チェックポイント阻害薬は肺がん再発を減少させるのに有望である(Abstract 8504)

NEOSTAR：早期肺がんに対する術前のチェックポイント阻害薬の併用は有効である

NEOSTAR: Combination checkpoint blockade effective in pre-surgical setting for early-stage lung cancer

免疫チェックポイント阻害薬を用いた術前補助療法による病理学的奏効率（MPR）は、治療された早期切除可能非小細胞肺がん患者において33% であった、と2019 ASCO Annual Meeting で発表された。第II相NEOSTAR 試験において、術前にニボルマブ（抗PD-1抗体）およびイピリムマブ（抗CTLA-4抗体）の併用療法を施行された患者21人中7人がMPR を達成したのに対し、ニボルマブ単独療法でMPR を達成したのは23人中4人であった。これら2群を比較するには検出力は不足しているが、併用療法は手術時点でviable な腫瘍を減少させるのにより有効と思われた。

Full Text

Neoadjuvant treatment with nivolumab plus ipilimumab resulted in an overall major pathologic response (MPR) rate of 33 percent of treated patients with early-stage, resectable non-small cell lung cancers, meaning these patients had less than or equal to 10 percent viable tumor remaining at surgery. With these results, the combination immunotherapy met the pre-specified trial efficacy endpoint of the phase II NEOSTAR trial conducted by researchers at The University of Texas MD Anderson Cancer Center.

The trial arm testing nivolumab alone in the treated population of patients achieved a 17 percent MPR rate, for an overall MPR rate across both trial arms of 25 percent. The results of the trial were presented in an oral presentation at the 2019 American Society of Clinical Oncology Annual Meeting by principal investigator Tina Cascone, M.D., Ph.D., assistant professor of Thoracic/Head & Neck Medical Oncology.

"The NEOSTAR trial results definitely tell us this combination is clinically promising and warrants further investigation, possibly in combination with other therapies" said Cascone. "By learning from these results and from our preclinical and translational findings, we can identify the best combination and make a major step forward in the field to limit tumor recurrence for our early-stage lung cancer patients."

Patients with early-stage or locally advanced lung cancer have the potential to be cured of their disease, but more than half of those patients will have a recurrence if treated with surgery alone, explained Cascone. Therefore, there is an urgent need to identify the most effective neoadjuvant therapy options to reduce the risk of relapse.

Preclinical studies in mice revealed that increased expression of PD-L1, an immune checkpoint protein, in lung adenocarcinoma tumors is critical for the development and survival of metastases, providing the rationale for testing immunotherapy in the neoadjuvant setting.

"Prior to this study, we knew that single agent neoadjuvant immunotherapy has achieved an MPR rate of 22 to 45 percent, but the combination of anti-PD-1 and anti-CTLA-4 immune checkpoint blockade before surgery in resectable NSCLC patients had not yet been tested," said Cascone. "In mouse models of resectable and spontaneously metastatic non-small cell lung cancer, the combination of immunotherapy prior to surgery was superior to adjuvant combined therapy in prolonging survival and reducing the frequency of lung metastases, supporting further investigation of neoadjuvant combined immune checkpoint blockade in the clinical setting."

The researchers designed the trial to test the effectiveness of combination immune checkpoint inhibitors priory to surgery. The trial enrolled 44 patients who were randomized to receive either neoadjuvant nivolumab (anti-PD-1) alone or nivolumab plus ipilimumab (anti-CTLA-4).

The trial's primary endpoint was MPR, hypothesized to be higher for single and/or combination immune checkpoint inhibitors compared to the rate induced by historical neoadjuvant chemotherapy controls. The pre-specified trial efficacy endpoint for a specific treatment to be considered promising was greater than or equal to six MPRs in the intent to treat population.

MPR has been adopted as a surrogate endpoint in neoadjuvant trials for patients with resectable non-small cell lung cancer patients, as it has been shown to positively correlate with improved overall and recurrence-free survival outcomes, explained Cascone.

Seven out of 21 patients treated pre-operatively with the combination therapy achieved an MPR, and four of 23 patients treated with nivolumab alone achieved an MPR.

Although the trial was not powered to make a comparison between the two arms, the combination therapy appeared more effective at reducing viable tumor at surgery. Six patients (38 percent) that received the combination therapy and underwent surgery on trial achieved a complete pathological response compared to just two patients (10 percent) receiving nivolumab alone. Also, the majority of patients with more than 50 percent viable tumor remaining at surgical resection received single-agent nivolumab therapy.

The treatments were generally well-tolerated, said Cascone, with no unacceptable toxicity or increased perioperative morbidity and/or mortality noted, however, careful perioperative monitoring is advised with these agents.

The trial also collected a variety of biospecimens from patients before, during and after treatment, which enabled researchers to investigate why results vary from patient to patient and understand the dynamic changes induced by therapy in potential biomarkers. They discovered that elevated tumor expression of the immune checkpoint protein PD-L1 prior to therapy was positively correlated with radiographic responses and with pathologic tumor regression at surgery.

Preliminary immunologic characterization of resected tumors from patients treated with immunotherapy indicated that the combination therapy is associated with an increased number of tumor-infiltrating lymphocytes as compared to monotherapy, and that some of these T cells might have tumor reactive activity. Additional results presented in a poster session show that combination therapy appeared to be associated with greater diversity and reactivity of T lymphocytes in resected tumors as compared to pretreatment tumor specimens.

"This is important because we don't see patients with early-stage lung cancer as often as patients with metastatic disease in the clinic, and we want to take advantage of this opportunity for our patients. There are limitations to this trial, as it was overall a small cohort, but the positive results suggest we should continue to evaluate neoadjuvant combination immunotherapy as an option for our patients. Our ongoing exploratory analyses will help us to better understand this response and to identify potential biomarkers that could inform future trials," said Cascone.
The researchers already have added and are nearing complete enrollment in a third arm of the NEOSTAR trial to evaluate neoadjuvant nivolumab plus platinum-based chemotherapy. Because of successful accrual, additional arms are being considered to evaluate further combination approaches.

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