Preliminary Observations of Blood-Mediated Molecular Testing in a Subset of Patients with Pancreatic Cancer in the Know Your Tumor (KYT) Initiative

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Abstract #268

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Background:

While molecular profiling in solid tumors remains routine practice in cancer diagnosis, modern techniques have enabled detection of biomarkers in stray cells, exosomes, and traces of DNA in blood and other bodily fluids that are relevant to diagnose and follow oncologic disease. In many cases, liquid biopsy can reveal mutations that are otherwise unattainable, particularly for lesions in advanced stages. Each of these techniques has distinct advantages, and it is likely that in the future, patients will benefit from multi-modality strategies.

Methods:
The Pancreatic Cancer Action Network (PanCAN) and Perthera initiated an IRB-approved registry for patients with pancreatic cancer when we identified commercially available, CLIA-validated multi-omics profiling including next generation DNA sequencing (NGS) and cfDNA testing as a research platform. In a subset of these patients, we incorporated BB DNA testing.

Results:

From 05/2019 to 12/2019, molecular profiling was available for 175 pts. Achievable findings, defined as a high response to therapy in patients with an identified molecular abnormality in any cancer type, was 40% of pts. In those pts, the response to treatment was identified in 40% of pts, primarily based on NGS. A KRAS mutation has been identified (146/162) of KYT patients confirmed based on NGS on 27 NGS in 30 BB tests. In 22 pts, we were able to compare the cDNA NGS directly with NGS testing for a KRAS mutation identified as compared to 122/38 (63%) from the tumor tissue. Of the 8 pts that did not correspond, an average of 9% of the patients had isolated mutations, inhibited by inter-sample variation. While 797 (30%) of the 2600 BB samples had mutations identified in the 30 BB patients overall was 83 (27%). When the 20 BB cases were compared to patients with advanced metastatic disease and progressive disease at the time of blood sampling, the KRAS mutation was increased to 413 (17%). Achievable findings and a limited to a specific therapeutic option were identified in 830 (27%) of the patients.

Conclusions:

Although we are aware of the limitations of this study, we recommend that for patients who have biopsiable disease, a tumor biopsy should still be the gold standard for molecular profiling.

For those without biopsyable disease, the KYT program presents an opportunity to offer these patients the chance to be able to get actionable information pertaining to molecular profiling information from a BB sample.

Methodologic Details

Background

• To date, hundreds of PDA genomes have been sequenced identifying multiple actionable pathways that maybe "druggable" including: 1) DNA repair; 2) VNT signaling; 3) mutant KRAS signaling; 4) chromatin remodeling (2).
• The best example of a personalized approach in PDA is where tumors that harbor a BRCA1/2, ATRX, AML, or PALB2 mutations (i.e., BRCA1/2 for PARP inhibition/Precision based therapy (3)).
• BB-DNA testing is a novel, noninvasive "liquid biopsy" with the potential utility of identifying actionable mutations in patients where a concept must be rigorously validated as these are histologically less amenable to genetic analysis. Notably, we have not identified duodenal adenocarcinomas (PDA) because there is >90% of PDA harboring KRAS mutations (2) thus providing a "liquid biopsy" taken from a PDA patient a blood sample.  

Results

Table 1: Specific mutations identified in the BB sample

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation Type</th>
<th>Sample</th>
<th>Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>Missense</td>
<td>Sample1</td>
<td>18%</td>
</tr>
<tr>
<td>TP53</td>
<td>Missense</td>
<td>Sample2</td>
<td>22%</td>
</tr>
<tr>
<td>CDKN2A/2B</td>
<td>Loss</td>
<td>Sample3</td>
<td>33%</td>
</tr>
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</table>

Table 2: Summary of patient demographics

<table>
<thead>
<tr>
<th>Trait</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (range)</td>
<td>55-75</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Primary Site (pancreate)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Conclusions and Future Directions

• Based on this pilot study, given that BB-DNA testing could not be validated. KRAS mutations in a small percentage of patients with disseminated and metastatic disease, we conclude that BB-DNA testing is not ready for clinical decision making, especially in the arena of precision therapy for PDA.

Future studies evaluating BB-DNA platforms in PDA cohorts should consider: 1) side by side testing with TT and 2) the use of RAD51 mutations as a gold standard biomarker for this disease. Sequencing germline (constitutional) cDNA not from the tumor should be considered an effort to define true somatic events.

References:


Citations and Acknowledgements

Figure 1: The PanCan/Panthera KYT Workflow. Algorithms identified patients for enrolled in the KYT platform. Algorithm guides patients through the workflow and results with the disease-specific protocol. A patient is then identified through a dataset review.

Figure 2: Patient enrollment

Figure 3: Status of Key PDAC Mutations.

Figure 4: Analysis of “Actionable” Mutations. A number of gene alterations are identified by both TT and NGS DNA testing. Highlighted in blue are the “actionable” mutations, as defined in the methods. Yellow, “possible actionable” mutations associated with treatment benefit (5). Green, identified by both NGS DNA and BB-DNA testing. In some cases, mutations identified by NGS DNA testing but not identified by BB-DNA testing. Additionally, mutations that are "actionable" are defined by the identification of the "activity" of the mutation. The lowest section highlights mutations analyzed for NGS DNA and BB-DNA testing.

Figure 5: Comparison of variants of exons containing mutations identified by TT and BB-DNA cDNA testing. Both TT/Cloaked (Red) and BB-DNA (Blue) cDNA testing reveal a number of different. The red box highlights the one or two mutations that are the same in both platforms and the blue box highlights the mutations that are unique to each platform.