Rare Ovarian Tumors Survive and Thrive

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VERBAL DISCLOSURE
NONE

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Rare Tumors: Challenges

Rare tumors

Very rare tumors

Very very rare tumors

<u>Challenges in studying rare tumors:</u>

1- numbers overall and numbers accrued to clinical trials

2- funding for basic science research

3- funding for clinical trials

Challenges are being addressed within Rare Tumors Committee of NRG

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Rare ovarian tumors

- Favorable features:
  - Low grade tumors
  - Diagnosed early due to low grade features and thus, improved outcomes
  - Some in advance stages are highly curable with chemotherapy
  - Some in advance stages are slow growing providing long progression free survivals with good quality of life

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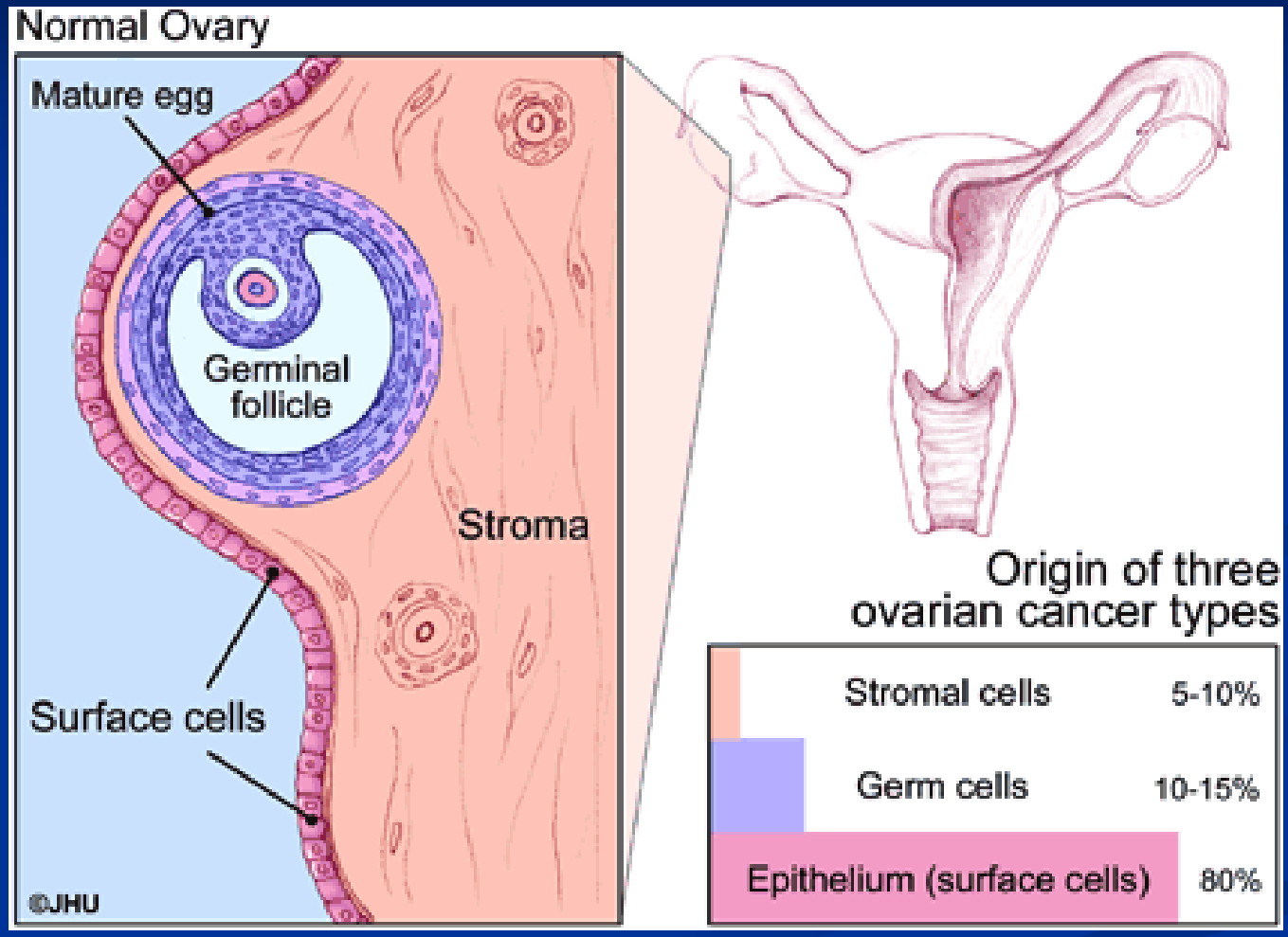
Normal Ovary
Mature egg
Germinal follicle
Stroma
Surface cells
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Origin of three ovarian cancer types
Stromal cells 5-10%
Germ cells 10-15%
Epithelium (surface cells) 80%

Rare Ovarian Tumors

- Epithelial ovarian tumors
- Ovarian sarcomas
- Sex cord stromal tumors
- Germ cell tumors

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Rare Epithelial Ovarian Tumors

- Endometrioid carcinoma (10 %)
- Clear cell carcinoma (5-10 %)
- Mucinous carcinoma (3-4 %)
- Low grade serous carcinoma (< 5%)
- Carcinosarcoma (2-5%)
- Transitional cell carcinoma (< 2%)
- Small cell carcinoma (< 3%)

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Endometrioid (10%)

- Usually diagnosed in 40's and 50's (mean age- 56 years)
- Most often diagnosed in early stage
- Typically low grade
- Chemosensitive (compared to mucinous, low grade serous and clear cell carcinomas)
- Better prognosis relative to other subtypes

  – Seidman JD et al. Int J Gynecol Pathol. 2004 Jan;23(1):41-44

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Endometrioid

- Associated with endometriosis (noted in approximately 45% of patients)
- Associated with endometrial cancer in 15-20% of cases
- *CTNNB-1* and PTEN gene mutation most common genetic abnormality
- Most common ovarian carcinoma associated with Lynch Syndrome

  – Mureno-Bueno et al., Diagn Mol Pathol. 2001 Jun:10(2): 116-22

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Clear cell carcinoma (5-10%) (OCCC)

- Most common in peri-menopausal women, late 40s-50s
- More common in early stage and thus, good prognosis
  - Fertility sparing surgery and adjuvant treatment for stage IA?
- In advance stage, worse prognosis than serous and endometrioid carcinoma
- Less sensitive to platinum
- Associated with higher incidence of thrombosis and hypercalcemia
- Associated with endometriosis (somatic mutations in *ARID1A associated with clear cell carcinoma and endometriosis)*
  - Chan JK, et al., Gynecol Oncol. 2008; 109(3):370-6
  - Goff BA, et al., Gynecol Oncol. 1996;60(3):412
  - Sugiyama T, et al., Cancer 2000: 88(11):2584

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Clear cell carcinoma (OCCC)

- Negative for ER and WT-1
- Positive for HNF-1 beta (hepatocyte nuclear factor 1-beta)
- High levels of MSI in OCCC. Associated with Lynch syndrome
- PIK3CA mutations (noted in 40% of OCCC)
  - Targeting the phosphatidylinositol 3-kinase (PI3K)/Akt/ mammalian target of rapamycin (mTOR) pathway

    - Kato N, et al., Mod Pathol. 2006 Jan;19(1):83-9

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Clear cell carcinoma

- **GOG trials:**
  - **GOG 254-Phase II evaluation of Sunitinib Malate in the treatment of persistent of recurrent clear cell ovarian carcinoma (Closed to patient entry September 2013; late breaking abstract at 2015 SGO))**
  - **GOG 268 A Phase II Evaluation of Temsirolimus (CCI-779) (NCI Supplied Agent: NSC# 683864, IND# 61010) in Combination with Carboplatin and Paclitaxel followed by Temsirolimus (CCI-779) Consolidation as First-line Therapy in the Treatment of Stage III-IV Clear Cell Carcinoma of the Ovary (Closed to patient entry January 2014)**
  - **GOG 283: A Phase II Trial of DCTD-Sponsored Dasatinib (NSC #732517 IND #73969) In Recurrent/Persistent Ovary, Fallopian Tube, Primary Peritoneal, Endometrial, or Endometriosis-Associated Clear Cell Carcinoma Characterized for the Retention or Loss of BAF250a Expression. (suspended)**
  - **GY-001: A randomized phase II study of XL-184 (cabozantinib) in recurrent clear cell carcinoma (Dr Farley)**
    - **(VEGFR2 inhibitor)**

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Mucinous carcinoma (3-4%)

- Usually presents in 40's-50's with age range in teen's to 80's.
- Mostly stage I at presentation. Large tumors
- Most mucinous carcinomas in the ovary are frequently metastasis from the GI tract (bilateral more common)
  - Usually, primary ovarian mucinous carcinomas have an associated transition from borderline to high grade intraepithelial neoplasm within the same tumor (unilateral more common).
  - Pseudomyxoma peritonei- almost always met to ovary from appendiceal primary

    - Riopel MA et al., Am J Surg Pathol. 1999 Jun: 23(6):617-35

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Mucinous carcinoma

- Molecular
  - KRAS mutation > 75% of tumors.
  - KRAS mutation also noted in mucinous borderline. Support transition concept from borderline to invasive-maybe?
  - KRAS mutation as molecular targets for future trials.

- Gemignani ML et al., Gynecol Oncol. 2003 Aug;90(2):378-81

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Mucinous carcinoma

- **GOG-0241**

  A GCIG INTERGROUP MULTICENTERPHASE III TRIAL OF OPEN LABEL CARBOPLATIN AND PACLITAXEL +/- NCI-SUPPLIED AGENT: BEVACIZUMAB (NSC #704865, IND #113912) COMPARED WITH OXALIPLATIN AND CAPECITABINE +/- BEVACIZUMAB AS FIRST LINE CHEMOTHERAPY IN PATIENTS WITH MUCINOUS EPITHELIAL OVARIAN OR FALLOPIAN TUBE CANCER (MEOC).

  (Closed to patient accrual in December 2013; abstract 2015 ASCO)

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Low grade serous carcinoma (<5%)
LGSC

- Biological distinct from high grade serous tumors
- Indolent, slow growing, mostly insensitive to platinum
- Usually present in advance stages
- Usually found in association with or derived from borderline serous tumors

  - Gershenson DM et al., Obstet Gynecol. 2006;108(2):361

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LGSC

- LGSC thought to represent progression from borderline tumors
- Immunohistochemistry
  - Low Ki 67 proliferation rate
  - Weak p53 expression compared to HGSC

- Molecular biology
  - BRAF and KRAS mutations also noted in borderline serous tumors but not in HGSC
  - Targeting of BRAF and KRAS mutation pathways (MEK inhibitors)

    - Kohn EC, Hurteau J. Cancer. 2012 Dec 11.

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LGSC
Targeted clinical trials

- **The MILO Study (MEK Inhibitor in Low-Grade Serous Ovarian Cancer): A Multinational, Randomized, Open-Label Phase III Study of MEK162 vs. Physician's Choice of Chemotherapy in Patients with Recurrent or Persistent Low-Grade Serous Carcinomas of the Ovary, Fallopian Tube or Primary Peritoneum (open June 2013, to complete accrual 2016).**

- **Phase II Randomized Double Blind Placebo Controlled Trial of Combination of Pimasertib with SAR245409 or of Pimasertib with SAR245409 Placebo in Subjects with Previously Treated Unresectable Low Grade Ovarian Cancer (open 2013, to be completed May 2016-currently ongoing but not recruiting participants)**

- **GOG 281: A Randomized Phase II/III Study to Assess the Efficacy of Trametinib (GSK1120212) in Patients with Recurrent or Progressive Low-grade Serous Ovarian Cancer or Primary Peritoneal Cancer (open)**

- **RTM 1313: A randomized phase II trial of paclitaxel/carboplatin vs. Trametinib monotherapy in patients with stage III/IV LGSC.**

- **<u>Most recent trials will evaluate hormones.</u>**

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Carcinosarcoma (2-5%)
(CS)

- More common in older women (mean age ~ 75 years)
- Usually present in advanced stages
- Monoclonal in origin like the uterine CS
- Histology: combination of malignant epithelial and stromal elements.
  - Epithelial element: similar to HGSC
- Behave like HGSC and treated like HGSC

  - Mano MS et al., Int J Gynecol Cancer. 2007 Mar;17(2): 316-24

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Carcinosarcoma

- Molecular biology:
  - PTEN mutations in approximately 17% of CS (Amant F, et al. Gynecol Oncol. 2002 Apr; 85 (1):165-9.
  - Agents that target the PI3K/AKT/mTOR pathways seem to be future direction.

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Carcinosarcoma

- **GOG0232C: A Phase II Evaluation of Paclitaxel, Carboplatin, and BSI-201 (Iniparib [Parp1 inhibitor] in the Treatment of Advanced, Persistent, or Recurrent Uterine Carcinosarcoma. Protocol Activated-04-feb-2008, Protocol Temporarily Closed-27-jul-2009, Protocol Closed-06-jul-2010, Protocol Terminated-29-jul-2012.**
  Gynecol Oncol. 2012 Sep;126(3):424-7. doi: 10.1016/j.ygyno.2012.05.024. Epub 2012 May 24 (Negative study)

- **GOG 130-F: A phase II evaluation of ixabepilone (anti-microtubule) in the treatment of recurrent persistent carcinosarcoma of the uterus. (closed August 2013)**

- **GOG 261: A randomized phase III trial of Paclitaxel and Carboplatin versus Ifosfamide and Paclitaxel in chemo-naïve patients with newly diagnosed Stage I-IV persistent or recurrent carcinosarcoma of the *uterus OR ovary*. (Closed March 2014)**

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Sex Cord Stromal Tumors (SCST)

- 5-8% of ovarian malignancies
- Derive from sex cords and ovarian stroma
- Granulosa cell; Sertoli Leydig cell tumors
- Adult granulosa cell tumors; most common of the group
- Considered low grade tumors; indolent
- Secrete estrogen and androgens

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Granulosa Cell Tumors

- Median age; 54
- 2-5% of ovarian cancers
- 5% juvenile-prepubertal age group
- Usually unilateral (< 5% bilateral)
- 70% secrete estrogen- concurrent endometrial cancer in 5-10%
- Most stage 1 at diagnosis
- Late recurrences 10-30 years post diagnosis can occur
    - Median time to recurrence-5-6 years

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Sertoli-Leydig cell tumors

- Median age: 25 years
- < 1% of ovarian cancers
- < 10% noted in prepubertal age or after menopause.
- Most common presenting symptoms: menstrual disorders, virilization and non specific symptoms from the abdominal mass. (frank virilization in 35% of patients due to androgen excess)
- Most are stage 1 at presentation (>97%)

Management

- Unilateral oophorectomy in children or women of reproductive age group with complete staging (can omit lymphadenectomy)
- Bilateral tumors uncommon (<5%)
- TAHBSO in post menopausal women with cytoreductive surgery if required (no prospective trials but seems reasonable due to indolent nature)
- No lymph node dissection required unless bulky nodes are palpated as LN mets are rare.
  - Brown J et al., Gynecol Oncol. 2009;113(1):86
- No evidence that adjuvant chemotherapy prevents recurrence-but no prospective randomized trials to guide. Can be considered in selective patients

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Adjuvant treatment

- Granulosa cell tumor
  - No adjuvant treatment recommended in Stage IA/IB
- Sertoli-Leydig cell tumor
  - No adjuvant treatment recommended in Stage 1A well or intermediate-differentiated SLCT. (no prospective data)
  - Adjuvant treatment for Stage 1A poorly-differentiated (60% risk of recurrence) and SLCT with heterologous elements (20% risk of recurrence). (no prospective data)
- Recommend adjuvant platinum based chemotherapy for all Stage IC-IV but no prospective data to support survival benefit

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GOG 264 (Dr Brown)

SCHEMA

Patients diagnosed with histologically confirmed SCST. Newly diagnosed, Stage IIA – IVB disease OR biopsy-proven recurrent disease with no prior chemotherapy (open)

↓

Randomization

- Arm I
  - Treatment:
    - Paclitaxel 175 mg/m2 IV over 3 hours
    - Carboplatin AUC = 6 IV over 1 hour
    - Every 3 weeks x 6 cycles (=18weeks)
- Arm II
  - Treatment:
    - Bleomycin 20 units/m2 IV Push day 1 (MAX 30 units/ cycle; Total lifetime cumulative dose should not exceed 120 units)
    - Etoposide** 75 mg/m2 IV Day 1,2,3,4,5
    - Cisplatin 20 mg/m2 IV Day 1,2,3,4,5
    - Every 3 weeks x 4 cycles (=12 weeks)

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Bevacizumab in SCST

- GOG 251-A Phase II Trial of Bevacizumab (rhuMAB VEGF)(NSC# 704865, IND# 7921) for Recurrent Sex Cord-Stromal Tumors of the Ovary
  - Bevacizumab 15 mg/kg IV. Repeat every 21 days until disease progression or adverse effects prohibit further treatment
    - 36 patients with recurrent SCST (90% Granulosa cell tumors)
    - 90% of patients received prior chemotherapy
    - Median number of regimens – 2
    - Overall response rate – 17%
    - Stable disease – 78%
    - Median PFS – 9 mo
    - Median F/U – 33 mo
    - Median OS – not reached
    - 11% discontinued treatment 2/2 toxicities
    - No GI perforation

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Hormonal treatment

Agent	Number of patients	Response %
LHRH agonist	13	50
Progestin-MPA	5	90
Tamoxifen-progestin	Case reports	
Aromatase-inhibitors	Case reports	

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Granulosa Cell Tumors
Future Directions

- Agents proposed in 2015 concepts at NRG
  - Enzalutamide: androgen-receptor inhibitors (used in prostate cancer treatment)
  - Abiraterone: CYP17 inhibitor (used in prostate cancer treatment)
  - Cediranib: Tyrosine kinase inhibitor

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Germ cell tumors
(Lance Armstrong tumor)

- Approximately 10-15% of all ovarian cancers
- Principally in adolescent girls and young women
- Median age- 16-20 yrs of age
- Range- 6-46 yrs of age
- A number of cases described in post menopausal women

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Modified Classification

- **Dysgerminomas-50%**

- **Non-dysgerminomatous malignant ovarian germ cell tumors (NDMOGCT)-50%**
  - **Yolk sac tumors-22%**
  - **Immature teratomas-20%**
  - **Mixed primitive germ cell tumors-8%**
  - **Embryonal carcinomas**
  - **Choriocarcinomas**
  - **Polyembryomas**

Tavassoli et al. Pathology and Genetics of Tumors of the Breast and Female Genital Organs. Lyon, France, International Agency for Research on Cancer, 2003 (modified WHO classification)

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Malignant Ovarian Germ Cell Tumors

Management differences between gynecologic oncology and pediatric oncology

- 18 year old female. 10 cm left adnexal solid mass confined to ovary on CT scan. AFP 3,000.
  - Gynecologic Oncology management (NCCN guidelines).
    - Fertility sparing surgery with comprehensive surgical staging.
    - Diagnosis: YST confined to ovary
      - 3 cycles BEP chemotherapy
  - Pediatric Oncology management.
    - Fertility sparing surgery with standard pediatric surgical staging
    - Diagnosis: YST confined to ovary
      - Surveillance

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Surgical staging: Is it really necessary for ovarian germ cell tumors

- NO study has compared comprehensive surgical staging with standard pediatric staging in patients undergoing active surveillance in a prospective manner until now.
  - **MaGIC study-AGCT 1531- Activated May 2017.**
    - **Malignant Germ Cell International Collaborative (MaGIC) initiative.**
  - Open to NRG group.
  - Active surveillance for FIGO stage IA/IB MOGCT- YST, Mixed, Embryonal carcinoma, Choriocarcinoma, Stage I grade II, III Immature Teratoma.

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Chemo Brain and Fatigue

Chemotherapy Related Cognitive Impairment

Chemotherapy Related Fatigue

Alok Pant, MD

Northwestern Medicine

Chemotherapy Related Cognitive Changes

- Attention
- Concentration
- Learning
- Memory
- Information processing
- Language
- Visuospatial skill

Scope of the Issue

- CRCI has been described since the 1970s
- Poorly understood
- Most of the data comes from breast cancer literature
  - 94% of BCS reported significant PCI 1 year following completion of chemotherapy
- 69% of OC survivors reported cognitive decline
- Even minimal impairment can profoundly impact QOL
  - As OS improves, attention to all aspects of QOL become more important

Description of the Experience

- “Walking into a room and forgetting what I was doing”
- Repeating themselves
- Misplacing keys and cell phones
- Names and phone numbers
- Trouble with word finding
- Repeating themselves
- Inability to multitask
- Reading comprehension and staying absorbed in a book
- Tasks taking longer
- Repeating themselves
- Feeling “foggy” and “spacy”

Impact of the Experience

- Depression, anxiety, frustration and embarrassment
- Family tension
- Withdrawing from social activities
- Job security
  - Difficulty returning to work when treatment is done
- Cognitive decline exacerbated by fatigue and stress

Timing of Cognitive Issues

- Wide range
- Sometimes no symptoms until chemotherapy completed
- Many symptoms after 1-2 cycles of chemotherapy
- Some noted improvement between cycles
- Some noted improvement 6-12 months following treatment
  - Some noted no improvement more than a year after chemotherapy

Direct effect of chemotherapy on CNS

- MTX and 5-FU cause progressive damage to myelin
- Minimal data on carboplatin and paclitaxel
  - One study of 28 Ov CA patients showed no EEG changes after 6 cycles of treatment
  - Reduced EEG processing speed 4 years following platinum in breast cancer patients
- Difficult to pinpoint specific chemotherapy agents

Indirect effects of chemotherapy on CNS

- Certain chemotherapeutics cause increased inflammation
  - Cytokine activation linked to:
    - Fatigue, sleep issues, poor concentration
  - Paclitaxel and docetaxel linked to increased levels of IL-6, 8, 10
- Increased free radical formation leads to neuron death
  - Especially in Adriamycin (Doxil)
    - Co-administration with anti-oxidants reversed these effects in mice

Non-treatment Causes

- Studies have shown cognitive decline before initiation of therapy
- Pain, fatigue and anemia
  - All have been shown to result in cognitive decline
- Hormone regulation
  - Increased glucocorticoid levels associated with cognitive decline
    - Dexamethasone for Taxol
  - Estrogen deficiency
    - Breast cancer patients who underwent both chemo and hormonal therapy showed the most deterioration and persistent decline

Official Diagnosis

- Difference in self-reported versus objectively measured
  - Some studies show up to 90% of patients exhibit cognitive decline
  - Some studies show no decline by objective measures
    - Prospective study in OC patients using carbo/taxol showed no decline
- 17 neuropsychological tests used to assess cognitive function
  - Heterogeneous group makes data interpretation difficult
- Imaging
  - Reduction in brain volume on MRI following chemotherapy in breast cancer
  - Lower resting metabolism on PET imaging of the brain following chemo

Patient Desires

- Information about possible cognitive decline BEFORE treatment starts
- Information to be shared with family, co-workers and friends
- Acknowledgement of the existence of cognitive decline

Coping Strategies

- Minimal quality research
- Needing to write things down
- Keep items in consistent locations
- Appropriate amounts of rest/sleep
- Structure and organize daily routine
- Relaxation techniques
- Meditation
- Exercise
- Crossword puzzles

Pharmacologic Interventions

- Erythropoietin (EPO)
  - 7 studies done – 3 with significant improvement
  - EPO no longer widely used due to significant risks
- Psychostimulants (Dexmethylphenidate and methylphenidate)
  - 8 published studies – mixed results
  - Minimal improvement in attention, memory
- Donepezil (cholinesterase inhibitor)
  - Two published trials – mixed results

Non-pharmacological Interventions

- Traditional Chinese Medicine
  - RCT of 81 Ov CA patients undergoing chemotherapy (carbo/taxol)
    - TCM consisted of herbs (?)
    - No difference in QOL noted and no difference in cognitive function
  - RCT of Medical Qigong showed improvement in cognition (all cancers)
    - 90 minutes/week for 10 months
    - Increased perceived cognition
  - RCT of Ginko biloba showed no improvement in cognition (all cancers)

Alternative Approaches

- Nature walks (breast cancer data)
  - 120 minutes/week of exposure to nature → improved attention/focus
- Exercise
  - Extensive research showing improvement in cognition
  - Tai Chi
    - 1 hour/week for 10 weeks
    - Improved perceived cognition but minimal objective response
- Cognitive Behavioral Therapy
  - Programs to improve/restore mental function
  - 4 large studies – 3 showed significant improvement in cognitive function
- Fruits and vegetables
  - CRC patients showed improved cognitive function

Cancer Related Fatigue

- Distressing, persistent, subjective sense of physical, emotional or cognitive tiredness/exhaustion related to cancer or therapy
  - Not proportional to recent activity
  - Significantly interferes with normal functioning
  - Not relieved by rest

Causes of Cancer Related Fatigue

- Progressive tumor growth
  - Metastatic disease
- Cancer therapy
  - Chemotherapy, surgery, RT
- Anemia
- Pain
- Emotional distress/depression
- Sleep disturbances
- Poor nutrition
- Medical co-morbidities

Prevalence of CRF

- Majority of patients undergoing treatment experience CRF
  - 75-90% of all patients
- 30% note persistent fatigue years following therapy
- Thought to be underreported
  - ASCO and NCCN recommend regular screening during treatment and surveillance/survivorship
- Most cases are mild-moderate
  - Recommend energy conserving activities

Severe CRF

- Focused history and evaluation
  - Anemia, metabolic disorders, endocrine issues, cardiac/pulmonary
  - Substance abuse, depression, sleep disturbance
- Non-pharmacologic interventions
  - CBT
  - Moderate aerobic exercise 150 min/week and strength training
    - Less fatigue/emotional distress, better sleep and QOL
  - Relaxation/stress reduction techniques, yoga

Pharmacologic Interventions

- Psychostimulants
  - Methylphenidate/dexmethylphenidate
    - Only 2 of 8 RCTs showed an improvement in fatigue scores
  - SSRI – only seem to benefit when fatigue accompanied by depression
- Vitamins – not effective
- Ginseng – beneficial while on treatment
  - Potential interaction with certain chemotherapies

Conclusions

- Cognitive Changes on Chemotherapy
  - It's real!
  - Hard to officially diagnose but it is common
  - Multifactorial
  - Medication has mixed results
  - Exercise, mind-body techniques, CBT all seem effective
- Chemotherapy-Related Fatigue
  - Very common with a wide range of severity
  - Rule out underlying medical causes
  - Multifactorial
  - Medication has mixed results
  - Exercise, mind-body techniques, CBT all seem effective