メラノーマのファーストライン治療としてipilimumabは有効である（Abstract No.LBA5）

モノクローナル抗体ipilimumabと化学療法の併用は転移性メラノーマの全生存率を改善する

Monoclonal antibody ipilimumab plus chemotherapy improves overall survival in metastatic melanoma

2011年ASCOで発表されNew England Journal of Medicineオンライン版に掲載されたPhase III無作為化スタディの結果、免疫療法薬ipilimumabと標準的な化学療法薬dacarbazineの併用によるファーストライン治療により未治療の転移性メラノーマ患者の全生存率が改善することが示された。昨年の2010年の学会において、ipilimumabはメラノーマワクチンgp100と比較し生存率を改善することが示された。今回のスタディにおいて転移性メラノーマ患者502人がipilimumabとdacarbazine併用群（250人）またはプラセボとdacarbazine投与群（252人）に無作為に割り付けられた。1年後の全生存率は併用療法群において47.3%であったのに対しdacarbazine単独療法群では36.3%であった。2年後の全生存率は2剤併用群で28.5%であったのに対しdacarbazine単独群では17.9%であった。3年後の総生存率は2剤併用群で20.8%であったのに対し化学療法単独群では12.2%であった。全生存率中央値はipilimumabとdacarbazine投与群で11.2ヵ月であったのに対しdacarbazine単独投与群においては9.1ヵ月であった（死亡のハザード比[HR] 0.72）。無増悪生存期間中央値は併用療法の2.8ヵ月に対しdacarbazine単独群では2.6ヵ月であり、ほぼ同等であった。

Full Text

A Phase III randomized study found that first-line treatment with a combination of the immunotherapy drug ipilimumab (Yervoy) and the standard chemotherapy drug dacarbazine (DTIC) improves overall survival in patients with previously untreated metastatic melanoma. It is the first study to show that combining chemotherapy and immunotherapy is safe and effective for patients with advanced melanoma. At the 2010 Annual Meeting, ipilumumab was shown to improve survival when compared to a melanoma vaccine, gp100.

"These findings show the same kind of important results announced last year with the use of ipilimumab alone in improving overall survival in metastatic melanoma," said lead author Jedd Wolchok, M.D., director of immunotherapy clinical trials and associate attending physician at Memorial Sloan-Kettering Cancer Center in New York. "This trial's three-year endpoint is significant. No randomized trial for metastatic melanoma has followed patients for this long, and it demonstrates the durability of this survival benefit, now out to three years in this population, and even four years in some cases. It's one of the advantages of immunotherapy. The immune system is a 'living drug,' able to adapt itself to changes in the tumor that might otherwise lead to resistance when treated with chemotherapy or a pathway inhibitor."

Advanced melanoma is one of the most deadly forms of cancer, and over the past three decades, melanoma incidence has climbed faster than any other cancer type. Ipilimumab is a monoclonal antibody that represents a new class of drugs that activate the immune system's T cells, which then seek and destroy melanoma cells. The drug targets the cytotoxic T-lymphocyte associated antigen 4, which acts like a brake on the T-cell. Ipilimumab removes this brake, enabling T cells to attack the cancer.

In this study, 502 patients with metastatic melanoma were randomized to ipilimumab plus dacarbazine (250) or placebo and dacarbazine (252). The overall survival rate for the combination after one year was 47.3 percent compared to 36.3 percent for DTIC alone. After two years, the overall survival rate was 28.5 percent for the two drugs, versus 17.9 percent for DTIC alone. At three years, overall survival was 20.8 percent for the combination compared to12.2 percent for chemotherapy alone.

Investigators found that the median overall survival was 11.2 months for patients who received ipilimumab and DTIC versus 9.1 months for those given only DTIC. The median progression-free survival times, however, were nearly the same: 2.8 months for the combination compared to 2.6 months for DTIC. Dr. Wolchok attributed this finding to the way ipilimumab - and immunotherapy - may work. The effects of immunotherapy treatment can take much longer to be seen than those from traditional chemotherapy or targeted therapies, and patients' scans may accurate way to gauge treatment effectiveness than progression-free survival.

The combination of ipilimumab and dacarbazine had a good safety profile, with no gastrointestinal perforations and a lower rate of colitis than was expected based upon prior studies with ipilimumab alone. Still, approximately 56 percent of patients in the ipilimumab-DTIC group and 27 percent of those who received only DTIC had significant grade 3/4 adverse events from their therapy, including elevated liver enzymes.

The next step in the research, according to Dr. Wolchok, is to investigate combinations of different therapies with ipilimumab, such as the targeted drug vemurafenib in melanoma patients with BRAF mutations, and to test other combinations of targeted agents and immune-modifying agents together as well.

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