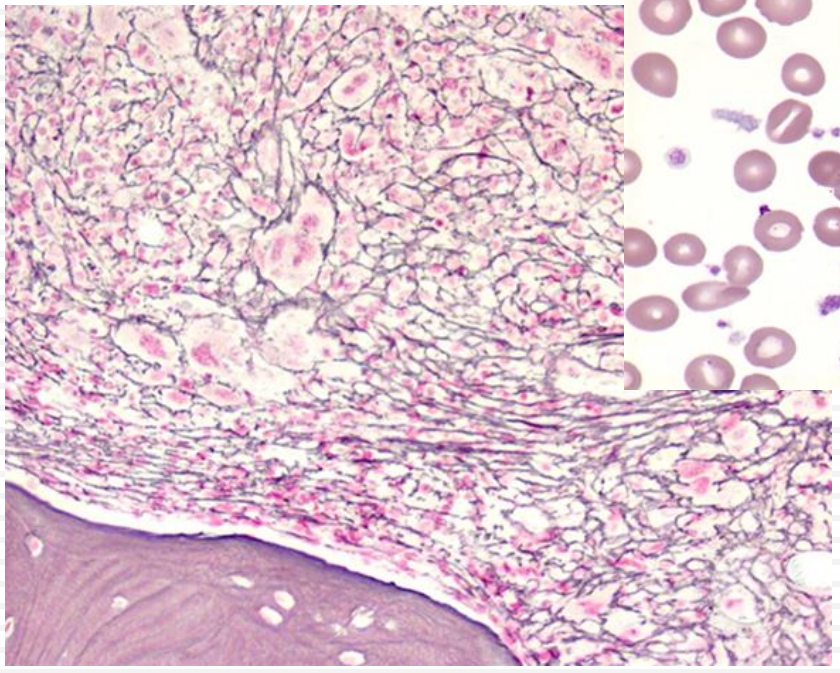
Adverse event (any grade)	**HC** (n=36)	**PEG-IFN** (n=36)
Fatigue	28%	50%
Flu-like symptoms	3%	33%
Depression	0%	28%
Dyspnoea	3%	19%
Headaches	11%	19%
Injection-site reactions	-	25%
Leukopenia	8%	22%
Anaemia	17%	19%
Thrombocytopenia	19%	17%
Overall grade ≥1	89%	100%
Overall grade ≥3	14%	47%

Mascarenhas Blood 2016;128:479

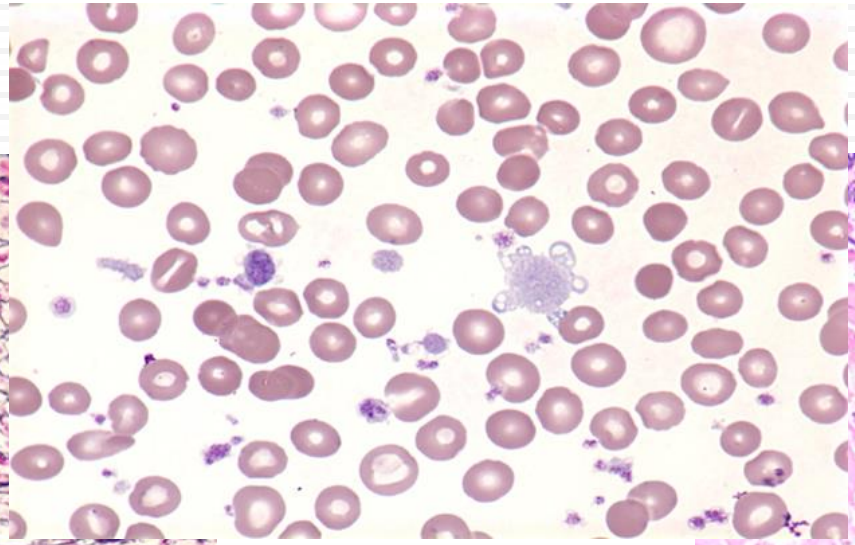
PEG-IFN in ET and PV

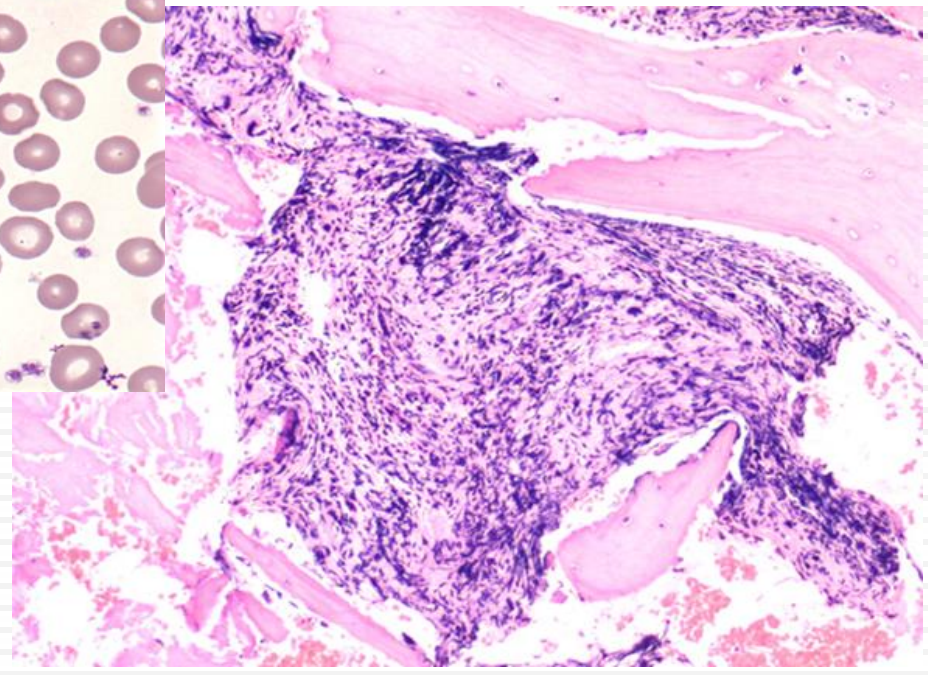
- PEG-IFN therapy considered as
  - First-line cytoreduction
    - Pts <60 yrs requiring therapy
    - Pregnant women
    - Pts >60 yrs
      - Motivated and capable of self-injection
      - Fewer comorbidities
      - Good performance status
  - Second-line
    - After hydroxycarbamide failure

Myelofibrosis



Reticulin stain: extensive fibrosis





Extensive fibrosis with clustered megakaryocytes

PMF Symptoms

- 20% of pts have no symptoms at dx
  - Abnormal blood count
  - Splenomegaly
- 80% of pts have symptoms
  - Low blood counts:
    - Anaemia - fatigue, weakness or shortage of breath
    - Frequent infections
    - Easy bruising or bleeding
  - Splenomegaly related abdominal discomfort
  - Bone pain
  - Constitutional symptoms
    - Anorexia, unexplained weight loss, night sweats
  - Gout

MF Prognostic information

- Accurate prognostic information essential
  - Important for pts and their families
  - Influences therapy
  - Survival varies with risk group
    - Low risk pts: >20 yrs
    - Very high risk pts: 1.7 yrs
- Prognostic scores
  - Age, blood count, symptoms, transfusion need, chromosomes
    - IPSS (at diagnosis)
    - DIPSS (during course of disease)
    - MIPSS+
      - Incorporates molecular abnormalities
      - Essential for pts being considered for alloSCT

PMF Therapy: Indications

- Observation alone unless
  - Significant symptoms
  - Symptomatic or progressive anaemia
  - Splenomegaly
    (palpable spleen >10 cm)
  - Leukocytosis
    (WCC >25 $\times 10^9$/L)
  - Marked thrombocytosis
    (platelets >1000 $\times 10^9$/L)

PMF Therapy

- MF-associated anaemia
  - Androgens, prednisone, Aranesp (ESA)
  - Blood transfusion support
  - Thalidomide rarely used
    - Toxicity and only modest efficacy
    - Not reimbursed for MF in Australia
- Cytoreductive therapy
  - Indicated for myeloproliferation (WCC, platelets, spleen)
  - Options
    - HC
    - rIFNα
    - Ruxolitinib

PMF Therapy: Ruxolitinib

- JAK inhibitor
  - Oral medication
  - Significantly improves
    - Splenomegaly
      - ≥35% reduction in 45%
    - Constitutional symptoms
      - Promotes weight gain
      - Improves pruritus
    - May reduce thrombosis risk
  - 50% pts remain on therapy at 2-3 yrs
  - Adverse effects
    - Anaemia – esp first 3 mths
    - Thrombocytopenia (low platelets)

PMF Therapy: Ruxolitinib

- 5-yr updates of COMFORT-I/II studies
  - Best response rates improve over time
    - 60% of pts achieve 50% palpatory SVR
      - Median duration of response 3.2 yrs
  - No new safety signals
  - Survival
    - Trials not powered for survival
    - Spleen response is dose-dependent and predicts for survival
    - Pts initially assigned to RUX lived longer than those assigned to PBO/BAT
      - COMFORT II: 5-year survival 44% (BAT) c/w 56% (RUX)

Patel Blood 2015;126:790-797
Verstovsek J Hematol Oncol 2017;10:55
Harrison Leukemia 2016;30:1701-1707

PMF Therapy: Ruxolitinib

- Ruxolitinib therapy considered for pts with
  - Intermediate-2 or high-risk disease
    - Symptoms
    - Severe splenomegaly (>10+ cm)
  - Intermediate-1-risk disease
    - Symptomatic or severe splenomegaly unresponsive to cytoreductive therapy
    - Symptomatic and severe splenomegaly with no prior cytoreductive therapy
  - Disease associated symptoms
    - MPN10
      - Pts scoring >44 points
      - Severe itching (score 6)
    - Unexplained fever
    - Unintended weight loss (>10% in 6 mths)

Marchetti et al. Leukemia (2017) 31, 882–888

PMF Therapy: Ruxolitinib

- Potential adverse effects
  - Thrombocytopenia
    - Dose modification in pts with low platelets
    - Risk of bleeding 2-3%
    - Avoid other antiplatelet drugs
  - Infection
    - Increased risk in MF pts
    - Resp/urinary/herpes zoster 6-8% of pts
    - Rare reports of HCV, HBV, TB reactivation
  - NMSC may be increased
      - Baseline and regular dermatology reviews

Lussana Am J Hematol 2018;93:339-347
Al-Ali Haematologica 2016;101:1065-1073
Talpaz J Hematol Oncol 2013;6:81

RUX: Survival advantage?

- Evidence supports a survival benefit
  - Quality of evidence is very low
- RUX not recommended solely to improve survival
- Factors contributing to possible survival advantage
  - Improved clinical status
    - Spleen size reduction
    - Reversal of cachexia
    - Alleviation of cytokine-driven symptoms and inflammation
  - Improvement in BM fibrosis occasionally seen

Vannucchi Haematologica 2015;100:1139–1145

HSCT in JAKi era

- HSCT indications remain unchanged in JAKi era
  - Intermediate-2 and high risk MF
  - Intermediate-1 risk disease and high-risk features
  - RUX improves transplant-specific risk factors
    - Reduces splenomegaly
    - Improves symptoms
  - Most pts are treated with RUX before HSCT
    - Clinical improvement with JAKi associated with favourable HSCT outcome

LIFESTYLE CHANGES FOLLOWING A DIAGNOSIS WITH MPN

Dr Cecily Forsyth

Lifestyle changes following a diagnosis with MPN

- Reducing complications
  - Vascular
  - Thrombosis
  - Skin cancer (NMSC)
- Living with a chronic illness
  - Psychological strategies
  - Improving physical function

Reducing risk of vascular disease

- Regular physical activity
- Smoking cessation
- BP control
- Dietary modification
- Weight reduction
- Limiting alcohol

Regular physical activity

- Cardioprotective effects:
  - Lowers BP
  - Controls weight
  - Improves quality-of-life
- 30 mins of moderate-intensity physical activity daily
- Sit less and move more - any activity counts
  - Gardening, housework, dancing, bowls and sports
  - Incidental physical activity important
- Strength training helps maintain core and stability
- Reduces fatigue

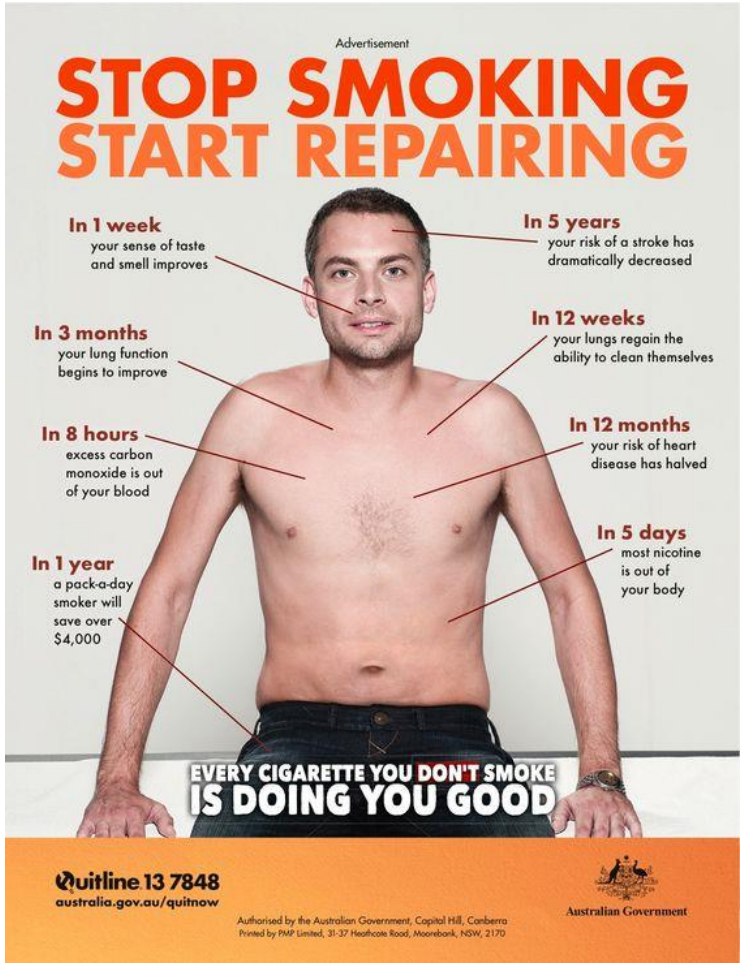
Risks of smoking

- Smokers lose 10 yrs of life
- Deaths due to smoking
  - 2 in 3 long-term smokers die due to smoking-related disease
  - 12% of all deaths in Australia
  - 30% of all deaths from cancer
- A smoker loses an average 3 months of life for each yr they smoke after 35 yrs of age

Risks of smoking

- Non-malignant risks:
  - COPD (1 in 4 smokers)
  - AMI x 3 risk
  - CVA x 2 risk
  - Peripheral vascular disease
  - Macular degeneration
  - Osteoporosis
  - Abdominal aortic aneurysm
- Malignancy risk
  - Lung cancer
    - Male smoker has 21 x increased risk c/w non-smoker
  - ENT: mouth and throat, larynx
  - Haematological: AML, MDS
  - GIT: oesophageal, stomach, pancreas, liver, colon
  - Urological: kidney, bladder

Benefits of smoking cessation



- Measures to assist smoking cessation:
  - My Quit buddy (mobile phone app)
  - Nicotine replacement products
    - Gum, lozenges, tablets, inhaler
  - Medication (Zyban, Champix)
  - Hypnotherapy
  - Acupuncture
  - E-cigarettes
    - Limited evidence on quality, safety, efficacy for smoking cessation or harm reduction
    - Not recommended

Lipid targets

- Target levels
  - TC <4.0 mmol/L
  - LDL <2.0 mmol/L
  - TG ≤2.0 mmol/L
- Strategies
  - Diet: 10-20% lowering
  - Weight loss: Aim for healthy BMI <25 kg/m^2
  - Medications
    - Statins
    - Ezetimide - decreases cholesterol absorption
  - Fish oil
    - Reduces TG
    - Anti-platelet effect at 3000 mg/d

Dietary modification

- Balance energy intake and expenditure
  - Maintain desirable body weight
  - Prevent weight gain
- Diet principles:
  - High intake of fruit and vegetables
  - Whole-grain, high-fibre foods
  - Consume fish at least 2 x week
  - Reduce sugar intake
  - Reduce salt intake
  - Consume alcohol in moderation only

Risk factors for venous thrombosis

- Obesity (BMI >30 kg/m2)
  - Significantly increased risk
- Smoking:
  - Small increased risk only
- Age
  - Increased risk if >60 yrs
- OCPs
  - 2-3 x increased risk
- HRT results in 2 x increase in risk
  - Max in 1st yr of use
- Pregnancy/postpartum
  - 20-30 x increased risk
- Testosterone
  - Increases Hct
  - Increases risk of VTE
- Other medications
  - Tamoxifen
  - Steroids (prednisone)
- Air-travel
  - Risk increases with flight distance
- Others
  - Medical illnesses
  - IVDU
  - Immobilisation

Skin cancers and MPNs

- Skin cancers in pts with MPNs
  - Medication may increase risk
    - Hydroxycarbamide
    - Ruxolitinib
  - Prevention
    - Clothing, hat, shade, sunscreen
  - Cutaneous surveillance essential
- Aspirin
  - May reduce risk of skin cancer (BCC, SCC)
  - Lowers risk of GIT cancer (by 40%)

Zhu. Oncol Lett. 2015; 9(3):1073-1080
Cuzick. Annals of Oncol. 2015;26:46-57

Travelling with a MPN

- Prior to overseas travel
  - Consult with your doctor
    - Confirm fitness for travel
    - Ensure you have all medications required while away from home
      - Consider taking a copy of recent FBC results +/- haematologist report
    - Check vaccination requirements prior to travel
      - Inactivated vaccines are safe
        - Influenza, pneumococcal, hepatitis A and B, and meningococcal vaccines
      - Live vaccines not always appropriate
        - MMR, (measles, mumps, rubella), oral typhoid, yellow fever and **zoster**
    - Inform your travel insurance company of your MPN diagnosis

Quality of life in MPN

- MPN-SAF
  - Validated QoL instrument
  - Provides valuable information on impact of MPNs on pts
  - Significant symptomatic burden
    - Fatigue in 88% of pts
    - Compromised daily functioning is common
    - Reduced QoL in majority of pts
    - PMF pts have most significant symptoms
  - Severe symptoms for which ruxolitinib should be considered
    - Score of >44 points
    - Severe itching (score 6)

Geyer. Cancer. 2016. 15;122(12):1888-96
Scherber. Blood 2011.118(2):401-408

Living well with chronic illness

- Chronic illness reduces QoL
  - Illness-related factors
  - Potential life interruptions
  - Psychological changes
- Goals for living well
  - Be proactive in managing one's own health in a holistic manner
  - Maintain an active and fulfilling life
  - Deal with physical and psychological issues of chronic illness
    - Frustration, fatigue, pain and isolation
  - Exercise for maintaining and improving strength, flexibility, and endurance
  - Interact effectively with health care professionals
    - Appropriate use of medications and side-effect management
    - Evaluate and negotiate therapies

Live your best life every single day with a MPN

- Even when times are tough, things aren't going to plan or the outcome is grim we never give up. Hope is not a fairy-tale ending but a gritty commitment to the journey. Hope is engaging in life with every cell in your body
  - Briony Scott.
  - Headmistress, Wenona School for Girls

Talk to your haematologist

- Doctors are funny souls…
  - They have hope
  - They believe in the human spirit to take on the big challenges and to give life its best shot…

Briony Scott.