GP CME

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Consultant Haematologist

Date:

Created by:

Scenario

- 52 year old European male
  - Fit and well
  - Brother recently diagnosed with diabetes
- PMHx
  - Nil
- Social Hx
  - Ex-smoker stopped 5 years ago (20 pack-year)
- Medication
  - Nil regular
  - NKDA

Continue

- Examination
  - Essentially normal
  - Mildly Elevated BMI 28
- Routine bloods
  - CBC, LFT, U&Es, HbA1c, cholesterol…etc

		Ref. Range
Haemoglobin	164	(130 – 175)
RBC	5.14	(4.30 – 6.00)
HCT	0.48	(0.30 – 0.44)
MCV	93	(80 – 99)
MCH	31.9	(27.0 – 33.0)
Platelets	188	(150 – 400)
WBC	13.1	(4.0 – 11.0)
Neutrophils	6.1	(1.90 – 7.5)
Lymphocytes	5.69	(1.00 – 4.00)
Monocytes	0.93	(0.20 – 1.00)
Eosinophils	0.32	(<0.51)
Basophils	0.05	(0.00 – 0.20)

Blood Film: Lymphocytosis with reactive lymphocyte morphology is suggestive of infection (especially viral). Suggest repeat in 4 – 6 weeks.

CBC

	21/11/2016	13/02/2017	
Haemoglobin	164	165	(130 – 175)
RBC	5.14	5.15	(4.30 – 6.00)
HCT	0.48	0.49	(0.30 – 0.44)
MCV	93	95	(80 – 99)
MCH	31.9	32.0	(27.0 – 33.0)
Platelets	188	165	(150 – 400)
WBC	13.1	12.1	(4.0 – 11.0)
Neutrophils	6.1	5.17	(1.90 – 7.5)
Lymphocytes	5.69	5.79	(1.00 – 4.00)
Monocytes	0.93	0.85	(0.20 – 1.00)
Eosinophils	0.32	0.21	(<0.51)
Basophils	0.05	0.06	(0.00 – 0.20)

- Reactive lymphocytosis eg due to infection, inflammation, medication or autoimmune disorder should be considered first. If the lymphocytosis persists without an obvious clinical explanation then **an indolent lymphoproliferative disorder including Monoclonal B cell Lymphocytosis** can be considered. Suggest continue monitoring the lymphocyte count. **If the lymphocyte count is above 7 E+9/L, or if the patient has unexplained lymphadenopathy, hepatosplenomegaly or systemic symptoms of unexplained fever, night sweats or weight loss, then a cell marker study on the peripheral blood lymphocytes will be a useful initial test.**

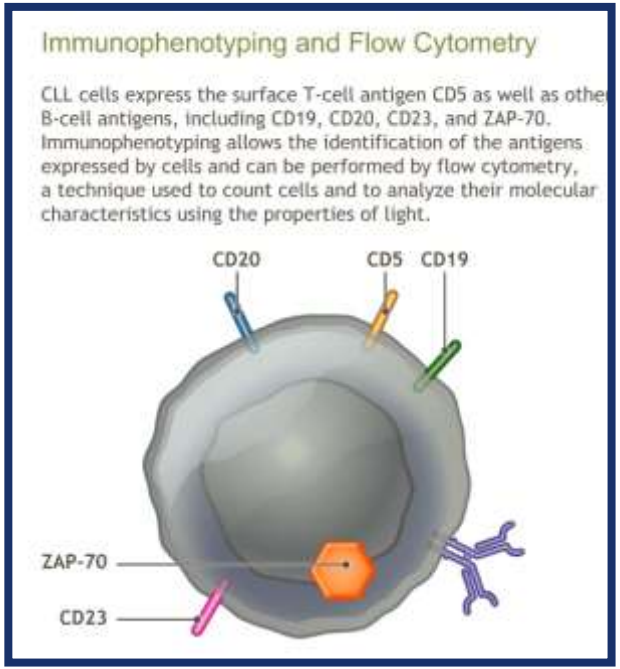
Lymphocytosis

- Reactive
  - Infection
  - Medication
  - Autoimmune
  - Smoker (female
- Clonal
  - Lymphoproliferative disorder
    - Lymphoma
    - Leukaemia
      - **Chronic lymphocytic leukaemia (CLL)**

CLL

- Epidemiology
  - Most common Leukaemia in Adult
  - Incidence 3 to 4 per 100,000 per year
  - Median age of onset ~67
  - Male > Female
  - 10% will have family history

- Diagnosis
  - 70% incidental finding on FBC
  - Requires ≥ $5x10^9$ circulating clonal B-cells
    - 3 month
    - Characteristic immunophenotype
      - CD5+, CD 23+, CD200+, weak CD20, weak surface immunoglobulin and CD79b- and FMC-.



“Types” of CLL

- Monoclonal B-cell lymphocytosis (MBL)
  - “Pre” CLL
  - 1%/year chance of transform to symptomatic CLL
- Small Lymphocytic Lymphoma (SLL)
  - Predominantly nodal involvement
- CLL
  - Predominantly bone marrow involvement

	MBL	SLL	CLL
Clonal B Lymphocytes > 5	N	N	Y
Cytopenia	N	N	Y
B symptoms	N	Y/N	Y/N
Lymphadenopathy /Splenomegaly	N	Y	Y/N

Staging (obsolete)

- Binet

Stage	Features	Median Survival (mo)
A	< 3 lymphoid areas	>120
B	≥ 3 lymphoid area	>84
C	Hb <100g/L or platelet <100	>24

- *FISH has trumped the clinical staging*
  - **17p deletion (TP53)**

- Rai

Stage	Risk Group	Features	Median Survival (mo)	Median Survival Mayo (mo)
0	Low	Lymphocytosis	>120	143
I	Intermediate	Lymphadenopathy	95	125
II	Intermediate	Hepatosplenomegaly	72	100
III/IV	High	Hb <110g/L or Plt <100x10^9	30	57

Management

- Key points
  - Indolent disease
  - Not curable but treatable
    - Therefore, most of these patient will be managed in primary care
    - Current gold standard therapy are R-FC (strong chemotherapy)
      - Use this as an opportunity for lifestyle modification
  - Monitoring
    - CBC
      - 6 monthly for a year and consider yearly if stable
    - Clinically
      - Lymphocyte count don't necessary reflect severity of disease
  - Special consideration
    - Increase infection
      - Acquire hypogammoglobulinaemia
      - Annual flu vaccination
    - Increase risk of malignancy

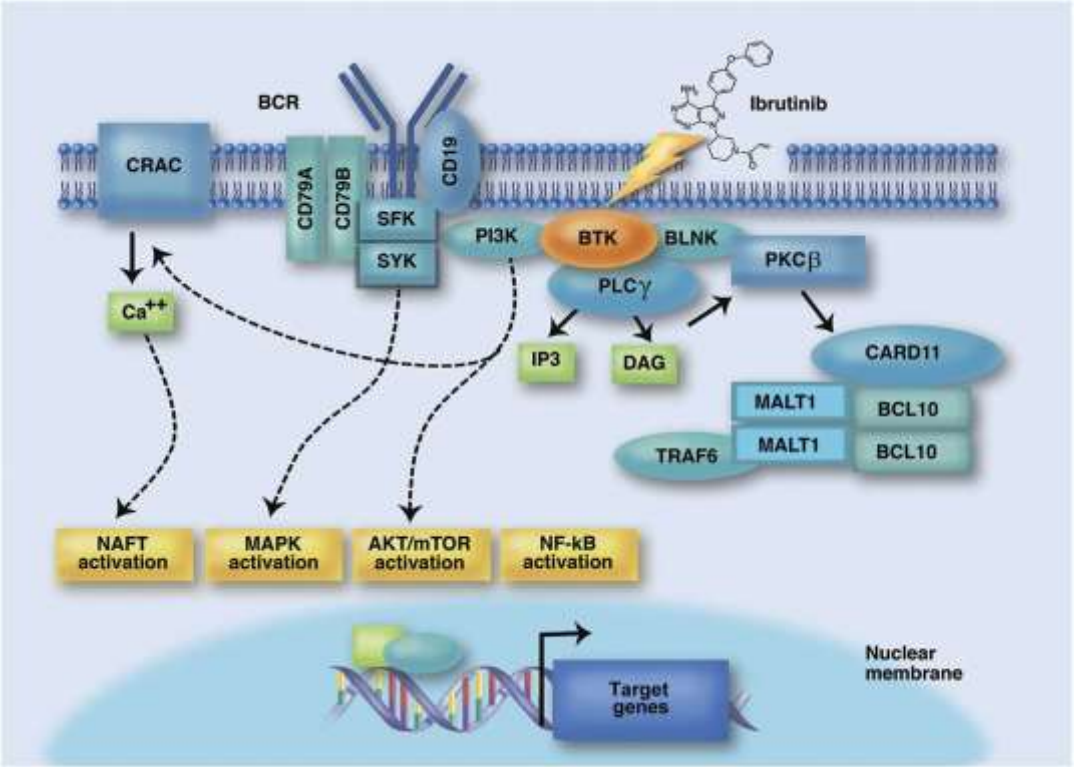
Indication to Treat

1. Cytopenia attributed to CLL
   - Binet stage C
2. Bulky lymphadenopathy
   - Splenomegaly (> 6cm below costal margin)
3. B symptoms
   - Fever, night sweats > 1 month
   - Weight loss > 10%
   - Fatigue (affecting daily activities)
4. Autoimmune disease
   - Autoimmune haemolytic anaemia or ITP
5. Progressive lymphocytosis (when baseline lymphocyte count is > $30x10^9$)
   - Lymphocyte doubling time < 6 month
   - Consider treatment once lymphocytes > $60x10^9$
     - This indication do not apply when patient has infection!

When to Refer?

- Indication to treat
- Cytopenia
  - If related to CLL
- Age <55
  - Debatable
    - I personally would see to educate these patients
    - Highly likely will need treatment in their lifetime and possibly die from CLL
- Frequent infections
  - May benefit from IVIG replacement (must be severe)

Future Direction

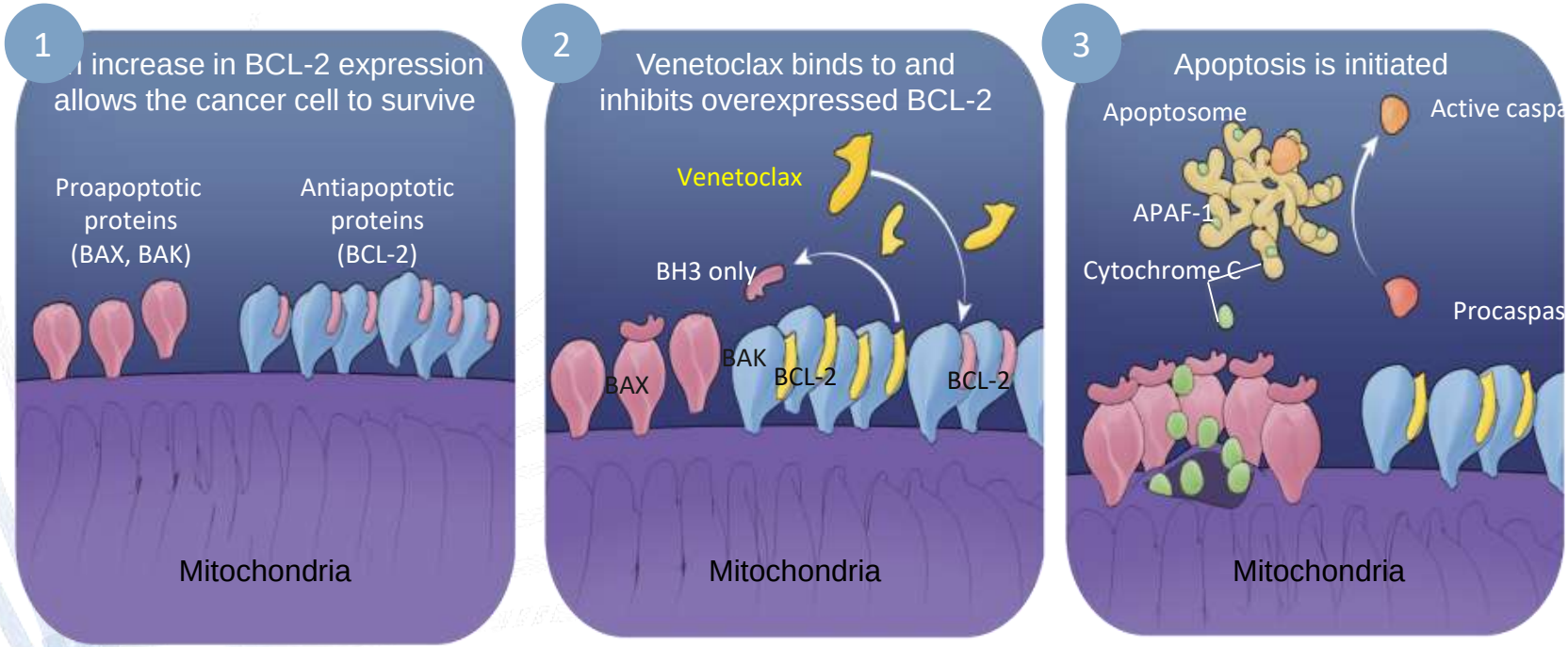


Key Points for Ibrutinib

- Excellent drug for CLL
  - Overcomes the 17p deletion
  - Not funded in NZ but FDA approved for first line therapy
    - Lifelong oral therapy

- Practice points
  - The lymphocytes actually increases!!
  - Increase risk of atrial fibrillation/arrhythmia
    - 5-8% of patient develop AF in trial
  - Increase risk of bleeding
    - Should not be on concurrent warfarin (can be on DOAC)
    - Effect like aspirin
  - Uncertain about long term effects on immune system

Venetoclax: Mechanism of Action



Kumar S, et al. ASCO 2015. Abstract 8576. Reproduced with permission.

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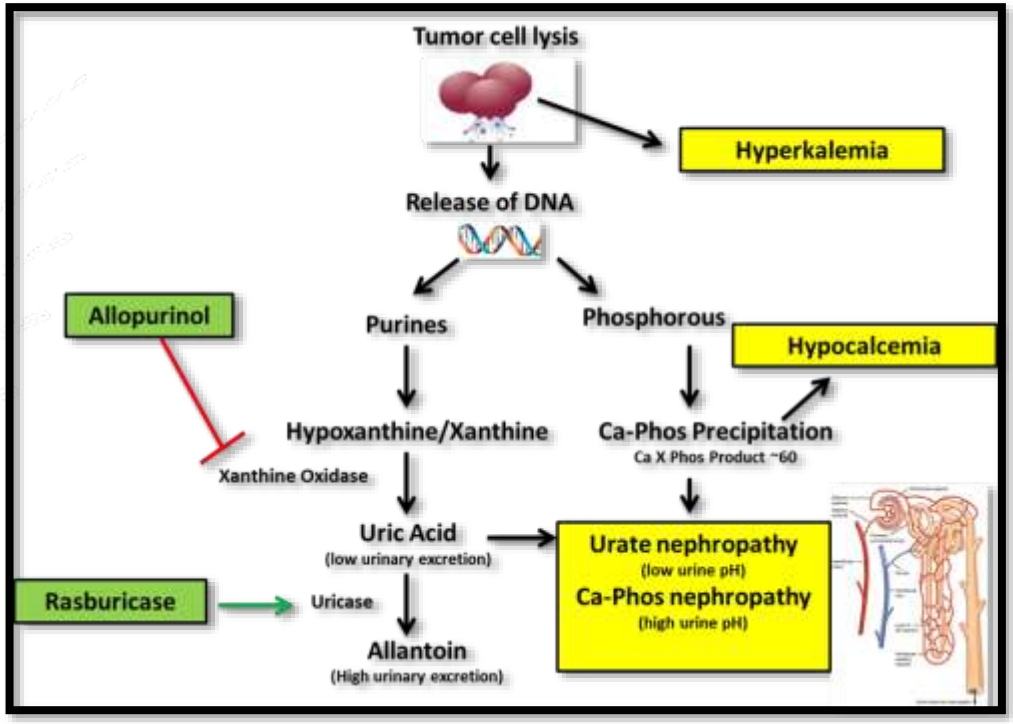
Key Points for Venetoclax

- Currently been tested in all sorts of malignancy
  - Risk of tumourlysis
  - Severe neutropenia
  - Uncertain about long term effects



Interaction

Table 1

CYP3A4 Inhibitors	
Amiodarone	Indinavir
Amprenavir	Itraconazole
Aprepitant	Nelfinavir
Atazanavir	Posaconazole
Clarithromycin	Quinupristin-dalfopristin
Conivaptan	Ritonavir
Cyclosporine	Saquinavir
Darunavir	Telithromycin
Delavirdine	Verapamil
Diltiazem	Voriconazole
Erythromycin	

Table 2

CYP3A4 Inducers	
Bosentan	Phenobarbital
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Efavirenz	Rifabutin
Fosphenytoin	Rifampin
Nafcillin	Rifapentine
Nevirapine	St. John's wort
Oxcarbazepine	

- Both are metabolised via the CYP3A4
  - Be careful of drug interaction
  - Best to consult haematologist

Summary

- Lymphocytosis
  - Reactive vs malignant (clonal)
  - Perform a flow cytometry if
    - Red flags
      - Rash, constitutional symptoms, lymphadenopathy or hepatosplenomegaly
    - Persistent lymphocytosis > $7x10^9/L$
- CLL
  - Think about the indication for referral
  - Always good to use the opportunity for lifestyle modification