Principles of Chemotherapy in Gynecological Cancer

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Conflicts of interest

Honoraria for lectures and advisory boards:

- Amgen
- Astra-Zeneca
- Celgene
- Daiichi-Sankyo
- Eisai
- Lilly
- MSD
- Mylan
- Nanostring
- Novartis
- Pfizer
- Pierre Fabre
- Puma
- Roche
- Vifor
Learning objectives

• Basic classification of chemotherapeutic agents
• Role of chemotherapy in ovarian cancer, uterine cancer, cervical cancer, vulvar cancer
• Assess the response for chemotherapy
• Management of toxicity
• General considerations
Chemotherapy in Gynecological Oncology
Indications – Achievements - Challenges

Breast Cancer – high risk of distant metastases:
- Early breast cancer  Adjuvant therapy leads to >50% less mortality / 15yrs!
- Metastatic breast cancer  Prolongation of PFS, palliation; OS benefit possible

Gynaecological Cancers – mainly locoregional / abdominal diseases:
- Ovarian cancer  Prolongation of OS (1L and 2L)
- Cervical cancer  Radiochemotherapy – alternative to radical surgery in 1L. Prolongation of progression and OS in 2L. Role of ICPi
- Endometrial Cancer  OS benefit in 1L. Later: Small effects. Options: endocrine therapy, immune checkpoint inhibitors (ICPi)
- Vulvar cancer  Rare indication, palliation (analogue to cervical cancer)
- Gestational trophoblastic neoplasia (GTN) – Chemotherapy - high chance of cure
Classification of antineoplastic drugs - cytotoxic chemotherapy -

- Platin-salts (cisplatin - CDDP, carboplatin - CDBCA)
  - Interaction with DNA-replication
    - Side effects: Nephrotoxicity, neurotoxicity, hearing loss, alopecia
- Spindle poisons (taxanes, vinca-alkaloids)
  - Inhibiting microtubule depolymerization: paclitaxel, docetaxel
  - Inhibiting microtubule polymerization: vinorelbine
    - Side effects: peripheral neuropathy, alopecia, myelosuppression
- Anthracyclines (doxorubicin, pegylated doxorubicin)
  - DNA-intercalation, topoisomerase II-inhibition
    - Side effects: vein toxicity, heart failure, alopecia, myelosuppression
- Alkylating compounds (cyclophosphamide)
  - DNA interstrand and intrastrand crosslinkages => apoptosis
    - Side effects: Myelosuppression, urotoxicity (in higher doses)

Chemistry:
- Coordination Complex (cis-diamino-dichloro-platinum)
- Natural products (taxanes: yew tree, vinorelbine: vinca plants (periwinkle))
- Bacterial product (Streptomyces)
- Nitrogen mustard-derived alkylating agent like ifosfamide

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Classification of antineoplastic drugs
- targeted drugs -

- Anti-angiogenic drugs
  - **Bevacizumab**: Antibody against VEGF (ligand capture to inhibit VEGF-R based activation of vessel growth) => tumour hypoxia
    - *Side effects: nephrotoxicity (protein loss), hypertension, impaired wound healing, GI-perforations; thrombo-embolic events*
  
- PARP-inhibitors
  - **Olaparib, niraparib, rucaparib**: Single strand DNA repair, most effective, if double strand repair is impaired (homologous repair deficiency - HRD, BRCA-mutation) – „synthetic lethality“
    - *Side effects: myelotoxicity, fatigue*

- Immune checkpoint inhibitors (anti-PD1-/antiPD-L1-antibodies)
  - **Pembrolizumab, nivolumab, durvalumab** (antiPD1-MoAb): blocking interaction between immune cells and tumor cells => activation of immune reaction
    - *Side effects: autoimmune-like (hypo-/hyperthyreodism, hepatitis, colitis, etc.)*

- Tyrosine kinase inhibitors (TKI)
  - **Lenvatinib**: oral multikinase inhibitor that targets VEGFR 1–3, FGFR 1–4, PDGFRe, RET, and KIT
    - *Side effects: hypertension, fatigue, diarrhea, stomatitis, decreased appetite*
Medical therapy in cancer - Toxicity

- Toxic drugs – indication important
- Tolerance depends on supportive care
  - Nausea, emesis  - prophylactic anti-emetic drugs
  - Myelosuppression  - dose, interval; G-CSF
  - Peripheral neuropathy  - compression gloves (& stocking)
  - Alopecia  - artificial hairs, wig
  - Renal failure  - hydration (also IV)
  - Pain  - analgetics (incl. opioids)
• Ovarian Cancer (EOC) – First-line
Current Treatment Concepts for Ovarian Cancer

Improve prognosis

Surgery

Drug therapy

OVARIAN CANCER
Ovarian cancer – Standards in first-line

• Standard
  – Surgery  Macroscopically tumor free
  – Medical therapy
    • Chemotherapy  Carboplatin\textsubscript{AUC5}/Paclitaxel_{175mg/m^2} q3w *6
    • antiVEGF-th.  Bevacizumab\textsubscript{7,5mg/kg} q3w for 15m (FIGO IIC+)

• New
  – Additional PARP-inhibitor (Niraparib, Olaparib) tablets for 2 years in pts with homologous repair deficiency (HRD) or germline BRCA1/2-mutation (BRCA1/2\textsuperscript{MUT})
Cisplatin/Paclitaxel (PT) vs Carboplatin/Paclitaxel (TC) (AGO Ovar-3 trial)

TC: Higher frequency of hematologic toxicity, but a lower frequency of gastrointestinal and neurologic toxicity, than in PT.

TC: Higher mean global quality-of-life scores at end of treatment than in the PT arm.

du Bois A et al., JNCI 2003;95:1320–30
Inhibition of angiogenesis

- VEGF, secreted by tumor cells, activates vessel growth

=> Anti-VEGF-MoAb (bevacizumab) catches the ligand VEGF, thus inhibiting its function by binding to the receptor VEGF-R and inhibiting vessel growth („Tumor starving“)

"Synthetic lethality"

- PARP-inhibition (no repair of single-strand DNA-breaks),
- Homologous recombination deficiency (no repair of double strand DNA-breaks)

=> PARP-Inhibition (niraparib, olaparib, rucaparib) effective in pts. with homologous repair deficiency (HRD, BRCA1/2\textsuperscript{mut})

* 20% in pts <50yrs with HG-EOC without family history
20-40% in pts with family history for EOC or BC
FIGO III/IV: Effect on PFS by surgery (residual tumor) and PARP-inhibitor (olaparib)

Surgery

\[ \Delta \text{PFS} \approx 30 \text{ m} \]

Olaparib

(76% optimally debulked)

\[ \Delta \text{PFS} > 30 \text{ m} \]

Postoperative residual tumor

Olaparib maintenance therapy after primary therapy in BRCA\text{mut}- pts. (OP + CBDCA/Paclitaxel)

PRIMA (niraparib vs placebo – FIGO III/IV) (HG-serous, FIGO III / optimally debulked excluded)

Homologous Recombination Deficient (HRd)

HRd/BRCAmut

HRd/BRCAwtn

HR-proficient

PFS Benefit in Biomarker Subgroups

PAOLA-1 (bevacizumab ± olaparib) (HG-serous, FIGO III/IV, 60% optimal debulking)

\[ \Delta \text{PFS} = 5.5 \text{ m} \]

Therapy 1L EOC – standards and perspectives

- Optimal surgery (without residual disease) plus 1L-therapy with carboplatin / paclitaxel – standard of care in EOC

- Molecular oncology provides new prospects of therapy (e.g. VEGF-inhibition, PARP-inhibition)
  - Inhibition of angiogenesis prolongs DFS (Bevacizumab)
  - Inhibition of PARP in HRD/BRCA\textsuperscript{mut} prolongs PFS (HG-EOC)
    - Patients with EOC should undergo genetic counseling and analysis (probability of BRCA1/2-mutation: up to 20%!)
      - Higher frequencies (-40%) with high-grade, family history, younger age
    - PARP-inhibitors - a substantial benefit in HRD/BRCA\textsuperscript{mut} patients

Paradiso AV et al. BMC Cancer 2019;19:641
Fumagalli C et al. Cancers (Basel) 2019;11:1641
• Ovarian Cancer (EOC) – Second-line
First question: Platinum sensitive or not?

- **Platinum-sensitive (≥6 months therapy-free)**
  - consider re-operation
  - re-challenge platinum-combinations (e.g. carboplatin-PEG-liposomal doxorubicin)
  - consider bevacizumab-containing regimen
  - consider PARP-inhibitors (independent from BRCA\textsuperscript{mut})

- **Platinum-resistant (<6 months therapy-free)**
  - topotecan
  - consider molecular tumorboard (NGS-analysis)

- **Platinum resistant and low grade**
  - Consider re-operation and chemotherapy. With low-grade disease consider maintenance with endocrine therapy (e.g. aromatase inhibitors)
Platin-combinations in platinum-sensitive recurrences of ovarian cancer

• Re-challenge regimen with similar efficacy

  – Carboplatin – paclitaxel*

  – Carboplatin – gemcitabine*

  – Carboplatin – pegylated doxorubicin

*analyzed also in combination with bevacizumab (antiVEGF-MoAb), if not given during 1L-therapy
OCEANS-trial: Bevacizumab-maintenance after carboplatin-gemcitabine

Carboplatin-gemcitabine + placebo

Carboplatin-gemcitabine + bevacizumab

Events, n (%): 187 (77%) 151 (62%)
Median PFS, months: 8.4 12.4
(95% CI): (8.3 to 9.7) (11.4 to 12.7)
Stratified analysis HR: 0.484
(95% CI): (0.388 to 0.605)
Log-rank P: <.0001

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• Role of PARP-inhibitors in therapy of relapse of HG-EOC (high grade serous ovarian cancer)
Olaparib maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21 – Phase 3)

**PFS-analysis (SOLO2)**

HR 0.30 (95% CI 0.22–0.41)  
*p*<0.0001  
Olaparib PFS\textsubscript{median} 19.1m  
Placebo PFS\textsubscript{median} 5.5m

**OS-analysis (Study 19 – Phase 2)**

HR 0.62 (95% CI 0.41–0.94)

Pujade-Lauraine E et al. Lancet Oncol 2017; 18: 1274–84 (SOLO2 - Phase 3)  
PARP-inhibition (niraparib) only with BRCA$^{\text{mut}}$?

- **BRCA1/2$^{\text{mut}}$**: HRD-positives (HRD-pos.)
- **BRCA1/2$^{\text{WT}}$**: HRD-negatives (HRD-neg.)

Treatment of **platinum-sensitive** recurrent ovarian cancer

- Re-challenge with a carboplatin-containing combination *(preference carboplatin-pegyl. doxorubicin)*
  - if not done before, add bevacizumab-maintenance (effect: $HR = 0.48$)

- Targeted option:
  **PARP-inhibitors** (niraparib, olaparib) should be given as maintenance therapy until disease progression (effect: $HR = 0.27^{BRCA_{mut}} - HR = 0.058^{BRCA_{wt-HRD_{neg}}}$)
  - combination with bevacizumab (unknown)
Treatment sequence in Ovarian Cancer

Platinum-resistant recurrence of ovarian cancer (<6 months therapy-free)

**Chemotherapy** (combination not better than single agent)
- Pegyliertes liposomales Doxorubicin (±Bevacizumab)
- Topotecan (±Bevacizumab)
- Gemcitabin
- Paclitaxel wöchentlich (±Bevacizumab)

Particularly in low-grade ovarian cancer (LGSC)
- Endocrine therapy (aromatase inhibitors; >70% stable disease, 7-11m PFS)

**Molecular tumor board (Next Generation Sequencing)**
- e.g. KRAS, BRAF etc. (MEK-inhibitors)
• Endometrial Cancer
Endometrial cancer

- Differentiate endometrial cancer types
  - Type 1 (low-grade, endocrine sensitive)
  - Type 2 (high grade, ER-negative)

- 1L-therapy:
  - Type 1: no endocrine adjuvant therapy
  - Type 1/2: chemotherapy, depending on stage and histology

- 2L-therapy (metastases)
  - Type 1: MPA 200mg/d or MGA 160mg/d – high CR rate
  - Type 2: chemotherapy, immune-checkpoint inhibitors
Adjuvant/additive concepts in endometrial cancer

Regimen: Carboplatin AUC5(or 6) + paclitaxel 175mg/m² q3w*6

<table>
<thead>
<tr>
<th>Type 1 pT1a/b cN0 G1/G2</th>
<th>=&gt; no chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 pT1a G3 cN0</td>
<td>=&gt; no data</td>
</tr>
<tr>
<td>Type 1 pT1b pN0 G3</td>
<td>=&gt; chemotherapy as option</td>
</tr>
<tr>
<td>Type 1 pT2 pN0</td>
<td>=&gt; chemotherapy as option</td>
</tr>
<tr>
<td>Type 2 any stage</td>
<td>=&gt; chemotherapy as option</td>
</tr>
</tbody>
</table>

- Carcinosarcoma, serous EC => chemotherapy recommended*

- pT3 or pN1 => chemotherapy recommended
- pT4a or M1 (no tumorrest) => chemotherapy recommended

(*for carcinosarcoma alternatively: ifosfamide 1,6 g/m² d1–4 + cisplatin 20 mg/m² d1–4)
Endometrial cancer – high risk (FIGO III or G3 LVI or serous/clear cell)

GOG 258
• Chemoradiotherapy* (CRT) vs chemotherapy** (CT)

• Overall:
  – Recurrence-free survival: **Hazard ratio 0.90** (90% CI, 0.74–1.10); *p=0.20*

Median follow-up 47.0 months
* Cisplatin 50 mg/m² q4w *2 during radiotherapy followed by carboplatin AUC5 / Paclitaxel 175 mg/m² q3w *4.
  Target (45 Gy): cN0 only pelvic, cN1 lower or upper aortic fields
** Carboplatin AUC6 / Paclitaxel 175 mg/m² q3w *6
Adjuvant concepts for high risk endometrial cancer
(FIGO III or G3 LVI or serous/clear cell)

- Adjuvant chemotherapy with carboplatin/paclitaxel (*6)
  - FIGO III
  - Serous/clear cell cancer

- Vaginal brachytherapy optional (also in high risk FIGO I)

- Percutaneous radiotherapy
  - May reduce locoregional recurrences
  - May enhance rate of distant metastases
  - Can be reserved for secondary irradiation in case of particularly as pelvic and/or paraaortic recurrence
Endometrial cancer – recurrence / metastases

- Most effective chemotherapy regimen
  - Carboplatin / paclitaxel, also as re-challenge
  - Alternative: doxorubicin / cisplatinum

- Other options
  - G1, ER-positive: MPA 200mg/d or MGA 160mg/d
  - dMMR (mismatch-repair deficiency)
    - Pembrolizumab
    - Pembrolizumab plus Lenvatinib
  - Trastuzumab if HER2-positive (serous EC)

=> molecular analysis in recurrent disease
Immune checkpoint-inhibitor (ICPIs)
Advanced endometrial cancer
KEYNOTE-158 / KEYNOTE-146

KEYNOTE-158 (Pembrolizumab 200 mg q3w for 35 cycles (approx 2 yrs) or PD, tox, withdrawal)

<table>
<thead>
<tr>
<th>MSI-H, N=49 (cohorts D+K)</th>
<th>Cohort D, N=107 (Biomarker unsel.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>57.1 (42.2–71.2)°</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>8 (16.3)</td>
</tr>
<tr>
<td>Partial response</td>
<td>20 (40.8)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>8 (16.3)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>11 (22.4)</td>
</tr>
<tr>
<td>Not evaluable°</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Not assessed°</td>
<td>1 (2.0)</td>
</tr>
</tbody>
</table>

Progression-free survival assessed by RECIST v1.1 per central review for participants with MSI-H endometrial cancer

KEYNOTE-146 (Lenvatinib and Pembrolizumab)
Change in Sum of Diameters of Target Lesions at Postbaseline Nadir

O’Malley D et al. ESMO 2019, Abstract No. 1044P (mod.)
Makker V et al. ESMO 2019, Abstract No. 994O (mod.)

Lenvatinib: oral multikinase inhibitor that targets VEGFR 1–3, FGFR 1–4, PDGFRα, RET, and KIT
• Cervical cancer
Cervical cancer

- **Radiochemotherapy** (instead of radiotherapy alone) if indication of irradiation is given (primary or adjuvant / recurrence)
  - Cisplatinum 40 mg/m² IV q1w during irradiation (5-7 weeks, minimum 5 applications)
  - Alternatively (e.g in kidney failure) **vinorelbine** (15mg/m² IV q1w or 40 mg/m² PO q1w) (5-7 weeks, minimum 5 applications)

Cervical cancer advanced/metastatic

• OS-Benefit shown for
  – **CDDP / topotecan** vs CDDP alone
    • CDDP-containing regimen less effective if CDDP-pretreated
  – Adding **bevacizumab** to standard regimen (CDDP/paclitaxel, topotecan/paclitaxel, carboplatin/paclitaxel)

• **NEW!**
  – Immune checkpoint inhibitors (Pembrolizumab, Nivolumab)

*CDDP = cisplatinum*
Antitumor activity of pembrolizumab (Keynote-158)

N=98; 3rd-line 65.3%; 82 (84%) PD-L1 pos.

Clinical Benefit (CR+PR+CSD) 33%; OS_{median} 9.4 m; duration of response >12m: 75% (9 of 12)

Medical therapy in gynaecological cancer

- Adjuvant / first-line (incl. RCT) use provides survival benefit
  - Ovarian cancer, endometrial cancer, cervical cancer
- Early use of targeted drugs (BEV, PARPi) is effective
  - Ovarian cancer (1L and 2L)
- Combination chemotherapy effective in 2L-situations
  - Ovarian cancer, cervical cancer, endometrial cancer
- Immune-checkpoint inhibitors in 2L
  - Cervical cancer, endometrial cancer
- Individualised effective therapy in GTN
  - Curative intention