Cytochrome P450 2D6 Function And Tamoxifen Therapy In Breast Cancer: An Evaluative Survey of Canadian Cancer Care Agencies and their Translation of Pharmacogenetic Research into Clinical Practice

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INTRODUCTION
Tamoxifen continues to be an important endocrine therapy for the prevention and treatment of estrogen receptor positive breast cancer. Tamoxifen is a pro-drug requiring hepatic metabolic activation to be effective. This results in tamoxifen being converted into a variety of primary and secondary active metabolites.

The production of highly active tamoxifen metabolites is dependent on the presence of cytochrome P450 2D6 (CYP2D6) enzymes in the liver. (Figure 1) Such conversion may be dramatically impaired where a patient has inherited a CYP2D6 genetic variant that is devoid of enzymatic activity and/or where a patient ingests a medication or herbal that inhibits a functioning CYP2D6 enzyme. Examples of classes of such inhibitors are the SSRIs and the SNRIs. (Figure 2)

Goetz assessed the impact of the combined effect of CYP2D6 genetic variation and enzyme inhibition on breast cancer recurrence and death. Compared with extensive metabolizers*, poor metabolizers* had significantly shorter time to breast cancer recurrences (P = 0.007), shorter relapse-free survival (P = 0.005) and a trend to shorter overall survival (P = 0.077). (Table 1) The difference between poor metabolizers and extensive metabolizers is particularly striking for relapse-free survival at two years after randomization. The relapse-free survival for poor metabolizers is only 68% whereas the relapse-free survival for extensive metabolizers is 98%. (Figure 3)

Given this compelling data, we undertook to evaluate the extent of the translation of this new, clinically relevant, scientific data into practice in the context of the Canadian cancer care landscape.

METHODS
Canadian Federal and Provincial web sites were searched for information on tamoxifen use in breast cancer. Each site was then scrutinized for recommendations relating to CYP2D6 genetic testing and the concomitant use of medications with the potential to inhibit the CYP2D6 enzyme.

To gain insight into the use of known CYP2D6 enzyme inhibitors in patients on tamoxifen, we contacted a number of provinces that record medications prescribed for drug plan beneficiaries. Manitoba Drug Programs Information Network agreed to provide this data in a timely manner. The database was searched for patients on tamoxifen and then within this group how many patients also filled a prescription for a known CYP2D6 enzyme inhibitor such as a SSR1 or a SNRI. The search covered the fiscal years from 2006 to 2008.

To determine the actual clinical practice among Canadian oncologists treating breast cancer, we purchased a commercial mailing list of 678 names. Each oncologist was mailed an introductory letter along with a short survey. The response rate to our appeal was 10%.

Table 1
<table>
<thead>
<tr>
<th>Outcomes By CYP2D6 Metabolizer Status</th>
<th>Hazard Ratio Relative To Extensive Metabolizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time To Breast Cancer Recurrences</td>
<td></td>
</tr>
<tr>
<td>Poor [T-value]</td>
<td>Intermediate [T-value]</td>
</tr>
<tr>
<td>3.26 [1.07, 9.89]</td>
<td>1.00 [0.46, 2.20]</td>
</tr>
<tr>
<td>Relapse-free Survival</td>
<td></td>
</tr>
<tr>
<td>Poor [T-value]</td>
<td>Intermediate [T-value]</td>
</tr>
<tr>
<td>2.06 [1.37, 3.07]</td>
<td>1.00 [0.65, 1.74]</td>
</tr>
<tr>
<td>Overall Survival</td>
<td></td>
</tr>
<tr>
<td>Poor [T-value]</td>
<td>Intermediate [T-value]</td>
</tr>
<tr>
<td>2.06 [1.37, 3.07]</td>
<td>1.00 [0.65, 1.74]</td>
</tr>
</tbody>
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* Examples of agents that inhibit CYP2D6 activity
1. Inhibitors of cytochrome P450 2D6 enzymes and not only tamoxifen
2. Inhibitors of CYP2D6 enzymes and not only tamoxifen
RESULTS AND DISCUSSION

The frequency of differences in inherited CYP2D6 activity are highly variable between ethnic groups. For instance, up to 7.7 percent of white Americans can be poor metabolizers, but as many as 19 percent of San Bushmen of southern Africa can be poor metabolizers. The phenotypic variation among patients can be further complicated by the administration of medications and herbs. Prescription drugs such as pimozide, and other SSRIs and SNRIs, can be potent inhibitors of CYP2D6. (Figure 2) Co-administration of tamoxifen and a CYP2D6 inhibitor can render a genetically determined extensive or intermediate metabolizer into a functionally poor metabolizer. Herbals and natural remedies with poorly characterized metabolic inhibitory effects may also negatively impact the benefit of tamoxifen treatment.

In 2006, an advisory panel to the US Food and Drug Administration recommended a warning be added to the tamoxifen label informing prescribers that tamoxifen may be less effective in women carrying a mutation that compromises CYP2D6 activity. Since then additional literature has been published by Gozzi and Punja. 4 Further supporting the role of pharmacogenetic testing in tailoring endocrine therapy of estrogen receptor positive breast cancer. In light of this data we conducted a study of current practices in Canada. We reviewed published breast cancer practice guidelines on the use of tamoxifen, examined the Manitoba Drug Programs Information Network to determine how often certain known CYP2D6 inhibitors are prescribed concomitantly with tamoxifen and surveyed Canadian medical oncologists.

None of the three reviewed publicly available guidelines from Ontario, British Columbia and Saskatchewan recommended pharmacogenetic testing for CYP2D6 before initiating tamoxifen therapy. (Table 2) Only British Columbia’s guideline cautions against the use of potent inhibitors of CYP2D6. All three provinces are silent on the use of moderate or mild inhibitors of CYP2D6 which could render a genetically determined intermediate metabolizer into a functionally poor metabolizer.

The Manitoba Drug Programs Information Network provides insight into how many tamoxifen patients are treated with known inhibitors of CYP2D6 from one commonly co-prescribed class. We found that 16 to 19 percent of patients in Manitoba were co-prescribed an antidepressant (SSRI or SNRI) with CYP2D6 inhibitory effects. (Table 3)

Clinical practice often outpaces the publication of formal guidelines in an area as dynamic as oncology. In order to gauge clinical practice we conducted a mail survey of Canadian medical oncologists to determine what oncologists were doing in their daily practices. Most notably 91% of our sample do not test for CYP2D6 status prior to initiation of tamoxifen therapy. (Figure 4) Sixty-three percent of respondents do not conduct a pharmacogenetic test because they believe such a test is not available. Only 16% of those surveyed believe the literature is not strong enough to support a recommendation for CYP2D6 pharmacogenetic testing prior to the initiation of tamoxifen therapy. A further 27 percent stated they were unfamiliar with the current scientific evidence in this regard. (Table 4)

Twenty-four percent of oncologists surveyed routinely screen patients’ prescription drugs for inhibitors of CYP2D6. (Figure 5) This suggests that a significant number of Canadian oncologists believe that an active CYP2D6 enzyme is important for the successful treatment of patients with tamoxifen.

CONCLUSION

Pharmacogenetic testing of CYP2D6 function in estrogen receptor positive breast cancer patients along with a meticulous review of all medications and herbs ingested by such patients is underrated. Increased testing and screening could serve to improve the therapeutic benefit of tamoxifen.

REFERENCES