BRAF阻害剤は転移性メラノーマの生存率を改善する（Abstract No.LBA4）

Vemurafenibは進行メラノーマ患者の無増悪生存期間を改善する初めての薬剤である

Vemurafenib first drug to improve progression-free survival in patients with advanced melanoma

第47回ASCOで発表されNew England Journal of Medicineオンライン版に掲載された無作為化国際Phase IIIトライアルの結果、BRAF遺伝子のV600E変異を標的とするvemurafenib（PLX4032）は進行メラノーマ患者において標準的治療と比較し全生存期間を改善した初めての薬剤である。このトライアルでは、治療歴のない手術不能なステージIIICまたはステージIVの転移性メラノーマを有しBRAF遺伝子にV600E変異のある患者675人において、zvemurafenibを用いた治療と化学療法薬dacarbazineを比較した。計画されていた3ヵ月後の中間解析において、vemurafenib投与患者はdacarbazine投与患者と比較し死亡リスクが63%低かった（hazard ratio [HR]0.37；P<0.001）。Vemurafenib群はまたdacarbazine群よりも疾患進行（または死亡）リスクが74%低く（HR 0.26、P<0.001）奏効率が高かった(48.3vs5.5%、P<0.001)。最も多い副作用は発疹、光線過敏症、肝酵素上昇、および関節痛であった。これらの副作用のうちグレードIII以上であったのは10%未満であった。

Full Text

A randomized, international Phase III trial showed that vemurafenib (also known as PLX4032), which targets the V600E mutations in the BRAF gene, is the first drug to improve overall survival when compared to standard chemotherapy in patients with advanced melanoma. It is also the first drug to improve progression-free survival (PFS) and response proportion in these patients. If approved by the U.S. Food and Drug Administration, vemurafenib could become a new standard treatment for patients with melanoma who have this gene mutation. The drug has received extensive attention as a result of striking results from earlier-stage trials. This study is the first to demonstrate conclusively that the drug significantly improves survival better than the current standard.

"This is really a huge step toward personalized care in melanoma," said lead author Paul Chapman, M.D., attending physician in the melanoma/sarcoma service at Memorial Sloan-Kettering Cancer Center in New York. "This is the first successful melanoma treatment tailored to patients who carry a specific gene mutation in their tumor, and could eventually become one of only two drugs available that improves overall survival in advanced cancers." The other drug, ipilumumab, is an immune therapy also featured in ASCO's 2011 Annual Meeting plenary session.

Approximately half of all melanomas harbor a V600E mutation in the BRAF gene. The trial compared the effectiveness - overall survival and progression-free survival - of treatment with vemurafenib to the chemotherapy drug dacarbazine in 675 patients with previously untreated, inoperable stage IIIC or stage IV metastatic melanoma and a V600E mutation in the BRAF gene.

At the planned interim analysis at median three months, patients receiving vemurafenib had a 63 percent reduction in risk of death compared to those receiving dacarbazine. Those who received vemurafenib also had a 74 percent reduction in the risk of progression (or death) compared to dacarbazine. In addition, the researchers found that those receiving vemurafenib had a 48.4 percent response rate compared to 5.5 percent for the dacarbazine group. At the first trial interim analysis, it was recommended that those patients receiving dacarbazine switch to vemurafenib.

The most common side effects of vemurafenib were skin rashes, photosensitivity, elevated liver enzymes, and joint pain. Fewer than 10 percent of these side effects were grade three or worse. In addition, 18 percent of patients developed a low-grade non-melanoma skin tumor.

Dr. Chapman said that because the study findings showed improvements in PFS and response rate along with greater overall survival, PFS may now become a validated study endpoint for future trials with similarly targeted therapies in melanoma.

The researchers plan to next test vemurafenib in combination with other agents in patients with advanced melanoma. A Phase I trial has already begun with vemurafenib and ipilimumab, which received approval from the U.S. Food and Drug Administration earlier this year.

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