



Basic principles of oncological treatment - chemotherapy

WORLD HEALTH ORGANIZATION definition:

A MEDICINE IS A SUBSTANCE OR PRODUCT THAT IS USED TO MODIFY OR TEST PHYSIOLOGICAL SYSTEMS OR PATHOLOGICAL CONDITIONS FOR THE WELL-BEING OF THE RECIPIENT.

LAW ON DRUGS AND MEDICINE DEVICES OF REPUBLIC OF SERBIA definition:

A MEDICINE IS A PRODUCT CONTAINING A SUBSTANCE OR A COMBINATION OF SUBSTANCES MANUFACTURED AND INTENDED FOR THE TREATMENT OR PREVENTION OF DISEASE IN HUMANS OR ANIMALS, DIAGNOSING, IMPROVING OR CHANGING PHYSIOLOGICAL FUNCTIONS, AS WELL AS ACHIEVING OTHER, MEDICALLY JUSTIFIED GOALS

DRUGS ARE SUBSTANCES, THEIR COMBINATIONS AND PREPARATIONS USED FOR THE TREATMENT OF DISEASES

Drugs in oncology

Antineoplastic drugs

THE GOAL OF ONCOLOGY (TUMOR) TREATMENT – TO CAUSE THE DEATH OF TUMOR CELLS (BY DIRECT TOXIC EFFECTS OR INITIATING THE PROCESS OF APOPTOSIS) WITHOUT CAUSING DEATH OR SERIOUS CONSEQUENCES TO THE PATIENT'S HEALTH.

THE IDEAL GOAL IS TO ACHIEVE HEALING, AND IF THAT IS NOT POSSIBLE, THEN THE GOAL IS REDEFINED - TO ACHIEVE DISEASE CONTROL

BY CONTROLLING DISEASE, WE GET AN EXTENSION OF LIFE AND A BETTER QUALITY OF LIFE

Antineoplastic drugs

CYTOSTATICS

HORMONES

TARGET THERAPY

IMMUNOTHERAPY

OTHER MEDICINES

Antineoplastic drugs

- A SYSTEMIC TYPE OF THERAPY
- USED AS A SINGLE AGENT OR IN COMBINATION WITH OTHER TYPES OF TREATMENT
- THEY ARE COMBINED WITH TREATMENT THAT HAS LOCAL OR LOCOREGIONAL (SURGERY AND RADIOTHERAPY) EFFECT,

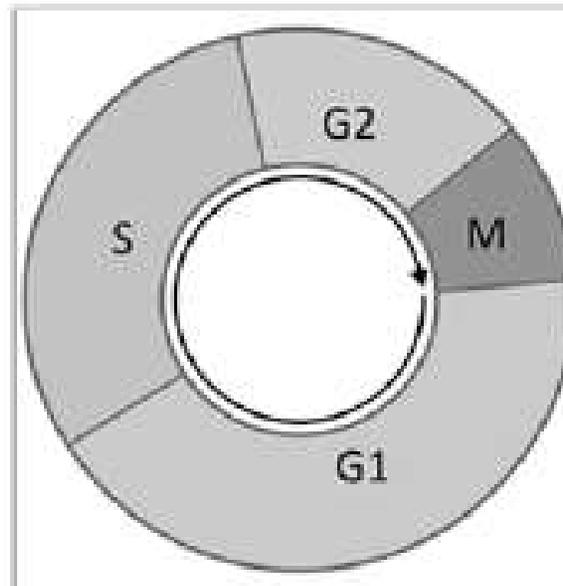
ANTINEOPLASTIC DRUGS

- THE FRACTION OF DIVIDING TUMOR CELLS IS THE PERCENTAGE REPRESENTATION OF CELLS THAT ARE IN THE PROCESS OF DIVISION IN RELATION TO THE TOTAL NUMBER OF TUMOR CELLS
- THE FRACTION OF TUMOR CELLS THAT ARE DIVIDING DIRECTLY INFLUENCES THE EFFECTIVENESS OF DRUG TREATMENT
- TUMORS WHOSE CELLS IN A HIGHER PERCENTAGE DIVIDE RAPIDLY ARE GENERALLY MORE SENSITIVE TO DRUGS
- CELLS WHICH ARE AT REST MOST OFTEN SURVIVE THE USE OF MOST ANTINEOPLASTIC DRUGS

Chemotherapy: Mechanism of action

- **Chemotherapy = cytotoxic medications**

- **Alkylating Agents**
- **Platinum agents**
- **Anti-metabolites**
- **Nucleoside analogs**
- **Topoisomerase inhibitors**
- **Anti-Microtubule agents**



G1 - Growth

S - DNA synthesis

G2 - Growth and preparation for mitosis

M - Mitosis (cell division)

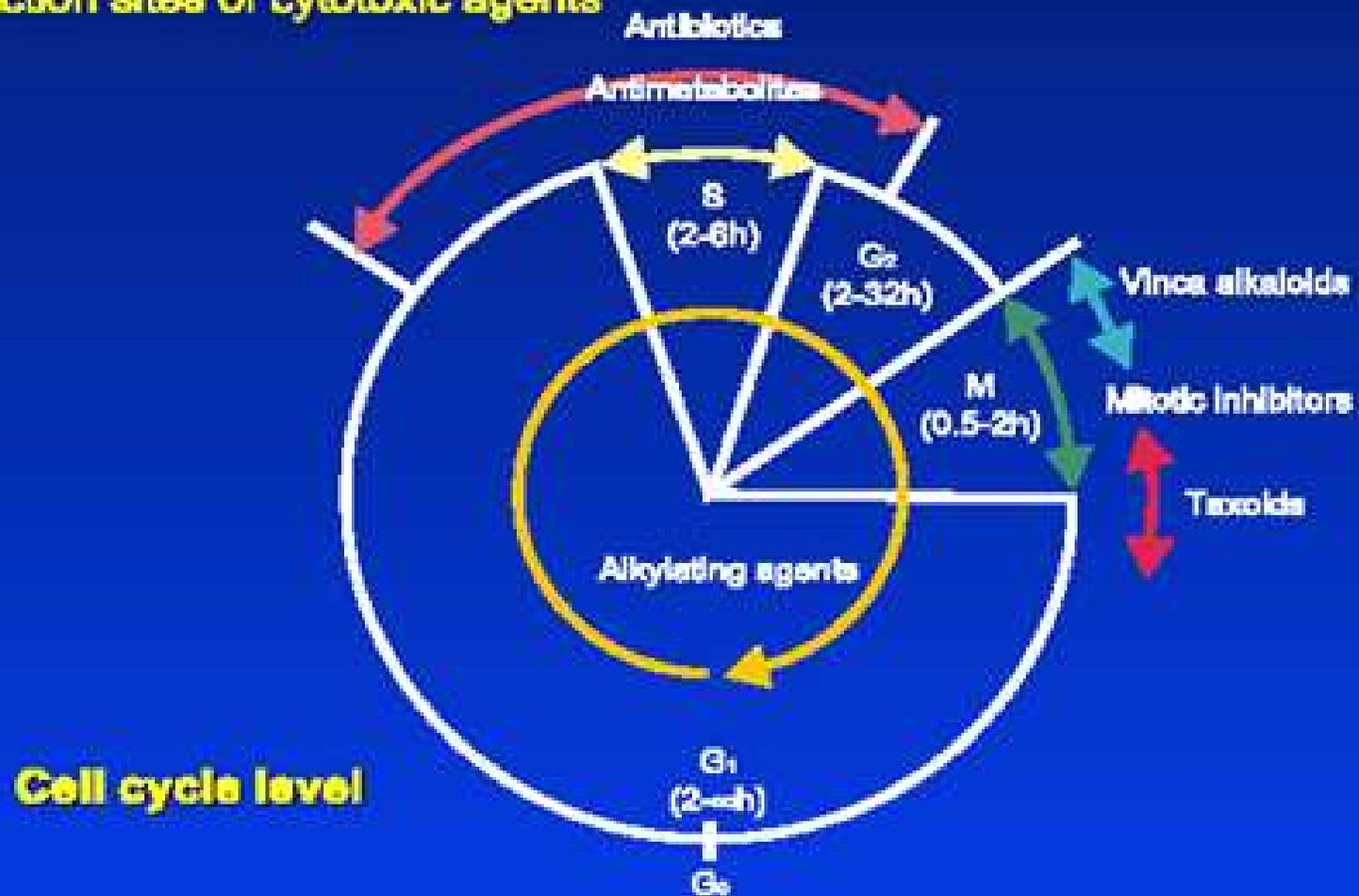
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ONCOLOGY

Principles of chemotherapy

Action sites of cytotoxic agents

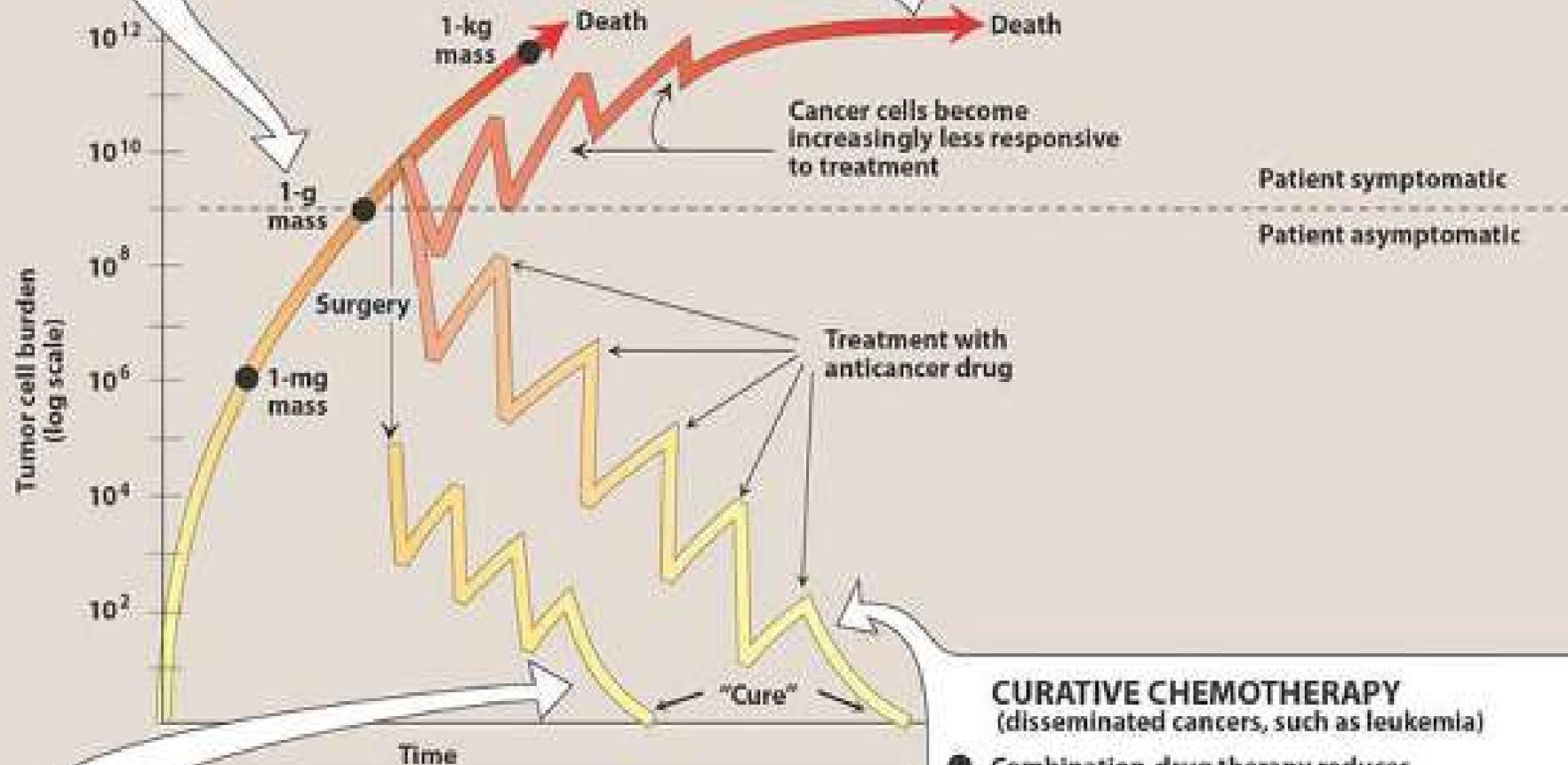


SIGNIFICANCE OF A 1-g TUMOR MASS

- A total of 10^9 cells is the smallest tumor burden that is physically detectable.
- These 1 billion cells represent a tumor weighing about 1 g or about the size of a small grape.
- Clinical symptoms usually first appear at this stage.

PALLIATIVE CHEMOTHERAPY

- Initial remissions are transient, with symptoms recurring between treatments.
- Survival is extended, but the patient eventually dies of the disease.



CURATIVE CHEMOTHERAPY (solid tumors, such as testicular carcinoma)

- Tumor burden is initially reduced by surgery and/or radiation.
- Treatment of occult micrometastases is continued after clinical signs of cancer have disappeared.

CURATIVE CHEMOTHERAPY (disseminated cancers, such as leukemia)

- Combination-drug therapy reduces the chance of drug resistance.
- Each drug is chosen to have a different cellular site of action or different cell-cycle specificity.
- Each drug is chosen to have a different organ toxicity.

Antineoplastic drugs

INDIVIDUAL DRUGS (MONOTHERAPY) OR COMBINATIONS OF MULTIPLE DRUGS (COMBINED CHEMOTHERAPY, POLYCHEMOTHERAPY) CAN BE USED DURING THE TREATMENT.

Antineoplastic drugs

- INDIVIDUAL DRUGS or SINGLE AGENT (MONOTHERAPY)
- ADVANTAGES:
 - SIMPLE APPLICATION
 - LOWER TOXICITY
 - POSSIBILITY OF APPLICATION IN PATIENTS WITH A LOWER PERFORMANCE STATUS
 - DEFICIENCY: LOWER EFFICIENCY
 - FASTER DEVELOPMENT OF RESISTANCE

Antineoplastic drugs

- ADVANTAGES OF COMBINED CHEMOTHERAPY:
 - ENSURES MAXIMUM EFFICIENCY
 - IT IS EFFECTIVE IN TREATING THE GREATER NUMBER OF DIFFERENT CELL LINES WHICH EXIST IN MOST TUMORS
 - PREVENTS OR DELAYS THE DEVELOPMENT OF DRUG RESISTANCE
- DISADVANTAGES OF COMBINED THERAPY:
 - MORE EXPRESSED TOXICITY
 - LIMITATION OF APPLICATION (PATIENT'S PERFORMANCE STATUS, COMORBIDITY,
 - DURATION OF THERAPY,
 - SIMULTANEOUS THERAPY OF OTHER MODALITIES)

Drug resistance

- MULTIPLE DRUGS RESISTANCE DUE TO MDR-1 OVEREXPRESSION
- RESPONSIBLE FOR THE MEMBRANE GLYCOPROTEIN P-170
- P-170 FUNCTIONS AS A PUMP THAT PUSHES HYDROPHOBIC CHEMICALS OUT OF THE CELL (RESISTANCE TO ANTHRACYCLINES, VINCA ALKALOIDS, EPIPODOPHYLOTOXINS)
- voltage-dependent calcium channels inhibitor (Verapamil) can block activity of P-170

Drug resistance

- RESISTANCE OVERCOMING CAN BE ACHIEVED/DELAYED INTRODUCING SHORT-TERM, INTENSIVE, INTERMITTENT TREATMENT USING DRUG COMBINATIONS

Antineoplastic drugs

WHEN DO WE USE CHEMOTHERAPY?

- WHEN WE WANT TO CURE A MALIGNANT TUMOR (CURATIVE INTENT)
- WHEN WE WANT TO DELAY DISEASE PROGRESSION AND IMPROVE THE QUALITY OF LIFE
- WHEN WE WANT TO ACHIEVE PALLIATION OF SYMPTOMS (PALLIATIVE CHEMOTHERAPY)
- WHEN WE WANT TO ENABLE SURGICAL TREATMENT – DOWNSTAGING, DOWNSIZING (NEOADJUVANT CHEMOTHERAPY)
- WHEN WE WANT TO REDUCE THE POSSIBILITY OF DISEASE RECURRENCE AFTER SURGICAL TREATMENT (ADJUVANT CHEMOTHERAPY)

Antineoplastic drugs

WHEN DO WE NOT USE CHEMOTHERAPY?

- WHEN THERE ARE NO ADEQUATE CONDITIONS FOR DRUG ADMINISTRATION AND PATIENT FOLLOW-UP
- WHEN THE EXPECTED LIFESPAN DOES NOT ALLOW TREATMENT BENEFIT TO ACHIEVE
- WHEN THERE ARE NO TREATMENT BENEFIT
- WHEN THERE ARE CONTRAINDICATIONS FOR THE ANTINEOPLASTIC DRUG USE DUE TO EXISTING COMORBIDITY

Antineoplastic drugs

HOW LONG DO WE USE CHEMOTHERAPY? THE LENGTH OF THE TREATMENT DEPENDS ON THE CHEMOTHERAPY REGIME AND THE INTENT

- CURATIVE-TO HEALING
- PALLIATIVE - UNTIL PALLIATION OF SYMPTOMS IS ACHIEVED
- NEOADJUVANT – PRECISE DEFINED PROTOCOLS AND LENGTH
IF SURGICAL TREATMENT DO NOT BECAME AN OPTION - THE TREATMENT GETS PALLIATIVE CHARACTER
- ADJUVANT – BASED ON TUMOR TYPE

IN CASE OF EXPRESSED TOXICITY AND/OR ADVERSE EFFECTS, THE TREATMENT IS DISCONTINUED (TEMPORARY OR PERMANENTLY)

Antineoplastic drugs

RECIST (Response Evaluation Criteria In Solid Tumors)

- **RECIST - Definitions**

Measurable Lesions

Non-Measurable Lesions

Target Lesions

Non-Target Lesions

RECIST is simple. Using RECIST is not.

Antineoplastic drugs

- *Complete response (CR)*: Disappearance of all target lesions
- *Partial response (PR)*: At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
- *Stable disease (SD)*: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
- *Progressive disease (PD)*: At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

CHEMIOPROTECTIVE DRUGS

THEIR ROLE IS TO PROTECT THE PATIENT OR MINIMIZE THE HARMFUL EFFECTS OF CHEMOTHERAPY

- AMIFOSTINE IS A CYTOPROTECTIVE ADJUVANT USED IN CANCER CHEMOTHERAPY AND RADIOTHERAPY INVOLVING DNA-BINDING CHEMOTHERAPEUTIC AGENTS - A ROLE IN KIDNEY PROTECTION
- DEXRAZOXANE- REDUCES THE CARDIOTOXIC EFFECT OF CHEMOTHERAPY
- MESNA - REDUCES OR DISABLES BLADDER IRRITATION

Antineoplastic drugs

Dosage recommendations

THE TUMOR TREATMENT GOAL IS TO CAUSE THE DEATH OF TUMOR CELLS (BY DIRECT TOXIC EFFECTS OR APOPTOSIS INITIATION) WITHOUT CAUSING DEATH OR SERIOUS CONSEQUENCES TO THE PATIENT'S HEALTH.

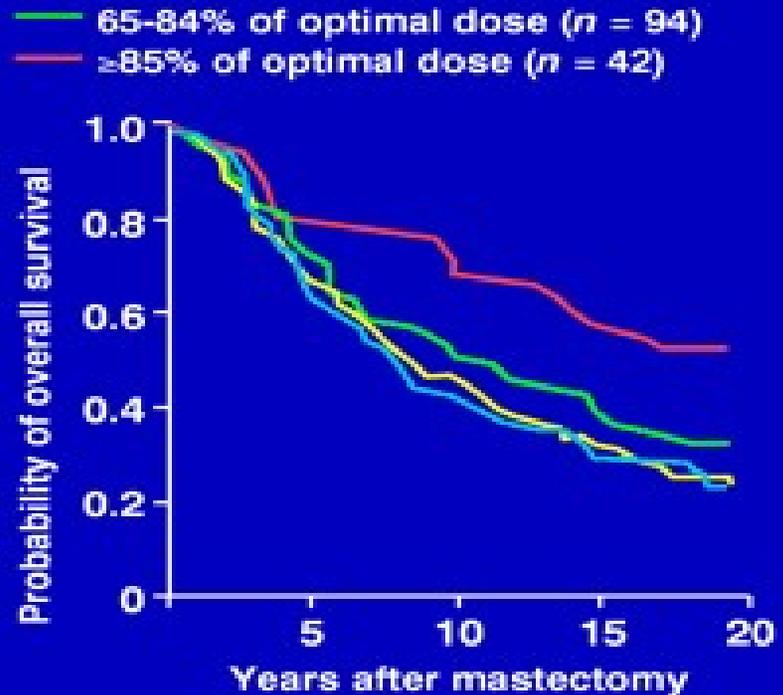
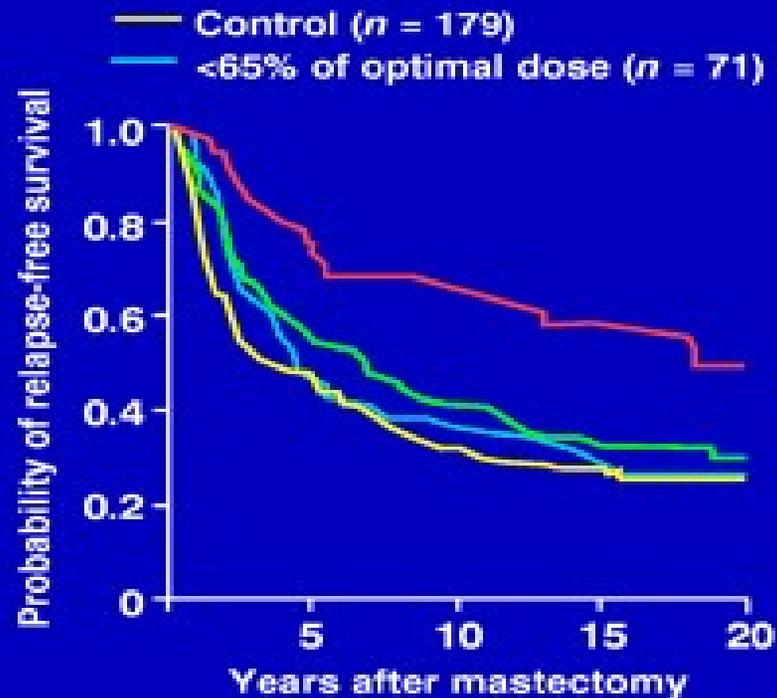
Antineoplastic drugs

DOSE-EFFECTIVENESS RELATIONSHIP

- LINEAR RELATIONSHIP?
- (INCREASING THE DOSE=BETTER TREATMENT EFFECT)20%
- DOSE REDUCTION IN EXPERIMENTAL MODELS REDUCES CURE RATE UP TO 50% WITH NO CHANGE IN COMPLETE RESPONSE RATE

Antineoplastic drugs

Adjuvant CMF in node-positive breast cancer: suboptimal doses associated with poorer outcome



Antineoplastic drugs

- DOSE INTENSITY IS THE DOSE OF DRUG PRESCRIBED IN A UNIT OF TIME
- HOW TO INCREASE THE INTENSITY OF THE DOSE (ACHIEVE BETTER OUTCOME)?

Antineoplastic drugs

Effect of chemotherapy dose intensity and density on tumor cell kill and regrowth between cycles



Antineoplastic drugs

SUCCESSFUL CHEMOTHERAPY ADMINISTRATION DEPENDS ON MULTIPLE FACTORS

- AGE
- PERFORMANCE STATUS
- COMORBIDITY
- RENAL AND LIVER FUNCTION
- HEMATOLOGICAL STATUS
- DRUG TOXICITY PROFILE
- INTERACTIONS BETWEEN DRUGS
- PREVIOUS OR CONCOMITANT TREATMENT

Antineoplastic drugs

Dosage in the elderly: No dose adjustment for the starting dose is required, but patients should be closely monitored and dose modification should be performed as described above. Older patients are more susceptible to the effects of fluoropyrimidine-based therapies with increased grade 3 / 4 adverse effects, especially when used in combination.

Description: Karnofsky scale	Karnofsky scale (%)	ECOG scale	Description: ECOG scale
No complaints; No evidence of disease	100	0	Asymptomatic; normal activity
Able to carry on normal activity; minor signs or symptoms of disease	90	1	{ Symptomatic; ambulatory; able to carry out activities of daily living
Some signs or symptoms of disease with effort	80		
Cares for self; unable to carry on normal activity or to do active work	70	2	{ Symptomatic; in bed less than 50% of the day; occasionally needs nursing care
Requires occasional assis- tance but is able to care for most personal needs	60		
Requires considerable assistance and frequent medical care	50	3	{ Symptomatic; in bed more than 50% of the day; needs nursing care
Disabled; requires special care and assistance	40		
Severely disabled; hospital- ization indicated, although death not imminent	30	4	{ Bedridden; may need hospitalization
Very sick; hospitalization necessary; requires active supportive treatment	20		
Moribund; fatal processes progressing rapidly	10		
Dead	0		Dead

Note: ECOG = Eastern Cooperative Oncology Group.

Antineoplastic drugs

COMORBIDITY

Cardiac toxicity is similar to that reported for other fluorinated pyrimidines and includes ECG changes, angina, infarction, dysrhythmias and cardiac failure. The risk may be increased in patients with prior coronary artery disease.

Antineoplastic drugs

Dosage with renal impairment: Moderate renal impairment results in an increase in severe toxicity.

<i>Creatinine Clearance (mL/min)</i>	<i>% of starting dose</i>
51 - 80	100 % with close monitoring
30 - 50	75 % (use with caution)
<30	CONTRAINDICATED

LIVER FUNCTION

- Creatinin 1.5xULN (Upper normals of limit)
- Liver enzymes (AST, ALT) up to 5xULN in case of metastases in liver
- Bilirubin 2.5xULN

Antineoplastic drugs

Dosage with hepatic impairment: In patients with mild to moderate hepatic impairment exposure is increased, but no dose adjustment is necessary, although caution should be exercised. Use dose modification table above for increases in bilirubin. The use of capecitabine in patients with severe hepatic impairment has not been studied.

Antineoplastic drugs

- **Dose reduction in hepatic dysfunction**

Drug	Mild	Moderate	Severe
• Adriamycin	50	75	Omit
• Daunorubicin	25	50	Omit
• Taxanes	Omit	Omit	Omit
• Vinca alkaloids	50%	Omit	Omit
• Epipodophyllotoxins	50%	Omit	Omit
• Synthetic alkaloid	50%	Omit	Omit
• Methotrexate	0%	25%	Omit
• Cyclophosphamide	0%	5%	Omit
• 5-Fluorouracil	0%	0%	Omit

Antineoplastic drugs

- **Dose reductions in renal dysfunctions based on CrCl (ml/min.)**

• Drug	30-60	10-30	<10
• Cisplatin	50%	Omit	Omit
• Carboplatin	20%	30%	30%
• Cyclophosphamide	0%	0%	50%
• Bleomycin	25%	25%	50%
• Methotrexate	50%	Omit	Omit
• Nitrosureas	Omit	Omit	Omit

Antineoplastic drugs

Hemathology:

White blood cells $> 3000 \times 10^9$

Neutrophyls $> 1500 \times 10^9$

Plateletes $> 100 (90) \times 10^9$

Hemoglobin $> 100 (90) \text{ g/L}$

Chemotherapy regime

DRUG COMBINATIONS – PRINCIPLES

- EACH INDIVIDUAL DRUG IN COMBINATION SHOULD HAVE ANTI-TUMOR ACTIVITY
- DRUGS IN COMBINATION SHOULD HAVE DIFFERENT MECHANISM OF ACTION
- THEY SHOULD HAVE DIFFERENT TOXICITY PROFILES
- THE MECHANISM OF RESISTANCE DEVELOPMENT SHOULD BE DIFFERENT
- SYNERGISM IN ANTI-TUMOR ACTIVITY IS DESIRED

Chemotherapy regime

- AC+T or TAC
 - A for adryamicin, C for cyclophosphamide and T for taxanes
 - For HER2 positive patients dual HER2 blockade is mandatory (Trastuzumab+Pertuzumab)
 - Indications: breast cancer
-
- Before each cycle, lab work
 - cardiac ECHO or MUGA scan - LVEF
 - Mandatory premedications

Chemotherapy regime

- Cisplatin-Fluorouracil
- Indications: head and neck cancer, esophagus, stomach, etc
- Every 28 days, four to six cycles

- Each cycle requires:
 - Lab work
 - Premedications
 - Hydration

Chemotherapy regime

- **FOLFOX** regime
- FOL(folinic acid/leucovorin)F(fluorouracil)OX(oxaliplatin)
- Indications: colon cancer

- Each cycle requires:
- Lab work
- Premedications
- Hydration