Matching Treatment to Genetic Changes in the Tumor Improves Survival Across Multiple Cancer Types

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ASCO Perspective

“It's been 20 years since the first targeted therapy was introduced. These first ‘precision medicine’ therapies revolutionized cancer care and helped many patients live longer. But we’ve just scratched the surface. Now with faster and more robust genetic tests, we can help even more patients by treating the cancer based on its genetic makeup rather than solely on its location in the body,” said ASCO Expert Catherine Diefenbach, MD.

CHICAGO – Researchers conducted a retrospective analysis of consecutive, prospectively molecularly profiled patients with advanced cancer who participated in a large, personalized medicine trial. They found that using molecular tests of tumors to select targeted therapy resulted in slower cancer growth and prolonged survival across a diverse set of cancer types. Of the 1,307 patients with at least one genetic change in the cancer, the 3-year overall survival rate was 15% in the matched targeted group compared to 7% in the non-matched group. The 10-year overall survival rate was 6% for the matched group and 1% in the non-matched group. Overall survival in the matched group plateaued, starting at 3.2 years (11% were still alive).
Participants in the trial who received matched treatment most commonly received an investigational medicine being tested in a clinical trial; a minority of patients received a commercially available targeted treatment that was FDA-approved for another indication (“off-label therapy”) as part of a clinical trial.

The study will be featured in a press briefing today and presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

“This is the first and largest study – with the longest follow-up – to assess the impact of precision medicine approaches on survival across multiple cancer types,” said lead study author Apostolia Maria Tsimberidou, MD, PhD, a tenured professor at The University of Texas MD Anderson Cancer Center in Houston. “Our findings show that molecular testing of tumors using next generation sequencing can be used to optimize therapy and should be taken into consideration when selecting therapy for patients with difficult-to-treat cancers.”

About the Study
The IMPACT (Initiative for Molecular Profiling and Advanced Cancer Therapy) clinical trial began in 2007 to evaluate the impact of personalized therapy selection based on molecular testing of tumors for people with difficult-to-treat cancers. Patients referred to the study had advanced cancer that worsened despite standard treatment (some had received as many as 16 prior therapies). Very few patients (2.8%) were newly diagnosed with a rare, incurable cancer. The most common types of cancer included gastrointestinal cancer, gynecologic cancer, breast cancer, melanoma, lung cancer, and thyroid cancer.

In the early years of the study, tumors were tested for mutations in individual genes, whereas in the late years of the study (until the end of 2013), next generation sequencing was used to test 20-50 different genes at once. Of the 3,743 patients who had molecular testing, at least one genetic change was found in 1,307 tumors. Of those, 711 patients received treatment matched to the biology of the tumor (e.g., a medicine that blocked the function of the mutated or altered gene) and 596 received a therapy that was not matched to the genetic change found in the tumor (i.e., because no matched treatment was available to the patient at the time). Matched therapies included single agent targeted therapy, as well as matched targeted therapy in combination with chemotherapy, or other treatments.

Key Findings
Overall survival in the matched targeted therapy group plateaued, starting at 3.2 years (11% were still alive). Matched targeted therapy was found to be an independent factor predicting longer overall survival in multivariate analysis. The 3-year overall survival rate was 15% in the matched
therapy group compared to 7% in the non-matched group. The 10-year overall survival rate was 6% for the matched therapy group and 1% in the non-matched group. The median overall survival was longer in the matched therapy group versus the non-matched therapy group (9.3 months vs. 7.3 months), as was the median time until cancer worsened (progression-free survival: 4 months vs. 2.8 months).

The investigators developed a prognostic score to predict overall survival of patients based on their baseline characteristics. Taking into consideration baseline characteristics in 1,307 patients, molecular alterations in the PI3K/AKT/mTOR pathway were an independent factor predicting shorter overall survival compared to other alterations. Other independent factors predicting shorter survival were liver metastases, elevated lactate dehydrogenase levels, poor functional status, low albumin levels, elevated platelet counts, and age ? 60 yrs.

Next Steps
The ongoing follow-on study, IMPACT 2, is a randomized phase II study comparing progression-free survival in patients who receive targeted therapy matched to the molecular characteristics of their tumor versus in those for whom treatment is not selected based on the molecular analysis of their tumor. Dr. Tsimberidou notes that the implementation of precision medicine using next-generation sequencing, as well as immune features and new drugs, including immunotherapy, hold the promise to significantly improve the clinical outcomes of patients with cancer.

This study received funding from the following donors: Alberto Barretto, Jamie Hope, and Mr. and Mrs. Zane W. Arrott.

Study at a Glance

<table>
<thead>
<tr>
<th>Disease</th>
<th>Multiple Cancers</th>
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<tbody>
<tr>
<td>Study Type</td>
<td>Retrospective analysis</td>
</tr>
<tr>
<td>Patients Analyzed</td>
<td>3,700+</td>
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<tr>
<td>Intervention</td>
<td>Matched targeted therapy vs. non-matched therapy</td>
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<tr>
<td>Primary Finding</td>
<td>Rates of response, overall survival, and progression-free survival were higher when treatment was matched to genetic changes in the tumor. Overall survival in the matched targeted therapy group plateaued, starting at 3.2 years (11% were still alive).</td>
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<tr>
<td>Secondary Finding(s)</td>
<td>Best outcomes with matched targeted therapies. Best outcomes in non-PI3K/AKT/mTOR pathway abnormalities.</td>
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For your readers:

- Understanding Targeted Therapy
  (Qué es la terapia dirigida)
- Types of Cancer

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