Angiogenesis Markers in Breast Cancer
Potentially Useful Tools for Priority Setting of Anti-Angiogenic Agents

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Breast Cancer

- The most common non-skin malignancies in females
- The 2\textsuperscript{nd} most lethal cancer after lung cancer
- 1:8 to 1:10 females
- Molecular subclasses are preferred for classification
Molecular Subclasses of Breast Cancer (BASIS)

- ER (Estrogen Receptor)
- PR (Progesteron Receptor)
- HER-2 (Human epithelial growth factor receptor)
Molecular Subclasses of Breast Cancer

- Luminal-like (Luminal A & Luminal B)
- HER-2 enriched (HER-2 positive)
- Triple Negative
Other Markers

- Ki-67

- P53

AS REQUESTED
Angiogenesis Markers

- AGF (angiopoietin-related growth factor)
- Angiogenin (ANG)
- Angiopoietin-1
- Angiopoietin-2
- ARP4 (angiopoietin-related protein 4)
- bFGF (basic fibroblast growth factor)
- CD97
- CD31 (PECAM-1)
- CD34
- CD97
- CD146 (MUC18)
- CECs (circulating endothelial cells)
- CEPs (circulating endothelial precursor cells)
- Collagenase-1 (C1)
Angiogenesis Markers (con.)

- COX-2 (Cyclooxygenase-2)
- E7820
- EG-1 (endothelial-derived gene-1)
- Extra-Domain B (ED-B) of Fibronectin
- Endoglin (CD105)
- ESAF (Endothelial cell stimulating angiogenesis factor)
- Flt-1 (Fms-like tyrosine kinase 1)
- Integrins
- KDR
- N-Cadherin
- NG2 proteoglycan
- V-1 (Plasmalemmal vesicle associated protein-1)
- S100A13
- Syndecan-1
Angiogenesis Markers (con.)

- T-Cadherin
- TEM-5 (Tumor endothelial marker 5 & 8)
- Thy-1
- Tie-1
- Tie-2
- Tn-C (Tenascin-C)
- TP (Thymidine phosphorylase)
- VCAM-1 (vascular cell adhesion molecule-1)
- VE-cadherin
- VEGF
- VWF (von Willebrand Factor)
- Others (Pulmonary microvessel density, ……..)
Molecular Subclasses of Breast Cancer

- Luminal- A (ER, PR pos., Her-2 neg.)
- Luminal B (ER, PR pos., Her-2 pos.)
- HER-2 enriched (ER, PR neg., HER-2 pos.)
- Triple negative (ER, PR, Her-2 neg.)
The Angiogenic Switch Is Necessary for Tumor Growth and Metastasis

- Tumor is dormant
- Angiogenic switch

Somatic mutation → Small avascular tumor → Tumor secretion of angiogenic factors stimulates angiogenesis → Rapid tumor growth and metastasis

Neovascularization
- Makes rapid tumor growth possible by supplying oxygen and nutrients and removing waste
- Facilitates metastasis

Objectives

- Anti angiogenic agents for priority setting in breast cancer using angiogenic markers
- Evaluation of Her-2 and P53 status
- Comparison of clinical parameters with the above markers
- Comparison of other histopathological parameters with the above markers
- Comparison of MVD-CD34 status with the above markers
Materials & Methods

• 111 breast cancer cases
  Female
  Primary
  Invasive
  Negative history of neoadjuvant therapy
• Tissue processing
• Paraffin blocks
• 4-5 microns sections
• H&E staining
• ER, PR, HER-2, P53, Annexin 5 immunostaining
• CD34 immunostaining
Tissue Stained Slides
CD34 Antibody
IHC
RESULTS
HER-2 & Tp53 Results

Group 1 : Her-2 + / Tp53 –

Group 2 : Her-2 - / Tp53 +

Group 3 : Her-2 + / Tp53 +

Group 4 : Her-2 - / Tp53 –
### Association of Her-2 & P53 Status with Angiogenesis (CD34)

<table>
<thead>
<tr>
<th>Status</th>
<th>Number (N)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Her-2 positive</td>
<td>N=25</td>
<td>p=0.001</td>
</tr>
<tr>
<td>P53 positive</td>
<td>N=37</td>
<td>p=0.002</td>
</tr>
<tr>
<td>Her-2 positive</td>
<td>N=13</td>
<td>p=0.001</td>
</tr>
<tr>
<td>P53 positive</td>
<td>N=13</td>
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Angiogenesis Marker (CD34)

- MVD is scored as Low (0-19.9), Moderate (20-29.9) and High (>30)
- MVD has an indirect relationship with Age (Bone Marrow Effect)
- MVD has higher score in Her-2 positive cases
- MVD has higher score in P53 positive cases

Higher MVD score is associated with poorer prognosis
DISCUSSION
Global Burden of Disease (GBD)

- Increasing rate of various cancers in developing countries
- Increasing survival rate of various cancers in industrialized countries
- Appropriate therapy needs financial resources
- Priority setting strategy
Antiangiogenic Drugs

- Bevacizumab (Avastin) is a monoclonal antibody
- Decreases or stops angiogenic process
- Antiangiogenic drugs are considered for metastatic Breast Cancers (2013 Xu et al, 2011 Lee et al)
The Facts...

- Increased angiogenesis could increase the rate of metastasis (Folkman, 2002)

- This fact needs to be treated

- ERBB2 subtype are treated by a kind of mAB (Herceptin)

- Avastin (Bevacizumab) could be saved for marker negative cases
Conclusion

- Bevacizumab should be saved for Triple Negative Breast Cancer (TNBC):

1. TNBC occur in young patients
2. TNBC has poor response to other drugs
3. TNBC has higher scores of angiogenesis
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