

# PRINCIPLES OF CHEMOTHERAPY IN CANCER

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# DISCLOSURE OF INTEREST

Nothing to declare

# 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**.

# 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**

# 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

# 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**

# 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)**

# 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**

# 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**

**Vincristine**

**Paclitaxel**

**Vinblastine**

**Paclitaxel Albumin**

**Vinorelbine**

**Cabazitaxel**

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

# 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.

## **Topoisomerase I inhibitors**

**Irinotecan**

**Topotecan**

## **Topoisomerase II inhibitors**

**Etoposide**

**Teniposide**



# **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 (meningeal metastasis)**

**Intra-peritoneal (ovarian cancer, peritoneal carcinomatosis)**

**Intra- pleural (pleurisy / pleural metastases)**

**Intra-pericardial (malignant pericardial effusion)**



# **PRINCIPLES OF COMBINATION CHEMOTHERAPY**

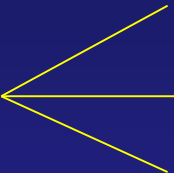
- **Use drugs active as a single agent**
- **Use drugs with different mechanisms of action**
- **Use drugs with different mechanisms of resistance**
- **Use drugs with different side-effects**
- **Be aware of drug-drug interactions**

# COMMON COMBINATION CHEMOTHERAPY REGIMENS

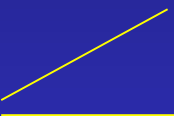
Cancer Type	Drugs	Acronym
Breast Cancer	Cyclophosphamide, methotrexate, 5-FU Doxorubicin (Adriamycin), cyclophosphamide Doxorubicin (Adriamycin), Paclitaxel (Taxol)	CMF AC AT
Hodgkin's disease	Mustine, Vincristine (Oncovin), Procarbazine, Prednisone Doxorubicin (Adria), bleomycin, vinblastine, dacarbazine	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

# **RATIONALE OF SYSTEMIC CHEMOTHERAPY**

## 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 3<sup>rd</sup> space occupation (excessive ascites or pleurisy)**
- **Performance status (ECOG Scale)**



TABLE 12.1

## 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.

# 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**  
**Alkylating**

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



# 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.



# **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.**



## **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.**

THANK YOU