Disclosures

• None
Outline

• Cases
• Introduce Oncofertility and Survivorship
• Cancer and cancer treatment effects on male fertility
• Fertility Preservation options for men prior to cancer treatment
Cases

• 14 year old post-pubertal adolescent with new diagnosis of ALL
  – Ill appearing
  – Needs treatment ASAP
  – He’s “not interested in fertility”
  – Do you recommend fertility preservation?
Cases

• Recently married 28 year old male with left testicular mass consistent with testicular cancer, contralateral testis atrophic, w/ nodes and pulmonary mets
  - Stated interest in having children
  - Semen sample showed azoospermia
  - What are his options?
Cases

- 38 year old divorced male with 2 children, one month s/p APR for invasive rectal cancer
  - Did not bank prior to surgery
  - Soon starting adjuvant chemo/radiation
  - Do you bring up sperm banking?
    - Patient is unable to obtain an erection or produce a semen sample
    - What are his options now?
Oncofertility Defined

- Oncofertility
  - Fertility management for young cancer patients
  - Oncologists and fertility specialists work together through issues of both cancer treatment as well as potential fertility threats in that immediate moment of diagnosis
Fertility Preservation

- Fertility preservation is essential component of treatment for young men with a new cancer diagnosis
- Novel advances in cancer therapy have increased survival
Cancer in Young Patients

- ~10% of cancers are diagnosed in people under age 45
- 5 year survival rates for many childhood cancers >90%
- 75% of all cancer patients SURVIVE
Survivorship

• Survivorship issues becoming more recognized
  – Report from Institute of Medicine, 2005: “From Cancer Patient to Cancer Survivor: Lost in Translation”
Survivorship

There are 14.5 million cancer survivors in the US. By 2024, there will be almost 19 million.*

*projected
Age of Fathers in the USA

How much sperm is needed for Fertility Preservation?

• Earliest Fertility Preservation literature began in the 1980’s
• Many opinions formed prior to the ubiquitous availability of in vitro fertilization
• Some docs may not be aware of minimal requirements of sperm needed for Assisted Reproductive Technology (ART) today
Assisted Reproductive Technology

**IUI**
Intrauterine Insemination
- 5 million motile sperm

**IVF**
In Vitro Fertilization
- 75,000 motile sperm
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
<th>Sperm Count</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IUI</strong></td>
<td>Intrauterine Insemination</td>
<td>5 million motile sperm</td>
</tr>
<tr>
<td><strong>IVF</strong></td>
<td>In Vitro Fertilization</td>
<td>75,000 motile sperm</td>
</tr>
<tr>
<td><strong>ICSI</strong></td>
<td>Intracytoplasmic Sperm Injection</td>
<td>~20 sperm</td>
</tr>
</tbody>
</table>
Intracytoplasmic Sperm Injection (ICSI)

- Revolutionized the treatment of male infertility (1993)
- Injection of a single sperm/egg
- Enabled men to be biologic fathers despite severe testicular damage or obstruction
Assisted Reproductive Technology

- ART contributes to 1.4% of all births in the US (2009 data)
- Combination of increased survival, delayed fatherhood, and utilization of ART magnifies the importance of long-term Fertility Preservation in young cancer survivors
Society Recommendations

**Fertility preservation and reproduction in cancer patients**

**Preservation of Fertility in Pediatric and Adolescent Patients With Cancer**

Mary E. Fallat, MD, John Hutter, MD, the Committee on Bioethics, Section on Hematology/Oncology, and Section on Surgery
ASCO recommendations for Fertility Preservation for a cancer patient:
- Discuss at the earliest possibility the risk of fertility impairment
- Prompt referral to a qualified specialist if patient interested
- Promote clinical trials to advance state of knowledge
Why not cryopreserve sperm?

• “No time, too many more important issues”
• “Semen parameters are poor – not worth freezing”
• “No need to bank – patient is on ‘favorable’ protocol”
• “Uncomfortable discussing it”
• “We should be focused on survival”
Physician Perspective

- American Society of Clinical Oncology (ASCO) members survey, 1999
  - 165 members, 28% response rate
  - 100% discuss FP with patients
  - Recommendation for sperm banking
    - 5.8 (1=mention it, 10=insist on it)
  - Importance for patients
    - 6.2 (1=not important, 10=critical)
  - Heard of ICSI? 26%
Patient Perspective

• 904 men with cancer (14-40 year old)
  – Informed about fertility issues? 60% yes
  – Informed about banking? 51% yes
• Do you want children after cured?
  – Yes 51%, and 77% if no previous children
• How many patients actually banked?
  – Overall: 24%
  – Those without children: 27%

Schover LR et al, 2002
Cancer Treatments

• **Every type** of cancer treatment contributes to reduced male fertility
  – Germ cell loss/destruction
  – Damage Hypothalamic-Pituitary-Gonadal Axis
  – Damage the ductal system for sperm transport
  – Damage to pelvic nerves
Table 1. Risk of impaired fertility potential with commonly utilized chemotherapeutic and radiation therapy regimens

<table>
<thead>
<tr>
<th>Chemotherapy High Risk</th>
<th>Treatment</th>
<th>Dose</th>
<th>Common Indication</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Alkylating agent</td>
<td>Transplant conditioning</td>
<td>BMT / SCT Testicular, hematopoietic malignancies, neuroblastoma, BMT / SCT</td>
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<tr>
<td></td>
<td>Alkylating agent + radiation</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Busulphan</td>
<td>600 mg/kg</td>
<td>Multi-agent protocols</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil</td>
<td>1.4 g/m2</td>
<td>Multi-agent protocols</td>
</tr>
<tr>
<td></td>
<td>Chlormethine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>600 mg/m2</td>
<td>Multi-agent protocols</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>&gt;7.5 g/m2</td>
<td>Hematopoietic malignancies, sarcoma, neuroblastoma</td>
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<tr>
<td></td>
<td>Dacarbazine</td>
<td></td>
<td>Multi-agent protocols</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>42 g/m2</td>
<td>Multi-agent protocols</td>
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<tr>
<td></td>
<td>Melphalan</td>
<td>140 mg/m2</td>
<td>Multi-agent protocols</td>
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<tr>
<td></td>
<td>MOPP / COPP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Procarbazine</td>
<td>4 g/m2</td>
<td>Multi-agent protocols</td>
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</table>

<table>
<thead>
<tr>
<th>Chemotherapy Intermediate Risk</th>
<th>Treatment</th>
<th>Dose</th>
<th>Common Indication</th>
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<tr>
<td></td>
<td>ABVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BEP</td>
<td>2-4 cycles</td>
<td>Testicular malignancy  Testicular malignancy</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>&lt;400 mg/m2</td>
<td>Testicular malignancy  Testicular malignancy</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>&lt;2 g/m2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy Low Risk</th>
<th>Treatment</th>
<th>Dose</th>
<th>Common Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bleomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dactinomysin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mercaptopurine</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Methotrexate</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Vinblastine</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Vincristine</td>
<td></td>
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</tbody>
</table>
Alkylating Agents

- St Jude Lifetime Cohort Study (2014)
  - Correlated SA w/ cumulative alkylating agent exposure in 214 adult male survivors of childhood cancer treated w/ chemo but not radiation

Alkylating Agents

• St Jude Lifetime Cohort Study (2014)
  – 53% low concentration, 25% azoospermic
    • CED negatively correlated with sperm concentration
  – 89% w/ CED <4 g/m² were normospermic
    • But… No lower CED threshold below which azoospermia did not occur
      » CED cannot be definitive prognostic marker for semen quality after treatment
      » CED should not be sole guiding parameter determining risk to fertility

Methods to Preserve Fertility

- Cryopreservation of ejaculated sperm
- Post-ejaculate bladder retrieval after retrograde ejaculation
- Penile vibratory stimulation (PVS) or electroejaculation (EEJ)
- Surgical sperm extractions: Testicular sperm extraction (TESE), Epididymal sperm aspiration (MESA)
- Prepubertal: Immature testicular tissue extraction – Must be on a protocol
Cryopreservation of Sperm

- Masturbation
- Collected in the office
- Can be brought in from home/hospital <1 hour
- ~90% successful for adolescents
- OK after chemo starts

What if the patient cannot produce a semen sample?

- Adolescents, hormone derangements, nerve damage, ED, emotional inability
  - Penile vibratory stimulation (PVS)
  - Electroejaculation (EEJ)
  - Surgical sperm extraction
    - Testicular sperm extraction (TESE)
    - Epididymal sperm aspiration (MESA)
What if the patient is Azoospermic?

- Azoospermia is not an end-point for Fertility Preservation!!!

- Surgical sperm extraction necessary
  - Overall ~50% sperm retrieval rate for azoospermic cancer patients

Sperm Extraction Techniques

- RETA
- PESA
- TESA
- SPAS
- MESA
- TESE
TESE (Testicular sperm extraction)
### TESE Performed in Azoospermic Men: Prior to Chemotherapy for Testis Ca

**Clinical Stage (Testis Ca)** | **# of patients** | **Successful sperm retrieval** | **Maturation Arrest** | **Sertoli Cell Only**
--- | --- | --- | --- | ---
I | 2 | 2/2 (100%) | 0/2 | 0/2
IIA-IIB | 8 | 3/8 (37%) | 3/8 | 2/8
≥ IIC | 4 | 1/4 (25%) | 0/4 | 3/4

TESE Performed in Azoospermic Men: Prior to Chemotherapy for Lymphoma

<table>
<thead>
<tr>
<th>Disease</th>
<th># of patients</th>
<th>Successful sperm retrieval</th>
<th>Maturation Arrest</th>
<th>Sertoli Cell Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s</td>
<td>7</td>
<td>3/7 (43%)</td>
<td>2/7</td>
<td>2/7</td>
</tr>
<tr>
<td>NHL</td>
<td>10</td>
<td>5/10 (50%)</td>
<td>3/10</td>
<td>2/10</td>
</tr>
</tbody>
</table>

Future of Fertility Preservation

Cases

• 14 year old post-pubertal adolescent with new diagnosis of ALL
  – Ill appearing
  – Needs treatment ASAP
  – He’s “not interested in fertility”
  – Do you recommend fertility preservation?
• “I highly recommend it, you’ll thank me later”
Recently married 28 year old male with left testicular mass consistent with testicular cancer, contralateral testis atrophic, w/ nodes and pulmonary mets

- Semen sample showed azoospermia
- What are his options?

Back table TESE during orchiectomy – If negative, re-attempt SA prior to chemo and if azoo, TESE of contralateral testis
• 38 year old divorced male with 2 children, 1 month s/p APR for invasive rectal ca
  – Did not bank prior to surgery
  – Soon starting adjuvant chemo/radiation
  – Do you bring up sperm banking?
    • Patient unable to obtain erection or produce a semen sample
    • What are his options now?
  – MESA/TESE or EEJ
Summary

- Fertility preservation is essential with cancer treatment for young men.
- In age of ART, fertility can be preserved in the majority of post-pubertal patients.
- All men with a new diagnosis of cancer, including adolescents, should be offered fertility preservation, regardless of the diagnosis or treatment plan.
Thank you!

“Urology department. Can you hold?”