Risk of Malignancy & Infertility with Cyclophosphamide: policy implications

Clifford Lo, PharmD, MHA, BCPS
Pharmacy Lead, Special Projects and Initiatives
BCPRA

Sean Barbour, MD, FRCPC
Assistant Professor
University of BC, Division of Nephrology

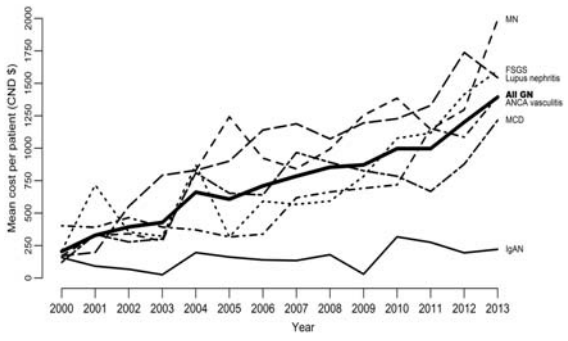
Costs of IS treatment of GN

- In kidney transplantation, IS medication costs have increased dramatically 1990's -> 2000's
  - Newer biologic induction agents
  - CsA -> Tacrolimus; Azathioprine -> MMF
- Population-level IS medication costs to treat GN have not been quantified
- Hypothesize a similar effect in the IS treatment costs of GN over time:
  - Cohort identification: incident biopsy-proven GN from SPH pathology database from 2000-2012
  - IS medication costs: linkage to PharmaNet from 2000-2013

Objectives

1. Quantify the cost of immunosuppression (IS) treatment of GN over time
2. Review the purpose of the BC Provincial Renal Agency GN Formulary, and its coverage
3. Discuss the increasing fiscal pressure of rituximab (RTX) on GN treatment
4. Review the risk of malignancy and infertility with cyclophosphamide and its impact on funding policy

IS medication costs per treated GN patient



No conflicts of interest.

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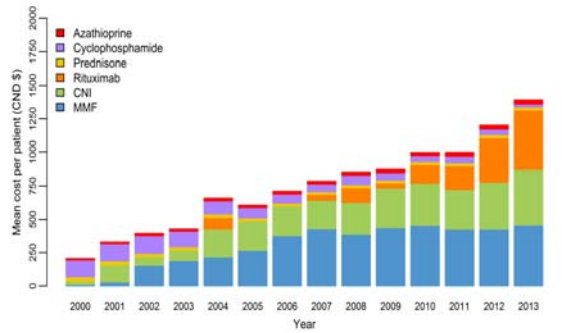
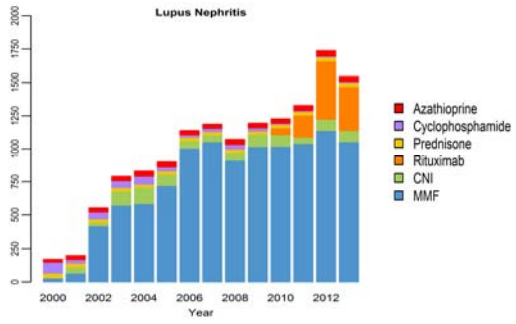
IS medication costs per treated GN patient



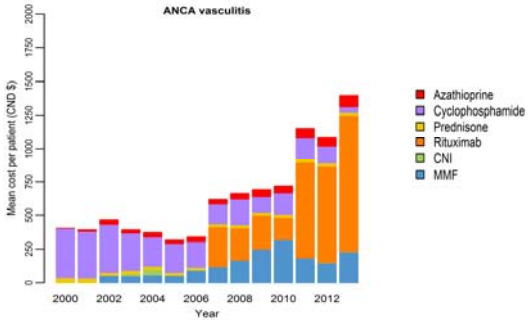
Example: lupus nephritis



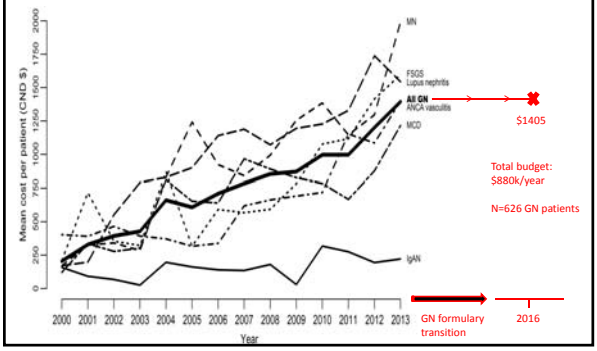
BCPRA GN formulary

- Opportunity:
  - Control increasing GN treatment costs
  - Improve patient access to IS medications
- GN formulary started April 15th 2014:
  - Includes prednisone, azathioprine, MMF, Myfortic, CsA, tacrolimus, oral CYC, RTX
  - Patient access without deductibles or co-pays
  - Easier, more streamlined renal-focused approval processes
  - Improved access to RTX (especially ANCA vasculitis)
  - Cost containment:
    - Provincial contracts
    - Generic MMF and tacrolimus

Example: ANCA vasculitis



IS medication costs per treated GN patient



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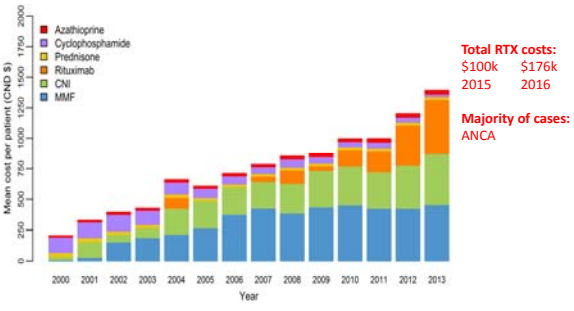
RTX: an area for fiscal concern



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Questions about CYC toxicity relevant to RTX approval process

1. What dose of cumulative CYC is associated with reduced fertility?
2. What dose of cumulative CYC is associated with increased cancer risk?

RTX approval for ANCA vasculitis

- Induction:
  - Failure of cyclophosphamide
  - Contraindication of cyclophosphamide
- Maintenance:
  - Contraindication to azathioprine
  - Relapse while on appropriate dose of azathioprine

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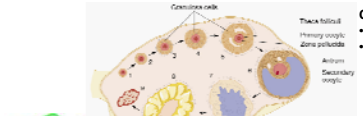
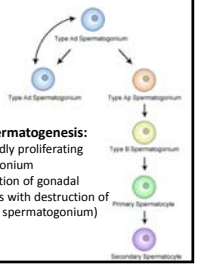
RTX approved cases for ANCA vasculitis

	N	Comments
Total	19	
Induction	17	
Maintenance	2	
Intolerance to CYC	1	Mucositis
Resistant to CYC	3	
Fertility concern male	1	Age 17, no prior CYC use
Fertility concern female	3	Age 22, 30, 44, no prior CYC use
Prior cumulative CYC too high	7	Doses: 10.5g, 11.3g, 12g, 27g Not provided: 3
Prior malignancy history	1	No prior CYC use
Intolerant azathioprine	1	
Flared on azathioprine	1	

Cyclophosphamide Pharmacology



CYC's effect on the menstrual cycle:
- Toxic to growing ovarian follicles
- Accelerates depletion of ovarian follicles leading to amenorrhea/premature menopause



CYC's effect on spermatogenesis:
- Most toxic to rapidly proliferating type B spermatogonium
- Severity and duration of gonadal damage correlates with destruction of stem cells (type A spermatogonium)

CYC alkylates guanine:
1. Prevents cell division by inhibiting DNA synthesis/transcription
2. Causes DNA mutation
3. Causes cell apoptosis

Literature Review

Medline 1946 to October 2016

MeSH: cyclophosphamide, ovarian failure, azoospermia, lupus, vasculitis

Identified 57 papers and appraised 23

When interpreting the data, please keep in mind:

- Patients of any age may have baseline deficiencies in semen quality, have subclinical ovarian damage or have diminished ovarian reserve
- Fertility in females will decline in the last 2 decades prior to menopause (average age of menopause = 51)
  - In a healthy 40 yo who is trying, there is a < 5% chance of becoming pregnant per cycle
  - Most women in their mid-40s are unable to have a successful pregnancies [ASRM 2012]
- *Amenorrhea or azoospermia may result from stress to the body, such as during acute illness*
  - 54% of SLE patients (age 18-39) experienced amenorrhea without CYC [Pasoto et al. 2002]

MALIGNANCY 2º CYC

Leukemia:

- IRR 59 (95% CI; 12 to 172) with > 36 g of exposure

Non-melanoma skin cancer:

- IRR 3.9 (95% CI; 1.4 to 8.4) with 1 - 36 g of exposure

Bladder cancer:

- Risk is non-significant when exposure < 20 g
- Risk increases 6.3x after 20 to 49 g
  - 3 more cases per 100 patients treated
- Risk increases 14.5x after 50 g
  - 7 more cases per 100 patients treated

Amenorrhea 2º CYC

There are 2 predominant approaches used in evaluation:

1. **Average cumulative dose at onset of amenorrhea**

	< 20 yo	20 - 30 yo	31 - 40 yo	> 40 yo
Keep cumulative dose under →	20 g	15 g	10 g	5 g

1. **% of patients who experienced amenorrhea when treated with a certain CYC regimen (e.g. 0.5 - 1 g/m² IV monthly)**

1.73 m² or 75 kg individual	< 20 yo	20 to 30 yo	31 to 40 yo	> 40 yo
10 - 20 g	0%	6%	23 – 45%	75 – 83%
15 – 30 g	4%	27 - 29%	54 - 62%	No data

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Azoospermia 2º CYC

The literature reports azoospermia by average cumulative dose in **pre/post pubertal** males rather than by age categories.

- Incidence of azoospermia in **prepubertal males** (75 kg) according to cumulative dose:

	≤ 30 g of CYC	> 30 g of CYC
Azoospermia	0	30%

- Incidence of azoospermia in **sexually mature males** (75 kg) according to cumulative dose:

	≤ 7.5 g	7.5 - 15 g	16 - 20 g	21 - 30 g	> 30 g
Azoospermia	0	20 - 100%	50 – 100%	80 – 100%	100%

Modifications to RTX funding criteria

- Proposed approximate guidelines for cumulative prior CYC exposure:
  - Fertility concern women: 10 g if age < 40, age > 40 fertility not considered
  - Fertility concern men: 10 g any age
  - Malignancy concern: 20 g
- These are not hard cut-offs
  - Each application will continue to be adjudicated on a case-by-case basis

Modifications to RTX funding criteria

- Recognize these are very sensitive and controversial topics
  - Chosen very conservative dose thresholds from the literature
- Goals:
  - Transparent and standardized approach to adjudicating RTX applications especially for sensitive indications
  - Mitigate rising costs from "controversial" indications for RTX

Thank You

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