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

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	No, nothing to disclose
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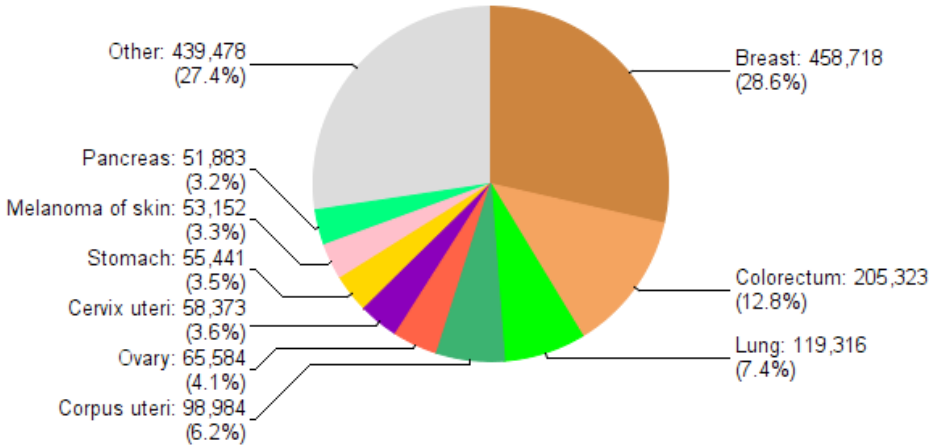
Astra Zeneca		X						
Merck Sharp & Dohme		X						
Boehringer-Ingelheim		X						

EACH YEAR 1.6 MILLION FEMALES DIAGNOSED WITH CANCER IN EUROPE

Europe: Female

Estimated number of cancer cases, all ages (total: 1606,252)

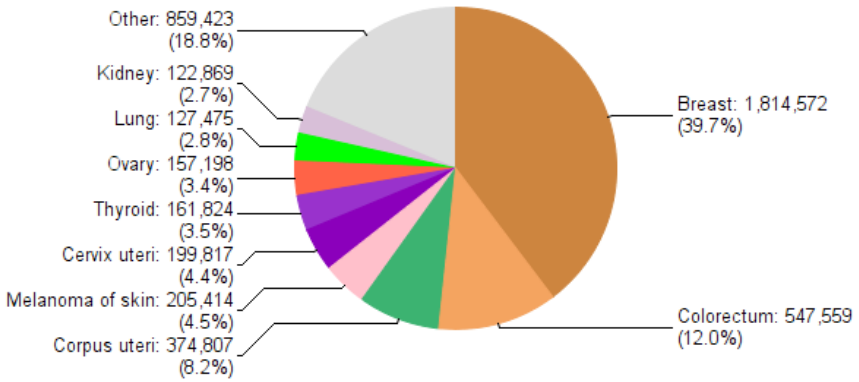


GLOBOCAN 2012 (IARC) - 3.10.2017

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

Europe: Female
Estimated 5-year prevalent cancer cases, adult population (total: 4570,958)



GLOBOCAN 2012 (IARC) - 3.10.2017

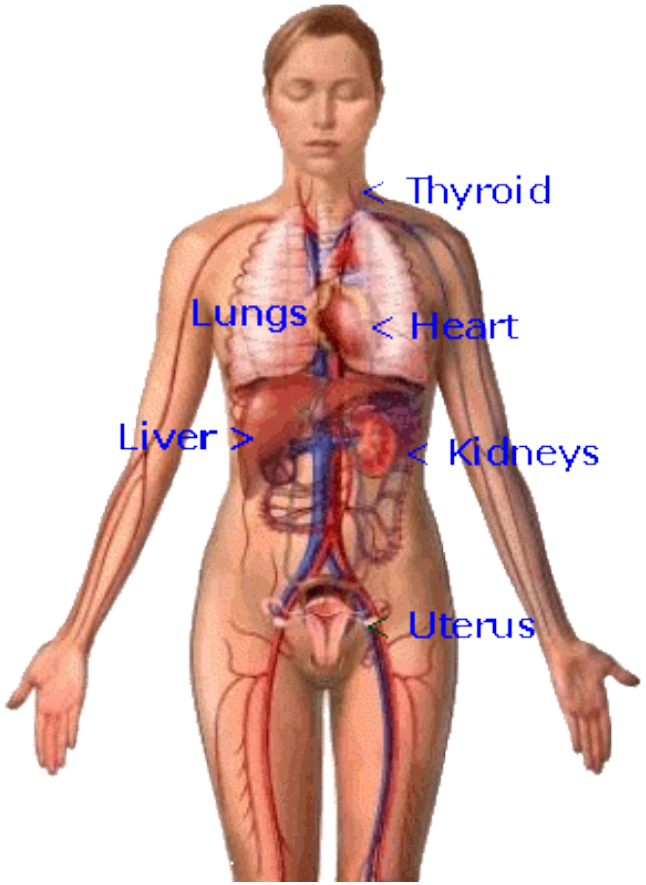
>2.5 million were gynecological cancer survivors

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

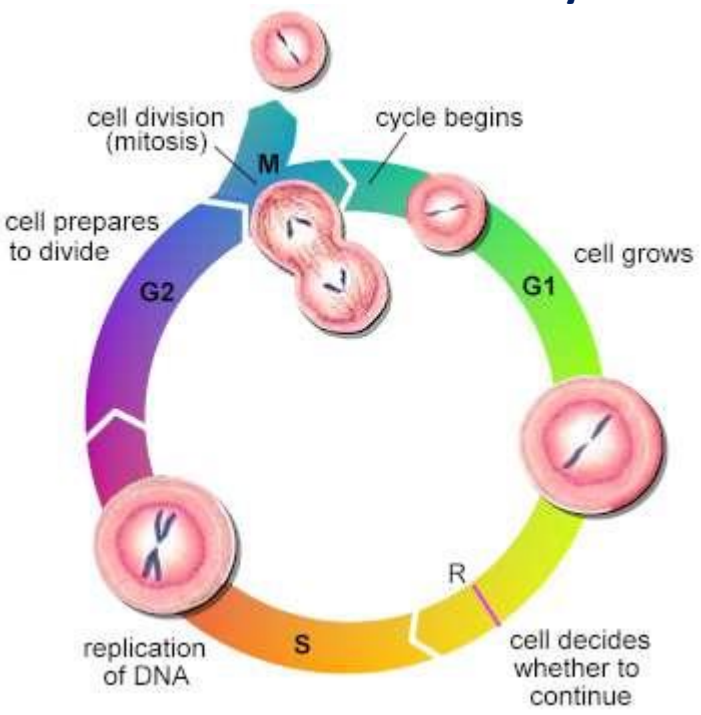
  e.g. taxanes

- Cytotoxic antibiotics

  e.g. anthracyclines

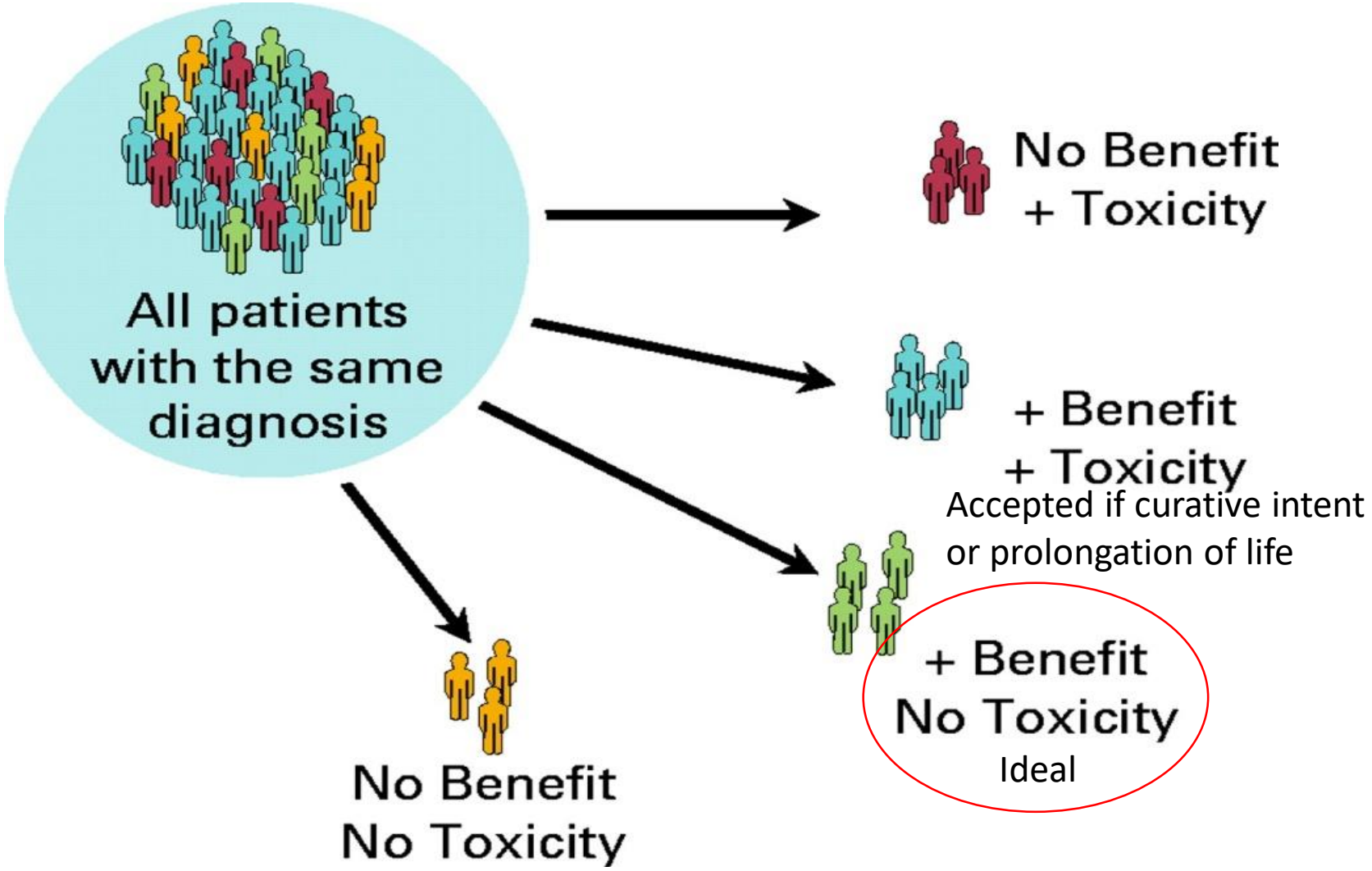
- Others

Cell life cycle



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

Cancer

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

Previous cancer treatments

- Surgery
- Radiotherapy
- Chemotherapy
- Targeted therapy
- Endocrine therapy

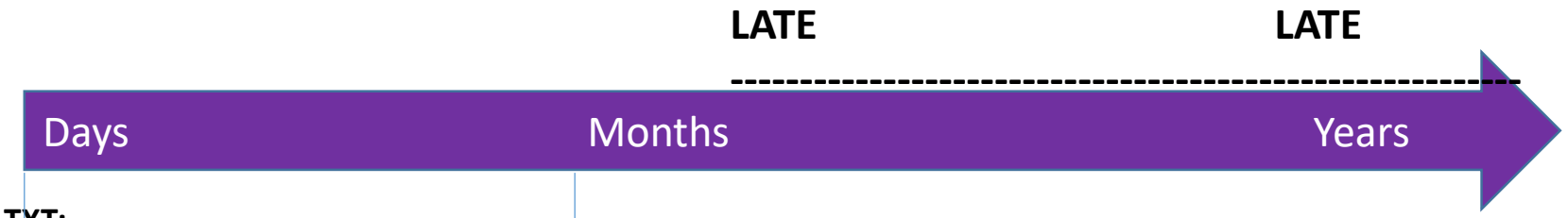
Patient characteristics

- 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

ACUTE----------
ACUTE----------LONGTERM----------PERSISTENT---



TXT:
Day 1

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

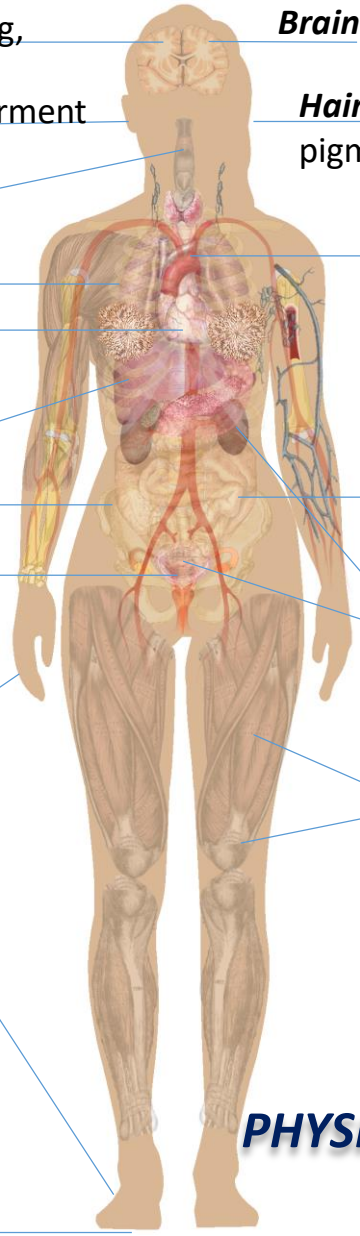
Last Day, Last TXT

Peripheral neuropathy

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

TXT=treatment
CNS=central nervous system

Runowitz et al. JCO 2016



Central nervous system: nausea, vomiting, encephalitis, fatigue

Brain: cognitive dysfunction

Hearing impairment

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

Mucous membranes e.g.Mouth, Eyes sores

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

Lung: pneumonitis

Circulatory: cardiac failure, hypertension, tromboembolism

Hepatic: hepatitis

Immune system: hypersensitivity

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

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

Renal/urological: renal failure, cystitis, electrolyte loss

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

Muscle and joint: pain

Fingers and toes: nail changes

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:

- **<u>educate</u> patients and health care providers about longterm and late side-effects**
- **<u>have access to multiprofessional team of experts</u> dedicated to cancerrehabilitation**

Koppelmans 2012; Hogendams 2015; Skalleberg 2017

THE SIDE-EFFECTS OF CANCER AND ITS TREATMENT

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

PHYSICAL

PSYCHOLOGICAL

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

SOCIAL

EXISTENTIAL

Doubt
Faith
Inner strength
Hope
Meaning
Religiously

IMPACT QUALITY OF LIFE

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 longterm and late effects of treatment
  - Patients should also be counseled on sexual health, life-style adaptation, nutrition, exercise, obesity and cessation of smoking

ESGO-ESTRO-ESP Guidelines cervical cancer 2017

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
  - Cancerrehabilitation 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

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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