Long term side effects: the wolf in the cage

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Progress in the adjuvant treatment of breast cancer in the last 20 years

CT
- Addition of taxanes to antracycline based regimens
- Dose dense regimens
- Better selection of who benefits from CT

HT
- Longer therapy
- Addition of ovarian suppression

Anti-HER2
- Addition of trastuzumab
- Addition of double anti-HER2 blockage

CT: chemotherapy, HT: hormonotherapy, HER2: human epidermal growth factor
Breast cancer mortality 1950-2003 (USA/UK)

UK and USA 1950–2003/2: Females
Breast cancer mortality at ages 35–69

*Mean of annual rates in the seven component 5-year age groups

Source: WHO mortality & UN population estimates

WHO Mortality and UN Population Estimates
High rates of long term survival among breast cancer patients

1) What are the ‘costs’ of cancer therapy?

2) How can we mitigate long term side effects associated with cancer therapy?
1) What are the ‘costs’ of cancer therapy?
The ‘cost’ of breast cancer survivorship

Chemotherapy & Biologics
- Neuropathy
- Secondary leukemia
- Cardiac dysfunction
- Autoimmune problems

Local Therapy
(Surgery & Radiation)
- Pain, numbness, lymphedema, restricted motion or weakness
- Cosmetic breast or reconstruction changes
- Cellulitis, nerve damage, rib fracture, pneumonitis
- Heart disease, sarcomas, skin & other second cancers, lung fibrosis

Due to Either/All
- Menopausal symptoms, infertility, sexual dysfunction
- Osteoporosis
- Weight gain
- Cognitive impairment
- Fatigue
- Metabolic syndrome
- Psychological distress

Hormonal Therapy
- Menopausal symptoms
- Sexual dysfunction
- Myalgias, arthralgia
- Cataracts
- Hyperlipidemia
- Uterine malignancies
- Vascular events

Adapted from Neklyudov and Partridge, 2013
The ‘cost’ of breast cancer survivorship

Ganz et al., N=864 and Couzi et al., N=225

Vasomotor symptoms  Vasomotor symptoms  Vaginal dryness  Dispaneuria  Joint pains  Difficulty in sleeping  Forgetfullness

< 50 (Ganz et al.)  50-59 (Ganz et al.)  ≥ 60 (Ganz et al.)  Couzi et al.

The ‘cost’ of breast cancer survivorship

CANTO cohort, N=5801 Stage 1-3 breast cancer

Poor QoL defined by a score <60 on functional scales (poor functions) or ≥40 on symptoms scales (severe symptoms) of EORTC QLQ-C30

Cottu, SABCS, 2017; CANTO cohort, Unpublished data
Impact of side effects

• Compared with matched controls, cancer survivors have a substantially increased burden of illness:
  
  Days lost from work, inability to work
  Poorer general health perception
  Need for help with daily activities

Side effects can impact: social function, quality of life, adherence to treatments

2) How can we mitigate side effects associated with cancer therapy?
First step to mitigate symptoms

Systematically ask about common concerns:
- Vasomotor symptoms
- Musculoskeletal symptoms
- Vulvo-vaginal symptoms
- Anxiety,
- Depression, distress
- Sleep disorders
- Fatigue

Avis et al., Qual Lif Re, 2005; Chopra et al., Health Qual Life, 2012; Ganz et al., JCO, 2012; NCCN and ASCO survivorship guidelines
First step to mitigate symptoms

Comprehensive Assessment and Targeted Intervention of Menopausal Symptoms and Sexual Dysfunction in Breast Cancer Survivors

Randomized controlled trial (RCT), N= 76 patients

Usual care vs. treatment (assessment, education, counselling, interventions directed at severe menopausal symptoms)

Treatment group reported improved menopausal symptoms and sexual functioning

Ganz PA et al., JNCI, 2000
Mitigation of side effects associated with cancer therapy

Vasomotor symptoms
Musculoskeletal symptoms
Vulvo-vaginal symptoms

Sleep disorders
Fatigue
Cognitive impairment
Cardiovascular Risk
Bone health

Avis et al., Qual Lif Re, 2005; Chopra et al., Health Qual Life, 2012; Ganz et al., JCO, 2012; NCCN and ASCO survivorship guidelines
Vasomotor Symptoms

- Pharmacological Non-hormonal Rx: anti-depressives
  - RCT of 4 weeks placebo vs. venlafaxine, N=229

Loprinzi et al., JCO, 2000
Vasomotor Symptoms

- Pharmacological Non-hormonal Rx: low dose anti-depressives

SSRI- caution with tamoxifen (inhibition of CYP2D6), although controversial

Selective serotonin re-uptake inhibitors (SSRI)

Serotonin neuroepinephrine re-uptake inhibitors (SNRI)

Loprinzi et al., JCO, 2008
Vasomotor Symptoms

- Pharmacological Non-hormonal Rx: anticonvulsants
  RCT of 8 weeks placebo vs. gabapentin, N=420

![Graph showing change in hot flush severity over time](image)

Low-dose (900-mg/d) effective

- N=240
- \( P < 0.0001 \)

Pandya et al., Lancet, 2005; Reddy et al. Obgyn, 2006
Vasomotor Symptoms

- **Non Pharmacological therapy:**
  1. CBT
     - RCT of CBT vs. usual care, N=96
  2. Hypnosis
     - RCT of hypnosis vs. no Rx, N=51

CBT: cognitive behavioral therapy

Vasomotor Symptoms

- **Pharmacological Non-hormonal Rx**
  - Anti-depressives: SSRI/SNRI → effective
  - Anti-convulsants: gabapentin/pregabalin → effective
  - Clonidine → mixed

- **Non-Pharmacological therapy**
  - Hypnosis, CBT → effective
  - Weight control, stop smoking → probably effective
  - Stellate ganglion blockage → effective (preliminary)
  - Acupuncture → mixed
  - Paced respiration, exercise, yoga → mixed
  - Vitamin E, omega-3, black cohosh, soy, magnesium → ineffective

Rada et al., Cochrane Review 2010; Salehi et al., Supp Care Cancer 2016; Stu et al., BCRT, 2010; Sternfeld et al., Menopause, 2014; Chen et al., J Cancer Res Ther 2016; Ann Partridge courtesy
Musculoskeletal Symptoms

• **Switching Rx**
  
  ATOLL, N=179: anastrazole to letrozole:
  
  at 6 months, 71.5% still taking letrozole

  ELPh, N=83: one AI to another:
  
  at 13 months, 38.6% taking 2nd AI

  Switching to Tamoxifen

Briot et al., BCRT, 2010; Henry et al., JCO, 2012
Musculoskeletal Symptoms

- **Pharmacological Rx: Duloxetine**
  
  RCT of 13 weeks of duloxetine vs. placebo, N=299

  **Improvement:**
  
  - Worst joint pain
  - Pain interference
  - Knee/hip/hand arthritis scales
  - Stiffness
  - Quality of life

  Henry et al., JCO, 2018
Musculoskeletal Symptoms

- **Non Pharmacological therapy: Exercise**

  RCT of exercise vs. usual care, N=61

  [Graph showing pain interference over time (months)]

  Irwin et al., JCO, 2015
Musculoskeletal Symptoms

- Non Pharmacological therapy: Acupuncture

  RCT of 12 weeks of true vs. sham acupuncture vs. waitlist, N=226

Crew et al., JCO, 2009, Hershman et al., JAMA, 2018
Musculoskeletal Symptoms

• **Switching Rx** → effective

• **Pharmacologic Rx**
  – Duloxetine → effective
  – NSAIDs → ? *(highly used)*
  – Weight control → probably effective
  – High dose vitamin D → mixed
  – Glucosamine/chondroitin → minimally effective
  – Omega-3 Fatty acids → ineffective *(placebo effect)*

• **Non-pharmacological options**
  – Acupuncture → effective
  – Exercise → effective

Vulvo-vaginal Symptoms

- Pharmacological Non hormonal Rx: moisturizers and lubricants

RCT crossed over of moisturizers vs. lubricant, N=45

Loprinzi et al., JCO, 1997
Vulvo-vaginal Symptoms

• Pharmacological Non Hormonal Rx: Lidocaine
  RCT of local vaginal saline vs. lidocaine, N=46

Goetsch et al, JCO, 2015

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Vulvo-vaginal Symptoms

- Pharmacological Hormonal Rx: Local estrogen replacement therapy **effective**

  Low dose or ultra low dose vaginal estrogens
  - Studies focused on the impact of serum hormone levels **mixed**
  - Studies focused on breast cancer recurrence or mortality **limited**

SAFETY CONCERNS
Vulvo-vaginal Symptoms

- **Pharmacological Hormonal Rx: Local Androgens/Estrogens**
  
  RCT of intravaginal testosterone cream vs. vaginal estrogen ring, N=69

  Barton et al., ASCO, 2014; Melisko et al., JAMA Onc, 2016

Vaginal atrophy, sexual interest & function improved for all patients
Vulvo-vaginal Symptoms

• **Vaginal dryness (Dyspareunia)**
  - Hormonal options
    - Estrogens
    - Androgens
  - Non-Hormonal options
    - Moisturizers
    - Lubricants
    - Lidocaine
    - Laser therapy

(Atrophy/Stenosis/Pelvic floor weakness, Libido)
Sleep disorders

Sleep Hygiene

**Bedroom practices:** Environmental control, bed for sleep, in bed when tired, empty bladder, same wake-up time, get out of bed if unable to fall back asleep, worry notebook

**Lifestyle:** Exercise, avoidance of naps and evening use of caffeine, alcohol, cigarettes

**Target contributing factors:** hot flashes, pain, anxiety

**Target sleep disturbance:**

CBT

Hypnotics: zolpidem, eszopiclone
Fatigue

Target contributing factors: sleep, hot flashes, medical conditions

Target Fatigue:

- Physical activity
- Psychosocial interventions: CBT
- Mind body interventions

Cognitive impairment

**General management**: organizational strategies (notebooks, planners), avoid multi-tasking, relaxation

**Healthy lifestyle**: Exercise, limit use of alcohol

**Target contributing factors**: depression, sleep, pain, fatigue, medical comorbidities

**Target cognitive impairment**

- Brain fitness exercise ([www.brainhq.com](http://www.brainhq.com); [www.lumosity.com](http://www.lumosity.com))
- EEG biofeedback ([www.zengar.com/research](http://www.zengar.com/research)) (preliminary)

**Refer patients for neurocognitive assessment and rehabilitation**

Cardiovascular risk

Thrombosis prevention:
Exercise, compression aids if long immobilization

Optimize risk factors:
Monitor lipid levels, blood pressure, and provide cardiovascular monitoring and treatment, as indicated
Educate breast cancer survivors on healthy lifestyle, potential cardiac risk factors, and when to report relevant symptoms
Screen survivors for risk of osteoporosis with DEXA:
   Age > 65
   Age 60-64 with family history osteoporosis, < 70 kg, prior fracture, other risk factors (smoke, alcohol)
   Treatment with aromatase inhibitor
   Young survivors with premature menopause (or on ovarian suppression)

Health behaviors: Exercise, Calcium + Vit D

Treat osteoporosis:
   Initiate bisphosphonate/denosomab therapy
For patients under treatment with aromatase inhibitor, regular DEXA
Resources available

http://www.journeyforward.org/
https://nccih.nih.gov/health/providers
http://www.cancerandcareers.org/en
http://www.canceradvocacy.org/resources/employment-rights/
http://www.canceradvocacy.org/resources/health-insurance/
https://www.cancer.org/treatment/finding-and-paying-for-treatment/understand
http://www.cancer.org/treatment/survivorshipduringandaftertreatment/stayingac
American College of Sports Medicine: ACSM ProFinder: Search for Certified
http://www.cancersupportivecare.com/whyexercise.html
http://www.livestrong.org/YMCA
https://www.silversneakers.com

Guidelines:
ASCO
NCCN
ESMO
National guidelines
Conclusions

- Substantial proportion of patients suffering from side effects of cancer therapy
- It is important to address side effects and individualize treatment options
- Substantial progress was made to mitigate long term side effects of treatment but many challenges remain in optimizing breast cancer survivorship care and long term effects management
- Additional research is needed to better understand, prevent and manage the long-term and late effects of cancer therapy
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