薬物により骨髄線維症の奏効率が改善する（Abstract No. LBA6501）

JAK阻害薬は高リスク骨髄線維症患者の奏効率を改善する

JAK inhibitor improves response rate for patients with high-risk myelofibrosis

あるヨーロッパの無作為化Phase IIIトライアルの結果、Janusキナーゼ（JAK）阻害薬ruxolitinibが、しばしば白血病に到る致死的な可能性のある骨髄疾患である骨髄線維症の3つの型の治療の奏効率を顕著に改善することが示されたと第47回ASCOで発表された。全ての患者においてJAKシグナリングパスウェイが活性化していたが、JAK2遺伝子の変異を有していたのは全体の約半数であった。RuxolitinibはJAK阻害薬でありJAK2変異の有無にかかわらず有効である。COMFORT IIトライアルは、原発性骨髄線維症、真性多血症後骨髄線維症または本態性血小板血症後骨髄線維症の成人患者におけるruxolitinibの有効性、安全性および忍容性を現在可能な最適な治療法と比較調査した。このスタディでは中等度または高リスクの患者をruxolitinib（146人）または可能な最適な治療法（73人）に無作為に割り付け、有効性のエンドポイントは脾臓サイズの35%以上の減少とした。Ruxolitinib群では24週後に31.9%の患者が、48週後には28.5%がこのエンドポイントを達成した。可能な最適な治療を受けたコントロール群患者においてはこのレベルの脾臓サイズの縮小を認めた者はいなかった。

Full Text

A randomized Phase III European trial showed that the Janus kinase (JAK) inhibitor ruxolitinib resulted in dramatically improved response rates in treating three forms of myelofibrosis (MF), a potentially deadly bone marrow disorder that frequently leads to leukemia according to researchers at the American Society of Clinical Oncology's 47th Annual Meeting. The trial - dubbed COMFORT II - and a companion Phase III study (COMFORT I) - are the first randomized drug trials for MF. In showing significant benefit compared to currently available therapies, the findings promise to change the standard of care for many patients with MF.

"There aren't really any therapies that work for a sustained period in myelofibrosis, and we've urgently needed new treatments for this condition," said study co-author Alessandro Vannucchi, M.D., associate professor of hematology at the University of Florence in Florence, Italy. "These patients responded very quickly to ruxolitinib - within two to four weeks. This therapy has the potential to significantly change the treatment landscape for these patients, and could greatly improve their outlook."

MF is a myeloproliferative disorder characterized by the progressive accumulation of scar tissue in the bone marrow, causing anemia and a variety of debilitating systemic symptoms, in addition to an enlarged spleen. Twenty-seven percent of patients eventually develop acute myeloid leukemia or bone marrow failure. While bone marrow transplantation is the only potentially curative therapy currently available, only 10 percent of patients are eligible; other therapies, including blood transfusion, anabolic steroids and thalidomide, are considered largely palliative because they do not alter the course of the disease and their activity usually is not sustained.

While the median overall survival for myelofibrosis can exceed five years, high-risk patients only live about two to four years after diagnosis. About half of all patients carry a mutation in the JAK 2 gene, though all have an activated JAK signaling pathway. Ruxolitinib is a JAK inhibitor and is active for patients regardless of whether or not they have a JAK2 mutation.

The COMFORT II trial studied the effectiveness, safety and tolerability of ruxolitinib compared to best available therapy (BAT) in adults with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF). In the study, 219 patients with intermediate or high-risk disease were randomized to either ruxolitinib (146) or BAT (73), with a response endpoint of a 35 percent or greater reduction in spleen size. After 48 weeks, 28.5 percent of patients receiving the drug achieved this reduction compared to 0 percent with BAT. At 24 weeks, the response rate was 31.9 percent for ruxolitinib versus 0 percent for BAT.

According to the authors, ruxolitinib had an adverse event profile similar to earlier studies. Adverse events including anemia and thrombocytopenia caused 8.2 percent of patients who received ruxolitinib to halt treatment, while 5.5 percent of those given BAT stopped therapy. There was one death that may have been related to ruxolitinib treatment.

Several research questions remain, including how ruxolitinib may be used with other treatments such as thalidomide, bone marrow transplantation or more novel agents, and whether ruxolitinib improves overall survival. Several such studies are in progress.

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