PATIENT SEMINAR: LONG-TERM AND LATE SIDE-EFFECTS OF CHEMOTHERAPY

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EACH YEAR 1.6 MILLION FEMALES DIAGNOSED WITH CANCER IN EUROPE

Of these, 682 657 diagnosed with gynecological cancers, incl. breastcancer
IN 2012, 4.6 MILLION WOMEN LIVED IN EUROPE WITH A HISTORY OF CANCER DIAGNOSED PREVIOUS 5 YEARS

>2.5 million were gynecological cancer survivors

Many received chemotherapy

Millions of women in Europe living with consequences of cancer and cancer treatment
CHEMOTHERAPY – A SYSTEMIC CANCER THERAPY

• Chemicals/drugs travel in the bloodstream throughout the body

• It usually refers to cytotoxic drugs* i.e. cell killing drugs (*cytostatic inhibits tumor growth*)

• Affects all dividing cells, especially those with high turnover i.e. cancer cells

• Normal cells, especially with high cell turnover such as hair, bone marrow and mucosa, are also affected - give rise to adverse events (unwanted side-effects)

• Normal cells in general recover faster

*Kummar Br J Clin Pharm 2006*
CHEMOTHERAPY – SEVERAL SUBCLASSES

Basic subclasses

- **Alkylating and platinum agents**
  - e.g. cyclophosphamide, cisplatin
- **Antimetabolites**
  - e.g. methotrexate, 5-FU
- **Antimitotic**
  - e.g. taxanes
- **Cytotoxic antibiotics**
  - e.g. anthracyclines
- **Others**

Some drugs are cell cycle specific but many are cell cycle non specific (targets the entire cell cycle)
PATIENTS REACT DIFFERENTLY TO CHEMOTHERAPY - As of today no predictive marker for adverse events
THE RISK OF UNWANTED SIDE-EFFECTS IS ASSOCIATED WITH SEVERAL FACTORS

Chemotherapy related factors
- Specific type of chemotherapy
- Duration and dose of treatment
- Route of administration
  - Intravenous
  - Oral
  - Intraperitoneal
- Interval
  e.g. q3 weeks (normal cells allows to recover)
- Single or combination chemotherapy

Cancer

Previous cancer treatments
- Surgery
- Radiotherapy
- Chemotherapy
- Targeted therapy
- Endocrine therapy

Patient characteristics
- Age
- Co-morbidity, Performance status
- Body Mass Index
- Smoking
- Genetic variants e.g. peripheral neuropathy
**ACUTE, LONGTERM AND LATE SIDE-EFFECTS**

**Acute side-effect** starts during treatment (TXT) and resolve after end of TXT

**Longterm side-effects** starts during TXT but do not resolve e.g. pain, fatigue, cognitive impairment

**Late side-effects** develops much later, after TXT has ended, e.g. second malignancy, heart failure

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**Rapidly proliferating tissue e.g. GI, blood counts, hair**

**Peripheral neuropathy**

**Slowly proliferating tissue e.g. CNS, cardiovascular, second primary malignancies**

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TXT=treatment
CNS=central nervous system

Runowitz et al. JCO 2016
**Central nervous system**: nausea, vomiting, encephalitis, fatigue

**Hearing**: impairment

**Mucous membranes e.g. Mouth, Eyes**: sores

**Lung**: pneumonitis

**Circulatory**: cardiac failure, hypertension, tromboembolism

**Hepatic**: hepatitis

**Immune system**: hypersensitivity

**Genitals**: Ovarian failure: premature menopause (sweating, hot flushes, osteoporosis), Infertility, Sexual dysfunction, Vaginal dryness

**Peripheral nervous system**: Sensory neuropathy (numbness, tingling hands and feet, pain) Motor neuropathy (muscle weakness)

**Brain**: cognitive dysfunction

**Hair and skin**: hairloss, rash, cracked skin, altered pigmentation, hand-foot disease (PPE)

**Hematological/blood**: Anemia Leukopenia Neutropenic sepsis Trombocytopenia – bruises, bleeding Secondary malignancies

**Gl tract**: no appetite, diarrhoea, nausea, vomiting, reflux, constipation

**Renal/urological**: renal failure, cystitis, electrolyte loss

**Fingers and toes**: nail changes

**Muscle and joint**: pain

**PHYSICAL SIDE-EFFECTS OF CHEMOTHERAPY**
LONG-TERM AND LATE EFFECTS OF CHEMOTHERAPY

• The frequency (prevalence) of various longterm and late side-effects of chemotherapy is difficult to quantify
  • Few longitudinal longterm studies
  • Many patients receives combination of different treatment modalities e.g. surgery and chemotherapy

• Estimations that at least 50% of cancer survivors experience longterm or late side-effects

Valdivieso et al. 2012
# SIDE-EFFECTS OF CHEMOTHERAPY

## Longterm side-effects e.g.

- **Peripheral neuropathy**, especially after taxanes; sensory -numbness, tingling, pain and motor dysfunction (slow fine moves); ≥ 20 yrs

- **Cognitive dysfunction**: immediate and delayed verbal memory, processing speed, executive function, psychomotor speed; ≥ 20 yrs

- Fatigue

- **Menopaus-related symptoms**: flash, sweat, vaginal dryness, urinary complaints, arthralgia etc.

- Sexual dysfunction

- Infertility

- Oral and dental health issues

- Hair loss

- Sleep disorders

- **Hearing impairment**, especially after cisplatin

## Late side-effects e.g.

- **Osteoporosis/ osteopenia (ovarian failure)**

- Anthracycline-induced heart failure

- Secondary primary malignancies e.g. leukemia, myelodysplastic syndrome

## Important to:

- **educate** patients and health care providers about longterm and late side-effects
- **have access to multiprofessional team of experts** dedicated to cancer rehabilitation

*Koppelmans 2012; Hogendams 2015; Skalleberg 2017*
THE SIDE-EFFECTS OF CANCER AND ITS TREATMENT

Fatigue
Infertility
Lymphedema
Pain
Cognitive impairment
Premature menopause
Sexual dysfunction
Secondary cancers

Fatigue
Anxiety/Depression
Fear of recurrence
Loss of control
Distress, post-traumatic stress disorder
Identity

Relations & Roles
Family distress & Fear of recurrence
Employment
Economy burden
Enjoyment
Isolation

Doubt
Faith
Inner strength
Hope
Meaning
Religiously

Stein Cancer 2008; Ricceri IJC 2015; Hodgkinson 2006;
Burg Cancer 2015

Nordic Cancer Union
Rehabilitation of cancer patients
www.ncu.nu
OBJECTIVES OF FOLLOW-UP AFTER CANCER TREATMENT

• Not only early detection of recurrent disease but also

• Assess side-effects; by physicians and patients

• Patient education and support
  • Patients should be educated about symptoms of potential recurrence and potential long-term and late effects of treatment
  • Patients should also be counseled on sexual health, life-style adaptation, nutrition, exercise, obesity and cessation of smoking
OBJECTIVES OF FOLLOW-UP AFTER CANCER TREATMENT

• Cancer rehabilitation, with the goal to prevent and reduce physical, psychosocial, social and existential consequences of cancer and its treatment
  • Family members/caregivers should be included
  • Several professions for counseling should be available e.g. psychologist, sexual therapist, physiotherapist, and dietitian

• Follow-up schemes may be individualized taking prognostic factors, treatment modality and estimated risk and/or occurrence of side-effects into account

ESGO-ESTRO-ESP Guidelines cervical cancer 2017
TAKE HOME MESSAGE

- Millions of women in Europe have survived cancer and/or are living with gynecologic cancer
- Many of them suffer from longterm and/or late side-effects after cancer and its treatment, such as chemotherapy
- Patients, next-to-kin and health care providers needs to be educated about longterm and late side-effects
- Multiprofessional/multidisciplinary networks of dedicated specialists needed and the care needs to be coordinated
  - Cancer rehabilitation start from diagnosis and a rehabilitation plan should be created and provided to all cancer patients
- Predictive markers needed to identify those with highest chance of benefit and those with highest risk of side-effects – so that treatment is tailored to the individual patient
- Knowledge of the mechanism behind side-effects has led to advances in treatment techniques – needs to be continued.
Always tell your doctor about your history of cancer and treatment
WE SEE MORE OF THE ICEBERG

More research needed about longterm and late side-effects

THANK YOU
CHEMOTHERAPY – GOAL OF TREATMENT/SETTINGS

Curative
To completely destroy cancer cells by chemotherapy
Mostly hematological malignancies, also GTD, MGCT
*Severe adverse events may be accepted*

Adjuvant
Postoperative/postRT to get rid off remaining microscopic cancer cells and prevent recurrence

Neoadjuvant
Reduce tumor size and metastases to facilitate surgery and/or RT

Maintenance
To postpone recurrence/tumor progression, may be given for long time

Palliative
Relieve symptoms and improve QoL by reducing tumor size or prolonging time to progression
*Severe adverse events not acceptable*

GTD=gestational trophoblastic disease
MGCT=malignant germinal cell tumors
RT= radiotherapy
QoL=quality of life