転移性メラノーマに対する有望な免疫療法の組み合わせ（Abstract＃CRA9007）

IpilimumabにGM-CSFを併用することにより転移性メラノーマ患者の生存率が改善する

Adding GM-CSF to ipilimumab significantly improves survival in patients with metastatic melanoma

第49回American Society of Clinical Oncology年次集会で発表された第Ⅱ相試験の結果、遺伝子組換え型顆粒球マクロファージコロニー刺激因子（GM-CSF, sargramostim）を高用量ipilimumabに併用することにより転移性メラノーマ患者の生存期間が延長することが示された。IpilimumabもGM-CSFも免疫系に働きかけることで作用する。Ipilimumabは免疫T細胞を不活化状態に維持する蛋白CTLA-4を標的とする。GM-CSFは一般的に化学療法または幹細胞移植後に白血球数を増加させるために使用される増殖因子である。今回のスタディでは過去に治療を多くて1回施行された転移性メラノーマ患者245人が、ipilimumabとGM-CSFの併用またはipilimumab（10mg/kgの用量）のみを投与される群に無作為に割り付けられた。腫瘍縮小率は両群で同等であった（11～14%）が、全生存期間は併用群で長かった：治療開始後1年の時点での生存率は併用群で68.9%であったのに対し、ipilimumab単独群では52.9%であった。死亡リスクは併用群でipilimumab単独群よりも35%低かった。さらに、併用療法の方がipilimumab単独治療よりも重篤な副作用が少なかった。

Full Text

A proof-of-principal phase II study shows that the recombinant granulocyte macrophage colony-stimulating factor (GM-CSF, sargramostim) added to an increased dose of the immunotherapy ipilimumab extends survival for patients with metastatic melanoma. More than two-thirds of patients were alive after one year of combination therapy vs. half of those treated with ipilimumab alone, a significant advance for metastatic melanoma. Interestingly, the combination also appears to be safer for patients than ipilimumab alone — GM-CSF decreased some of the serious side effects of ipilimumab.

Both ipilimumab and GM-CSF work by activating the immune system to fight cancer. Ipilimumab is a new treatment for advanced melanoma targeting CTLA-4, a protein that keeps immune T-cells in an inactive state. GM-CSF is a growth factor commonly used to boost white blood cell counts after chemotherapy or stem cell transplantation.

"This is the first randomized phase II study looking at the combination of ipilimumab and GM-CSF in any cancer," said lead author F. Stephen Hodi, M.D., an associate professor of medicine at Dana-Farber Cancer Institute in Boston, Massachusetts, USA and principal investigator for this ECOG-ACRIN clinical trial. "The results of the E1608 study provide another important sign that immunotherapy can have a big impact for patients with advanced melanoma. At the same time, we still need to clarify the best way to apply these findings in everyday practice."

In this study, 245 patients with metastatic melanoma who had undergone up to one prior treatment were assigned to receive ipilimumab plus GM-CSF or ipilimumab alone (at a dose of 10 mg/kg). The median follow up time was 13.3 months. Tumor shrinkage rates were comparable in both arms (11-14 percent) but the overall survival rate was longer in the combination treatment arm: one year after the start of therapy, 68.9 percent of patients who received the combination were alive, compared to 52.9 percent of patients who received ipilimumab alone. Patients who received the combination treatment had a 35 percent lower risk of dying compared with those that received ipilimumab alone.

In addition, the combination treatment was associated with fewer serious side effects compared to ipilimumab alone. The most significant differences were in lung and gastrointestinal toxicities. There were two possible treatment-related deaths in the combination arm vs. seven in the single-drug arm.

"This melanoma study builds upon the remarkable successes and advances we have seen for patients with advanced melanoma over the past two years," said Lynn Schuchter, M.D., ASCO spokesperson and melanoma expert.

The researchers noted that additional immune system boosters are being explored in early clinical trials, though the advantage of GM-CSF is that it improves both efficacy and safety of immunotherapy. The next step is to better define the role of GM-CSF in combination with other immune checkpoint targeting drugs, such as PD-1 and PD-L1.

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