CURRENT TREATMENT OF AGCT AND FUTURE PERSPECTIVES

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• No conflicts of interest
AGCT

- Prognosis
  - 5-year survival 90-97% in stage I (*Colombo et al 2007, Bryk et al 2015*)
    22-75% in stage II-IV (*Björkholm et al 1981, Fujimoto et al 2001*)

- 30% relapse
  - median time 4-8 years (*Lee et al 2008, Sun et al 2012, Bryk et al 2015*)
  - mortality to recurrent disease 50% (*Bryk et al, unpublished*)
Treatment of AGCT

• Surgery, primary tumor:
  • Laparotomy (open) or laparoscopic surgery
  • Removal of the uterus, ovaries and fallopian tubes, peritoneal washings, biopsies and omentectomy
  • Lymphadenectomy not recommended as routine procedures, suspicious nodes should be removed
  • Tumor rupture is an adverse prognostic factor
    -> centralization of the treatment to specialized units!
• Fertility-sparing surgery (in stage I (a)): uterus and healthy ovary conserved, biopsies and endometrial sampling should be performed
• Younger age may be associated with relapse
• Long latency to relapse -> No consensus what to do when reaching menopause
Recurrent tumors

- Often multifocal
- Pelvis as the most common site
- Metastasis to distal organs are rare
- Optimal surgery is important
  - Debulking surgery (ESMO guidelines)
  - Even repeated operations (Mangili 2013)
  - Residual tumor is a significant adverse prognostic factor
- Optimal surgery achieved in 71-85 % of the recurrences (Ertas 2014)
Chemotherapy

Malignant Sex Cord-Stromal Tumors

CLINICAL PRESENTATION

Malignant sex cord-stromal tumors

Stage IA/IC: Desires fertility

Stage I Low risk

Fertility-sparing surgery with complete staging

Stage I High risk (eg, ruptured stage IC or poorly differentiated stage I) or Intermediate risk (eg, heterologous elements)

Stage II-IV

Platinum-based chemotherapy (category 2B) or RT for limited disease (category 2B)

Stage II-IV Low risk

Observe (category 2B)

Observe (category 2B) or Consider platinum-based chemotherapy (category 2B)

Stage II-IV High risk

Observe (category 2B) or Consider platinum-based chemotherapy (category 2B)

Observe (category 2B)

Observation

Stage III-IV

Clinical trial or Consider secondary cytoreductive surgery or Recurrence therapy

RECURRENT DISEASE

TREATMENT

RECURRENT THERAPY
Chemotherapy

- ESMO guidelines
  - Recommended as adjuvant in stage Ic/II primary tumor or higher and in recurrent AGCT
  - BEP=Bleomycin, Etoposide, Carboplatin (3-6 cycles)
- other options
  - Etoposide, Cisplatin
  - Cyclophosphamide, Doxorubicin, Cisplatin
  - Paclitaxel, Carboplatin
  - Platinum agent alone
  - PVB (Cisplatin, Vinblastine, Bleomycin)
  - VAC (Vincristine Dactinomycin Cyclophosphamide)
## BEP/BEC response rates

<table>
<thead>
<tr>
<th>Patients</th>
<th>Response rates</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>5 (2 res, 3 rec)</td>
<td>2 x CR (40%)</td>
<td>Gershenson 1996</td>
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<tr>
<td></td>
<td>3 x PR (60%)</td>
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<tr>
<td>25</td>
<td>6 x CR (24%)</td>
<td>Homesley 1999</td>
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<tr>
<td></td>
<td>4 x PR (16%)</td>
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<tr>
<td></td>
<td>14 x SD (56%)</td>
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<tr>
<td></td>
<td>1 x PD (4%)</td>
<td></td>
</tr>
<tr>
<td>20 (5 res, 15 rec)</td>
<td>9 x CR (45%)</td>
<td>Pautier 2008</td>
</tr>
<tr>
<td></td>
<td>9 x PR (45%)</td>
<td></td>
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<tr>
<td></td>
<td>1 x SD (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 x PD (5%)</td>
<td></td>
</tr>
<tr>
<td>9 (9 rec)</td>
<td>1 x CR (11%)</td>
<td>Van Meurs 2013</td>
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<td></td>
<td>1 x PR (1%)</td>
<td></td>
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<tr>
<td></td>
<td>7 x SD (78%)</td>
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Adjuvant therapy – effect for relapse?

- Park 2012
  - Adjuvant BEP chemotherapy not significantly associated with DFS
  - 6/13 completed 6 cycles of BEP: no recurrence
  - 7 patients received fewer than 6 cycles, 5/7 had recurrences

- Meisel 2015
  - BEP did not improve the recurrence free interval
BEP/BEC adverse effects

- Pulmonary toxicity
  - Bleomycin induced pneumonitis > lung fibrosis
- Skin reactions
- Bone marrow suppression
- Gastrointestinal symptoms

- Cisplatin vs carboplatin
Taxanes

• Brown et al 2005: same efficacy with less toxicity when compared with BEP

• GOG trial ongoing: Paclitaxel and Carboplatin or Bleomycin Sulfate, Etoposide Phosphate, and Cisplatin in Treating Patients With Advanced or Recurrent Sex Cord-Ovarian Stromal Tumors
Targeted treatments

• Bevacizumab
  • Angiogenesis inhibitor
  • AGCTs highly vascularized, VEGF elevated in AGCT
  • Brown 2009: Bevacizumab showed activity: response rate 38%
    • 8 GCTs, 1/8 CR, 2/8 PR, 3/8 disease progression
  • Brown 2015: GOG phase II trial, activity in AGCT (PR 16%), toxicity acceptable

• Adverse effects
  • hypertension
  • proteinuria
  • bowel perforation
Hormonal treatments

• AGCT is a hormone secreting tumor
  • Inhibins, estradiol (E2)

• Drugs
  • Aromatase inhibitors
  • Selective Estrogen Receptor Modifiers (Tamoxifen)
  • Progestins
  • GnRH agonists

• Efficacies : CR 25.8%, PR 45.2%, aromatase inhibitors most efficient (van Meurs 2014)

• Recent studies: CR 4.5%, PR 14%, SD 64%, progression 18% (van Meurs 2015)
Future perspectives

• Targeted treatments
  • Less side effects
  • Biological background

• Mechanisms of hormonal modulation
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AGCT patients and samples

Original Cohorts
Diagnostic Histology: AGCT

- Helsinki 1956-2016 n=245
- Turku/AURIA 1984-2015 n=50
- Amsterdam 1974-2013 n=127

Histological re-evaluation
FOX1L2 402C>G mutation analysis

- FOXL2 verified AGCTs n=315*
- Other/missing n=63/46*

Final cohort 1956-2016 n=315*

Prospective study 2007-> n=110

TMA
- Helsinki 1956-2016 n=198
- Turku 1984-2015 n=50*
- Amsterdam 1974-2013 n=110

- Survival, recurrences, treatment responses
- IHC expression profiles

Fresh tumor samples
- Primary and recurrent n=60

Blood samples
- Primary cell cultures
- Genomic and expression analyses
- Serum and plasma biomarkers

Helsinki
- Pretreatment and follow-up n=900
GCT Research Group Helsinki

- Clinical and translational studies
  - Comprehensive database
  - Primary GCT cell culture model
  - Fresh AGCT samples
  - GCT cell lines
  - Tumor tissue microarrays
  - Serum samples

- 5-10 new AGCTs every year
Serum markers in AGCT

- Diagnostic markers for patients with Ovarian Granulosa Cell Tumors; comparative analysis of CA125, HE4, Inhibin B and AMH

  - CA125 levels usually not elevated in AGCT but no studies on HE4-levels in AGCT
  - Preoperative diagnosis is important
    - Referral of patients to specialized units
  - To find most optimal serum marker/marker combination for AGCT
Conclusion

• HE4 levels are not elevated in AGCT

• Inhibin B is the best marker to differentiate AGCT from both malign and benign ovarian cysts.

• For differentiating AGCT from EOC, Inhibin B alone is sufficient

• For differentiating AGCT from endometriomas, Inhibin B and AMH in combination is most optimal

• In this study, Inhibin B was the best follow-up marker for AGCT
Primary cell cultures of AGCTs

2-10 cm tumor → 0.5% collagenase → filtration → single cells

experiments
Drug sensitivity and resistance testing (DSRT)

- Measures how efficiently different drugs inhibit tumor cells
- Over 300 drugs screened at the same time (approved cancer drugs and novel agents)
- Drugs plated on 384-well plates at five different concentrations (from 1 nM to 10 µM)
- Isolated primary cultured GCT cells added > Incubation for 3 days
DSRT results

- Drug efficacy measured by the amount of viable (ATP-producing) cells
- IC50-value
  - Required dose to kill 50% of the tumor cells
- Drug sensitivity score-value (DSS)
  - Algorithm developed for comparing drug responses between drugs and between patients
Selective drug sensitivity score sDSS

• Differential activity of the drugs in GCT cells in comparison to healthy bone marrow cells

Unpublished data
Conclusions

- AGCT cells are more sensitive to paclitaxel than to bleomycin
- The most efficient compound in reducing cell viability of AGCTs was tyrosine kinase inhibitor dasatinib
- Dasatinib and paclitaxel seem to have synergy effect in AGCT cells when used in combination
- *In vivo* studies are needed
AGCT and hormones

Granulosa cells produce estradiol from androgens (aromatase enzyme active in granulosa cells)

AGCTs “estrogen-dependent” – are they really?
Clinical questions

• Estrogen replacement therapy after AGCT surgery?
  • Bryk 2015: HRT not risk for survival

• Aromatase inhibitors in AGCT, is there a rationale?
AGCT and hormones

- AGCTs secrete estradiol, but what does estradiol do to AGCT?

- Strong GPER intensity at primary diagnosis showed a significantly reduced overall survival (Heublein 2014)

- Does estrogen stimulate AGCT cell growth?
  - $17\beta$-estradiol inhibits spreading of metastatic cells from granulosa cell tumors through a non-genomic mechanism involving GPER1 (Francois 2015)
The role of FSH in AGCT?
Future studies

• Hormonal characterization of AGCT
  • Clinical correlations

• The efficacy of aromatase inhibitors in AGCT
  • Can hormone receptors be used as predictive markers for hormonal treatments (clinical data)
  • Aromatase inhibitors in cell cultures

• AGCT cells and hormonal stimulations
  • Do we have to avoid ERT or not??
Thank you!

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