

OPTIMAL MANAGEMENT OF MPN IN AUSTRALIA

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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

Thrombotic and Haemorrhagic Events

	All Pts <i>n</i>=438	PV <i>n</i>=139	ET <i>n</i>=132	PMF <i>n</i>=109	Post-PV/ET MF or MPN-U <i>n</i>=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

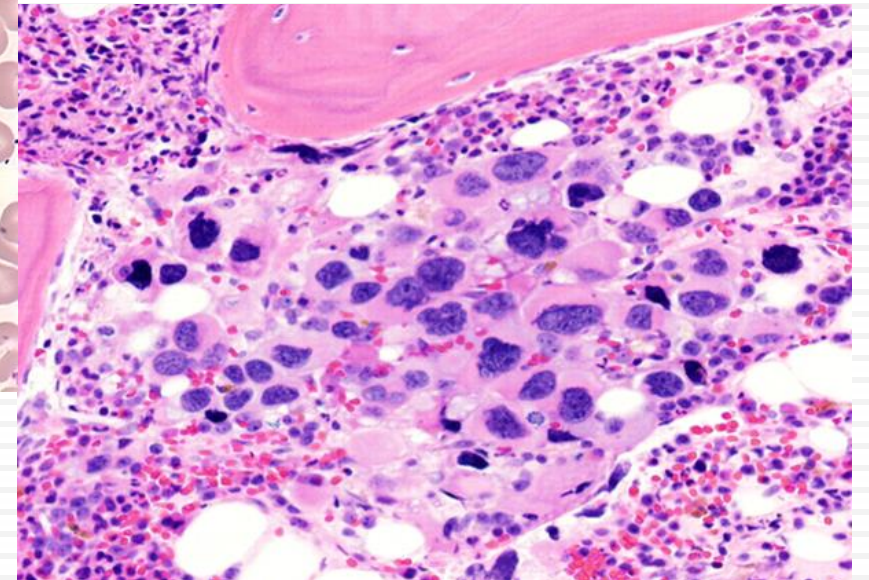
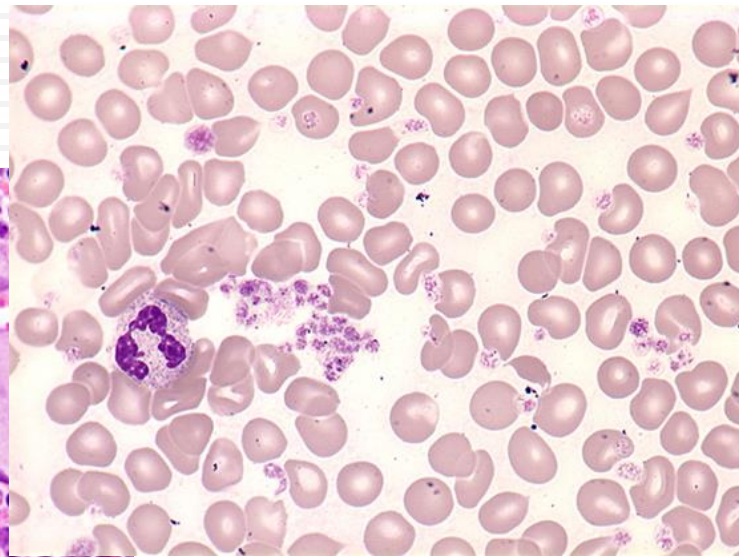
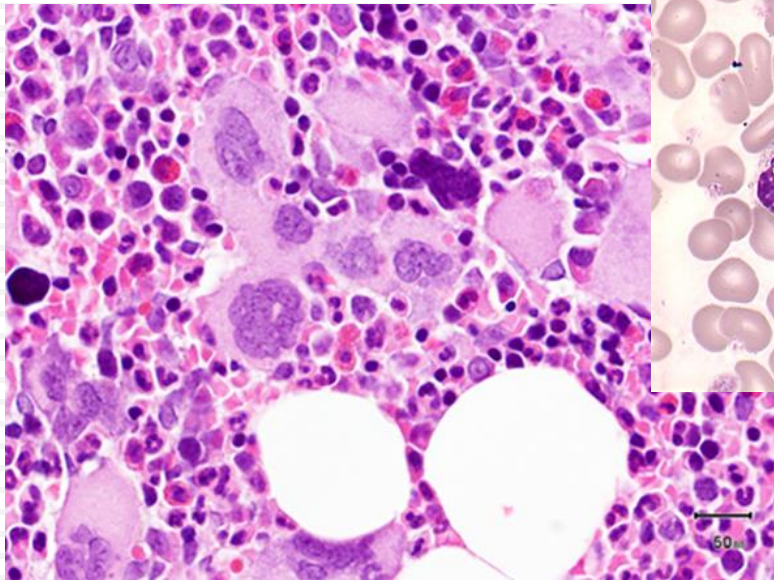
▣ Thrombotic risk

- 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 ($>1500 \times 10^9/L$)
 - Reduction in platelets corrects defect and reduces bleeding

Essential Thrombocythemia



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

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 $<1500 \times 10^9/\text{L}$ should not receive cytoreductive therapy

ET: Therapy

□ Indications for cytoreduction

□ High-risk pts

- Age ≥ 60 yrs
- Major thrombotic event

□ Additional indications

- Platelets $> 1500 \times 10^9/L$
- Uncontrolled myeloproliferation (e.g. symptomatic splenomegaly)
- Uncontrolled ET-related systemic symptoms

□ First-line cytoreduction

- Hydroxycarbamide (HC)
- Interferon (rIFN α)

□ Second-line cytoreduction

- HC
- Anagrelide
- rIFN α
- Busulfan

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 $<600 \times 10^9/L$)

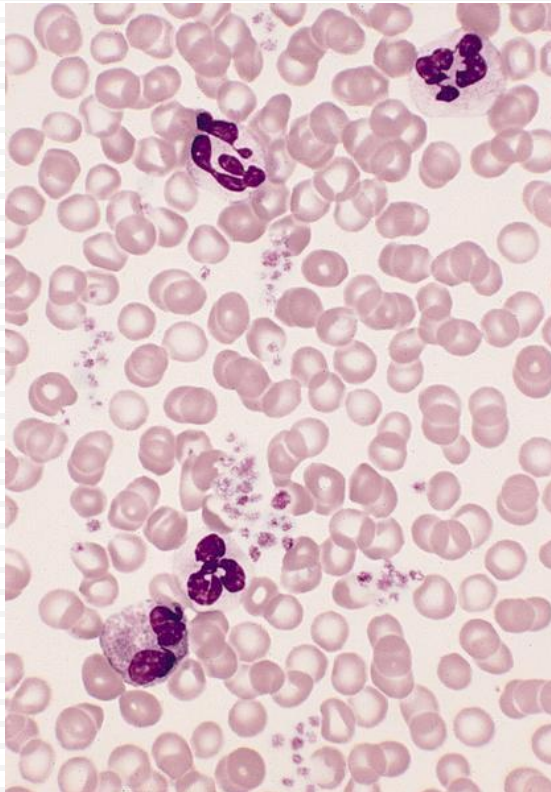
Hydroxycarbamide

- 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

PV Therapy

□ Indications for cytoreduction

□ High-risk pts

- Age ≥ 60 yrs, or
- Previous thrombotic event

□ Additional indications

- Poor tolerance of phlebotomy
- Platelets $> 1500 \times 10^9/L$
- WCC $> 15 \times 10^9/L$
- Uncontrolled myeloproliferation (e.g. increasing splenomegaly)
- Uncontrolled PV-related systemic symptoms

□ First-line cytoreduction

- HC (hydroxycarbamide)
- rIFN α (interferon)

□ Second-line cytoreduction

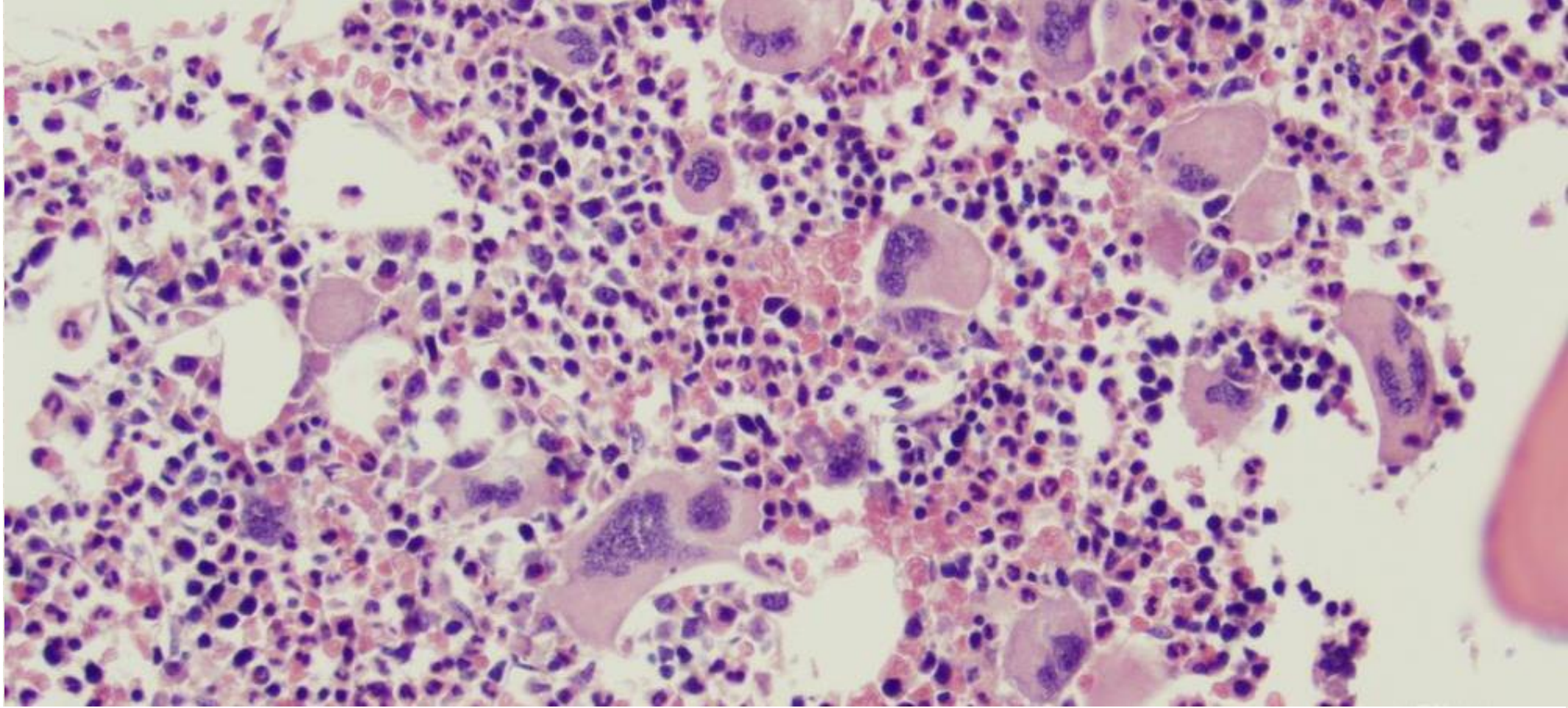
- HC
- rIFN α
- Busulfan
 - Intermittent therapy in very elderly
- Ruxolitinib
 - Not available in Aust for PV

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



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 rIFN α discontinuation

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

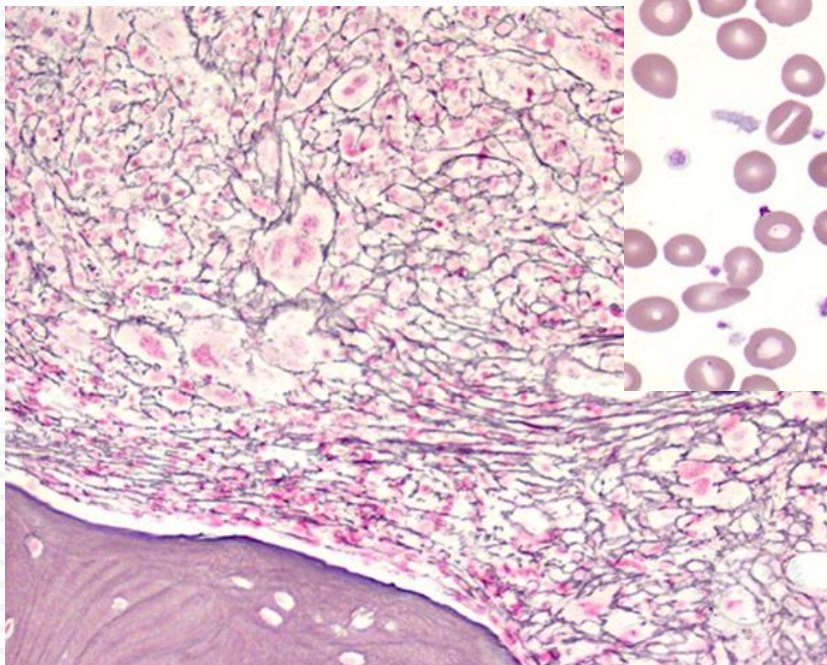
MPD-RC 112: Adverse events

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%

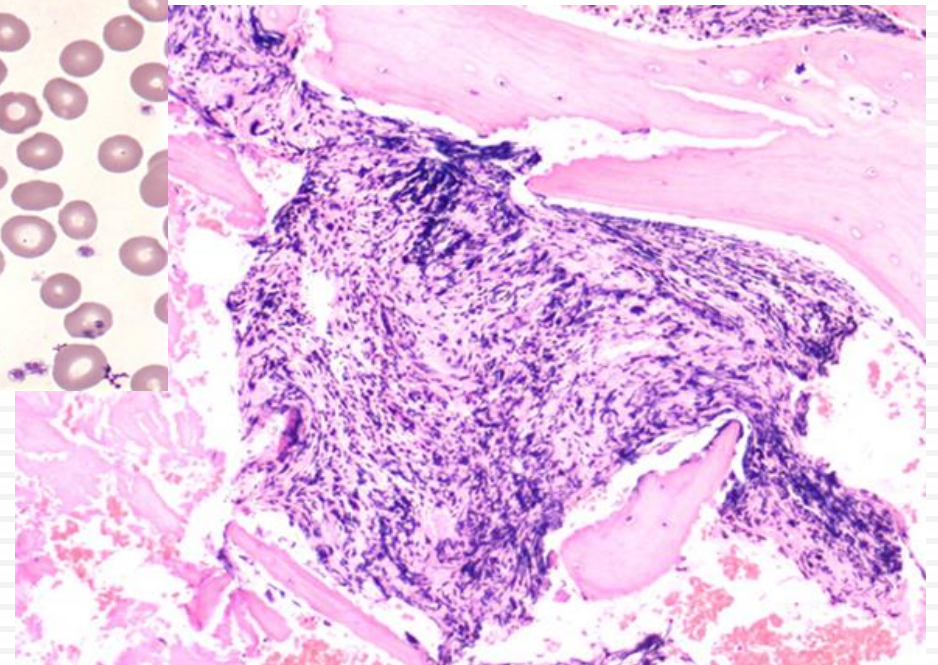
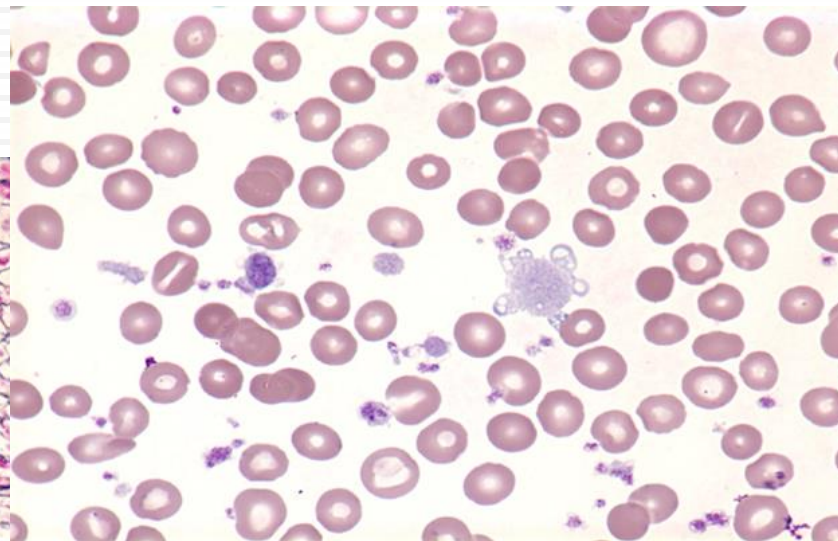
PEG-IFN in ET and PV

- 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 ×10⁹/L)
 - ▣ Marked thrombocytosis
(platelets >1000 ×10⁹/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
 - rIFN α
 - Ruxolitinib

PMF Therapy: Ruxolitinib

- JAK inhibitor
 - Oral medication
 - Significantly improves
 - Splenomegaly
 - $\geq 35\%$ 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% palpable 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)

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)

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

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

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

Advertisement

STOP SMOKING START REPAIRING



In 1 week
your sense of taste and smell improves

In 3 months
your lung function begins to improve

In 8 hours
excess carbon monoxide is out of your blood

In 1 year
a pack-a-day smoker will save over \$4,000

In 5 years
your risk of a stroke has dramatically decreased

In 12 weeks
your lungs regain the ability to clean themselves

In 12 months
your risk of heart disease has halved

In 5 days
most nicotine is out of your body

**EVERY CIGARETTE YOU DON'T SMOKE
IS DOING YOU GOOD**

Quitline 13 7848
australia.gov.au/quitnow

Authorised by the Australian Government, Capital Hill, Canberra
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Australian Government

- 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 \leq 2.0 mmol/L
- Strategies
 - ▣ Diet: 10-20% lowering
 - ▣ Weight loss: Aim for healthy BMI <25 kg/m²
 - ▣ 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%)

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)

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

**I'M GONNA MAKE
THE REST OF MY LIFE,
THE BEST OF MY LIFE.**

- 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.