Matching Genetic Mutations to Targeted Therapy Improves Survival

Using molecular tests to select the most appropriate treatment leads to better outcomes.

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Testing the genetic characteristics of tumors and using the results to guide the choice of treatment led to longer survival in a large study of people with hard-to-treat cancer, according to a presentation at the American Society of Clinical Oncology (ASCO) annual meeting last week in Chicago. However, the 10-year overall survival rate in the matched treatment group reached only 6 percent, showing much room for improvement.

“Precision medicine requires complete understanding of tumor biology,” lead researcher Apostolia Maria Tsimberidou, MD, PhD, of the University of Texas MD Anderson Cancer Center in Houston told reporters at an ASCO press briefing. “I’m optimistic that in the next few years we will dramatically improve outcomes of patients with cancer with the increasing use of precision medicine.”

Precision medicine refers to treatment tailored to individual patients. Unlike traditional chemotherapy, which kills fast-growing cells throughout the body including cancer cells, targeted therapies work against cancer with specific genetic characteristics. For example, they may interfere with signaling pathways that regulate cell proliferation or blood vessel formation. Genetic testing of tumors is becoming more widely used to determine which drugs are most likely to work for a particular person.

The first targeted therapy was introduced two decades ago. Before the advent of precision medicine—and often still today—cancer was traditionally treated based on where it was located in the body, according to ASCO expert Catherine Diefenbach, MD, of NYU Langone Perlmutter Cancer Center. “To treat cancer based on its neighborhood ignores all of these genetic differences,” she said.

Tsimberidou and fellow investigators with the IMPACT (Initiative for Molecular Profiling and Advanced Cancer Therapy) trial evaluated the effect of molecular testing on long-term survival among patients with refractory (nonresponsive) cancer referred for Phase I clinical trials between 2007 and 2013. Participants treated with matched targeted therapy selected by genetic testing were compared against those treated with nonmatched therapy.
This retrospective analysis included 3,743 people who had exhausted standard treatment options or had incurable rare cancers. About 60 percent were women and the median age was 57. The most common cancer types were gastrointestinal cancers (24 percent), gynecological cancers (19 percent), breast cancer (14 percent), melanoma (12 percent) and lung cancer (9 percent). The participants were highly treatment-experienced, having tried a median of four prior therapies.

Participants received molecular tests that identified up to 50 different targets. During the first years of the study patients’ tumors were tested for mutations in individual genes, but in later years next-generation sequencing was used to test many different genes at once.

Of these, 1,307 people (35 percent) were found to have at least one targetable genetic alteration or mutation. Within this group, 711 people (54 percent) received matched targeted therapy while 596 (46 percent) received unmatched therapy because no appropriate targeted drugs were available. Targeted therapies could be used alone or in combination with traditional chemotherapy. Most participants who received matched therapy received investigational agents in clinical trials, but some were given “off-label” treatment using available medications that were approved for another indication, usually a different type of cancer.

Treatment with matched therapy was associated with higher response rates and longer survival. The objective response rate, meaning complete or partial tumor shrinkage, was 16 percent in the matched therapy group compared with 5 percent in the nonmatched therapy group. Combining these with stable disease, 35 percent of patients who received matched therapy and 20 percent who received nonmatched therapy did not experience disease progression.

Progression-free survival (meaning patients were still alive without worsening of disease) and overall survival were both significantly longer in the matched therapy group, indicating that the differences were probably not attributable to chance alone. The median progression-free survival duration was 4.0 months in the matched therapy group compared with 2.8 months in the nonmatched therapy group. Overall survival duration was 9.3 months versus 7.3 months, respectively.

After three years, 15 percent of patients in the matched therapy group were still alive compared with 7 percent in the nonmatched therapy group. After 10 years, the overall survival rates were 6 percent and 1 percent, respectively.

In addition to use of nonmatched therapy, other factors associated with shorter overall survival were older age; poorer performance status (ability to carry out normal activities); cancer that had spread to the liver; abnormal albumin, platelet or lactate dehydrogenase levels; and having tumors with alterations in the PI3K/AKT/mTOR cell signaling pathway, which plays a role in regulating cell division.

“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,” Tsimberidou concluded. “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.”

The randomized IMPACT2 trial and ASCO’s TAPUR trial aim to shed further light on the benefits of personalized targeted therapy.

“These first precision medicine therapies revolutionized cancer care and helped many patients live longer,” Diefenbach said in an ASCO press release. “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.”

Click here to read the study abstract.

Click here to read an ASCO press release about the study.