DISCLOSURE OF INTEREST

Nothing to declare
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.
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
**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
**Mechanism of action**: Interfere with DNA synthesis. They are structural analogs or they inhibit several enzymes. S-phase specific

<table>
<thead>
<tr>
<th>Antimetabolites</th>
<th>Antimetabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aracytidine</td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td>Cytarabin</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Pemetrexed</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Pentostatin</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>Raltitrexed</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Thioguanine</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Trimetrexate</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>Uracil / Tegafur (UFT)</td>
</tr>
</tbody>
</table>


**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
- Paclitaxel
- Paclitaxel Albumin
- Cabazitaxel
- Vincristine
- Vinblastine
- Vinorelbine
- 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.

<table>
<thead>
<tr>
<th>Topoisomerase I inhibitors</th>
<th>Topoisomerase II inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan</td>
<td>Etoposide</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Teniposide</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Drugs</th>
<th>Acronym</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>Cyclophosphamide, methotrexate, 5-FU Doxorubicin (Adriamycin), cyclophosphamide Doxorubicin (Adriamycin), Paclitaxel (Taxol)</td>
<td>CMF AC AT</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>Mustine, Vincristine (Oncovin), Procarbazine, Prednisone Doxorubicin (Adria), bleomycin, vinblastine, dacarbazine</td>
<td>MOPP ABVD</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>Cyclophosphamide, doxorubicin, vincristine, prednisone</td>
<td>CHOP</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>Bleomycin, etoposide, cisplatin</td>
<td>BEP</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>Epirubicin, cisplatin, 5-FU</td>
<td>ECF</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Methotrexate, vincristine, doxorubicin, cisplatin</td>
<td>MVAC</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>5-FU, folinic acid, oxaliplatin</td>
<td>FOLFOX</td>
</tr>
</tbody>
</table>
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 3rd space occupation (excessive ascites or pleurisy)
• Performance status (ECOG Scale)
<table>
<thead>
<tr>
<th>Status</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal activity</td>
</tr>
<tr>
<td>1</td>
<td>Symptoms, but ambulatory</td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt;50% of time</td>
</tr>
<tr>
<td>3</td>
<td>In bed &gt;50% of time</td>
</tr>
<tr>
<td>4</td>
<td>100% bedridden</td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group.
CHEMOTHERAPY TOXICITY
CHEMOTHERAPY TOXICITIES

**TOXICITY**

- Bone marrow suppression (anemia, leucopenia, thrombocytopenia)
- Nausea-vomiting
- Alopecia
- Cardiotoxicity

**DRUG INDUCED**

- **Platinum**
  - Anthracyclines
  - Alkylating
- **Anthracyclines**
- **Taxanes**

**ANTIDOTE**

- Erythropoietin, G-CSF, blood transfusions
- 1. Serotonin receptors antagonists
- 2. NK 1 receptor antagonists
- 3. Tacikinin
- 4. Olanzapine
- Scalp-cooling techniques (not universally accepted)
- Early detection. Dexrazoxane
CHEMOTHERAPY TOXICITIES (II)

Pulmonary toxicity
- Bleomycin
- Alkylating agents
- Gemcitabine
- Early detection
- Corticosteroids

Nephrotoxicity
- Platinum
- Methotrexate (↑dose)
- Adequate hydration

Neurotoxicity
- Alkaloids
- Platinum
- Taxanes
- Early detection

Gonadal damage
- Alkylating agents
- Others
- Sperm preservation

Second malignancies
- Alkylating agents
- 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.
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 a mechanism that inactivates 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