Chemotherapy in Gynecologic Malignancies

Dr U.D. Bafna
Professor & Head, Department of Gynecologic Oncology, Kidwai Memorial Institute of Oncology, Bangalore
Chemotherapy in solid tumors is mainly adjuvant to surgery/radiotherapy and not by itself curative except in Gestational Trophoblastic Tumors.

Chemotherapy drugs act on the rapidly dividing cells by damaging the DNA/cytoplasmic organelles; and in the bargain destroy normal cells also.

Normal cells, however, recover faster by repairing the DNA.
Timing of chemotherapy

* Neoadjuvant – chemotherapy given before definitive treatment by surgery or radiotherapy
* Concomitant – given along with radiotherapy
* Adjuvant – Given postop or post RT to tackle potential microscopic disease
* Adjunctive – given postop to tackle gross macroscopic disease
Molecular targeted therapy (MTT)

- Molecular targeted therapy, on the other hand, act by targeting a specific target on the cell membrane (receptors)
- or target intra-cellular signaling pathways.

- They block or target a specific function – eg, angiogenesis and other growth factors
Cell signaling pathways in cancer
Chemotherapy

- Normal cells recover faster by repairing the damaged DNA
- In cancer cells this DNA repair mechanism is sub-optimal and takes longer time to recover
- Therefore, chemotherapy is given at intervals which allow the recovery of normal cells but not cancer cells
But over a period of time, unless completely destroyed, cancer cells develop mechanism to overcome damage caused by CT (Cellular intelligence).

Chemoresistance is the main reason why most cancers relapse and are not curable.
It is important to prevent development of chemotherapy resistance, if possible, by:

1. Follow proper dosage
2. Follow proper schedule weekly, 3 weekly etc)
3. Administer optimal number of cycles so as to destroy most of the cancer cells as soon as possible
4. Use appropriate chemotherapeutic drug
Curable cancers

* Are highly chemosensitive destroying 99% of cancer cells during each cycle
* Generally cured by 3-6 cycles eg GTT, GCT
* Chemoresistance is rare as most of the ca cells are destroyed.
Chemotherapy

- Ovarian cancer
- Endometrial
- Cervical ca
- Sarcoma
- GTT
- Vulva/vagina
Chemotherapy of ovarian ca

* **Epithelial cancers**
  - Type I epithelial ca – low grade serous, mucinous, endometroid and clear cell ca
  - Type II epithelial ca – high grade serous ca
* **Germ cell cancers** – Dysgerminoma, Yolk sac tumor, Immature teratoma, embryonal ca and mixed
* **Stromal cancers** – Granulosa and Sertoli Leydig cell
Epithelial Ovarian ca

* Type I – clear cell ca, mucinous adenoca, endometroid and low grade serous and borderline tumors.
* These are low grade cancers

They are relatively **unresponsive to chemotherapy** and are associated with kras and braf mutations which produce abnormal ras, raf proteins present in the cytoplasm (important for cell signaling).

In future targeted therapies with kras, braf etc inhibitors may play a role.
Type II ca – high grade serous cystadenoca

These tumors are aggressive, rapidly growing tumors

Commonest epithelial ovarian ca (>70%)

Are associated with p53 mutations producing abnormal TP53 protein

Familial ca also are generally high grade serous ca and in addition have BRCA, MMR gene mutations
* Type II cancers are moderately chemo-sensitive with response rates of 80%
* Chemotherapy is generally not curative except in stage I
* It can only increase the overall survival if properly used
Type II ovarian ca

- Conventional Standard chemotherapy has been a combination of Paclitaxel and carboplatin.
* P and C has been used in various ways
* Three weekly IV
* Weekly IV
* Intra-peritoneally
Paclitaxel and carboplatin

Standard regimen –
* Paclitaxel 175 mg/sq.m + Carboplatin AUC 6 given once in three weeks for six cycles

Dose Dense regimen (Chemotherapy given more frequently with same or more total dose)
* Paclitaxel 80 mg/sq.m + Carboplatin weekly or three weekly

Japanese trial showed overall survival of 100 months in advanced ovarian ca as compared to 39-45 months with standard regimen!!! This trial has not yet been replicated in other studies.
Intra-peritoneal chemotherapy

* Intra-operative normothermic -
* HIPEC- Heated IP intra-operative chemotherapy
* Late Post-operative repeated chemotherapy by placing a semi-permanent catheter with attached port
Postoperative chemotherapy using implanted peritoneal catheter with port has shown very promising results as compared to IV chemotherapy (60 months vs 45 months OS).

But it is cumbersome.

- Catheter can perforate bowel, result in infection.
- Results in abdominal pain due to fibrosis lasting for up to one year.
- More hematologic toxicity due to slow absorption in to the blood from peritoneal cavity.
Figure 6: An intraperitoneal catheter. The port is implanted under the skin. The attached rubber catheter delivers chemotherapy directly into the peritoneal cavity.
* Intra-peritoneal chemotherapy with indwelling catheter should be the standard of care in properly trained units.
Heated intraoperative intraperitoneal chemotherapy with temp of the peritoneal solution constantly maintained to 42 degree C for 60 to 90 minutes by HIPEC machine which constantly delivers and drains the solution mixed with chemotherapy drug (inflow and outflow) by a specially placed drains in to the abdominal cavity.

The abdominal cavity is kept open or closed during this process.

Subsequent 5 cycles are given IV once in three weeks
Closed technique of HIPEC
HIPEC

- Still experimental
- Has shown improved OS in retrospective studies even in chemoresistant tumors
- Is associated with prolonged paralytic ileus, metabolic and renal problems
- Expensive and needs critical care management and TPN
Other chemotherapy regimens in epithelial ovarian cancers

* Single agent IV carboplatin in older women/medically compromised patients
* **Liposomal doxorubicin and carboplatin** is non-inferior and alternative regimen to P+C
* The QOL is better, and it is given once in four weeks so frequent hospital visits are avoided.
Epithelial Ovarian ca – 5 year survival

- Stage I – 90
- Stage II – 70
- Stage III – 30
- Stage IV - <5%
- Most of the patients present with stage III & IV
Most of these patients have PFS of 18 – 24 months.
Most patients would recur and would require second line chemotherapy after 18-24 months.
With second line and subsequent chemo the OS is 38-60 months.
As most patients with advanced ovarian ca would recur maintenance therapy has been tried without much success,

Exercise, yoga and diet play important role in preventing relapse

Molecular Targeted Therapy – cediranib, pazopinib and olaparib may improve OS but QOL is not good – loss of taste, appetite etc.
Second Line chemotherapy

- First line the RR – 80%
- Second line chemotherapy response is better if the recurrence is delayed >12 months after last chemotherapy
- More is the disease free interval better is the response
* As platinum is the most active drug in ovarian ca – recurrence is classified based on platinum free interval after the last chemotherapy
Recurrence

- **Cisplatin refractory** – disease progression during CT. These patients do not respond to any chemotherapy.
- **Cisplatin resistant** – disease recurrence within 6 months of last chemo. Do not usually respond to any chemotherapy.
- 6-12 – Partially cisplatin sensitive
- > 12 months – cisplatin sensitive. These patients usually respond well to – either same or different chemotherapy regimen.
Germ Cell tumor of the ovary

- One of the most curable malignancies even is advanced stages III & IV
- Most chemosensitive
- Therefore, surgery is fertility preserving as these tumours occur mostly below the age of thirty years.
- Optimal debulking is done only if morbidity is not unduly increased.
- Lesser the tumor burden less is the number of chemotherapy cycles.
Chemotherapy of malignant germ cell tumours of the ovary

* Three to four cycles of BEP regimen (Bleomycin, Etoposide and Cisplatin) are generally curative.
* Proper dosing and schedule should be maintained to prevent chemoresistance
* Except stage I dysgerminoma, Immature teratoma Stage I &G1-2 - all malignant germ cell tumors – Yolk sac, embryonal ca, chorioca require adjuvant chemotherapy
* Contraception is advised for a period of one year after chemotherapy- to allow recovery /elimination of the damaged oocytes
* Risk of recurrence is mostly within the first year, if at all!!
Granulosa cell tumor/S-L cell tumours – most present in stage I and surgery is curative.

Stage > I may benefit from P+C or BEP

Slow growing hence response to chemo not very good and difficult to assess.
General Toxicity and principles of chemotherapy

* Paclitaxel + Carbo - myelosuppression. Usually recovers before the next cycle is due.
* If the recovery is delayed by > 1 week dose should be reduced by 20% or **CSF – filgrastim** should be used
* Total WBC count should be > 3500 and Neutrophil > 1500, Platelet > one lakh to start next cycle
* Chemotherapy should be delayed in the presence of stomatitis, mucositis.
Paclitaxel –
* Hypersensitivity due to cremaphor preservative
* Alopecia – almost total
* Peripheral Neuropathy occur in almost all causing tingling and numbness which last for many years.

Carboplatin has replaced **cisplatin which was more nephrotoxic, more emetogenic, causing more neuropathy**. Carboplatin causes more thrombocytopenia and allergic reactions as compared to cisplatin.
To avoid alopecia combination of Liposomal doxorubicin (PLD) + Carboplatin may be used in place of P+C
All stages may be managed by radiotherapy.

Stage IA and Ib1 surgery is preferred over radiotherapy.

Stage IB2 – IV – concomitant chemoradiation is the standard of care.
Cispaltin is given concomitantly with radiotherapy to:

- Potentiate the RT effect
- Tumoricidal by itself
- Has improved survival compared to RT alone.

Cisplatin is given weekly – 40 mg/sq.m X 6 cycles – during the entire course of RT which should be completed within 6-8 weeks.
* Cisplatin induced anemia should be corrected to have optimal radiotherapy response
* Hypoxia induced by anemia makes cancer less radiosensitive.
* Hemoglobin levels should be maintained to > 10 G% throughout the duration of the treatment
* Radiotherapy consists of both external radiotherapy and brachytherapy
Advanced Stage IV B(extra pelvic) and recurrent cancer is usually treated by P+C with or without bevacuzimab (Avastin) with palliative intent and to prolong survival.
Most present (>80%) in stage I or stage II unlike cervical cancer
Most are cured by surgery alone (with radiotherapy in some high risk cases)
Most do not require chemotherapy except in patients with adverse histology – clear cell, poorly diff ca etc. or
Advanced stages (Stage 3 & 4)– adnexal mets or Lymph node metastasis
Chemotherapy of endometrial cancer

- Cisplatin, doxorubicin and endoxan (CAP) regimen has been commonly used for many years.
- Recently, paclitaxel+ carboplatin is emerging as combination of choice.
Uterine Sarcoma – three main types

- Endometrial Stromal Sarcoma – low grade and high grade
- Leomyosarcoma
- Adenosarcoma

Note- Carcino-sarcoma also known as Malignant Mixed Mullerian Tumor is now classified as metaplastic endometrial ca and is not a true sarcoma
* Endometrial Stromal Sarcoma – low grade are usually ER and PR positive and may be treated with high dose progestins if there is extra-uterine spread
* High Grade ESS – all cases require chemotherapy
Uterine Sarcoma

- LMS are aggressive tumours with recurrence rates of 50% in stage I after surgery.
- Most cases require adjuvant chemotherapy to prevent recurrence.
Chemotherapy of uterine Sarcoma

- There is no Category I evidence in favor of chemotherapy.
- Combination chemotherapy may improve overall survival.
  - Ifosfamide + doxorubicin
  - Docetaxel + Gemcitabine
  - Trabectidin

  have shown promising response rates.
Gestational Trophoblastic Tumors

- Low Risk – single agent chemotherapy methotrexate is the choice
- High Risk – Combination chemotherapy should be used. EMACO regimen is the choice
- Low risk – 100% survival
- High Risk >85-90% cure rates.
 Generally 1-2 cycles in low risk and 2-3 cycles in high risk GTT are used after the serum bhcg levels have become normal
* Rare cancer
* Neoadjuvant chemotherapy has been used when it is difficult to excise the tumor with at least 1 cm margin-example when the tumor is close to the external urethral meatus, anal canal or involving vagina
* Neoadjuvant chemotherapy has also been used when there are fixed inguinal nodes.
Before and after chemotherapy
Managing Chemotherapy induced nausea and vomiting (CINV)

- Nausea and vomiting – very common
- Cisplatin is most emetogenic
- CINV is managed with lorazepam, palenosetron/granisetron/ondansetron (5HT3 antagonist), Steroids, aprepitant (acts on CTZ) and hydration
Fatigue

- Analgesics
- Walking
- Hydration and correcting electrolytes
Bone marrow suppression

- Peaks between 7-14 days
- Try and avoid cross infection
- Colony stimulating factors – Inj Filgrastim may be used if risk of severe neutropenia is high
- In case of febrile neutropenia institute antibiotic treatment immediately preferably as an inpatient. Could be fatal if not recognized and treatment is delayed > 24 hours.
Others

* Alopecia – wigs may be used or use chemotherapy with less risk of alopecia eg PLD + carbo
* Peripheral neuropathy – if it is severe change the drug. Vit E and gabapentin have been used
* Thrombocytopenia – platelet transfusion only if counts < 20,000
* Anemia – correct anemia preferably by erythropoetin to maintain hemoglobin around 11-12 g%
Hypersensitivity – Paclitaxel, carboplatin, liposomal doxorubicin are known to cause hypersensitivity reactions – recognize early and prevent it.
Thank You
Targeted therapy like PARP inhibitors – Olaparib (Lynparza) and VEGF inhibitors like bevacuzimab (Avastin), pazopanib (Votrient) appears promising.

- PARP protein is responsible for the repair of single strand DNA breaks.
- When PARP is inhibited DNA breaks are not repaired and result in double strand DNA breaks.
Double strand DNA repairs normally are repaired by homologous recombination.

This mechanism is hampered in BRCA mutations.

Hence PARP inhibitors cause accumulation of Double strand DNA breaks which are not repaired resulting in apoptosis and cell death.