Malignancy Risk in Pediatric IBD: What to tell parents and patients?

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Consultant/Advisory Board

Abbvie, Given Imaging, Janssen, Salix, Lilly, Pfizer, Prometheus, Sandoz, Takeda, Theradiag, UCB

Speaker for CME activities

Abbvie, Janssen, Pfizer, Takeda

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Abbvie, Janssen, Salix

Intellectual property

Dartmouth-Hitchcock Medical Center and Cedars-Sinai Medical Center have a patent pending for a “System and Method of Communicating Predicted Medical Outcomes”, filed 3/34/10. Dr. Corey Siegel and Dr. Lori Siegel are inventors and founders of MiTest Health, LLC.
Learning Objectives

- Communicating risk to patients and parents
- Cancer risk related to immunomodulators
- Cancer risk related to biologics
- Cancer risk related to having IBD
What patients and their parents hear and see

Serious Infection
Cancer
Tuberculosis

FDA
Black Box
Warning

Chemotherapy Drug
Toxic
Dispose of as BIO-HAZARD

3E 3332
What (how) do we tell them?

- NNT = 7
- SIR = 3.23
- RR = 1.48
- OR = 14.5
- P < 0.05
- 0.01%

Numbers are hard!

- Numeracy (quantitative literacy)
  - \( \frac{1}{2} \) of patients were unable to convert:
    - 1% to 10 in 1000
  - 80% of patients were unable to convert:
    - 1 in 1000 to 0.1%
  - Patient have difficulty determining which is the higher risk:
    - 1 in 27 *versus* 1 in 37

What types of cancer are we talking about as related to medications?

- Most patients and parents have no idea
- NOT talking about solid tumors
- The conversation needs to be focused on lymphoproliferative disorders and skin cancers
Immunomodulators
Overall lymphoma risk on thiopurines (2015 meta-analysis)

- Overall SIR = 4.92
- Overall SIR for ages 0-19=11

Absolute rate of lymphoma in children exposed to thiopurines:

- Absolute risk = 5.8/100,000
- SIR = 11 (for ages 0-19)
- \(5.8/100,000 \times 11 = 0.0006 \rightarrow 6/10,000\)
Risk of Developing non-Hodgkin’s Lymphoma

Patient receiving Immunomodulator +/- anti-TNF Therapy for 1 year

Risk of lymphoma with immune suppression

Siegel CA, Inflamm Bowel Dis 2010;16:2168.
Two other VERY important points about lymphoma

1. Risk is directly related to years of exposure
   - < 1 year risk not increased

1. Risk goes back to baseline after thiopurine withdrawal
Thiopurines and Lymphoproliferative disorders: Role of EBV

<table>
<thead>
<tr>
<th></th>
<th>Crude risk in patients exposed to thiopurines per 1000 patient-years *</th>
<th>Recommended</th>
<th>To be discussed in the near future</th>
<th>To be investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-transplant-like lymphoma with EBV reactivation</td>
<td>0.60</td>
<td><strong>6/10,000</strong></td>
<td>EBV viral load in case of unusual symptoms, unexplained biological inflammatory syndrome, with or without increase in the blood level of LDH and beta2-microglobulin and HLH</td>
<td>Monitoring EBV viral load or T cells cytotoxic functions</td>
</tr>
<tr>
<td>Early Postmononucleosis lymphoproliferation in EBV-seronegative young (&lt;35 years) male #</td>
<td>2.90</td>
<td><strong>3/1000</strong></td>
<td>Avoiding anti-TNFα and thiopurine treatment beyond two years in young (&lt;35 years) male</td>
<td>- Identify involved genes and mutations</td>
</tr>
<tr>
<td>Hepatosplenic T cell lymphoma in young (&lt;35 years) male treated with thiopurine alone or in association with anti-TNFα</td>
<td>0.06</td>
<td><strong>&lt;1/10,000</strong></td>
<td>Avoiding association of anti-TNFα and thiopurine treatment beyond two years in young (&lt;35 years) male</td>
<td>- Genetic testing before treatment</td>
</tr>
</tbody>
</table>

* Data from the CESAME study; # in the absence of EBV serological test for most patients in the CESAME study, the prevalence of EBV-seronegative young male was estimated to be 20%; $ unexplained headache, fatigue or fever, acquired adenopahies not attributable to intestinal inflammation, increase size of the spleen or the liver.
Risk of HSTCL is related to duration of thiopurine use

Consider this: Even in young males → Induce with our “best” therapy (thiopurine + anti-TNF) and stop thiopurine after 6-12 months when in deep remission
Other hematologic malignancies with immunomodulators

- DEVELOP registry
  - Prospective study of 5766 participants
  - < 18 years of age, Crohn’s disease and UC
  - Specifically interested in any malignancy and hemophagocytic lymphohistiocytosis (HLH)

<table>
<thead>
<tr>
<th></th>
<th>Thiopurine exposed +/- biologics</th>
<th>Thiopurine non-exposed +/- biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients, N</td>
<td>3857</td>
<td>1909</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>4.8 pt-years</td>
<td>3.0 pt-years</td>
</tr>
<tr>
<td>Malignancy (all)</td>
<td>7.5/10,000 95% CI (0.40-1.29)</td>
<td>2.7/10,000</td>
</tr>
<tr>
<td>HLH*</td>
<td>2.9/10,000 95% CI (0.09-0.68)</td>
<td>0</td>
</tr>
</tbody>
</table>

*None of the patients with HLH were exposed to biologics prior to HLH diagnosis.

No clear association between thiopurines and solid tumors in IBD

<table>
<thead>
<tr>
<th>Study</th>
<th>Types of cancer</th>
<th>Number of patients</th>
<th>Statistically significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armstrong 2010</td>
<td>lung, breast</td>
<td>1955</td>
<td>NO</td>
</tr>
<tr>
<td>Fraser 2002</td>
<td>breast, bronchial, renal</td>
<td>6262</td>
<td>NO</td>
</tr>
<tr>
<td>Connell 1994</td>
<td>gastric, lung, breast, cervical</td>
<td>755</td>
<td>NO</td>
</tr>
</tbody>
</table>
A false sense of security with MTX?

Methotrexate/iatrogenic lymphoproliferative disorders in rheumatoid arthritis: histology, Epstein-Barr virus, and clonality are important predictors of disease progression and regression.


Epstein-Barr virus infection and gene promoter hypermethylation in rheumatoid arthritis patients with methotrexate-associated B cell lymphoproliferative disorders.


Methotrexate-associated lymphoproliferative disorders of the tongue developing in patients with rheumatoid arthritis: a report of 2 cases and a review.

Hashimoto K, Naga T, Saito T, Kinoshita H.

Methotrexate-associated lymphoproliferative disorders mimicking angioimmunoblastic T-cell lymphoma.

Past and current thiopurine exposure increases the risk for non-melanoma skin cancer (NMSC)

Yearly incidence rate (per 1,000 patient-years)

- Continuing
- Discontinued
- Never received

Cases of NMSC (n)

- <50 years
  - 0.66
  - 0.38
  - 0

- 50-65 years
  - 2.59
  - 1.96
  - 0.60

- >65 years
  - 4.04
  - 5.70
  - 0.84

Peyrin-Biroulet. Gastroenterology 2011
Patient proposed to start immunosuppression (thiopurines/ antiTNF)

- Information about dermatological complications
  - Identify risk factors for development of skin cancer: premalignant skin lesions, evidence of HPV infection, sun exposure history, family history of skin cancer, skin type
  - Advice on adequate skin protection and on self-monitoring
  - Advice on modifiable risk factors protection
- Annual Skin checks
Biologics
Biologics used for IBD

- **Vedolizumab**
  - So far so good from trial experience
  - Too soon to tell, PASS study underway

- **Ustekinumab**
  - Too early in IBD
  - PSOLAR (psoriasis safety registry) includes over 12,000 patients $\rightarrow$ no increased risk of malignancy

- **Anti-TNFs**
8905 patients representing 20,602 pt-years of exposure

13 Non-Hodgkin’s lymphomas → 6.1 per 10,000 pt-years

Mean age 52, 62% male

10/13 exposed to IM* (really a study of combo Rx)

<table>
<thead>
<tr>
<th></th>
<th>NHL rate per 10,000</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEER all ages</td>
<td>1.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IM alone</td>
<td>3.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-TNF + IM vs SEER</td>
<td>6.1</td>
<td>3.23</td>
<td>1.5-6.9</td>
</tr>
<tr>
<td>Anti-TNF+ IM vs IM alone</td>
<td>6.1</td>
<td>1.7</td>
<td>0.5-7.1</td>
</tr>
</tbody>
</table>


*not reported in 2
What do we know about the risk of solid tumors and anti-TNF?

- **Rheumatoid arthritis**
  - 13,000 patients, ½ on biologics

- **Inflammatory bowel disease**
  - Fairly limited data

### Type of Cancer

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>All solid tumors</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Colon</td>
<td>0.8 (0.3-1.7)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.1 (0.7-1.8)</td>
</tr>
<tr>
<td>Breast</td>
<td>0.9 (0.5-1.3)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.5 (0.1-2.6)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.3 (0.9-5.4)</td>
</tr>
<tr>
<td>Non-melanoma</td>
<td>1.5 (1.2-1.8)</td>
</tr>
</tbody>
</table>

### Type of study

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Associated risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population based</td>
<td>SIR 0.7 (0.2-1.7)</td>
</tr>
<tr>
<td>651 patients</td>
<td></td>
</tr>
<tr>
<td>Single center</td>
<td>OR 0.97 (0.56-1.65)</td>
</tr>
<tr>
<td>734 patients</td>
<td></td>
</tr>
</tbody>
</table>

*No clear evidence that anti-TNF is associated with (non-skin) solid tumors*

Wolfe, Arthritis and Rheumatism 2007;56:2886.
Systematic Review: Risks of Serious Infection and Lymphoma with anti-TNF Therapy in Pediatric IBD

<table>
<thead>
<tr>
<th>Risk with anti-TNF</th>
<th>Risk with comparator</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphoma 2/10,000</strong></td>
<td><strong>Pediatric population 0.58/10,000</strong></td>
<td>3.5 (0.35-19.6)</td>
</tr>
<tr>
<td></td>
<td><strong>Thiopurines 4.5/10,000</strong></td>
<td>0.47 (0.03-6.44)</td>
</tr>
<tr>
<td></td>
<td><strong>Adults with anti-TNF 6.1/10,000</strong></td>
<td>0.34 (0.04-1.51)</td>
</tr>
</tbody>
</table>

No statistical significance, but possibly underpowered to detect a difference.
No increased risk of malignancy with biologics

*Excludes NMSC

No increased risk of malignancy with biologics

<table>
<thead>
<tr>
<th></th>
<th>Rate of malignancy /10,000 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected rate in general UC pediatric population</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>IBD patients treated with biologics</strong></td>
<td></td>
</tr>
<tr>
<td>Biologics with thiopurines</td>
<td>7.0</td>
</tr>
<tr>
<td>Biologics without thiopurines</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>IBD patients treated with non-biologics</strong></td>
<td></td>
</tr>
<tr>
<td>Non-biologics with thiopurines</td>
<td>5.2</td>
</tr>
<tr>
<td>Non-biologics without thiopurines</td>
<td>3.2</td>
</tr>
</tbody>
</table>

*Excludes NMSC

- No cases of HLH in patients exposed to biologics
- 1 case of B-cell lymphoma in with biologic monotherapy (rate = 2/10,000)

Risk of melanoma and anti-TNFs

IBD appears to be associated with a 37% increased risk of melanoma, independent of the use of immunomodulator and anti–TNFα therapy.

- The risk of melanoma was higher in studies performed before introduction of biologic therapies (before 1998) (8 studies: RR, 1.52; 95% CI, 1.02–2.25) but not in studies performed after 1998 (2 studies: RR, 1.08; 95% CI, 0.59–1.96)

Colon cancer in pediatric IBD

- EPIMAD registry (France, population based) 1988-2004
- 698 patients included, all < 17 years old
- Median follow-up 11.5 years

<table>
<thead>
<tr>
<th></th>
<th>Expected number</th>
<th>SIR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD (n=8)</td>
<td>2.70</td>
<td>3.0</td>
<td>1.3-5.9</td>
<td>0.012</td>
</tr>
<tr>
<td>UC (n=3)</td>
<td>0.65</td>
<td>4.6</td>
<td>0.9-13.5</td>
<td>0.06</td>
</tr>
<tr>
<td>CD (n=5)</td>
<td>2.03</td>
<td>2.5</td>
<td>0.8-5.8</td>
<td>0.11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer location</th>
<th>Expected number</th>
<th>SIR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer (n=2)</td>
<td>0.05</td>
<td>45.7</td>
<td>5.5-165.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Basal cell (n=2)</td>
<td>0.32</td>
<td>6.2</td>
<td>0.08-22.3</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Patients are Willing to Take High Risks in Exchange for Improved Health

Risk of dying from side-effect all < 1 per 1000

N = 580

Patients are Willing to Take High Risks in Exchange for Improved Health

Parents are willing to take even higher risks of lymphoma…but only if their kids are sick!

Maximal Acceptable Risk of Lymphoma (%)

- Adult patients
- Parents

Johnson et al. Risk Analysis 2009
Over a lifetime (in US), the chance of dying from:

Lightning → 1 out of 80,000
Bicycle accident → 1 out of 5000
Drowning → 1 out of 1000
Car accident → 1 out of 261
Cancer → 1 out of 8
Heart disease → 1 out of 5
Driving to the office visit about as risky as IBD therapy!

Annual risk of dying in a car accident

<table>
<thead>
<tr>
<th>Country</th>
<th>Annual Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>1.6 per 10,000</td>
</tr>
<tr>
<td>UK</td>
<td>0.6 per 10,000</td>
</tr>
<tr>
<td>France</td>
<td>0.9 per 10,000</td>
</tr>
<tr>
<td>Germany</td>
<td>0.7 per 10,000</td>
</tr>
<tr>
<td>Spain</td>
<td>1.2 per 10,000</td>
</tr>
<tr>
<td>Ukraine</td>
<td>2.0 per 10,000</td>
</tr>
</tbody>
</table>

www.medicine.ox.ac.uk/bandolier/booth/Risk/trasnsportpop.html
Challenges from Crohn's
You and your family may already be familiar with some of the challenges Crohn's can cause.

Making a decision
To make a decision about your treatment options, you need to weigh the risks and benefits of each option and figure out what's most important to you.

READY TO GET STARTED?
Visit www.goemmi.com/DECIDEIBD
Summary

- Immunomodulators appear to be associated with an increased risk of malignancy
- But the absolute risk, even in high-risk individuals, is small
- Biologics probably do not increase the risk of malignancy
- Clearly communicating these data is hard, but shared decision making tools can help

Dartmouth-Hitchcock IBD Center
Research Site
https://goo.gl/7o3ZbZ