

小児プレジジョン・メディシンの試験は予測を超える (Abstract 10011)

Pediatric MATCH: 試験の結果、小児がんにおいて標的とされる遺伝子変異が予測を上回る高頻度で認められた

Pediatric MATCH: Trial finds more frequent targetable genetic alterations in pediatric cancers than predicted

2017年のPediatric Molecular Analysis for Therapy Choice (NCI-COG Pediatric MATCH) 試験の開始時点で、難治性がんを有する小児、青少年、および若年成人における腫瘍シーケンシングにより、試験対象の標的薬に適合する遺伝子変異が発見されるのは、スタディ参加者の10% であろうと推定された。スクリーニングされた患者400人超の間解析の結果、適合率はそれよりもかなり高いようで、24% の患者が今回の試験対象となった薬剤の少なくとも1つを用いた治療に適合した。このスタディの最新情報が、2019 ASCO Annual Meeting で発表される。

Full Text

At the launch of the National Cancer Institute-Children's Oncology Group Pediatric Molecular Analysis for Therapy Choice (NCI-COG Pediatric MATCH) trial in 2017, it was estimated that tumor sequencing in children, adolescents, and young adults with treatment-refractory cancers would identify genetic alterations that matched an investigational targeted therapy in 10% of study participants. An interim analysis of more than 400 patients screened has revealed the match rate appears to be significantly higher, with 24% of participants eligible to receive treatment with at least one drug being tested in the trial. The first update on the study is being presented at the 2019 ASCO Annual Meeting in Chicago.

The expectation of a 10% match rate prior to the trial launch was based on experience from pediatric disease-specific research studies, the majority of which had focused on newly diagnosed pediatric cancers as opposed to treatment-refractory tumors, as well as similar adult trials, such as the NCI-MATCH study.

"Our study shows that we can successfully create a nationwide molecular screening trial for children, adolescents, and young adults with cancers that have been resistant to treatment," said COG study chair Will Parsons, MD, PhD, Associate Professor of Pediatrics-Oncology at Baylor College of Medicine in Houston, TX. "One of our key goals has been to expand access to targeted therapies for pediatric cancer patients across the country, and these early results suggest that goal is within reach."

"We're encouraged by these early results that underscore the value of public-private collaboration in understanding and treating cancers occurring in children, adolescents, and young adults," said NCI study chair Nita Seibel, MD, Head of Pediatric Solid Tumor Therapeutics in the Clinical Investigations Branch of NCI's Cancer Therapy Evaluation Program. "Pediatric MATCH depends on active partnership between NCI, COG, the U.S. Food and Drug Administration, pharmaceutical companies, and other and key pediatric cancer research stakeholders."

Precision medicine treatment approaches have not been routinely incorporated into the care of childhood cancer patients but are now being tested through trials such as Pediatric MATCH. To date, only a small number of targeted therapies have been approved for the treatment of pediatric cancer. By comparison, there are more than 150 U.S. approvals for targeted therapies in adult cancers. For these reasons, earlier this year ASCO identified "Increase Precision Medicine Research and Treatment Approaches in Pediatric Cancers" as a critical research priority.

NCI-COG Pediatric MATCH is the first nationwide pediatric precision oncology trial for patients with cancers that have not responded to standard treatments. The study seeks to identify the specific genetic alterations occurring in each patient's cancer, match patients to drugs targeted at those alterations (regardless of the cancer type), then evaluate the impact of the treatments. Study patients are first enrolled on a screening protocol in which their tumors are sequenced and any matching alterations are identified based on previous evidence linking the alterations to targeted therapies. If a match is found for a study patient, they are then offered enrollment on the corresponding Pediatric MATCH phase II treatment trial. Ten different targeted therapies are currently being studied as part of Pediatric MATCH.

As of the end of 2018, trial investigators had enrolled 422 children, adolescents, and young adults from one to 21 years of age (median age of 13 years) on the study, including patients from nearly 100 participating Children's Oncology Group sites across the U.S. This included 101 patients (24%) with brain tumors, 300 (71%) with other solid tumors, and 21 (5%) with lymphomas or histiocytic disorders, which are rare disorders affecting the immune system. Tumor samples from 390 patients were submitted for DNA and RNA sequencing of more than 160 genes in order to identify alterations that would match patients to one of the 10 targeted therapies being tested in the study. The treatments, many of which are being tested in children for the first time, included:

- Larotrectinib – targeting NTRK
- Erdafitinib – targeting FGFR
- Tazemetostat – targeting EZH2 and other SWI/SNF complex genes
- LY3023414 – targeting the PI3K/MTOR pathway
- Selumetinib – targeting the MAPK pathway
- Ensartinib – targeting ALK or ROS1
- Vemurafenib – targeting BRAF
- Olaparib – targeting defects in DNA damage repair
- Palbociclib – targeting cell cycle genes
- Ulixertinib – targeting the MAPK pathway

Tumor testing was completed for 357 patients (92%). Targetable genetic alterations – mutations, fusions or gene copy number changes targeted by one of the 10 medicines included in the trial – were identified in 112 (29%) patients, with 95 of those patients (24%) eligible to be assigned to one of 10 treatments available in the trial. As of the end of 2018, 39 patients (10%) had enrolled on a Pediatric MATCH treatment trial, with additional matched patients still eligible for treatment at a later date.

Targetable alterations were detected in more than 40% of patients with brain tumors and more than 25% of patients with the other cancer types tested (other solid tumors, lymphomas, and histiocytic disorders) demonstrating the utility of tumor screening for children with both common and rare cancers. No significant difference in detection rate was seen between younger patients (under 12 years of age) and older children, adolescents and young adults on the study.

The targetable alterations detected in Pediatric MATCH patients involved diverse cancer genes: most commonly RAS gene mutations, found in 16 patients; BRAF mutations or fusions, found in 14 patients; SMARCB1 mutations or deletions, found in 14 patients; NF1 mutations, found in 11 patients; and numerous alterations occurring in fewer than 10 patients each.

"Today we cure a large number of children with cancer, but there are still many patients needing better treatments. These results bring us one step closer to bringing the precision medicine era to pediatric cancer care. Now that we know that targetable genetic alterations are fairly common in pediatric cancers, we have an exciting opportunity to boost success rates," said ASCO President Monica M. Bertagnoli, MD, FACS, FASCO.

In addition to tumor samples, blood samples are also being sequenced as part of the study, in order to see if any of the mutations identified in each tumor are hereditary and require additional genetics evaluation for the patient and family. These results could assist doctors in informing families about cancer risk, the need for additional genetic testing, and screening strategies for cancer prevention.

Pediatric MATCH is anticipated to enroll at least 1,000 patients. Study investigators plan to continue to add new targeted therapies to the trial in an attempt to further increase the number of patients who could be matched to drug treatments on the study – protocols for four additional drugs are currently under development. Strategies for future adaptations of the trial may include testing combinations of drugs as well as immunotherapies, and optimized plans for molecular testing and assignment of patients to study treatment arms.

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