一部のがんにおいてゲノム異常は抗PD-1反応の予測因子となる (Abstract LBA100)

いくつかのタイプのがん患者において特定のゲノム異常によりpembrolizumabの有効性が予測できる

Specific genomic abnormality predicts response to pembrolizumab in patients with several types of cancer

第51回American Society of Clinical Oncology年次集会で発表された第II相試験において初めてのゲノムマーカーーミスマッチ修復（MMR）欠損ーにより広範ながんに対する抗PD-1抗体pembrolizumabの有効性が予測できることが示された。スタディには3群の患者ーMMR正常転移性大腸がん（CRC 25人）、MMR欠損転移性CRC(13人)、および他のMMR欠損がん（10人）ーが含まれた。全ての患者が過去の治療にもかかわらず悪化した進行性転移性がんを有していた。奏効率はMMR欠損CRCとMMR正常CRCとで大きく異なった（62%対0%）一方で、病勢コントロール率（腫瘍縮小または増殖抑制）の差はより大であったーMMR欠損群の92%に対しMMR 正常群では16%であった。有効性を示す血液マーカー変化は治療開始後数週間以内に認められ、患者はほぼ治療直後に体調が改善した。他のMMR欠損がん群（CRCsを除く）における全奏効率は60%であった。奏効は、進行子宮内膜がんおよび乳頭部、十二指腸、胆のうがん、および胃がんなどのいくつかのタイプの進行消化器がんにおいて認められた。最後の解析において、奏効は1人の患者以外においては継続中であり多くは1年以上持続していた。

Full Text

A phase II study presented by researchers at the American Society of Clinical Oncology's 51st Annual Meeting identified the first genomic marker – mismatch repair (MMR) deficiency – to predict response to the anti-PD-1 antibody pembrolizumab. This marker predicted responses across a range of cancers.

Among patients with colorectal cancer (CRC), 62% of those with MMR-deficient tumors experienced tumor shrinkage, while no responses were detected among those without this abnormality ("MMR-proficient"). The response rate among patients with other MMR-deficient cancers was similar – 60%.

MMR deficiency is found in 15-20% of sporadic (non-inherited) CRCs and in nearly all CRCs associated with Lynch syndrome, which constitute up to 5% of all CRCs. MMR deficiency is also found in other tumor types including stomach, small bowel, endometrial, prostate, and ovarian cancer.

Testing for MMR-deficiency is widely available and may enable doctors to identify a larger population of patients who might benefit from pembrolizumab and other PD-1 drugs.

"This study is really about bridging immunotherapy and genomics for the benefit of patients, and it has implications for a broad range of cancers," said lead study author Dung T. Le, MD, an assistant professor of oncology at Johns Hopkins Kimmel Cancer Center in Baltimore, M.D.. "Opening the door to this effective new therapy would be a breakthrough for this subset of patients with metastatic colon cancer and other hard-to-treat cancers."

MMR deficiency leads to an accumulation of genetic mutations in a tumor. "When you have a tumor that has thousands of mutations, this increases the probability that the immune system can recognize and destroy the tumor. So, we suspected that immune checkpoint inhibitors such as pembrolizumab would work particularly well against MMR-deficient tumors," added Dr. Le.

In this study, MMR-deficient tumors had an average of 1,782 mutations, compared to 73 mutations in MMR-proficient tumors. Higher numbers of mutations were linked to better response to pembrolizumab.

The study included three groups of patients: MMR-proficient metastatic CRC (25 patients), MMR-deficient metastatic CRC (13 patients), and other MMR-deficient cancers (10 patients). All patients had progressive metastatic cancer that had worsened despite prior treatment.

While researchers observed a large difference in response rates between MMR-deficient and -proficient CRCs (62 vs. 0%), the difference in disease control rates (tumor shrinkage or suppressed growth) was even greater – 92% in the MMR-deficient group and only 16% in the MMR-proficient group. Blood marker changes such as CEA levels indicating response were seen within the first few weeks of starting treatment, and patients tended to feel better almost immediately.

In the group of other MMR-deficient cancers (excluding CRCs), the overall response rate was 60%. Responses were detected in patients with advanced endometrial cancer and several types of advanced gastrointestinal cancers including ampullary, duodenal, cholangiocarcinoma, and gastric cancers. Few treatment options exist for such patients. At last analysis, responses were ongoing for all but one patient, and many responses have lasted for over a year.

Dr. Le indicated that the next step is to reproduce the findings of this prospective study in a larger group of patients to solidify the observation that MMR deficiency is a predictor of response to therapies targeting PD-1. She noted that the durability of response with little toxicity could eventually lead to testing this approach in initial treatment for these patients.

Pembrolizumab is currently only FDA approved to treat patients with advanced melanoma that has not responded to other standard therapies. Another PD-1 therapy, nivolumab, is approved for the same indication, as well as in advanced squamous lung cancer.

"This study helped identify a whole new population of patients who might benefit from PD-1 immunotherapy. MMR deficiency appears to be a predictor of response to nivolumab, and it's very encouraging that the responses in MMR-deficient tumors thus far have been long-lasting," said ASCO Expert Smitha S. Krishnamurthi, M.D..

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