GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

PRINCIPLES OF CHEMOTHERAPY IN CANCER

Prof. N. PAVLIDIS

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DISCLOSURE OF INTEREST

Nothing to declare

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HISTORY OF CHEMOTHERAPY THROUGH THE YEARS

The First Chemotherapeutic Agent Found

- **On *December 2, 1943* Bari's harbor was bombed by a flight of 105 German bombers. Among the 24 ships of the alliance, one ship named SS John Harvey was carrying a secret cargo of 100 tons of liquid mustard gas. Many seamen on surrounding ships who survived developed blistering of epithelial surfaces, reduced white blood cells and profound lymphoid and myeloid suppression on autopsies.**

- **Using this information Goodman and Gilman – two pharmacologists from the Yale School of Medicine - reasoned that this agent could be used to treat lymphoma.**

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INTRODUCTION

- **Cancer chemotherapy is a modality of cancer therapy that involves the administration of chemical agents to destroy cancer cells.**

- **The aim of cancer chemotherapy is to cure where possible and palliative where cure is impossible**

- **The effective use of chemotherapy needs a deep understanding of the principles of tumor biology, cellular kinetics, pharmacology and drugs resistance**

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RESULTS OF CHEMOTHERAPY THROUGH THE YEARS (1949-2015)

Chemotherapy

1. **Can cure cancer (even in advanced stages)**
   - Germ – cell tumors (i.e. testicular cancer)
   - Hodgkin's disease
   - Non –Hodgkin's lymphomas
   - Gestational choriocarcinoma
   - Pediatric tumors (i.e. lymphomas, leukemias neuroblastoma, bone sarcomas)

2. **Can achieve considerable prolonged survival (in advanced stages)**
   - Breast cancer
   - Ovarian cancer
   - Colorectal cancer
   - Lung cancer
   - Other hematological malignancies (i.e. leukemias, myeloma)

3. **Can achieve prolonged progression-free survival (as an adjuvant treatment in non-metastatic disease)**
   - Breast cancer
   - Colorectal
   - Ovarian cancer

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ALKYLATING AGENTS

Mechanism of action: **Target DNA, produce alkylation through formation of intermediates. No phase-specific drugs**

Busulfan

Chlorambucil

Cisplatin, Carboplatin, Oxaliplatin

Cyclophosphamide, Ifosfamide

Dacarbazine

Mechlorethamine (Nitrogen Mustard)

Melphalan

Nitrosoureas

Procarbazine

Streptozotocin

Temozolomide

Thiotepa

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ANTIMETABOLITES

Mechanism of action **: Interfere with DNA synthesis. They are structural analogs or they inhibit several enzymes. S-phase specific**

Aracytidine

Cytarabin

Fludarabine

Fluorouracil

Leucovorin

Capecitabine

Gemcitabine

Hydroxyurea

Mercaptopurine

Methotrexate

Pemetrexed

Pentostatin

Raltitrexed

Thioguanine

Trimetrexate

Uracil / Tegafur (UFT)

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ANTITUMOR ANTIBIOTICS

Mechanism of action **Cause linkage of double strands of DNA and prevent replication. They are derived from microorganisms. Cell cycle specific drugs.**

Actinomycin –D

Bleomycin

Daunorubicin

Doxorubicin

Doxorubicin Liposomal

Epirubicin

Idarubicin

Mitomycin

Mitoxantrone

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MITOTIC SPINDLE AGENTS

Mechanism of action: **Bind to microtubular proteins, thus inhibit microtubule assembly resulting in dissolution of the mitotic assembly structure. M- phase specific drugs.**

Docetaxel
Paclitaxel
Paclitaxel Albumin
Cabazitaxel

Vincristine
Vinblastine
Vinorelbine

Eribulin (Non-taxane tubulin binding agent
A marine sponge product)

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TOPOISOMERASE INHIBITORS

Mechanism of action: **DNA Topoisomerases I and II are essential enzymes for transcription, replication and mitosis. The following drugs are able to inhibit these enzymes.**

Topoisomerease I inhibitors

Irinotecan

Topotecan

Topoisomerase II inhibitors

Etoposide

Teniposide

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MISCELLANEOUS AGENTS

Asparaginase

Estramustine

Hexamethymelamine

Octreotide

Velcade

MODES OF CHEMOTHERAPY ADMINISTRATION

- **Intravenous**
- **Oral**

Local Drug Application

Intra-arterial (i.e. hepatic infusion, limb perfusion)

Intra-thecal (menengeal metastasis)

Intra-peritoneal (ovarian cancer, peritoneal carcinomatosis)

Intra- pleural (pleurisy / pleural metastases)

Intra-pericardial (malignant pericardial effusion)

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PRINCIPLES OF COMBINATION CHEMOTHERAPY

- Use drugs active as a single agent
- Use drugs with different mechanisms of action
- Use drugs with different mechanisms of resistance
- Use drugs with different side-effects
- Be aware of drug-drug interactions

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COMMON COMBINATION CHEMOTHERAPY REGIMENS

Cancer Type	Drugs	Acronym
Breast Cancer	Cyclophosphamide, methotrexate, 5-FU Doxorubicin (Adriamycin), cyclophosphamide Doxorubicin (Adriamycin), Paclitaxel (Taxol)	CMF AC AT
Hodgkin's disease	Mustine, Vincristine (Oncovin), Procarbazine, Prednisone Doxorubicin (Adria), bleomycin, vinblastine, dacarbazine	MOPP ABVD
Non-Hodgkin's lymphoma	Cyclophosphamide, doxorubicin, vincristine, prednisone	CHOP
Germ cell tumor	Bleomycin, etoposide, cisplatin	BEP
Stomach cancer	Epirubicin, cisplatin, 5-FU	ECF
Bladder cancer	Methotrexate, vincristine, doxorubicin, cisplatin	MVAC
Colorectal cancer	5-FU, folinic acid, oxaliplatin	FOLFOX

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RATIONALE OF SYSTEMIC CHEMOTHERAPY

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1. NEOADJUVANT CHEMOTHERAPY [PREOPERATIVELY]

Rationale

- To make non-operable tumors operable
- To achieve organ preservation
- To select sensitivity for specific treatment (biomarkers)

2. ADJUVANT CHEMOTHERAPY [POSTOPERATIVELY]

Rationale

- To kill micrometastatic disease
- To increase disease-free survival

3. PALLIATIVE CHEMOTHERAPY

Chemotherapy given to control symptoms or prolong life in a patient in whom cure is unlikely

4. SALVAGE CHEMOTHERAPY

A potentially curative, high-dose regimen given in a patient who has failed or recurred following a prior curative regimen.

5. **INDUCTION CHEMOTHERAPY**

The intent is to induce complete remission when initiating a curative regimen (usually applied to hematologic malignancies)

6. **CONSOLIDATION CHEMOTHERAPY**

Repetition of the induction regimen in a patient who has achieved a complete remission after induction, with the intent of increasing cure rate or prolonging remission.

7. **DOSE INTENSIFICATION CHEMOTHERAPY**

Strategy to overcome drug resistance through:

(i) highest possible dose
(ii) shortest possible intervals
(iii) with supportive use of G-CSF

8. **DOSE INTENSIFICATION CHEMOTHERAPY**

Marrow-ablative doses of chemotherapy to increase tumor cell-kill, while rescuing the host with:

(i) autologous bone marrow
(ii) donor bone marrow
(iii) peripheral stem-cells

9. MAINTENANCE CHEMOTHERAPY

Long – term, low dose, single or combination chemotherapy in a patient who has achieved a complete remission, with the intent of delaying the regrowth of residual tumor cells.

10. METRONOMIC CHEMOTHERAPY

Oral chronic administration of chemotherapy (i.e. cyclophosphamide, etoposide, vinorelbine) has both antitumorigenic and antiangiogenic effect on tumor endothelial tumor cell. Endothelial cells are 10-100 times more susceptible to chemotherapy.

11. CHEMORADIATION

- **Integration of chemotherapy with radiotherapy**
- **Drugs commonly use are 5-FU and Cisplatin**
- **Enhancement of tumor response (radiosensitization)**
- **Protection of normal tissue**

EVALUATION OF RESULTS
(EFFICACY)

PARAMETERS TO BE EVALUATED IN SYSTEMIC TREATMENTS

RESPONSE (Response Evaluation Criteria In Solid Tumours – RECIST – 2000)

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 targeted lesions

STABLE DISEASE (SD) : Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

PROGRESSIVE DISEASE (PD) : At least a 20% increase in the sum of the LD of targeted lesions.

DURATION OF RESPONSE *OR* TIME TO PROGRESSION (TTP) : The time from response to progression

PARAMETERS TO BE EVALUATED IN SYSTEMIC TREATMENTS

SURVIVAL

DISEASE-FREE SURVIVAL (DFS) : **From the time of treatment to first recurrence**

OVERALL SURVIVAL (OS) : **From the time of diagnosis to death**

PRE- CHEMOTHERAPY ASSESSMENT

- **Full blood count (Hb, WBCs, Plts)**
- **Renal function (creatinine, GFR)**
- **Liver function (enzymes, bilirubin)**
- **Avoid 3rd space occupation (excessive ascites or pleurisy)**
- **Performance status (ECOG Scale)**

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ECOG Performance Status Scale

Status	Definition
0	Normal activity
1	Symptoms, but ambulatory
2	In bed <50% of time
3	In bed >50% of time
4	100% bedridden

ECOG = Eastern Cooperative Oncology Group.

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CHEMOTHERAPY TOXICITY

CHEMOTHERAPY TOXICITIES (I)

TOXICITY	DRUG INDUCED	ANTIDOTE
Bone marrow suppression (anemia, leucopenia, thrombocytopenia)	Almost all	Erythropoietin, G-CSF, blood transfusions
Nausea-vomiting	Platinum Anthracyclines Alkylatings	1. Serotonin receptors antagonists 2. NK 1 receptor antagonists 3. Tacykinin, 4. Olanzapine
Alopecia	Anthracyclines Taxanes	Scalp-cooling techniques (not universally accepted)
Cardiotoxicity	Anthracyclines Cyclophosphamide 5-FU	Early detection. Dexrazoxane

CHEMOTHERAPY TOXICITIES (II)

Pulmonary toxicity	Bleomycin Alkylatings Gemcitabine	Early detection. Corticosteroids
Nephrotoxicity	Platinum Methotrexate (↑dose)	Adequate hydration
Neurotoxicity	Alkaloids Platinum Taxanes	Early detection
Gonadal damage	Alkylatings Others	Sperm preservation
Second malignancies	Alkylatings	Avoid if possible responsible drugs and/or RT in curable diseases

RESISTANCE TO CHEMOTHERAPY

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RESISTANCE TO CHEMOTHERAPY

- ***Primary Resistance***

  When the cancer does not respond to standard chemotherapy from the very first exposure

- ***Acquired Resistance***

  When the tumour initially responds to chemotherapy and then becomes resistant.

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MECHANISMS OF RESISTANCE TO CHEMOTHERAPY (I)

- **Cancer cells may be mutated & develop pathways that are independent of those blocked by cytotoxic drugs.**

- **Gene amplification may lead to overproduction of proteins that are blocked by anticancer drugs.**

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MECHANISMS OF RESISTANCE TO CHEMOTHERAPY (II)

- **Cancer cells may develop mechanism that inactivate anticancer drugs.**

- **They may learn to repair the DNA & protein damages induced by anticancer drugs.**

↓ (leading to)

- **Resistant clones of cancer cells may develop.**

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Thank You