



Risk of Malignancy & Infertility with Cyclophosphamide: policy implications

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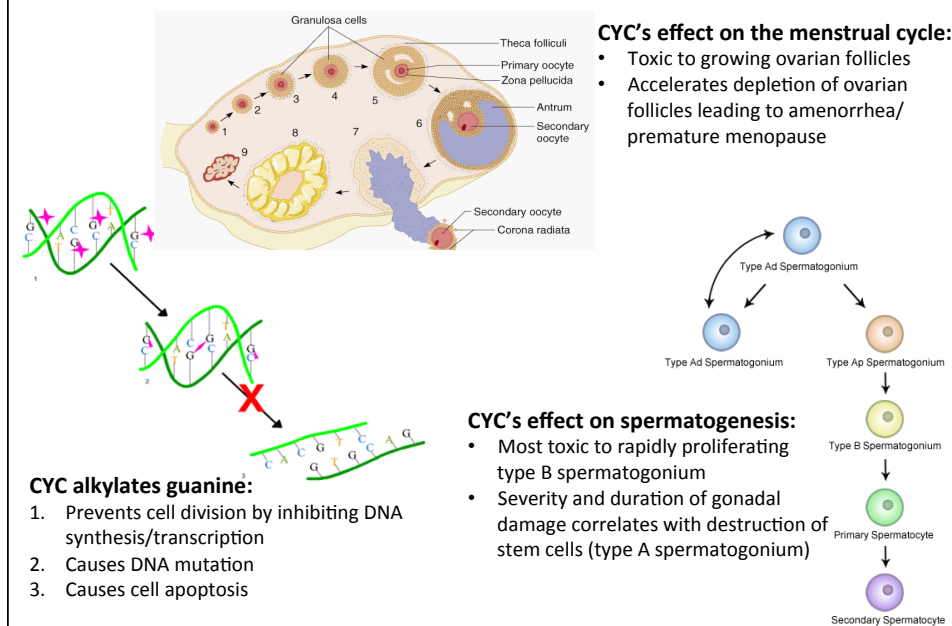
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Questions about CYC toxicity relevant to RTX approval process

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

Cyclophosphamide Pharmacology



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]

Amenorrhea 2° 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

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

1.73 m ² 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

Azoospermia 2° 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%

MALIGNANCY 2° 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

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