AR Expression in Breast Cancer and the Potential Role of Antiandrogens as Treatment: A Review

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Introduction

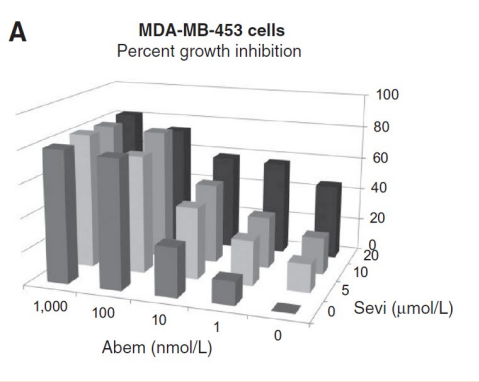
Androgen receptors are widely expressed in all breast cancer subsets, making them a potentially pervasive breast cancer therapeutic. 77% of invasive breast cancers are androgen receptor positive including 91% of luminal A breast cancer, 59% of HER2+ breast cancer, 32% of TNBC, and 46% of breast cancers that were ER, PR, HER2, CK 5/6, and EGFR negative. (Collins et al., 2011). AR:ER ratio is currently being investigated as a predictor of breast cancer survival and as a marker for those who will benefit from androgen treatment.

Triple Negative Breast Cancer (TNBC) has very little targeted therapy options. In addition, many patients have heavily pretreated breast cancer, which often shows resistance to aromatase inhibitors. The androgen receptor (AR) plays a promising role in treatment of treatment resistant breast cancer. There is controversy on whether an AR agonist or antagonist is best for breast cancer treatment.

In this review we discuss the pertinent literature on AR in both TNBC and ER+ breast cancer and we propose that there may be a way to determine how to predict for disease that will not respond to AI therapy using AR or AR regulated genes or circulating factors. We argue that AR expression can be used both as a prognostic indicator and as a target for treatment and discuss other therapies that it might work well in combination with.

Methods

Pertinent review articles relating to AR:ER ratio and androgen treatment were selected.



Brief Review of Literature/Results

Rangel et al studied 402 ER+, HER2- breast cancer patients

- AR expression was associated with a significantly longer disease specific survival.
- When stratifying for high AR:ER ratio, a high (2 fold or over) ratio was the most significant marker of poor prognosis.
- High AR:ER was associated with a larger tumor, higher grade, lower PR, more positive nodes, and more relapses.

In our recent work, Christenson et al, investigated the use of antiandrogens and CDK4/6 inhibitors

- Seviteronel, an AR antagonist, was able to inhibit proliferation of an AR+ TNBC PDX tumor model in a dose-dependent manner.
- Cell cycle related genes were upregulated with high AR expression.
- Seviteronel combined with abemaciclib (a CDK 4/6 inhibitor) showed a synergistic inhibitory effect on these cell lines

Hickey et al investigated the use of AR agonists in breast cancer treatment.

- ER+ breast cancer cell lines:
  - Estrogen treatment alone had higher proliferation than estrogen and DHT treatment, indicating that androgens may suppress estrogen driven proliferation.
    - DHT binding to AR caused ER binding elements to be displaced, decreasing ER activity.
- Endocrine resistant breast cancer cell line
  - DHT inhibited growth while Enza had no effect on tumor growth.
- CDK4/6 resistant breast cancer cell lines.
  - DHT increased the efficacy of CDK4/6 inhibitors

In a phase II clinical trial, Krop et al tested exemestane vs exemestane plus enzalutamide.

- Overall PFS did not significantly change between the groups.
  - Those with a high AR:ER ratio (high AR expression with low ESR1) had a large benefit from the addition of enzalutamide.
  - However, when stratified into AR:ER ratio:
    - Those with a low AR:ER ratio did better with exemestane alone.

Limitations

Each study had different methods and data collection, so comparing specific data was not performed. There was some conflicting data on use of AR agonists. Ongoing clinical trials are being performed to better elucidate this discrepancy.

Key Findings

AR expression is a positive prognostic indicator. High AR:ER is a marker of poor prognosis.

AR is involved in cell cycle regulation and combination treatment in AR+ TNBC may be efficacious.

Both DHT and Enza inhibited tumor growth. The effect of DHT lasted longer (90d vs 5d).

Those with a high AR:ER ratio had a large benefit from the addition of enzalutamide.

Conclusion

AR expression was shown to be a positive prognostic predictor in many different studies. However, a high AR:ER ratio was shown to be a marker of poor prognosis, indicating the complex role that androgens play in breast cancer.

There is still some controversy in whether an AR agonist or antagonist is most useful in breast cancer treatment. Antiandrogens are seen to be efficacious when the AR:ER ratio is high. Our lab has a current clinical trial for antiandrogen use in those with metastatic disease that was highly pretreated, which is showing positive results.

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Sevi (µmol/L)	Abem (nmol/L)	% Growth inhibition	Combination index (CI)
5	0	16.96	–
10	0	22.15	–
20	0	45.35	–
0	1	14.07	–
5	1	27.02	0.71
10	1	31.44	0.93
20	**1**	**56.87**	**0.57**
0	10	29.56	–
5	10	43.19	0.77
10	10	48.45	0.73
20	10	58.28	0.68
0	100	77.58	–
5	100	71.26	0.59
10	**100**	**78.78**	**0.33**
20	100	73.68	0.66
0	1,000	79.86	–
5	1,000	81.59	1.67
10	1,000	80.54	1.95
20	1,000	81.83	1.74

Figure 5.
Combination (combo) treatment of TNBC cells with an anti-androgen and cell cycle inhibitor. **A,** MDA-MB-453 cells were cultured in full-serum media. Cell viability was determined by crystal violet assay after a 5-day exposure to DMSO (0) or increasing concentrations of seviteronel (sevi) and (abemaciclib (abem; CDK4/6 inhibitor). Data were normalized to the mean absorbance of DMSO-treated cells and presented as mean percentage growth inhibition. Calcu-Syn software was used to calculate the degree of synergy between com-bination treatments, represented as the CI. CIs < 0.9 indicate synergy.