Dept of Cancer Care Service

Dr Kirk MORRIS

Haematologist

Metro North Health's vision
Creating healthier futures together—where innovation and research meets compassionate care and community voices shape our services.

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A CASE

- 16 year old (grade 12), sent to DEM on Saturday

Presented with her dad . C/o lump in the left neck for few months , getting bigger, no pain, no fever, no sore throat, no ear pain
also recent appetite loss, has lost few kg over past few months ?
some dry cough , no sob, has had BCG vaccination .

Examination
neck- left side, LN ++ , significant size ?

Blod shows - microscopic anaemia, low WCC, neutropenia , lymphocytopenia !
high ESR, CRP

US/scan - equivocal findings

sinister pathology ?

Appreciate your urgent assessment .
Thank you .

In DEM

- Assessed by intern -> called : nonspecific symptoms as described, somewhat vague about size of cervical nodes
- Had not performed any further investigation (incl bloods)

FULL BLOOD EXAMINATION

--	Haemoglobin		90	g/L	(115-160)
	Red Cell Count		5.2	x10^12 /L	(3.6-5.2)
-	Haematocrit		0.31		(0.33-0.46)
---	Mean Cell Volume		61	fL	(80-98)
---	Mean Cell Haemoglobin		18	pg	(27-35)
	Platelet Count		303	x10^9 /L	(150-450)
-	White Cell Count		3.9	x10^9 /L	(4.5-13.0)
	Neutrophils	64 %	2.5	x10^9 /L	(2.0-8.0)
-	Lymphocytes	21 %	0.8	x10^9 /L	(1.5-5.0)
	Monocytes	14 %	0.5	x10^9 /L	(0.2-1.0)
	Eosinophils	1 %	0.04	x10^9 /L	(0.04-0.40)
	Basophils	0 %	0.00	x10^9 /L	(< 0.21)

++	Erythrocyte Sedimentation Rate	78	mm/hr	(1-20)

-	Sodium	136	mmol/L	(137-147)
	Potassium	4.0	mmol/L	(3.5-5.0)
	Chloride	102	mmol/L	(96-109)
-	Bicarbonate	23	mmol/L	(25-33)
	Other Anions	15	mmol/L	(4-17)
	Urea	3.2	mmol/L	(2.0-7.0)
	Creatinine	49	umol/L	(40-100)
	Total Bilirubin	3	umol/L	(2-20)
	Alk. Phos.	97	U/L	(30-300)
	Gamma G.T.	24	U/L	(0-45)
	ALT	17	U/L	(0-45)
	AST	24	U/L	(0-41)
+++	LD	551	U/L	(120-280)
	Albumin	43	g/L	(35-50)
	Globulins	37	g/L	(20-40)

There are multiple prominent and mildly enlarged lymph nodes in the bilateral cervical regions, largest short axis 17mm in the bilateral level 2 regions. There nodes demonstrate preserved ovoid morphology and fatty hilum, with increased nodal hilar vascularity.

COMMENT

1. A 7mm left lower pole thyroid TI-RADS 4 nodule, ultrasound follow-up in 6 months suggested.
2. Multiple prominent and enlarged bilateral cervical lymph nodes. The largest nodes are mildly enlarged, however there is preserved ovoid morphology with increased nodal hilar vascularity. Appearance may represent reactive lymphadenopathy, other possibilities are not completely excluded. A shot interval follow-up ultrasound in 3-4 weeks can be considered. Otherwise, these nodes are amenable to ultrasound-guided FNA.

Hgb	:	102	L	WBC	:	3.6	L				
PLT	:	344			:	3.6	L				
RBC	:	5.82	H	HCT	:	0.36	L				
MCV	:	61	L	MCH	:	17.5	L				
RDW	:	23.9	H	MCHC	:						
Neut	(	56	%):	2.00							
Lymph	(	27	%):	0.98	L						
Mono	(	15	%):	0.53							
Eosin	(	2	%):	0.07							
Baso	(	0	%):	0.01							

Specimen type	Blood			Protein	86 H	g/L	(57 - 80)
Sample Appearance	Clear			Albumin	34	g/L	(29 - 42)
Sodium	137	mmol/L	(133 - 144)	Globulin	52 H	g/L	(25 - 45)
Potassium	4.5	mmol/L	(3.6 - 5.3)	Bilirubin	< 4	umol/L	(< 20)
Chloride	105	mmol/L	(97 - 110)	Bili(Conj)	< 4	umol/L	(< 4)
Bicarb.	22	mmol/L	(20 - 32)	ALP	104	U/L	(35 - 140)
Anion Gap	11	mmol/L	(4 - 13)	Gamma GT	22	U/L	(< 24)
Glucose	4.5	mmol/L	(3.0 - 7.8)	ALT	19	U/L	(5 - 20)
Fasting RR	-->		(3.0 - 6.0)	AST	27	U/L	(< 30)
Urea	3.1	mmol/L	(2.9 - 7.5)	LD	583 H	U/L	(107 - 207)
Creatinine	48	umol/L	(38 - 82)	Calcium	2.49	mmol/L	(2.20 - 2.65)
Urea/Creat.	65		(40 - 100)	Corr Ca	2.60	mmol/L	(2.20 - 2.65)

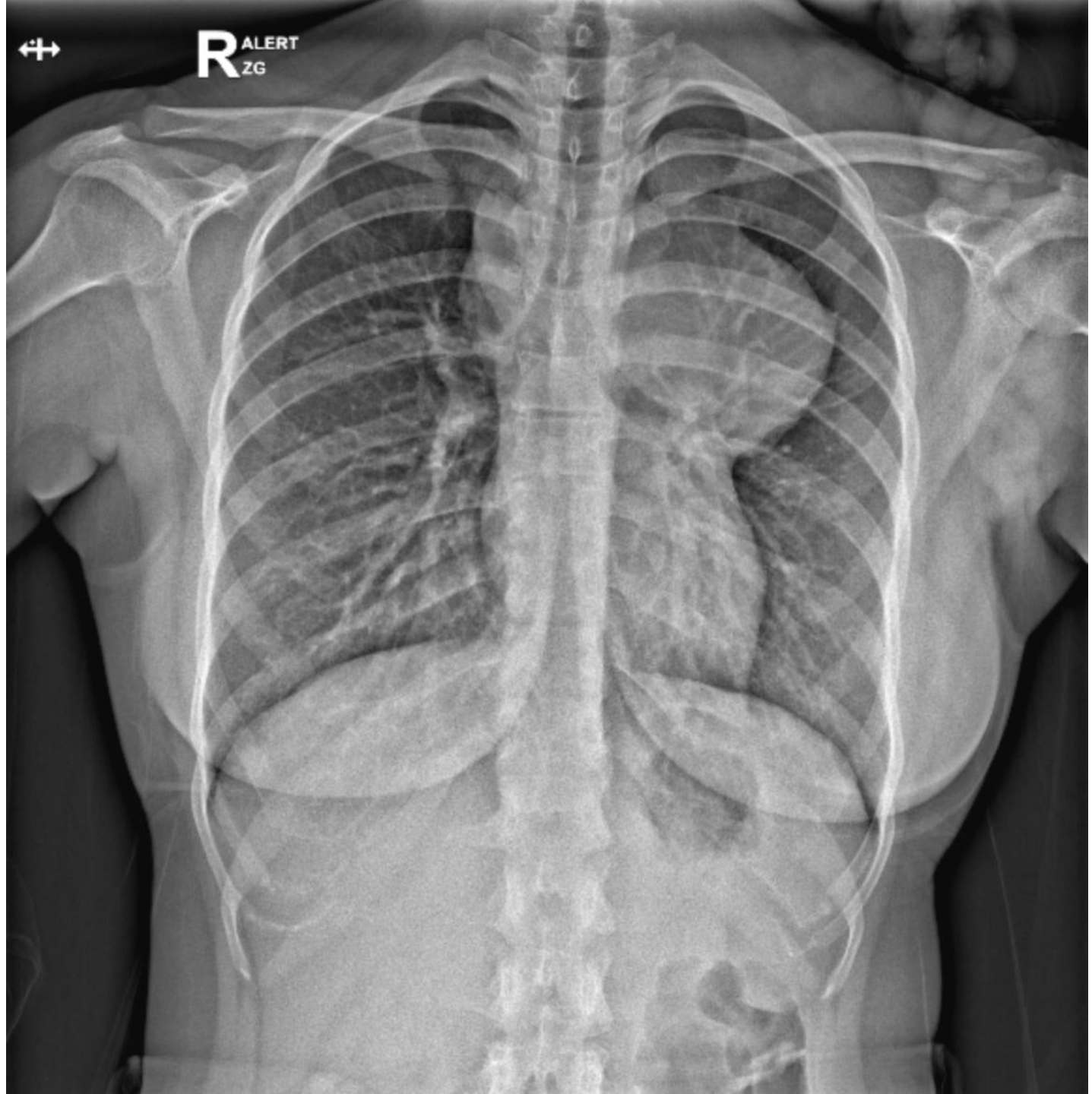
? thoughts

“skeptic”

- clearly significantly anaemic BUT other likely explanations
  - iron deficiency in young female
  - from India, mum and dad both have alpha thalassemia
- lymphadenopathy “at this point” sounds nonspecific
  - ??? EBV
- did she really need to come up on the weekend?

What test would you like to do?

- “Monospot” / EBV serology
- CMV serology
- iron studies
- B12, folate
- CXR
- Quantiferon gold
- All of the above


R
ALERT
ZG

RED FLAGS

- (… all nicely addressed in the referral)

- significant symptoms
  - painless lymphadenopathy
  - absence of overt infective symptoms (sore throat)
  - unexplained weight loss
  - “dry cough”
- that level of Hb is significant (despite other possibilities)
- lymphopenia (although this can happen with viral infections too)
- Isolated elevated of LDH (vs mixed elevation)
- “young female”

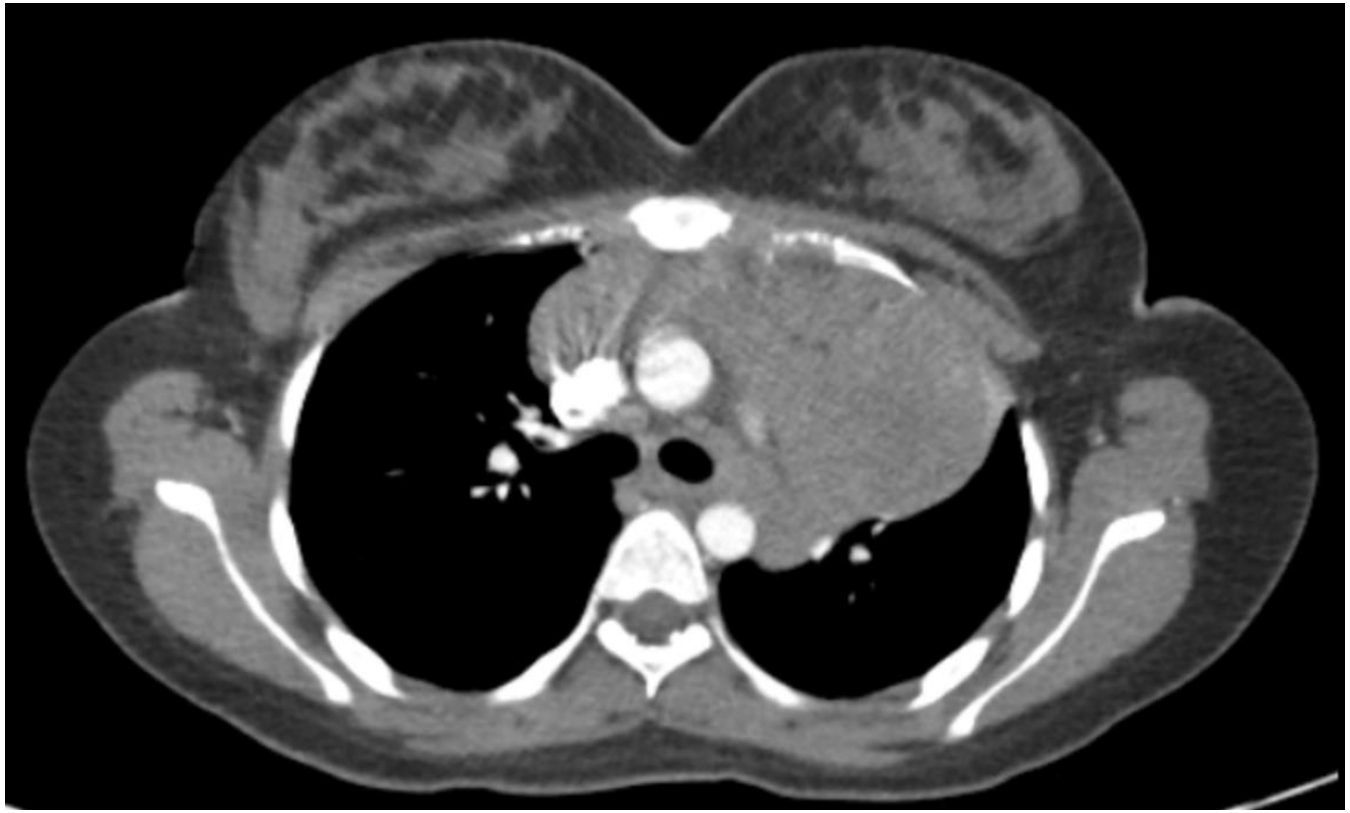
… enough in combination to suspect that this was not just EBV

CMV SEROLOGY			Loc.No.:RB
CMV IgG (EIA)	REACTIVE		
CMV IgM (EIA)	REACTIVE		
EBV SEROLOGY			
EBV (VCA) IgG (EIA)	REACTIVE		
EBV (VCA) IgM (EIA)	Non reactive		
IM Screen	Negative		

Iron	2 L	umol/L	(9 - 22)
Transferrin	3.2	g/L	(2.0 - 3.9)
Transferrin Saturation	2 L	%	(15 - 45)
Ferritin	27	ug/L	(10 - 80)

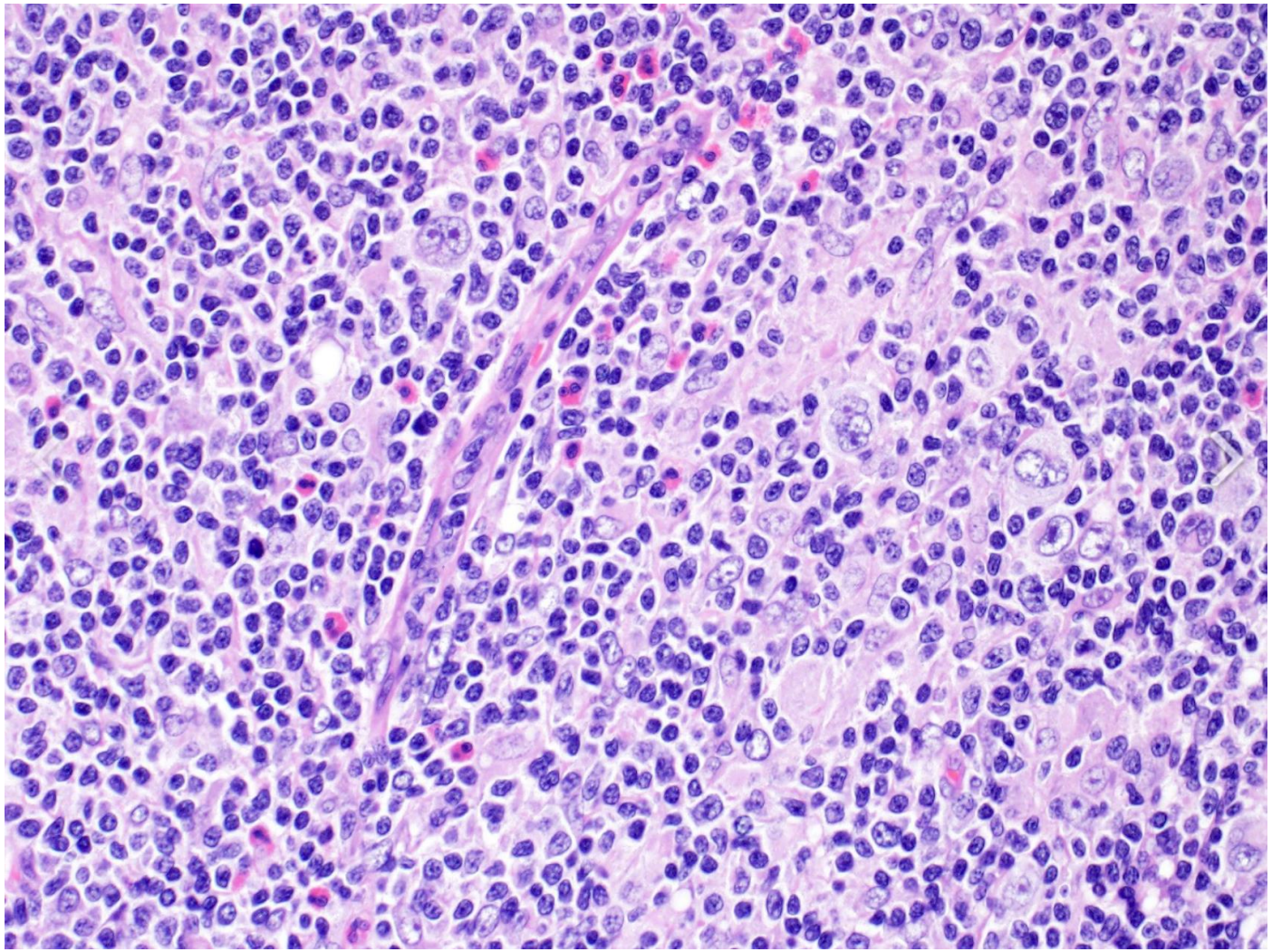
What did we do?

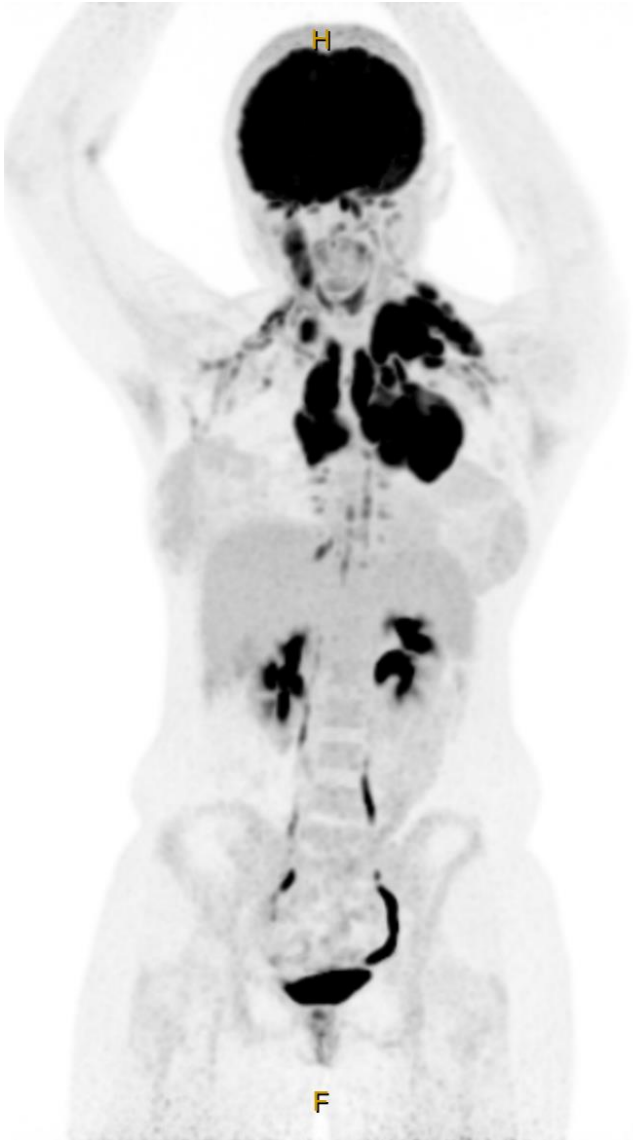
- ADMIT
- CT – on Saturday
  - confirms mediastinal mass, nothing critical eg vascular obstruction
- BIOPSY – on Monday
- PET – Wednesday



SUMMARY

1. Left supraclavicular lymph node core biopsy: Classic Hodgkin lymphoma;





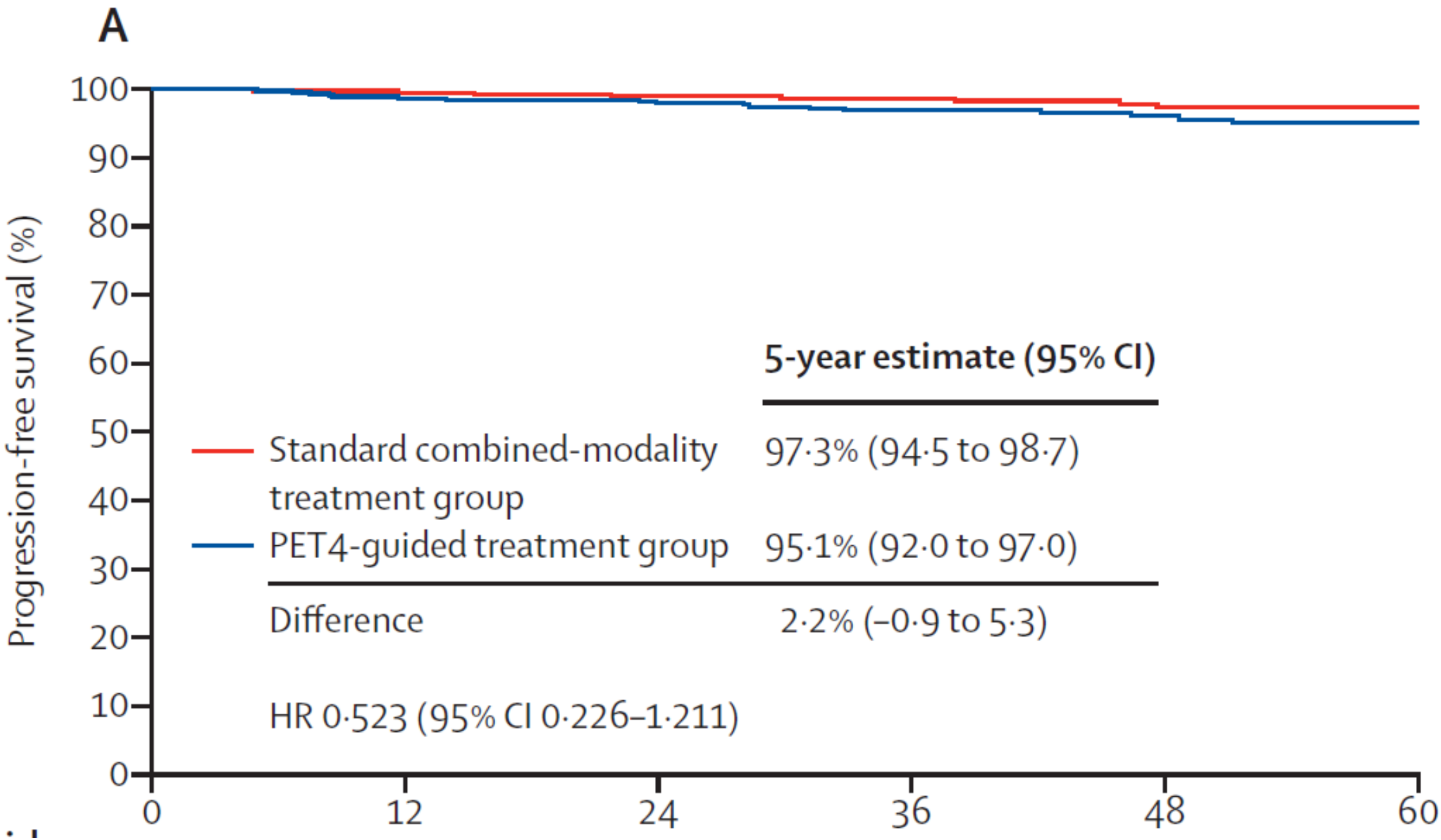
https://www.pathologyoutlines.com/topic/lymphomanonBclassic.html

“BIG MEDIASTINAL MASS”

- LYMPHOMA
  - HODGKIN
  - primary mediastinal
  - (others)
- OTHER CANCER
  - thymoma
  - germ cell tumour
- “vascular”
- …

Hodgkin lymphoma

- “most common cancer in adolescents”
- bimodal age distribution
  - most often presents in younger adults (age 15-25)
  - second peak in 7th – 8th
- “classical” presentation
  - young female
  - “B symptoms” : fever, sweats (“drenching”), weight loss (10% in 6 month)
  - pruritus
  - cervical and mediastinal masses
  - (spleen involvement in advanced stages)


A
Progression-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
5-year estimate (95% CI)
Standard combined-modality treatment group
97·3% (94·5 to 98·7)
PET4-guided treatment group
95·1% (92·0 to 97·0)
Difference
2·2% (–0·9 to 5·3)
HR 0·523 (95% CI 0·226–1·211)

Not always as clear as this case

- Common GP referral = “young adult with cervical lymphadenopathy … ultrasound showing mildly enlarged nodes +/- pathologic features”
- What would we like from you?
  - Description of symptoms, time course
  - Bloods : FBC, CHEM20, serology (EBV, CMV +/- HIV, hep C), (ESR)
  - Some form of imaging : plain (eg CXR), ultrasound vs CT
  - ?? biopsy
    - FNA is UNLIKELY to make diagnosis of Hodgkin lymphoma

Lymphadenopathy “RED FLAGS”

- BLOODS
  - cytopenias
  - hypercalcaemia
  - raised LDH
- IMAGING showing “critical mass”
  - bulky (? definition : 3 / 5 / 7 / 10cm)
  - obstructing something (or potential to do so) <-> extranodal
    - lung / bronchi
    - biliary tree
    - vasculature (eg SVC / IVC)
    - bowel
  - neurologic
    - paravertebral

GP “HOTLINE”

https://metronorth.health.qld.gov.au/refer-your-patient/clinic-advice-line

Metro North Clinical Advice Line

> Connecting GPs directly to Metro North specialties.
>
> **This service is for GPs ONLY and is not a patient advice phone line.**

Clinical Advice Line

1800 569 099

Open Monday to Friday

8.30am – 4.00pm

Treatment principles – Hodgkin lymphoma

- Front line remains chemotherapy +/- radiation therapy
  - BUT increasing “sophistication” all intended to maximise cure (> 90% in early stage disease) whilst minimising long term toxicity
    - reduce number of cycles of chemotherapy, avoiding bleomycin (lung)
    - shift away from radiation, minimising fields <- secondary malignancy risks, thyroid, cardiovascular

- Subsequent therapies include more sophisticated strategies esp immunotherapies

Long term toxicities

- secondary malignancy
  - radiation field effect
  - secondary blood cancer eg leukaemia
- cardiovascular <- anthracycline, mediastinal radiation
- lung (bleomycin)
- fertility
- psychosocial

- ARCHWAYS PROGRAM for youth cancer patients

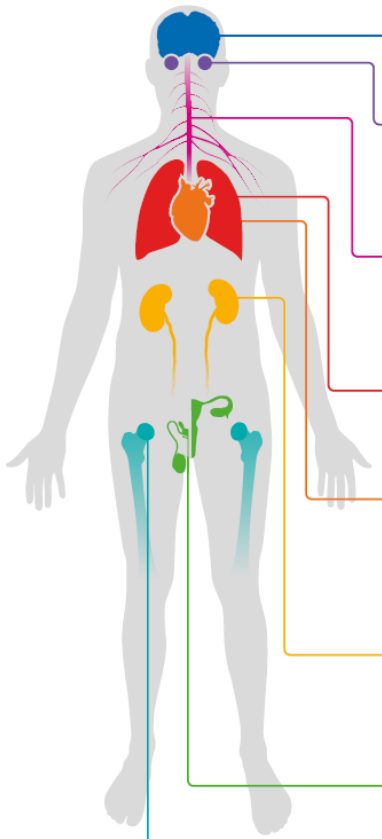
Managing long term side effects of chemotherapy

Teenagers and young adults (TYA) who survive cancer treatment can have a range of side effects later in life. If it is known which chemotherapeutic agents were used, the "Principal causative drugs" column can guide monitoring and management. Factors that further increase the risk of complications from chemotherapy are listed in the "risk groups" section.

Principal causative drugs

Alkylating agents: Busulfan, Cisplatin, Cyclophosphamide, Ifosfamide, Other

Anthracyclines, Antimetabolites, Bevacizumab, Bleomycin, Prednisolone HD[1], Taxanes, Trastuzumab, Vincristine, Vinblastine, Topo II inhibitors[2]



Risk groups

Managing those at risk

Loss of executive function / Memory loss

Risk: Concurrent cranial RT[3]

- Baseline MMSE[4] — Repeat if symptoms
- Consider: Neurorehabilitation; Psychotropic drugs
- Encourage communication with school/ university/ place of work
- Consider referral to: Social worker; Psychologist; Occupational therapist

Cataract

Risk: Concurrent RT[3]

- Funduscopy — Every year
- Refer to ophthalmology if symptoms

Peripheral neuropathy

Risk: Smoking

- Neurological examination — Every year for first 3 years | After this, reassess if symptoms change

Tinnitus / Deafness

Risk: Smoking

- Baseline audiological assessment — Repeat if symptoms
- Refer to ENT specialist if changes
- Consider: Hearing aid; Speech therapy; Assessment of reversible causes

Raynaud's phenomenon

Risk: Smoking

- Warm gloves in winter
- Calcium channel blockers

Pulmonary fibrosis

Risk: Smoking; Younger; HD[1]; Exposure to high O_2 concentration; +RT[3]; Renal dysfunction

- Baseline tests: Chest radiograph; Lung function
- Respiratory examination — Every year
- Vaccinations: Influenza; Pneumococcal
- Offer advice: Against smoking; Respiratory specialist review before anaesthesia or SCUBA diving

Ventricular failure / Coronary artery disease / Hypertension

Risk: CVS risks: Smoking; Diabetes; High cholesterol; Mediastinal RT[3]; High dose; Time since chemo; Pregnancy

- Encourage early presentation: Cardiac disease may occur at much younger ages in people who have had chemotherapy
- MUGA[5]/echocardiogram
- Consider ECG and blood pressure — Every year

Total anthracycline dose (mg/m²)

	< 200	200–300	> 300
Chest RT	Every 2 years	Every 2 years	Every 1 year
No chest RT	Every 5 years	Every 2 years	Every 1 year

Chronic kidney disease / Haemorrhagic cystitis / Renal tract malignancy

Risk: Prior renal dysfunction; Diabetes

Risk: Concurrent RT[3] to urinary tract

- Blood pressure — Every year
- Urinalysis — Every year
- Baseline urea and electrolytes — Repeat if symptoms or signs of renal failure
- Encourage self reporting: Advise patient to report potential symptoms
- Refer to renal specialist if deterioration in symptoms or results

Infertility / Primary hypogonadism

Risk: Older age at time of treatment; +RT[3] to gonadal region; Higher cumulative doses

- Fertility preservation: Refer all TYA[7] undergoing chemotherapy to fertility preservation services
- Baseline bloods: Men: Testosterone; Women: LH; FSH; Oestradiol
- Hormone replacement
- Mammogram — Every year; Breast MRI — from 8 years after RT / age 25 (whichever is later)
- Clinical breast exam: Every year from puberty to age 25; Every 6 months after age 25
- Breast self-exam — Every month

Necrosis of femoral head

Risk: Concurrent RT[3]

- Clinical examination — Every year
- Refer for MRI if clinical suspicion

Second malignant neoplasm

Risk: High dose; +RT[3]; t-AML survivors; Autologous stem cell transplant

- Full blood count for t-AML survivors — Every year
- After thoracic radiotherapy — Enhanced breast cancer surveillance

Psychosocial problems

Possible with all chemotherapy

Risk: CNS tumour; Hearing loss; Female; Younger; Cranial RT[3]; Learning difficulties; Lower SEG[6]

- Psychosocial assessment — Every year
- Support groups; Psychology referral; Counselling
- Antidepressants; Anxiolytics
- Assess impact on family members and carers

Fatigue

Most chemotherapeutic agents

Risk: Depression

- Screen for underlying depression
- Rule out reversible causes
- Advise short bursts of exercise

Osteoporosis

Risk: Smoking

- Bone density scan — Calcium and vitamin D according to results
- Rule out hypogonadism

Psychosocial effects of chemotherapy include:

- Post-traumatic stress disorder
- Financial burden
- Depression
- Employment difficulties
- Social isolation
- Educational difficulties
- Strained relationships with partner, family, and peers

[1] HD = High dose
[2] Topoisomerase II inhibitors
[3] RT = radiotherapy
[4] Mini Mental State Examination
[5] Multigated acquisition scan
[6] SEG = socio-economic grouping
[7] TYA = teenagers and young adults


CASE IH
MAGNUM
315

Thank you for seeing [redacted] for an opinion and management. Please can this 57M patient be seen for suspected b cell non-hodgkins lymphoma, with slow healing right right shin wound after exposure to thorns, noted during admission with hypercalcaemia, now with lymphocytosis and recent pathology interpretation.

Have ordered CT Chest Abdomen Pelvis - NAD, attached.

COPD / active smoker
peripheral vascular disease (documented arterial stenosis)
chronic leg ulcers
OSA - on CPAP
chronic back pain -> arthritis
hypertension
hyperlipidemia
chronic sinusisits
depression

Test Name	Result	Reference Interval	Units
Haemoglobin	138	125 - 175	g/L
Haematocrit	0.42	0.38 - 0.54	
Red cell count	4.3	4.2 - 6.5	10^12/L
MCV	100	80 - 100	fL
● **White cell count**	**12.3 H**	3.5 - 10.0	10^9/L
Neutrophils	5.27	1.5 - 6.5	10^9/L
● Lymphocytes	**5.90 H**	0.8 - 4.0	10^9/L
● Monocytes	**0.94 H**	0 - 0.9	10^9/L
Eosinophils	0.15	0 - 0.6	10^9/L
Basophils	0.05	0 - 0.15	10^9/L
Platelets	344	150 - 400	10^9/L

Test Name	Result	Reference Interval	Units
Sodium	140	135 - 145	mmol/L
Potassium	4.0	3.5 - 5.5	mmol/L
Chloride	107	95 - 110	mmol/L
Bicarbonate	26	20 - 32	mmol/L
Anion Gap	7	<16	mmol/L
● Calcium (Corrected)	2.68 H	2.10 - 2.60	mmol/L
Phosphate	1.14	0.80 - 1.50	mmol/L
Urea	4.5	3.5 - 8.5	mmol/L
Urate	0.430	0.200 - 0.500	mmol/L
Creatinine	80	60 - 110	umol/L
eGFR	>90	>59	
Glucose random	7.0	3.6 - 7.7	mmol/L
Total Protein	66	63 - 80	g/L
Albumin	38	32 - 44	g/L
Globulin	28	23 - 43	g/L
Bilirubin	6	<21	umol/L
ALP	95	35 - 110	U/L
AST	15	10 - 40	U/L
ALT	20	5 - 40	U/L
● GGT	52 H	5 - 50	U/L
LD	173	<250	U/L
Cholesterol	4.4	<5.6	mmol/L
● Triglyceride	3.8 H	<2.1	mmol/L
Magnesium	0.79	0.70 - 1.10	mmol/L
Haemolysis Index	2	<40	

? thoughts

would you like to do any further testing?

- No further testing, the changes are nonspecific
- Repeat FBC
- Bone marrow biopsy
- Flow cytometry
- PTH +/- vitamin D
- Need more information

Approach to mild lymphocytosis

- CAUSE?
  - reactive / secondary <- common, but hard to prov
  - lymphoproliferative neoplasm <- “don’t want to miss”
    - (but typically chronic, non aggressive)

- COMMON THEMES in reactive cases
  - documented over years, intermittent
  - low level (< 10 x 109/L)
  - **smoking**, chronic lung disease, obesity, autoimmune disorders
  - blood film just shows “bland” small lymphocytes
  - absence of other blood count abnormalities

Flow cytometry

Peripheral Blood Surface Markers

Lymphocytes comprise 26%.
T-cells 32% CD4/CD8: 3.1
B-cells 52% kappa/lambda: Unable to determine
NK-cells 14%
A monoclonal B-cell population comprises 50% of lymphocytes
The phenotype is:

CD5 +ve	CD10 -ve	CD19 +ve	CD20 +ve (weak)
CD23 +ve	CD79b -ve	CD200 +ve	CD43 +ve

SMIg Kappa (weak)

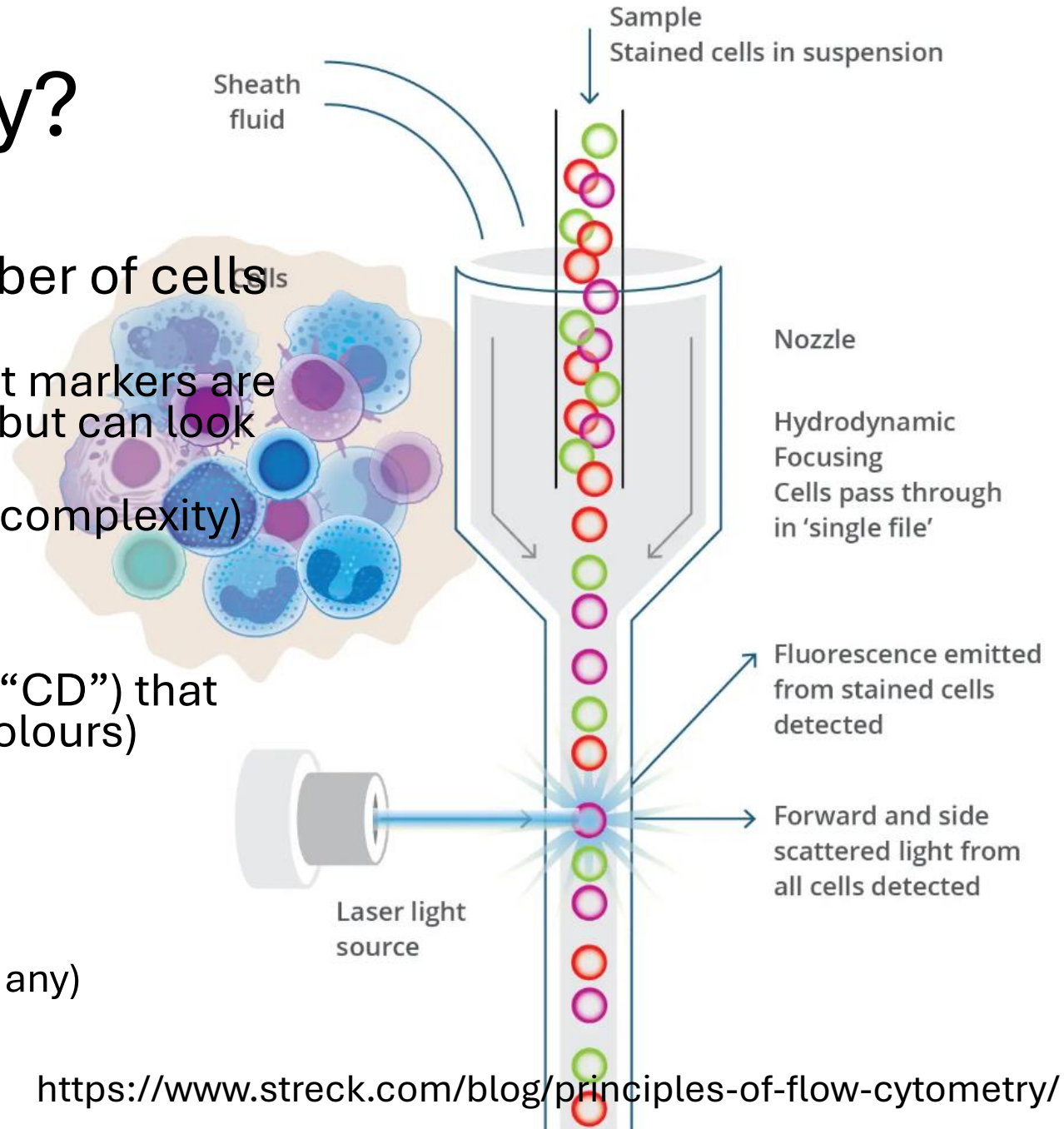
Comments

Conclusion: In the absence of extramedullary disease, this is most consistent with High count Monoclonal B-cell lymphocytosis (high count MBL) with chronic lymphocytic leukaemia phenotype (monoclonal B-cells between 0.5x10^9/L - 5x10^9/L). This subgroup of MBL has an increased risk of progression to chronic lymphocytic leukaemia and annual follow-up is recommended.

Parathormone	23 H	pmol/L (2.0 - 9.3)

What is flow cytometry?

- A means of analysing a very large number of cells to determine
  - immunophenotypic characteristics – what markers are expressed by the cell (mostly on surface, but can look at intracellular expression too)
  - certain physical characteristics (size and complexity)
- How does it work
  - suspension of cells (blood = easy!)
  - mix with antibodies against cell markers (“CD”) that have fluorochromes attached (different colours)
  - send through machine in single file
  - “shoot lasers” at the cells
    - how much shadow they make (~ size)
    - how much light bounces off (~ complexity)
    - what coloured flurochrome is detectable (if any)



https://www.streck.com/blog/principles-of-flow-cytometry/

Flow cytometry

- Can look at all cell populations in blood
- Particularly useful for lymphocytes
  - (easily) distinguish between T and B cell populations
  - **is there expansion of an abnormal population / clone?**
  - B-cells only express one of 2 light chains (kappa / lambda) on surface, and there is a normal / expected ratio
  - Abnormal populations may have aberrant gain or loss of expression of a marker
- (Can also detected abnormal myeloid populations eg MDS, AML)

Chronic lymphocytic leukaemia

- mature B-cell neoplasm characterised by progressive accumulation of monoclonal B-cell lymphocytes with a very specific (aberrant) phenotype
  - expression of CD5 (= T-cell specific marker) on a B-cell
  - week immunoglobulin expression
  - CD23+, CD200+
- “most prevalent leukemia” in adults
- Most commonly is diagnosed upon “incidental” finding of isolate lymphocytosis
- In more advanced stages
  - lymphadenopathy
  - splenomegaly
  - anaemia / thrombocytopenia – marrow failure, immunologic
  - constitutional (“B”) symptoms

CLL – treatment

- Like most “indolent” blood cancers (eg myeloma, low grade lymphoma such as follicular), regarded as “incurable”
  + no evidence that early treatment makes you live longer

= therapy reserved for patients who have “symptomatic” disease

what is “monoclonal B-cell lymphocytosis”?

- With the wider availability of testing such as flow, recognised that clonal B-cell populations (typically with CLL phenotype) are detectable in a sizable number of otherwise well patients
  - > 40 – 60 year old : 3.5 – 6.7%
  - > 60 years olf : 5 - 9%
- when the absolute level of these clonal cells is low (<5x109/L), and in the absence of other features of lymphoma, the expectation of progression to symptomatic disease requiring therapy is very low

= a desire to avoid labelling as “leukaemia” (/ cancer)

(… much like “MGUS”)

MBL

- Subclassify
  - “low count” MBL – clonal population < 0.5 x 109/L
  - “high count” MBL – above this

- Low count MBL :
  - extremely low risk of progression to CLL
  - some argue no monitoring necessary (+ not even tell patient)

- High count MBL :
  - risk of progression 1-2 percent per year. median OS 17.9 years.

MBL

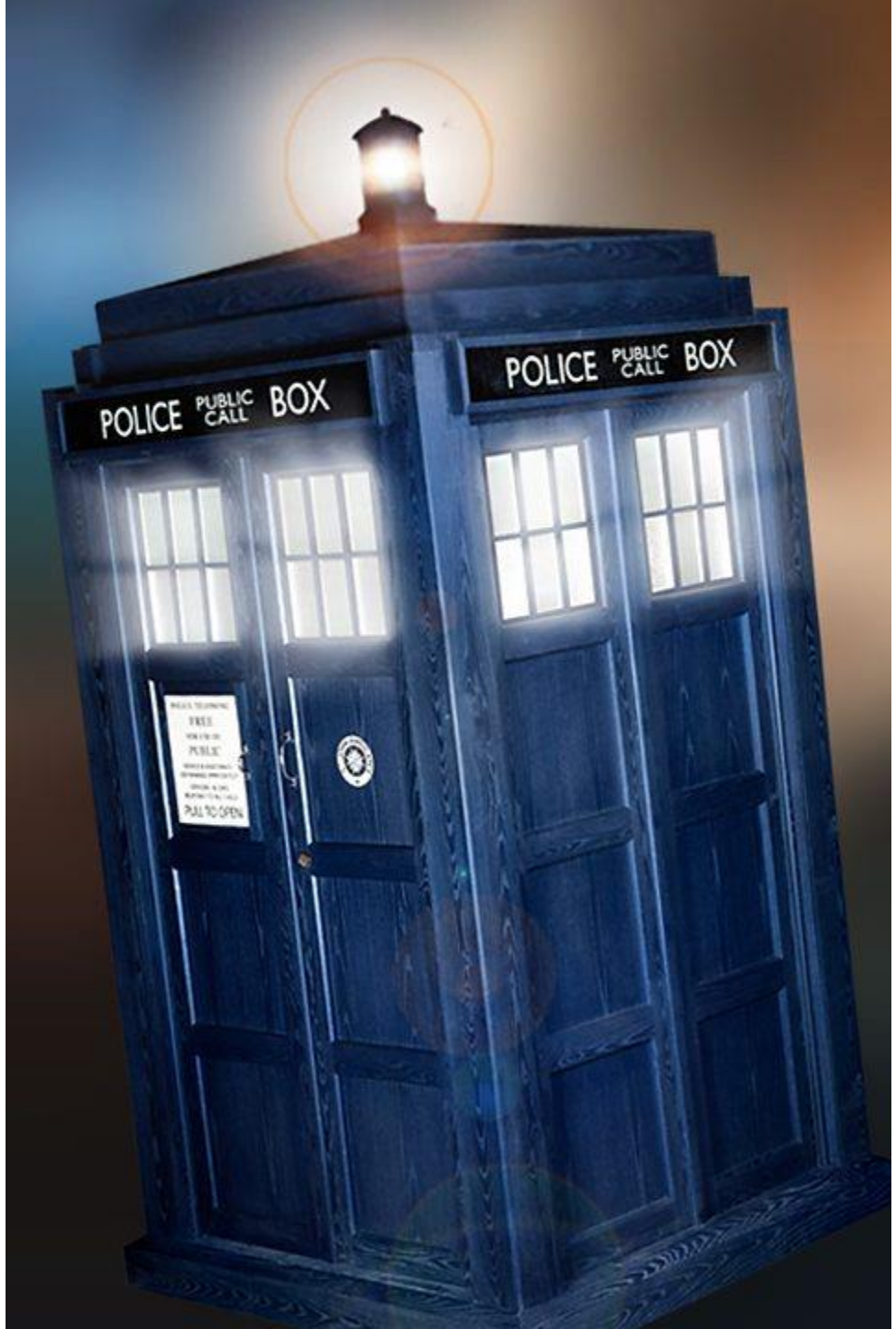
- Due to low risk of progression / need for treatment, we may ask you to monitor them (please!)
  - clinical monitoring for lymphadenopathy, splenomegaly
  - unexplained constitutional symptoms
  - annual FBC
    - progressive lymphocytosis (eg doubling, > 10)
    - development of other (unexplained) cytopenia

Other clonal lymphoproliferative disorders that might cause “isolated lymphocytosis”

- B-cell
  - CLL + monoclonal B-cell lymphocytosis
  - “other” B-cell lymphoma (… typically indolent)
    - lymphoplasmacytic lymphoma (IgM paraprotein)
    - marginal zone lymphoma (esp splenic)
    - hairy cell leukemia
    - follicular lymphoma

  ** flow cytometry will pick these up **
- T-cell
  - T-LGL (blood film important, associated neutropenia)
- NK-cell (rare!)

CLL – treatment



Tranditional therapy for (blood) cancers

“Cellular poison” – interfere with how cells replicate
Hope that more cancer cells are killed than normal cells
If that fails …

Bone marrow Transplant

What we really want

What is wrong with the cell?
(genetics, epigenetics, molecular, microenvironment)

-> design a therapy that targets this

IMMUNOTHERAPY

- “Harnessing the power of your immune system”
  - T-cells = most powerful cellular weapon

- (Bone marrow transplant)
- Antibodies targeting cell surface markers (rituximab – CD20)
- Antibodies – drug (chemo) conjugates
- Checkpoint inhibitors
- CAR-T
- BiTE

CLL

- Is in the growing list of blood cancers that we no longer primarily treat with chemotherapy (and / or bone marrow transplant)

- others include
  - Chronic myeloid leukaemia – TKIs (imatinib, dasatinib, nilotinib, asciminib)
  - Acute promyelocytic leukaemia – arsenic, ATRA
  - (Myeloma)

Ideal cancer therapy

- A pill
- Cures the disease
- No side effects

Ideal cancer therapy

✓ A pill

- Nobody likes needles

Cures the disease

No side effects

Ideal cancer therapy

A pill

Cures the disease

- Recurring theme = they often don’t
- Often remain on indefinitely / long period

No side effects

Ideal cancer therapy

A pill

Cures the disease

No side effects

- This drug does not exist

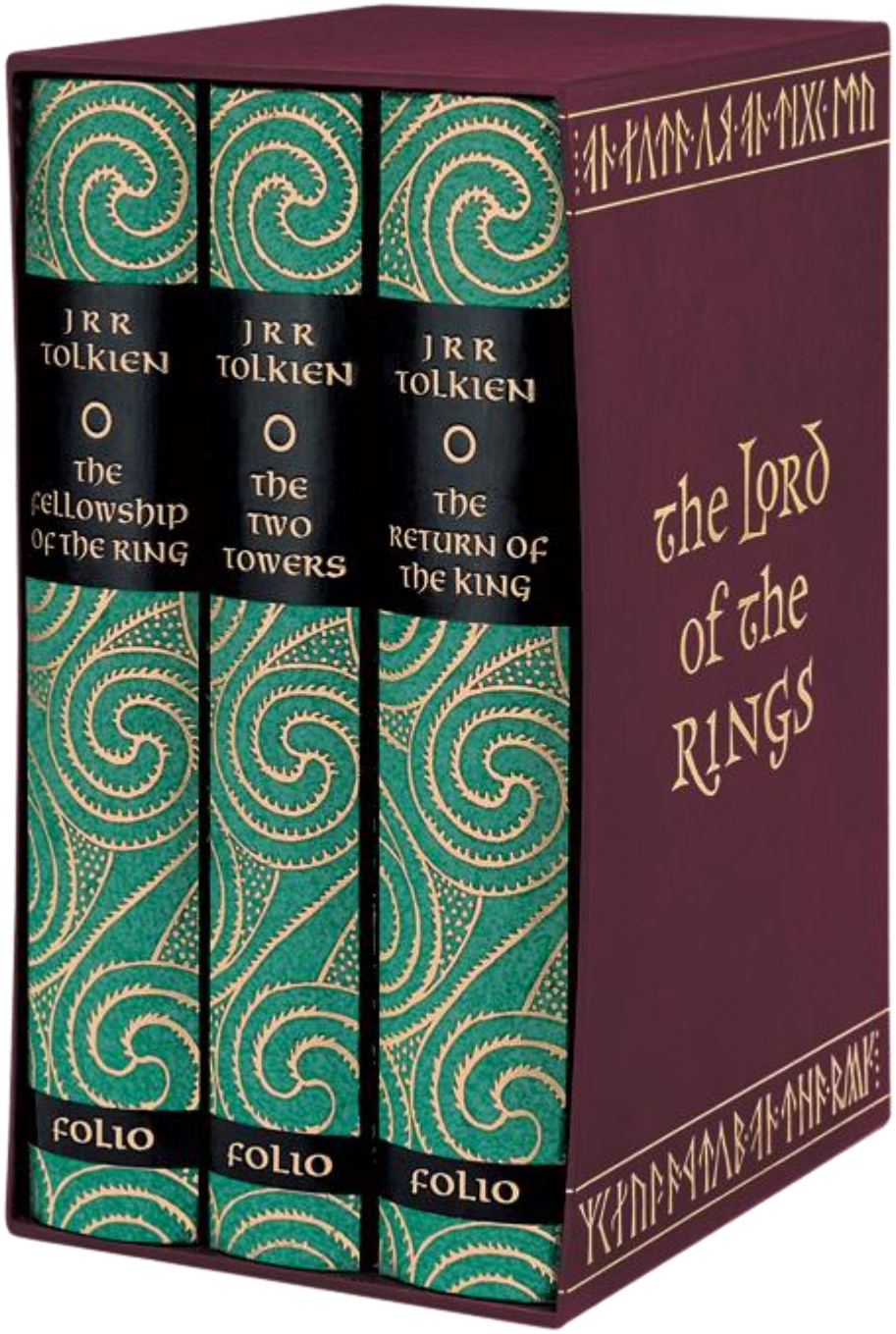
CLL - “Novel therapies”

- Monoclonal antibodies

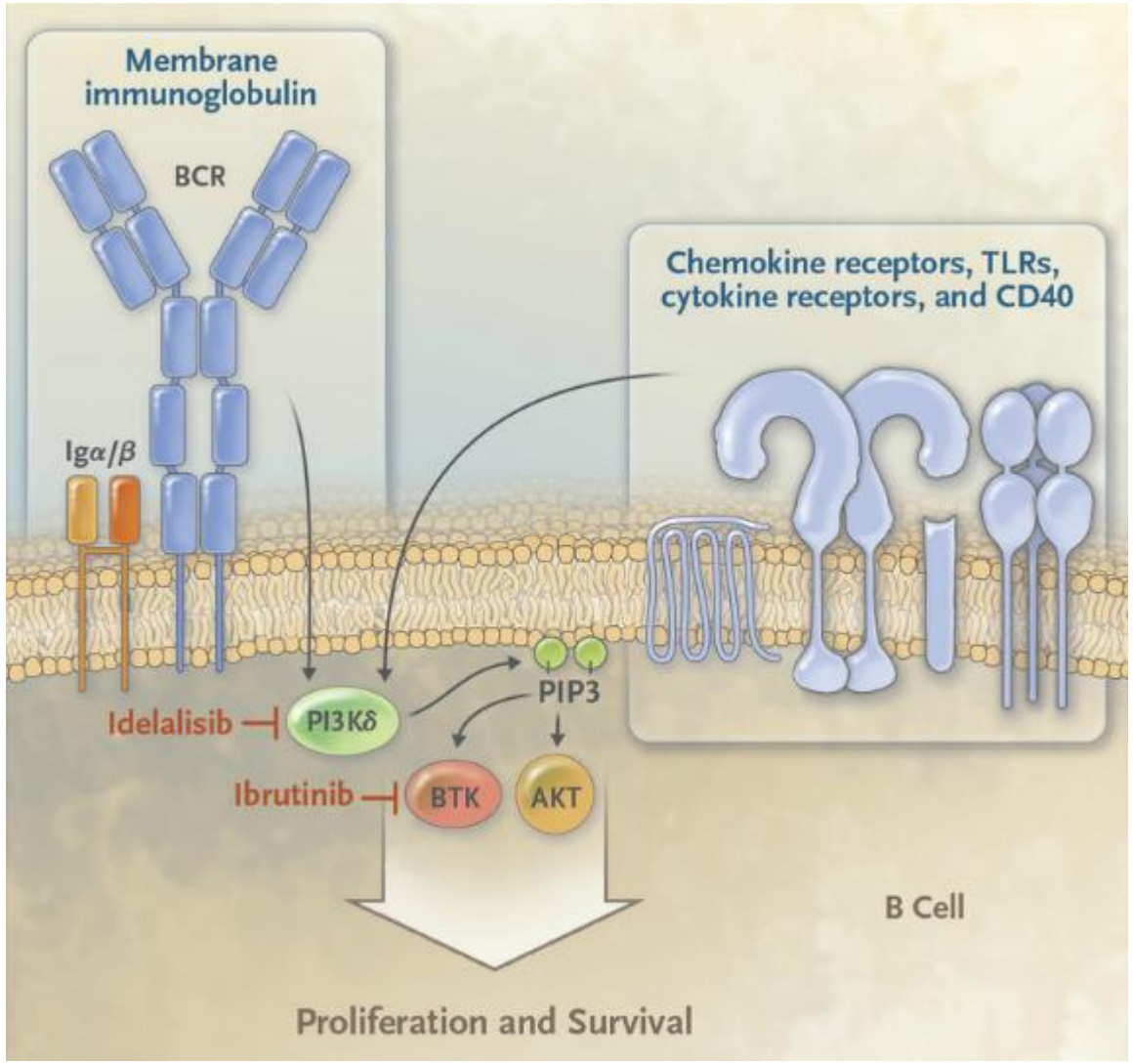
- BTK inhibitors **
  - ibrutinib (Imbruvica)
  - acalabrutinib (Calquence)
  - Zanubrutinib (Brukinsa)

- BCL-2 inhibition **
  - Venetoclax (Vencyto)

** ORAL THERAPIES that you will see patients taking



B-cell receptor signalling pathway



- Normal B lymphocyte : binding of ligands to surface receptors leads to cell proliferation and survival
- CLL : this pathway is constitutively activated / independent of ligand binding
  - “uncontrolled” cell activation
- BTKi inhibitors are designed to block this

NEJM 2014:370(11):1061

BTK inhibitors
- ibrutinib, acalabrutinib, zanubrutinib

- Once or twice daily oral therapy
- Intended to continue “indefinitely”
- expect lymphocytosis to worsen initially, and may not fully resolve
- POTENTIAL TOXICITIES
  - increased rates of tachyarrythmias esp AF
  - increased bleeding (? anti – platelet effect) … patients often on DOAC
  - immunosuppression / infection - ? prophylactic antimicrobials eg Bactrim, valaciclovir **
  - diarrhoea, nausea

** Shingrix and other vaccines please !!

Venetoclax = “BCL-2 inhibitor”

- BCL-2 protein = “anti-apoptotic” -> stops programmed cell death
  - **Pathologically overexpressed in CLL (amongst other)**
  - “keeps the cell alive”

= a target! <- Inhibit BCL-2 => allow the cell to die

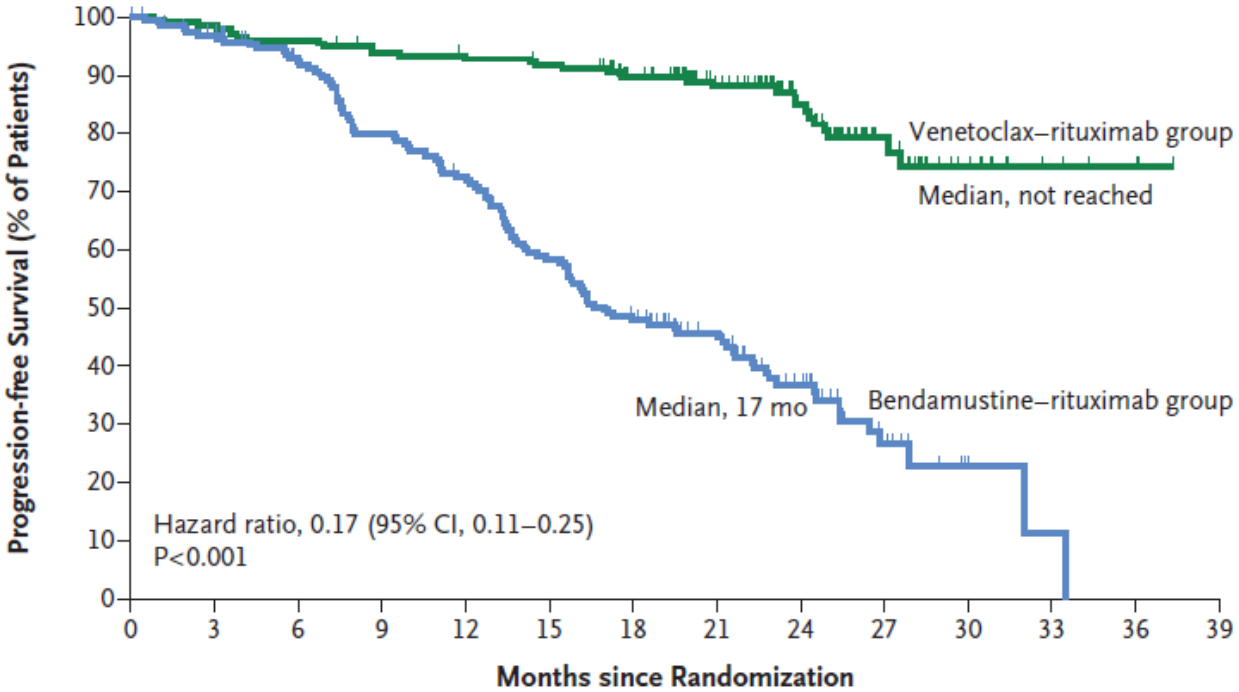
Venetoclax

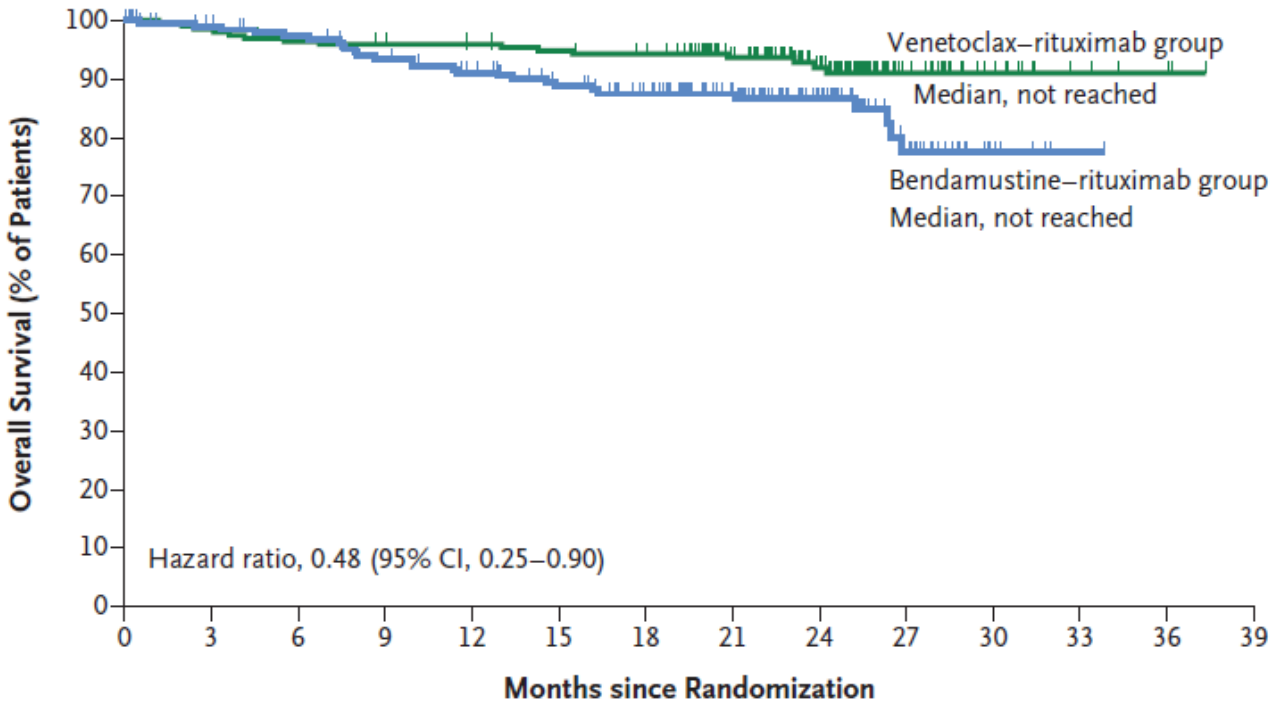
- Development pioneered by Australian Haematologists
- Once daily oral therapy, usually “time limited” (12 – 24 months)

- In early trials in CLL as monotherapy in heavily pretreated patients, people died from **tumour lysis syndrome**
  - rapid cellular death overwhelms kidneys with urate, potassium, phosphate (+ other bad things)

= start at very low dose, with escating to maximal dose over 5 weeks

(also used in non lymphoid blood cancers eg MDS, AML)





Seymour, J. F. *et al.* Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *New England Journal of Medicine* **378**, 1107–1120 (2018).

Venetoclax - toxicities

- Tumour lysis (3-6%)
- Neutropenia (43-62%) – higher overall incidence compared to chemo arm, but less infecton / infestations
- Anaemia, thrombocytopenia
- Diarrhoea (29 – 52%)
- Hyperglycaemia (10-16%)

($)

PERSPECTIVE

Approach to an FBC abnormality “key points”

- MILD, SINGLE LINEAGE CYTOPENIAS ARE RARELY ANYTHING BAD
  - ? Definition of mild
    - Hb > 100 [80]
    - neutr > 1.0 [0.5]
    - plt > 100 [75, 50]

- YOU ARE UNLIKELY TO MISS SOMETHING SERIOUS
  - there is usually something to see on the film (= trust your laboratory!)
  - you will know on repeat testing … at the very least, the most important thing to do is REPEAT THE TEST

- TALK TO US ANYTIME!
  - We would prefer to solve the problem by phone

Approach to blood count abnormality

- Severity
- duration / progression over time [acute vs chronic]
- single vs multi-lineage
- blood film

- Clinical history
  - is there any obvious cause (eg smoking, drug eg prednisolone)
  - are there red flags ?

Severity

- Our thresholds may differ from yours
  - BUT always dependent on clinical context (“red flags”)

- https://metronorth.health.qld.gov.au/specialist_service/refer-your-patient/haematology

	Cat 1	Cat 2	Cat 3
Anaemia	Hb < 80g/L Hb < 100g/L + symptoms	Hb 80-100g/L	Hb >100g/L
Erythrocytosis	Hb > 200g/L HcT >0.6 (men), >0.56 (women) Hb above normal with thrombosis or symptoms	Hb > upper limit normal with JAK2 mutation and/or suppressed EPO	(if no “red flags”) Hb up to 200g/L HcT 0.51-0.6 (males), 0.48-0.56 (females)
Thrombocytopenia	< 30x109/L	30-75x109/L	>75x109/L
Thrombocytosis	>1000x109/L >600x10^9/L + symptoms	>600x10^9/L	450-600x10^9/L
Neutropenia	< 0.5 x 10^9/L	0.5-1.0 x 10^9/L	1.0-1.5x10^9/L
Neutrophilia	CML, leucoerythroblastic	> 30x10^9/L	< 30x109/L
Lymphocytosis	Above normal with cytopenias or symptoms	CLL Aberrant T-cell lympocytosis	Monoclonal B-cell lymphocytosis

Blood film – RED FLAGS

- The “really serious” things (acute leukaemias, CML, MDS) will almost invariably have abnormalities that are visible down a microscope
  - dysplastic changes
  - “leukoerythoblastic”
  - red cell shape / size

- Presence of immature cells will be considered more significant than if all the cells appear “normal” and “mature”

“Persistent Leukocytosis”

- Very common referral
- Usually mild (WCC < 20)
- Common themes in history
  - SMOKERS, marijuana
  - obese, hepatic steatosis
  - diabetic
  - autoimmune conditions
  - on prednisolone (!)
  - mental health disorders esp schizophrenia

“Persistent Leukocytosis”

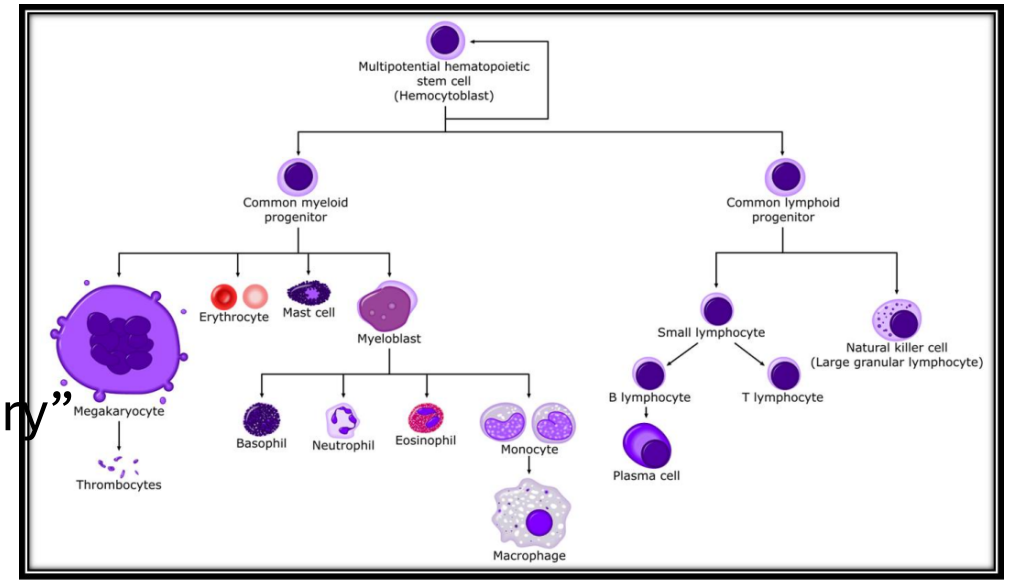


Figure 1: Hematopoiesis in Bone Marrow

- Most common explanation is “reactive” or “secondary”
- <u>Reassuring findings</u> on film / differential
  - variable / transient / “multilineage” (myeloid / neutrophil vs lymphoid / lymphocytosis) at different time points – this is unlikely clonal
  - Absence of anaemia or thrombocytopenia is always reassuring
  - No dysplasia (“cells look normal”)
  - Differential only shows mature cells (no myelocytes, blasts)
- Mild thrombocytosis (< 600) is common in inflammatory states
- Mild isolated neutrophilia is very rarely neoplastic

72 year old

Primary Reason for Referral

Thank you for seeing [redacted] for an opinion and management. [redacted] recent blood test showed moderate neutrophilic leucocytosis (WBC 22.0,neutriphils 16.1), Blood report attached.Previoulsy well,

I would really appreciate if you can see him for opinion and managment.

Detailed history or comments:

Please explain if you consider this referral urgent:

Date Collected	12/12/2016	17/07/2017	18/12/2017		Current
Time Collected	08:20	05:08	08:10		Reference
Episode				Units	Range
Hb	153	158	169	g/L	(130-180)
Total WCC	6.8	9.0	22.4 *	10^9/L	(4.0-11.0)
RCC	4.7	4.8	5.7	10^12/L	(4.5-6.5)
Hct	0.47	0.49	0.53		(0.38-0.54)
MCV	102 *	103 *	94	fL	(80-97)
MCH	33 *	33 *	30	pg	(27-32)
MCHC	323	323	318 *	g/L	(320-360)
Plt	233	149 *	NP	10^9/L	(150-450)
Neutrophils	56	52	69	%	
	3.8	4.7	15.5 *	10^9/L	(2.0-8.0)
Lymphocytes	34	36	18	%	
	2.3	3.2	4.0	10^9/L	(1.0-4.0)
Monocytes	7	8	3	%	
	0.5	0.7	0.7	10^9/L	(0.0-1.0)
Eosinophils	2	2	2	%	
	0.1	0.2	0.4	10^9/L	(0.0-0.5)
Basophils	1	2	5	%	
	0.1	0.2	1.1 *	10^9/L	(0.0-0.3)
Myelocytes			1	%	
Myelocytes			0.2		
Metamyelocyt.			2	%	
Metamyelocyte			0.4		
RDW	15.3	14.9	15.0		(9.0-16.5)

? thoughts

Approach to this referral

- CONSIDER OTHER CAUSES
- **REPEAT THE TEST**

Hb	165
Total WCC	**26.2**
RCC	5.5
Neutrophil	75
Neutrophils	**19.7**
Hct	0.52
Lymphocyte	16
Lymphocytes	**4.2**
MCV	94
Monocyte	4
Monocytes	1.0
MCH	30
Eosinophil	1
Eosinophils	0.3
MCHC	**317**
Basophil	5
Basophils	**1.3**
RDW	15.4
Platelets	169

FILM REVIEW!

Red cells appear normocytic normochromic. The white cells show a moderate neutrophilic leucocytosis. ? bacterial infection, ? reactive. Basophilia. Metamyelocytes and myelocytes are present. The film shows many platelet clumps making the platelet count unreliable, HOWEVER NUMBERS APPEAR INCREASED ON FILM.

COMMENTS : Film suspicious of chronic myeloproliferative disorder given neutrophilia, basophilia and thrombocytosis (frequent platelet clumpings or aggregations and occ large platelet, and raised LDH). Suggest repeat FBC in citrate tube to get more accurate platelet count. If no apparent reactive causes of leucocytosis and or thrombocytosis such as infection or inflammation, and blood picture remains uncharged, consider PCR for Jak2 mutation. Suggest clinical correlation and repeat FBC.

Common causes of thrombocytosis include reaction to infections, blood loss, malignancy and some haematological disorders. If persistent and clinically indicated, further investigation may be required.

MYELOPROLIFERATIVE NEOPLASM

- inappropriate overproduction of “mature” blood cells

• CML	<->	white (“myeloid”) cells
• polycythemia vera	<->	red cells
• essential thrombocytosis	<->	platelets
• myelofibrosis		

Rare : chronic eosinophilic leukaemia, chronic neutrophil leukaemia

Myeloproliferative neoplasia

- We have come to recognise that these conditions are driven by definable mutations that drive cell proliferation whilst maintaining normal maturation
  - BCR-ABL -> CML
  - JAK2 V617F -> PV, ET, myelofibrosis
  - CALR, MPL mutations -> ET

… you can directly test for these, on peripheral blood

“myeloproliferative screen”

Date Collected	12/12/2016	17/07/2017	18/12/2017		Current
Time Collected	08:20	05:08	08:10		Reference
Episode				Units	Range
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MCH	33 *		30	pg	(27-32)
MCHC	323		318 *	g/L	(320-360)
Plt		149 *		10^9/L	(150-450)
Neutrophils		52		%	
			15.5 *	10^9/L	(2.0-8.0)
Lymphocytes	34		18	%	
		3.2	4.0	10^9/L	(1.0-4.0)
Monocytes		8	3	%	
	0.5	0.7	0.7	10^9/L	(0.0-1.0)
Eosinophils	2	2	2	%	
	0.1	0.2	0.4	10^9/L	(0.0-0.5)
Basophils	1	2	5	%	
	0.1	0.2	1.1 *	10^9/L	(0.0-0.3)
Myelocytes			1	%	
Myelocytes			0.2		
Metamyelocyt.			2	%	
Metamyelocyte			0.4		
RDW	15.3	14.9	15.0		(9.0-16.5)

CHRONIC MYELOID LEUKAEMIA

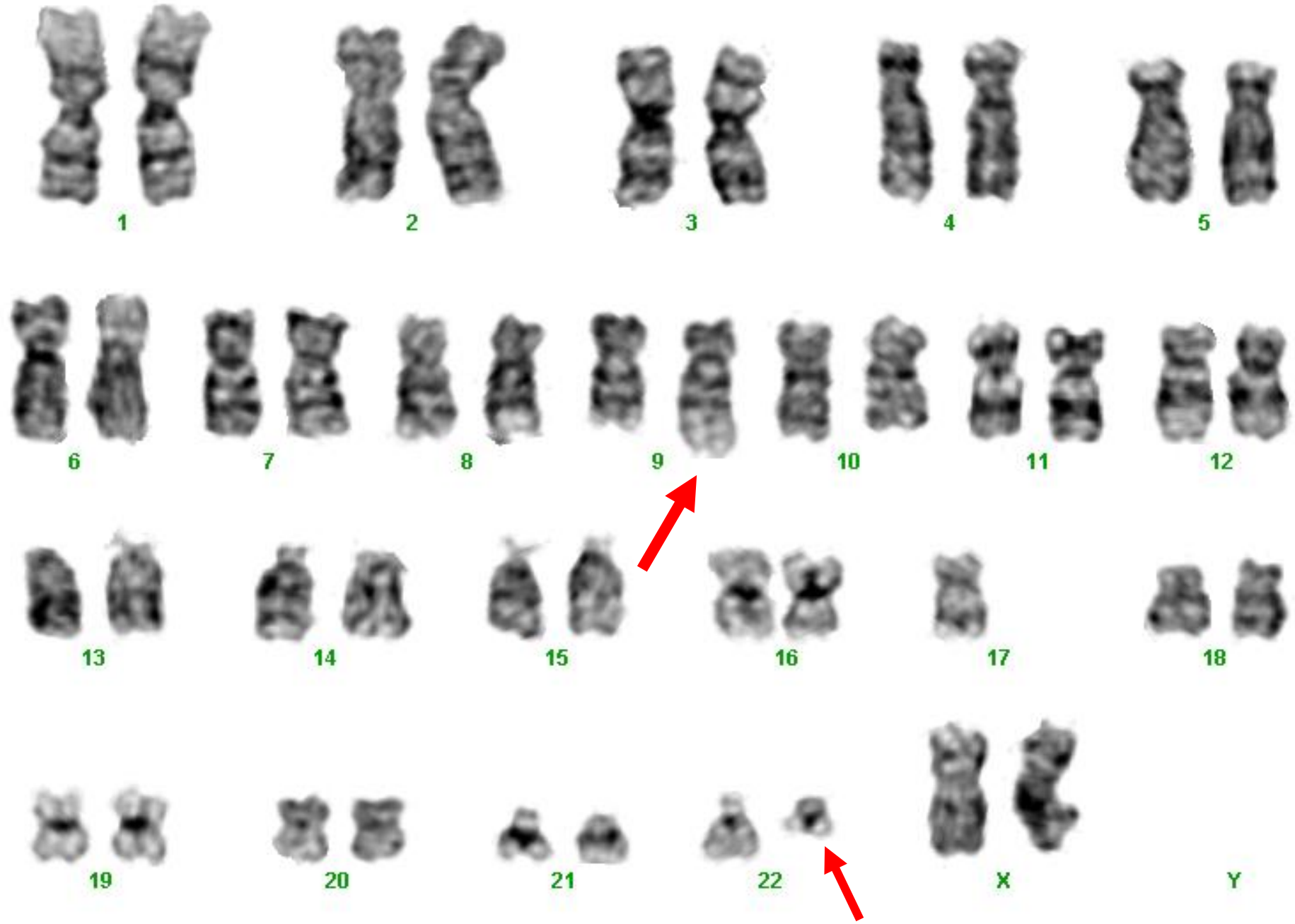
CML

- CML is genetically distinct from the other members of this oversimplified category = **BCR-ABL**

- Represents the first example of a disease for which a specific drug was designed and developed once the genetic basis of the disease was understood

CML –distinguishing features

- What would make a diagnosis of CML more likely in a patient with an elevated WCC?
  - No other infective / inflammatory cause
  - Splenomegaly on clinical examination
  - Elevated WCC is persistent, progressive and “excessive”
    - (<- ? definition : 20 - 30)
  - **Basophilia** (and to a lesser extent, eosinophilia <- broader DDx)
  - Presence of “slightly immature” white cells such as myelocytes, metamyelocytes)
    … but not blasts = more likely to represent acute leukemia (/ myelofibrosis)
  - Other blood count abnormalities
    - Elevated platelet count – not uncommon, but not specific
    - ? Low platelet count (+/- anaemia) – may represent either a more advanced stages of disease (chronic phase -> accelerated phase -> blast crisis)


1
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21
22
X
Y

CML – genetics

BCR-ABL translocation

↓

BCR-ABL fusion protein

↓

“constitutive tyrosine kinase”

↓

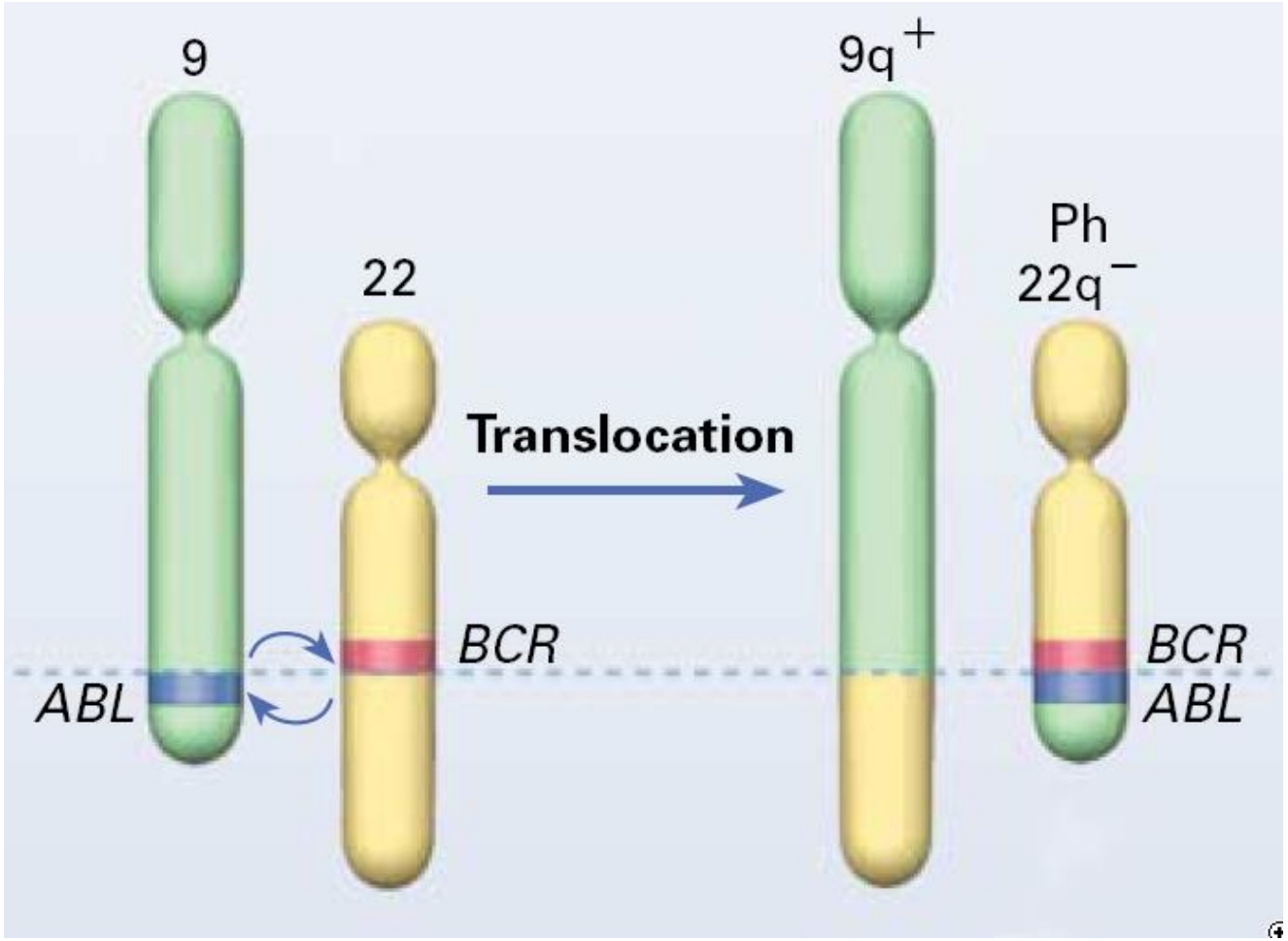
inappropriate activation of multiple downstream signal transduction pathways

↓

Proliferation and restance to apoptosis

↓

CML



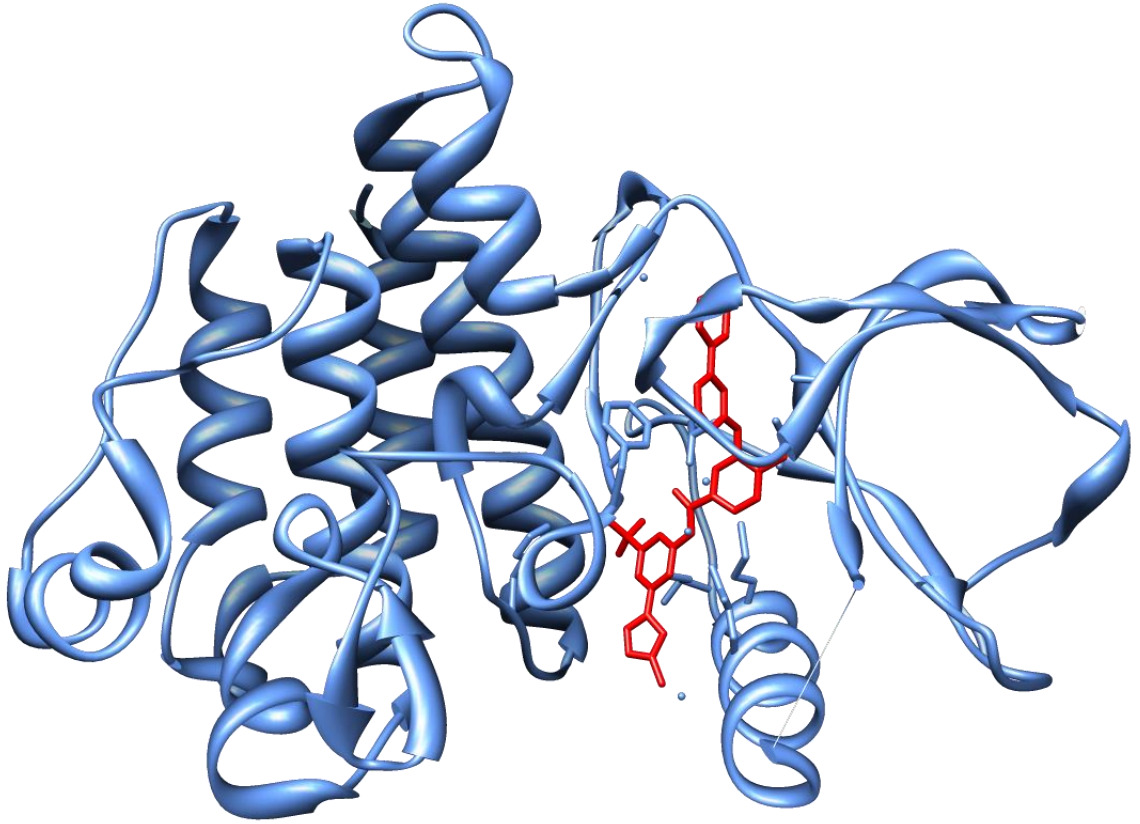
NEJM 2003

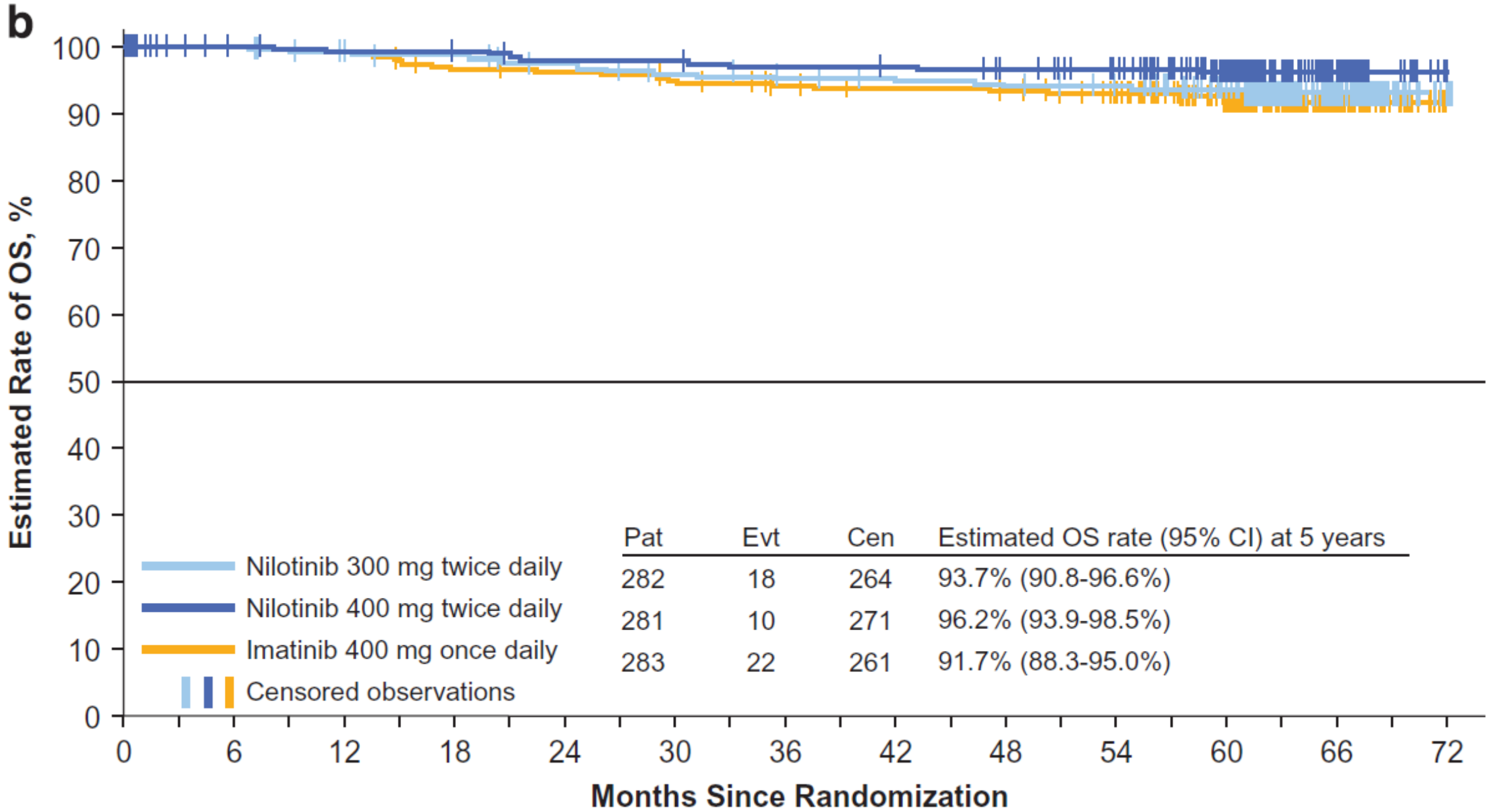
“Modern cancer therapy”

CML therapy
– pioneering targeted small molecule therapy

- Determine structure and function of fusion protein (BCR-ABL)
- Drug designed to interfere with function
  - specifically block the ATP binding site

- Tyrosine Kinase Inhibitors (“TKI”)
  - imatinib
  - nilotinib, dasatinib
  - ponatinib, bosutinib
  - asciminib




b
Estimated Rate of OS, %
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
48
54
60
66
72
Months Since Randomization
Nilotinib 300 mg twice daily
Nilotinib 400 mg twice daily
Imatinib 400 mg once daily
Censored observations
Pat
Evt
Cen
Estimated OS rate (95% CI) at 5 years
282
18
264
93.7% (90.8-96.6%)
281
10
271
96.2% (93.9-98.5%)
283
22
261
91.7% (88.3-95.0%)


12 BOTTLES X 65UM

Thank you for seeing Ms [redacted], age 38 yrs for further investigation and management of her persistent neutropaenia.
Normally quite well with no significant medical history, [redacted] was originally seen in our clinic for a different problem, but was found to be quite markedly and persistently neutropaenic. She is asymptomatic of this and has remained well with no signs of fever or infection.
She did suffer from a viral URTI 1 week prior to us performing the blood test.

Attached are further infective screening tests and markers recommended by the SNP haematologist, which are quite unremarkable besides a mild B12 deficiency.

Haematology	22/09/2014 16:30 AEST	02/06/2015 09:48 AEST	16/06/2015 09:08 AEST	19/06/2015 11:04 AEST	Reference
Haemoglobin	134	125	119	121	(115 - 165)
Haematocrit	0.41	0.36	0.36	0.35	(0.35 - 0.47)
RCC	4.5	3.9	3.7 L	3.7 L	(3.9 - 5.6)
MCV	91	93	96	95	(80 - 100)
WCC	7.3	1.2 L	1.0 L	1.0 L	(3.5 - 12.0)
Neutrophils	3.98	0.36 L	0.40 L	0.31 L	(1.5 - 8.0)
Lymphocytes	2.53	0.74 L	0.57 L	0.64 L	(1.0 - 4.0)
Monocytes	0.59	0.04	0.04	0.04	(0 - 0.9)
Eosinophils	0.16	0.04	0.03	0.03	(0 - 0.6)
Basophils	0.02	0.00	0.00	0.00	(0 - 0.15)
Platelets	281	149 L	155	150	(150 - 400)

NEUTROPENIA

- **ISOLATED AND MILD** neutropenia is very common, and rarely serious
- Definitions of severity
  - mild = 1.0 – 1.5x10^9/L
  - moderate = 0.5 – 1.0x10^9/L
  - severe = <0.5x10^9/L
- NOTE
  - reference range for “normal” is different (1.5 vs 2.0)
  - risk of infection not significantly increased until neutr < 0.5 (not 1.0)
    - “very serious” = <0.2x10^9/L

NEUTROPENIA - causes

- “primary marrow problem”
  - clonal lymphoproliferative disorders – eg T-LGL
  - myelodysplastic syndrome
  - (acute leukemia)
- “secondary marrow problem”
  - nutritional deficiency
  - excessive alcohol
  - medication esp antibiotic, methotrexate
  - viral infection
- (auto) immune
- “constitutional” – cyclic neutropenia, benign ethnic neutropenia, familial neutropenia

NEUTROPENIA

- WHEN TO WORRY
  - patient is unwell (infection / fever) … **just send to hospital**
  - FILM REVIEW :
    - presence of other cytopenias
    - immature cells (esp blasts) ** the lab will call you **
    - “leucoerythroblastic” [?? do I need to explain this]
  - Neutrophils < 0.5 ? call your friendly neighbourhood haematologist for advice

- WHEN NOT TO WORRY
  - isolated neutrophil count >0.5-1.0x109/L
    - if 0.5-1.0 and well : warn patient about fever / infection, repeat in a week
    - if > 1.0 : repeat in 2-6 weeks

BACK TO THE

Haematology	16:30 AEST	02/06/2015 09:48 AEST	16/06/2015 09:08 AEST	19/06/2015 11:04 AEST	Reference
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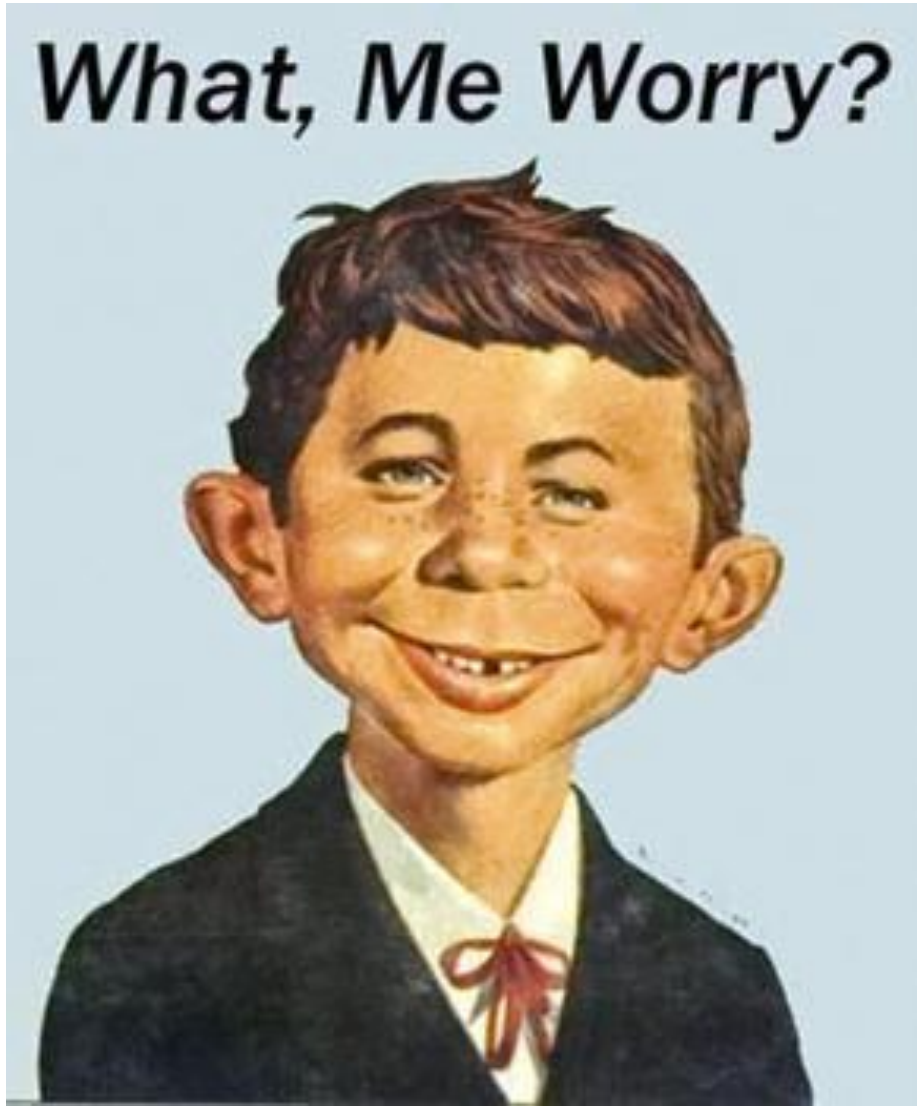


WHY NOT WORRY …

- patient is well
- not anaemic, thrombocytopenic
- film appears normal
- neutropenia AND lymphopenia
- “viral infection” could explain everything!

- flow cytometry (by GP) was NORMAL

WHY WORRY?

- The neutropenia is “severe” [$0.5x10^9/L$]
- IT HAS PERSISTED
- She is young
- REPEAT THE TEST

2 June -> 7 July

Test Name	Result	Units	Reference Interval
Haemoglobin	119	g/L	115 - 165
● Haematocrit	**0.34 L**		0.35 - 0.47
● Red cell count	**3.5 L**	10^12/L	3.9 - 5.6
MCV	96	fL	80 - 100
● **White cell count**	**0.8 L**	10^9/L	3.5 - 12.0
● Neutrophils	**0.29 L**	10^9/L	1.5 - 8.0
● Lymphocytes	**0.43 L**	10^9/L	1.0 - 4.0
Monocytes	0.03	10^9/L	0 - 0.9
Eosinophils	0.02	10^9/L	0 - 0.6
Basophils	0.00	10^9/L	0 - 0.15
● **Platelets**	**145 L**	10^9/L	150 - 400

What do you want to do?

- Continue FBC monitoring
- Other blood test
- Bone marrow biopsy
- Scan something
- Ignore - things don’t look too bad

Bone Marrow Aspirate & Trephine Report

INDICATION FOR PROCEDURE: Neutropenia ? cause. Associated mild anaemia and thrombocytopenia.

DIAGNOSIS: Acute Promyelocytic Leukaemia (APML).

FBC: Hb 112g/L, WBC 0.6x10E9/L, Plt 138x10E9/L, MCV 95fL, Neutrophils 0.2x10E9/L, Lymphocytes 0.3x10E9/L, Monocytes 0.02x10E9/L, Eosinophils 0.02x10E9/L, Basophils 0.0x10E9/L.

Blood Film: Normal neutrophil morphology; no blasts.

PROCEDURE: Right posterior iliac crest aspirate and trephine biopsy.

LESSONS

- Excellent referral
  - clinical information supplied
  - repeated tests at early interval
  - additional testing – flow, viral, autoimmune screen

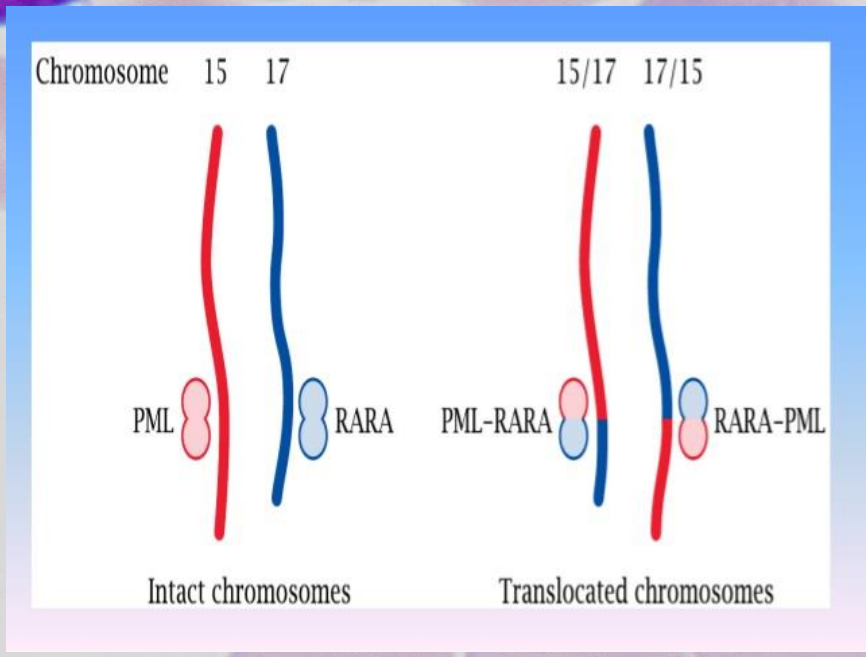
- Identification of “severe enough” abnormality = Cat 1

- repeated testing until the abnormality resolves OR declares

- Our system works!

Acute Promyelocytic Leukemia

- VERY specific subtype of acute myeloid leukemia
- (typically) associated with severe coagulopathy at presentation (bleeding, DIC)
  - historically often fatal, poor prognosis
- SPECIFIC genetic alteration involving retinoic acid gene (chromosome 17)
  - cell is unable to differentiate past promyelocyte stage
- We have “targeted therapy”



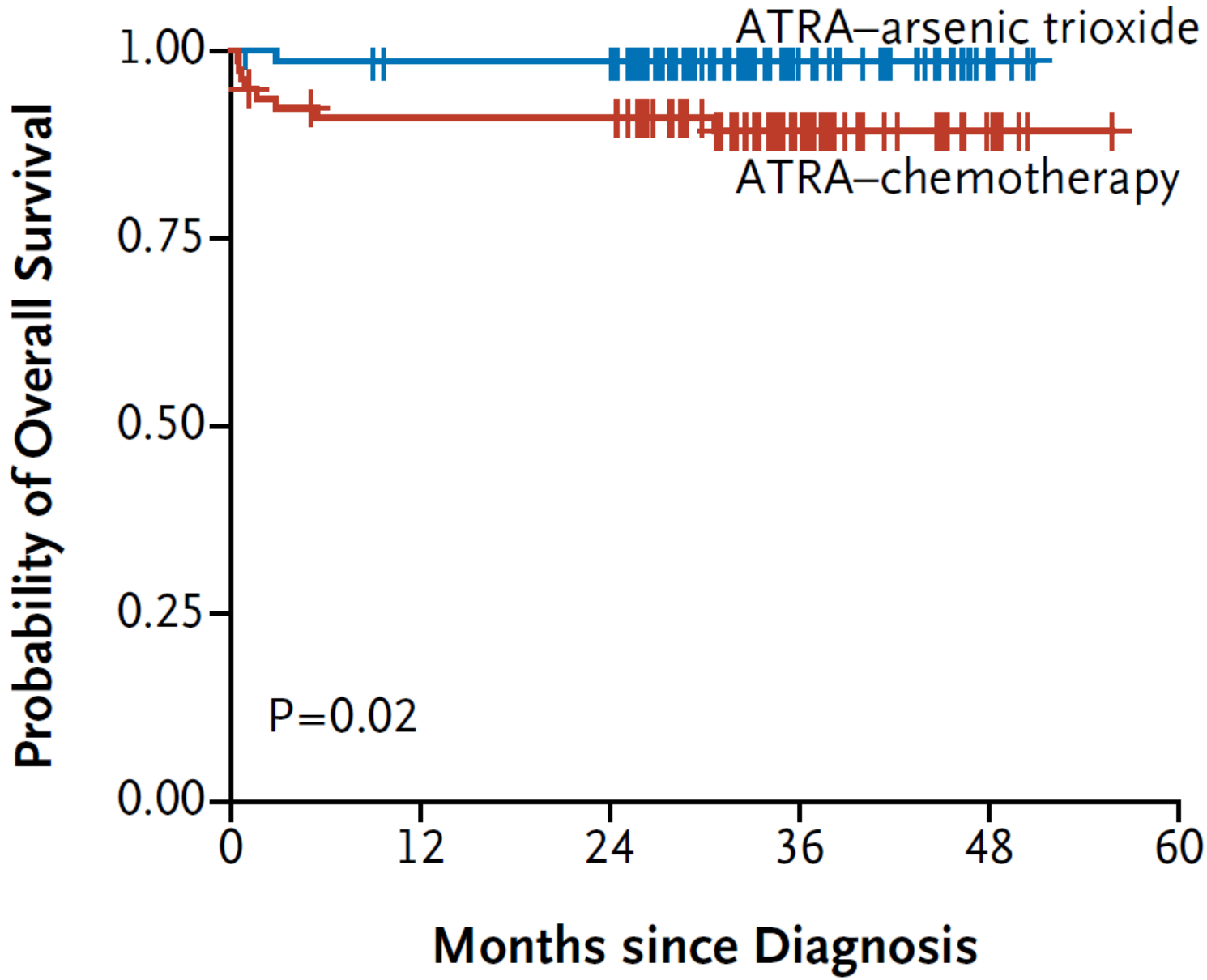
https://www.slideshare.net/Manikandan3131996/role-of-a-chimeric-transcription-factor-in-acute-promyelocytic-leukemi

Acute promyelocytic leukemia

ATRA
(retinoic acid)

+

ARSENIC


ATRA–arsenic trioxide
ATRA–chemotherapy
Probability of Overall Survival
1.00
0.75
0.50
0.25
0.00
P=0.02
0
12
24
36
48
60
Months since Diagnosis


The Beer Store

RED CELLS

ANAEMIA

- Mild (> 100g/L), chronic, isolated anaemia is rarely anything “bad”
  - common referral : elderly patient, “fatigued”, multiple comorbidities, Hb decr 120 -> 110g/L … this will likely get a Cat 3

- “Classic” approach is to use MCV
  - Microcytic : iron deficiency, thalassemia, sideroblastic anaemia, lead poisoning
  - Macrocytic : alcohol / liver disease, B12 + folate deficiency, hypothyroid, medication, myelodysplastic syndrome
  - Normocytic : “everything else” … “anaemia of chronic disease”

ANAEMIA

- Is it acute or chronic?
- “Red flag” symptoms / signs : bleeding, jaundice, weight loss, splenomegaly, lymphadenopathy
- Minimum Ix :
  - BLOOD FILM including RETICULOCYTE COUNT (<- is marrow responding appropriately?)
    - pancytopenia, early myeloid cells, dysplastic changes, “leucoerythroblastic”
  - ELFT/CHEM20 including LDH
  - IRON STUDIES
  - B12 + folate

ANAEMIA
- further investigation

- “Haemolytic screen” = retic, bilirubin / LDH, DAT, haptoglobin
- serum EPP +/- free light chain assay (esp if bone pain, hypercalcaemia)
- thalassemia screen (if microcytic and iron studies appear normal)

ERYTHROCYTOSIS (elevated Hb / HcT)

- MOST COMMONLY SECONDARY!
  - smoking, chronic lung disease
  - obesity
  - (testosterone therapy)
- What will get our attention (?? myeloproliferative)
  - no “obvious” explanation
  - “Severe” : Hb > 200g/L, HcT > 0.6 (male) / 0.56 (female)
  - history of thrombosis / ischaemia
  - splenomegaly
  - additional presence of thrombocytosis +/- leukocytosis
    - but note this is also common in smokers
  - positive molecular study (JAK2)
  - suppressed erythropoietin

JAK2

- Gene on chromosome 9
- “Just another (tyrosine) kinase” [NO]
- Janus kinase – structure of JAK dimers reminiscent of two faced Roman god

- Normal function = “proliferation signal”

- Mutations identified → constitutive / “inappropriate” proliferation, survival, differentiation
  - JAK2 V617F
  - JAK2 “exon 12” mutations

JAK2 V617F
- when to do the test?

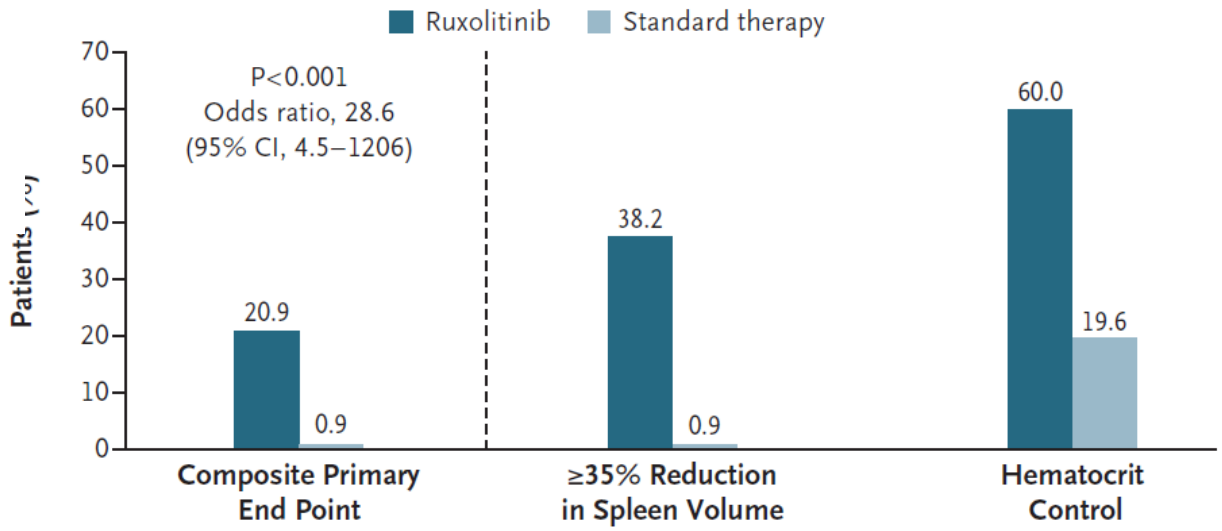
- Persistent, severe, unexplained erythrocytosis with no other explanation
- other blood film abnormalities eg leukoerthroblastic
  - lab will usually guide you here

- We will be reassured if negative → less urgency to consider venesect
  - role of venesection for secondary erythrocytosis poorly defined, even if severe

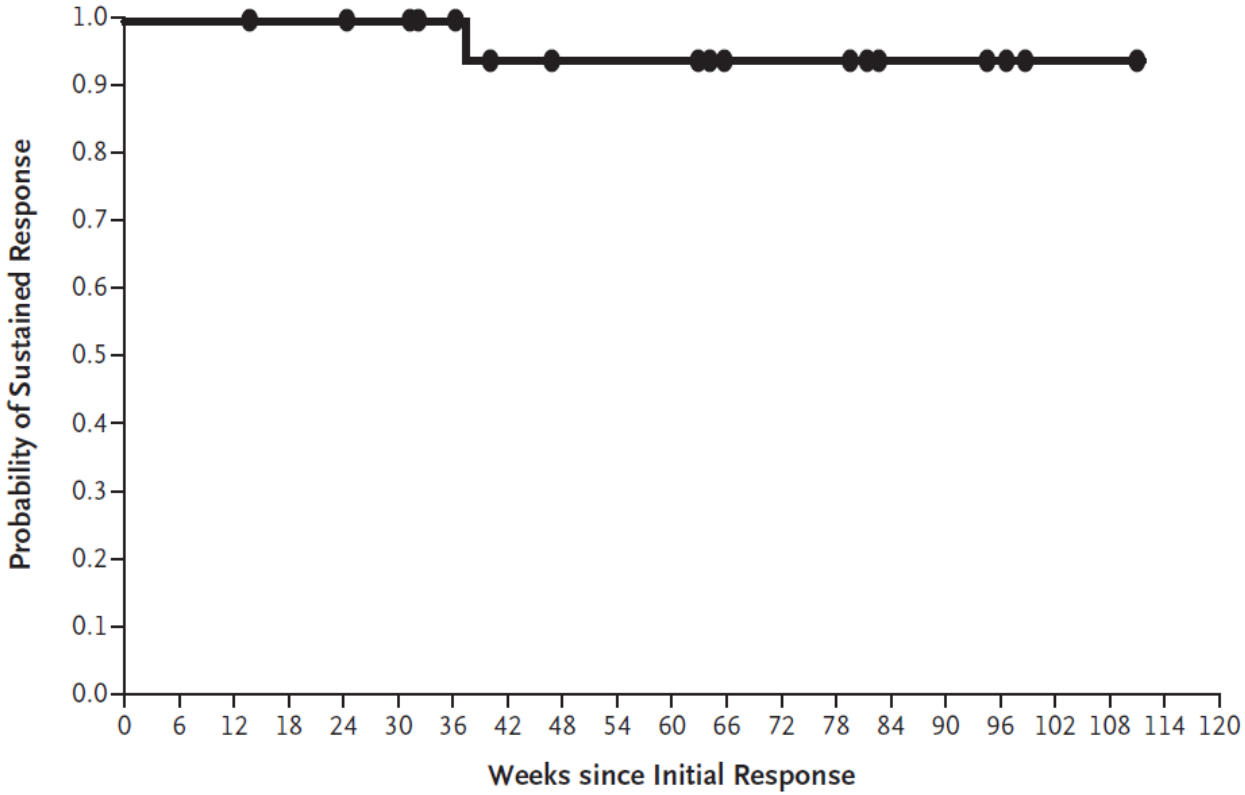
- Medicare rebated

Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

N ENGL J MED 372;5 NEJM.ORG JANUARY 29, 2015



- "JAK inhibitor"
- Symptomatic improvement especially with respect to splenomegaly
- Reduces haemactocrit
- ? Survival benefit



PLATELETS

THROMBOCYTOSIS
? reactive or myeloproliferative

Favour "reactive"

- "mild" (< 600g/L)
- comorbidities esp inflammatory
- iron deficiency
- splenectomy

Favour "myeloproliferative"

- platelets >600g/L [> 1000g/L]
- thrombosis / ischaemia (amaurosis), pruritis
- splenomegaly
- other blood film changes
  - (erythrocytosis, leukocytosis)
  - early myeloid cells
  - "leucoerythroblastic" (MF)
  - (dysplasia ? CMML)

THROMBOCYTOSIS - approach

- (Clinical history + examination esp spleen)
- FBC + film
- ESR / CRP
- iron studies
- ? JAK2 V617F +/- BCR-ABL
  - other mutations : CALR, MPL

THROMBOCYTOPENIA - “Classic approach”

- Consumption / sequestration
  - IMMUNE
  - splenomegaly / hypersplenism (eg chronic liver disease -> portal hypertension)
  - “microangiopathic” - TTP, HUS
- Reduced production (= marrow problem)
  - primary marrow neoplasm / malignancy
    - acute leukemia, MDS, myelofibrosis
    - marrow involvement with lymphoma, myeloma
  - marrow suppression – drugs, infection
  - aplastic anaemia
  - marrow infiltration by non haematopoietic cancer
  - congenital / constitutional

THROMBOCYTOPENIA - Severity

- Our threshold for severe will always be lower than yours

- (Generally) don't expect major spontaneous bleeding until platelets <$10x10^9$/L

- Platelet count > $50x10^9$/L "as good as normal" (mostly)
  - we're happy to deliver babies down to this level (+ below if we have to)
  - safe to do most surgical procedures (not eye, spinal, or neurosurgery)

- Common referral : platelet count range 110-130 over years, asymptomatic, blood count and film otherwise completely normal …

THROMBOCYTOPENIA
- What will get me interested?

- "Severe" : < 50 x 10^9/L (30 – 100 x 10^9/L)
- Bleeding!
- Other associated cytopenias + BLOOD FILM (trust your laboratory!)
  - "More lines" = "More likely the marrow"
  - Anaemia + Thrombocytopenia (without leukopenia, or with leukocytosis)
    - think about HUS, TTP = "microangiopathic" ** blood film **
      - diarrhoea, AKI, neurologic symptoms
    - "Evans syndrome" = autoimmune thrombocytosis AND haemolytic anaemia (rare)

https://www.ouhsc.edu/platelets/TTP/what%20is%20ttp.html