SPRMs, androgens and breast cancer

Dr Joëlle Desreux

BMS 04/06/2016
WHI : the nuclear explosion

- Looking for the perfect menopause treatment
  - Hot flushes relieve
  - Osteoporosis prevention
  - Cardio-vascular health protection
  - Sexual function preservation
  - Bleeding control
  - No excess of breast or endometrium cancer risk

- Alternatives to CEE + MPA
  - Phytoestrogens and other estrogens (estetrol)
  - Other progestins and progesterone
  - (Ultra) low doses
  - Transdermal and other routes
  - SERMs
  - TSEC
  - SPRMs
  - Androgens
Warning: to prove a BC risk induced by hormones = impossible mission?

Inter-individual variability of mitosis during menstrual cycle

Warning: no reliable surrogate marker of BC risk

- Breast cancers are multifactorial diseases.
- Each BC subtype has its own risk factors.
- Proliferation and apoptosis are only a part of oncogenesis.
- Excess of breast density induced by hormones is difficult to measure and is not proven as a true surrogate marker of BC risk.
Women’s Health Initiative

The WHI Steering Committee, *JAMA* 2004, 291 (14), 1701-1712

Hypothesis: the effects of menstrual cycle in mouse models

Brisken, Nat Rev Cancer 2013
SPRMs or PRMs or antiprogestins or mesoprogestins or partial agonist-antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onapristone</strong></td>
<td>Pure antagonist (PA or type 1 SPRM)</td>
</tr>
<tr>
<td><strong>Mifepristone</strong></td>
<td>(MIFEGYNE°, 200 mg) for abortion: predominantly antagonist effect on PR (type 2 SPRM), anti-glucocorticoid effect</td>
</tr>
<tr>
<td><strong>Ulipristal acetate</strong></td>
<td>(UPA) for preoperative treatment of fibroids (ESMYA°, 5 mg) and emergency contraception (ELLAONE°, 30 mg): agonist-antagonist (type 2 SPRM)</td>
</tr>
</tbody>
</table>
Progesterone

Pure antagonist

SPRM

Mixed Heterodimer
PA + Progesterone

Spitz M, Steroids 2003
SPRM effects on target tissues

- **Hypothalamic-pituitary-gonadal axis**: inhibit ovulation by inhibiting LH peak but maintain physiological levels of estrogens.

- **Endometrium**: induce unique and reversible morphology of unknown long term significance (PAEC: progesterone receptor modulator associated endometrial changes) leading to amenorrhea and prevention of implantation. No atypias. Potential effect on endometriosis.

- **Myometrium**: decrease fibroids volume and control bleeding.

- **Cushing’s syndrome**: anti-gluocorticoid effect of mifepristone decreases insulin resistance.

- **Meningiomas**: case reports.
Effect of PA on mammary tumors in rats

Fig. 1. DMBA-induced mammary tumors in rats: Effects of dosages of ORG 31710 (mg/kg/day). *Significantly different from control group.
Effects of PA and tamoxifen in mammary tumors in rats

Fig. 2. DMBA-induced mammary tumors in rats: Effects of ORG 31710, tamoxifen, ORG + tamoxifen.
Table 3
(Possible) mechanisms of action of antiprogestins in breast cancer*

1. Downregulation of PR
2. Blockade of AR (by some antiprogestins in selected models)
3. Blockade in G₀/G₁ phase of cell cycle
4. Induction of terminal differentiation
5. Induction of DNA fragmentation (apoptosis)
6. Downregulation of bcl2
7. Induction of TGF-beta
8. Blocking progesterone-induced VEGF secretion (T47-D)
9. Translocation of PKC activity from the soluble to the particulate and/or nuclear fraction

*PR = progesterone receptor; AR = androgen receptor; TGF = transforming growth factor; VEGF = vascular endothelial growth factor; PKC = protein kinase C.
Fig. 4. Antiprogesterone treatment inhibits mammary tumorigenesis by decreasing ductal branching and alveolar proliferation in Brca1f11/f11 p53f5&6/f5&6Crec mice.

A

% tumor free mice

0 20 40 60 80 100

Age (months)

no treatment placebo mifepristone

B

Control Mifepristone

100 μm

C

Control Mifepristone

1 mm

100 μm

Mifepristone

Aleksandra Jovanovic Poole et al. Science 2006;314:1467-1470

Published by AAAS
The effect of mifepristone on breast cell proliferation in premenopausal women evaluated through fine needle aspiration cytology

- 28 premenopausal women referred for fibroids surgery, mifepristone 50 mg every other day/84 days before surgery

![Graph showing Ki67 levels before and after treatment.](Graph.png)

**Antigonadotropic action and/or direct effect on breast?**

- Before treatment
- After 3 months of treatment

\[ P = 0.012 \]


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The effect of mifepristone on breast cell proliferation in premenopausal women evaluated through fine needle aspiration cytology

Table III. Breast symptom scores in women treated with mifepristone during 84 days.

<table>
<thead>
<tr>
<th>Symptom (BSI)</th>
<th>Baseline score (mean ± SEM)</th>
<th>End of treatment score (mean ± SEM)</th>
<th>P-value within group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soreness</td>
<td>2.43 ± 0.70</td>
<td>0.71 ± 0.58</td>
<td>0.035</td>
</tr>
<tr>
<td>Swelling</td>
<td>1.93 ± 0.78</td>
<td>0.0 ± 0.0</td>
<td>0.028</td>
</tr>
<tr>
<td>Increased breast volume</td>
<td>2.14 ± 0.90</td>
<td>0.36 ± 0.36</td>
<td>0.043</td>
</tr>
<tr>
<td>BSI-total (soreness, swelling, volume, stings, pain)</td>
<td>8.29 ± 3.03</td>
<td>2.46 ± 1.84+</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Maximum score is 10 for each parameter.
+Betweentreatment groups. $P = 0.049$, no significant changes were present within the control group.

Moderate but significant increase of hot flushes in mifepristone group ($p = 0.029$)
Clinical studies of SPRMs in postmenopausal women with metastatic BC

Antitumor effects of single treatment with antiprogestins in postmenopausal patients with metastatic breast cancer*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Antiprogestin</th>
<th>Dose (mg/day)</th>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romieux et al. [40]</td>
<td>Mifepristone</td>
<td>200</td>
<td>22</td>
<td>0</td>
<td>3</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>(third-line)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klijn et al. [9]</td>
<td></td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonat [41]</td>
<td></td>
<td></td>
<td>43</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

In total

<table>
<thead>
<tr>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>123</td>
<td>1</td>
<td>12</td>
<td>53</td>
<td>57</td>
</tr>
</tbody>
</table>

(1%), (10%), (43%), (46%)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Antiprogestin</th>
<th>Dose (mg/day)</th>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perrault et al. [42]</td>
<td>Mifepristone</td>
<td>200</td>
<td>28</td>
<td>0</td>
<td>3</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>(first-line)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robertson et al. [43]</td>
<td>Onapristone</td>
<td>100</td>
<td>18</td>
<td>0</td>
<td>10</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>(first-line)</td>
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</tbody>
</table>

*N = number; CR = complete response; PR = partial response; NC = no change; PD = progressive disease.

Most responders are PR+ tumors.

Median duration of response: 70 months. The anti-glucocorticoïd effect of mifepristone, rising the level of androstenedione, converted in estradiol by aromatase, could explain the short duration of response.

Stop development of onapristone because of liver toxicity.
Antiestrogenic effects of SPRM type 2 EC313 on mammary glands and uterus in ovariectomized mice (n=6)

- Mammary ductal length
- Terminal ductal buds count
- Apoptosis and proliferation
- Uterine weight

Nair HB PLOSone 2016
UPA effects on normal human breast cells proliferation

Anti-glucocorticoid effect of UPA on proliferation.
No effect on E2-induced proliferation.
UPA effects on proliferation in human breast grafts in mice

« No growth stimulation in normal breast tissue. »

Communal L, Human Reprod 2012
Current clinical studies of PA and SPRMs in breast cancer patients

- Clinical Trial NCT01493310. Nab-paclitaxel (Abraxane) with or without mifepristone in patients with advanced breast cancer.

- Clinical Trial NCT2014337. Mifepristone and eribulin in patients with metastatic triple negative breast cancer.

- Clinical Trial NCT02046421. Carboplatin, gemcitabine hydrochloride, and mifepristone in treating patients with advanced breast cancer or recurrent or persistent ovarian epithelial, fallopian tube, or primary peritoneal cancer.

- Clinical Trial NCT01898312. BRCA1/2 and effect of mifepristone on the breast.
SPRMs and breast
My conclusions

- No class effect
- Tolerance is an issue (hepatic toxicity, anti-glucocorticoid effect with rise of androgens levels).
- High complexity but promising field of research. It could be interesting in PMW in association with estrogens, if long-term endometrial safety is ascertained.
Androgens and normal breast

- Androgens inhibit the breast development in male adolescents.
- Androgens inhibit estrogens-induced mammary development during puberty and menstrual cycle.
- Androgens take part to mammary involution in PMW
- High doses of androgens induce mammary involution in female-to-male transsexuals.
- No excess of risk in male-to-female transsexuals: early exposure to androgens could have a long term protective effect?
Testosterone levels and breast cancer risk

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases</th>
<th>Controls</th>
<th>Subgroups</th>
<th>Testosterone levels in cases as a percent of control (P value)</th>
<th>Hazard or risk ratio (range)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premenopausal women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeleniuch-Jacquotte et al. (2012)</td>
<td>192</td>
<td>390</td>
<td>Luteal</td>
<td>103 (0.09)</td>
<td>2.00 (1.10–3.60)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dorgan et al. (2013)</td>
<td>370</td>
<td>726</td>
<td></td>
<td>108 (0.01)</td>
<td>1.73 (1.16–2.57)</td>
<td>0.005</td>
</tr>
<tr>
<td>Wang et al. (2000)</td>
<td>160</td>
<td>174</td>
<td></td>
<td>96 (NG)</td>
<td>0.92 (0.50–1.80)</td>
<td>0.387</td>
</tr>
<tr>
<td>Eliassen et al. (2002)</td>
<td>65</td>
<td>243</td>
<td>Luteal</td>
<td>NG (NG)</td>
<td>2.16 (0.60–7.61)</td>
<td>0.28</td>
</tr>
<tr>
<td>Kaaks et al. (2005a,b)</td>
<td>127</td>
<td>130</td>
<td></td>
<td>110 (0.022)</td>
<td>1.92 (1.00–3.65)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Thomas et al. (1997)</td>
<td>68</td>
<td>182</td>
<td></td>
<td>NG (NG)</td>
<td>1.22 (0.60–2.40)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Postmenopausal women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fourkala et al. (2012)</td>
<td>200</td>
<td>400</td>
<td></td>
<td>125 (0.04)</td>
<td>2.15 (1.26–3.17)</td>
<td>0.0006b</td>
</tr>
<tr>
<td>Farhat et al. (2011)c</td>
<td>111</td>
<td>594</td>
<td>ERα negative</td>
<td>94 (0.16)</td>
<td>0.58 (0.33–1.02)</td>
<td>0.08b</td>
</tr>
<tr>
<td></td>
<td>306</td>
<td></td>
<td>ERα positive</td>
<td>116 (0.004)</td>
<td>1.68 (1.04–2.67)</td>
<td>0.005b</td>
</tr>
</tbody>
</table>

Premenopausal women: no correlation BUT limitations (measurement methods, sample sizes, cyclic variations of testosterone levels)

Postmenopausal women: increased risk but not independent from estrogens

McNamara, Endocrine-Related Cancer 2014
Effects of exogenous androgens on breast cancer risk

- No risk increase in female to male transsexuals BUT mastectomy < 3 years after starting androgens.

- No risk increase in PMW treated by MHT + androgens for hypoactive sexual disorders BUT follow-up < 4 years.
Androgens metabolism

- In estrogenic milieu, 5α reductase > aromatase
- In the absence of estrogens, aromatase > 5α reductase

Adaptative intracrinology

McNamara, Endocrine-Related Cancer 2014
Effects of E2, P and T in 25 ovariectomized cynomolgus monkeys

- Con = placebo
- E = micronized E2 1 mg/d
- P = micronized P 200 mg/d
- T = subcutaneous pellet of Testosterone 15 mg (High-dose) during 8 weeks, removed and replaced by pellet 1,5 mg (Low-dose) for the next 8 weeks.

Wood C, Menopause 2009
Complexity of AR roles in breast cancer

McNamara, Endocrine-Related Cancer 2014
Complexity of AR roles in breast cancer

In the presence of comparable levels of AR and ERα, AR is an ERα competitor and can suppress ERα-mediated growth. Thus, AR serves as a TUMOR SUPPRESSOR.

In absence of ERα, AR levels increase, cofactor interactions change and AR becomes an ERα mimic. Therefore, AR functions as an ONCOGENE.

Hickey T Mol Endocrinol 2012
AR expression in ER-positive breast cancers

- AR expression is an independent predictor of reduced risk of relapse and/or death in luminal A and luminal B tumors.
- High ratio AR/ER expression is associated with tamoxifen resistance.
- Phase II SARM Enobosarm in metastatic ER+ BC: benefit in 6 out of 17 PMW patients.
AR expression in ER-negative breast cancers

- Apocrine breast cancers (100% AR +) : very poor prognosis
- Triple negative cancers (12% AR+) : better prognosis in some studies but not all
- Numerous ongoing clinical studies of SARMs in triple negative tumors : mixed results.
Androgens and breast: conclusion

- « As inhibitory therapies targeting AR have been established for prostate cancer, AR is an attractive ‘low-hanging fruit’ in the treatment of breast cancer. However, refining selection criteria and determining ‘in whom’ and ‘to do what’ will be essential in the effective clinical utilisation of agents that either specifically inhibit or selectively activate AR to improve the breast cancer outcomes. »