The Quest for Multi-Functional Medicines: Path for Progress
The Tamoxifen Story
Lecture 1

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Professor of Oncology and Pharmacology

Serendipity

• 1958: first nonsteroidal antioestrogen was reported;
  Discovery was by chance with the screening of a potential cardiovascular drug
• Excellent “morning-after pills” in rats
  but did exactly the opposite in women by inducing
• Ovulation (Clomiphene and Tamoxifen);
  Reinvention and patenting promoted progress in therapeutics and chemoprevention

Tamoxifen the early years

<table>
<thead>
<tr>
<th>Name</th>
<th>1950's</th>
<th>1960's</th>
<th>1970's</th>
<th>1980's</th>
</tr>
</thead>
<tbody>
<tr>
<td>MER25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRL41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upjohn U11109a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICI 46474</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI 628</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Jordan VC, Tamoxifen: a most unlikely pioneering medicine,
The Quest for Multi-Functional Medicines: Path for Progress

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Table 21. Induction of ovulation with Nolvadex in women with Anovulatory infertility

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Number of responders</th>
<th>% response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>16</td>
<td>80</td>
<td>Klopper and Hall (1971)</td>
</tr>
<tr>
<td>22</td>
<td>1</td>
<td>0</td>
<td>EI-Sheikha et al., (1972)</td>
</tr>
<tr>
<td>32</td>
<td>26</td>
<td>81</td>
<td>Williamson and Ellis (1973)</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>60</td>
<td>Smith et al., (1973)</td>
</tr>
<tr>
<td>24</td>
<td>17</td>
<td>71</td>
<td>Macourt (1974)</td>
</tr>
<tr>
<td>29</td>
<td>14</td>
<td>48</td>
<td>Koskimies and Hirvonen (1976)</td>
</tr>
<tr>
<td>48</td>
<td>30</td>
<td>63</td>
<td>Gerhard and Runnebaum (1979)</td>
</tr>
<tr>
<td>40</td>
<td>38</td>
<td>95</td>
<td>Ruiz-Velasco et al., (1979)</td>
</tr>
<tr>
<td>235</td>
<td>165</td>
<td>70</td>
<td>Bolis and Polatti (1981) reported a 75% response in 134 treated cycles</td>
</tr>
</tbody>
</table>

• BACKGROUND:
  Breast cancer chemotherapy commonly causes premature ovarian failure and infertility; because increased estrogen levels are thought to be potentially risky in breast cancer patients, natural cycle IVF (NCIVF) has been used to preserve fertility and treat infertility in these women...

• CONCLUSIONS:
  Tamoxifen stimulation appears to result in a higher number of embryos and may provide a safe method of IVF and fertility preservation in breast cancer patients.

Situation: 1972

• Cytotoxic chemotherapy the only way to treat cancer
• No hope for further development
• ICI 46,474 economically unviable as a drug to treat metastatic breast cancer and induce ovulation in sub-fertile women
Advantage of tamoxifen (ICI 46,474) to pursue further testing in USA for advanced breast cancer

• "The particular advantage of this drug is the low incidence of troublesome side effects"

• "Side effects were usually trivial"

Path for progress: 3P’s
people, passion, persistence

Annual report 1973-1974
Worcester foundation for experimental biology
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Treatment strategies with tamoxifen (1973-79)
- The DMBA rat mammary carcinoma model (Dimethylbenz(a)anthracene)
- This is a model of hormone responsive cancer

Longer vs. shorter Tamoxifen treatment 1977
- Control (1&3)
- Tamoxifen 1
- Tamoxifen 2
- ER+ pre-menopausal women

Effectiveness of long term adjuvant Tamoxifen
- Duration of Tamoxifen (Years)
- % Reduction in Recurrence
- % Reduction in Death Rates


Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials
- Breast cancer mortality
- 500,000 women are alive because of Tamoxifen

EBCTCG, Lancet 2005;365:1687-703

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Treatment practice 2010
Long term oestrogen deprivation treatment

- Combination: Coombes et al., J Clin Oncol, 26: 498-502, 2007

Approvals and indications

• Induction of ovulation
• ER positive metastatic breast cancer
• Long term adjuvant therapy
• Chemoprevention of high risk women
• Male breast cancer

And of course, the fourth P-Patenting:
A unique 45 year story

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TAMOXIFEN: A MOST UNLIKELY PIONEERING MEDICINE
V. Craig Jordan

For more than 25 years, tamoxifen has been the gold standard for the endocrine treatment of all stages of oestrogen receptor-positive breast cancer, and the World Health Organization lists tamoxifen as an essential drug for the treatment of breast cancer. It is estimated that more than 400,000 women are alive today as a result of tamoxifen therapy, and millions more have benefited from reduced mortality and extended disease-free survival. Interestingly, tamoxifen also became the first cancer chemopreventive approved by the Food and Drug Administration (FDA) for the reduction of breast-cancer incidence in both pre- and post-menopausal women at high risk. However, 40 years ago, it was hard to imagine that a non-toxic targeted treatment for breast cancer could be developed at all.

Box 2 | Patenting problems

- Adequate patent protection is required to develop an innovation in a timely manner. In 1962, ICI Pharmaceuticals Division filed a broad patent in the United Kingdom (UK) (Application number GB1962034898 19620913). The application stated, "The alkene derivatives of the invention are useful for the modification of the endocrine status in man and animals and they may be useful for the control of hormone-dependent tumours or for the management of the sexual cycle and aberrations thereof. They also have useful hypocholesterolaemic activity."

- ICI Pharmaceuticals Division was repeatedly denied patent protection in the US until the 1980s because of the perceived primacy of the earlier Merrell patents and because no advance (that is, a safer, more specific drug) was recognized by the patent office in the United States.

- Remarkably, when tamoxifen was hailed as the adjuvant endocrine treatment of choice for breast cancer by the National Cancer Institute in 1984, the patent application, initially denied in 1984, was awarded through the court of appeals in 1985.


Conclusion

- Tamoxifen was re-invented in the 1970s from a failed contraceptive to become the gold standard for the treatment of breast cancer
- Millions of women around the world have had increased survivorship because of long term adjuvant tamoxifen targeted to the oestrogen receptor
- Tamoxifen is the first successful targeted therapy for breast cancer
- Additionally, tamoxifen became the pioneering medicine for the chemoprevention of breast cancer in high risk women
- Most importantly, tamoxifen became the "lead compound" for the development of a new drug group called the selective oestrogen receptor modulators (SERMs)
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