レナリドミドは多発性骨髄腫の発症を遅延させる (Abstract 8001)

レナリドミドは、前がん状態の骨髄腫が明らかな多発性骨髄腫に進展する高リスク患者におけるリスクを軽減する

Lenalidomide reduces risk that precancer myeloma will progress to overt multiple myeloma in high risk individuals

2019 ASCO Annual Meeting で発表されたランダム化第II/III相試験 E3A06 で、レナリドミドは中等度または高リスク患者におけるくすぶり型多発性骨髄腫（SMM）－前がん病態－が、がんに進展するのを有意に減少させることを明らかにした。一般的に、多発性骨髄腫においては臓器障害がみられ、これがSMMと鑑別する方法である。3年後、レナリドミドを投与されたSMM患者の87%（第II相）および91%（第III相）で病態が多発性骨髄腫に進展しなかったのに対し、この治療を受けず病態進展の可能性を経過観察のみで行った患者におけるこの割合は66% であった（第III相）。経過観察がこの疾患における現在の標準治療である。

Full Text

The phase II/III E3A06 randomized clinical trial found that lenalidomide significantly reduces the risk of smoldering multiple myeloma (SMM) – a precancerous condition – from progressing to cancer in patients at moderate or high-risk. Organ damage is typically seen in multiple myeloma, which is a way to differentiate it from SMM. At three years, in 87% (phase II) and 91% (phase III) of people with SMM receiving lenalidomide, the condition did not progress to multiple myeloma compared with 66% of people who did not receive the therapy and were just observed for potential progression (phase III). Observation is the current standard of care. The study is being presented at the 2019 ASCO Annual Meeting in Chicago.

"We typically see two types of patients – those who are anxious and want to do something to prevent cancer from developing, and those who are more cautious and are willing to watch and wait," said lead study author Sagar Lonial, MD, Chief Medical Officer at Winship Cancer Institute of Emory University, Atlanta, GA. "It's gratifying to know that especially for the first group of patients there may now be a viable treatment option."

Lenalidomide is an analog of thalidomide, a therapy developed decades ago as a sedative. Lenalidomide prevents the formation of blood vessels that can feed tumors, such as those found in multiple myeloma, and it also carries the risk of serious side effects.

A recent study looking at over 86,000 people with multiple myeloma found that 13.7% were first diagnosed as having SMM, with a median age of 67 at diagnosis. When extrapolated to multiple myeloma diagnosis data for the entire United States, this amounts to roughly 4,400 people in the United States being diagnosed with SMM each year. In only half of people diagnosed with SMM, however, the condition progresses to multiple myeloma in the first five years. Once diagnosed with multiple myeloma, the 5-year survival rate is over 50%. Survival rates have steadily increased over the last decade thanks to the availability of several new therapies.

Earlier this year, ASCO included "Identifying Strategies to Detect and Treat Premalignant Lesions" in its list of Research Priorities to Accelerate Progress Against Cancer. The findings of this trial support this critical need and help provide a new preventive therapy for patients with this precancerous condition.

The E3A06 trial enrolled people with intermediate or high-risk SMM in two phases. In phase II, 44 people received lenalidomide to assess potential efficacy. In phase III, investigators randomly assigned 182 people to a 25 mg pill of lenalidomide daily for 21 of the first 28 days of a therapy cycle, or observation, and stratified them based on whether they were diagnosed with high-risk SMM within that past year or more than a year after enrollment.

In this trial, researchers used MRIs of the spine and pelvis to detect disease at enrollment, which is more sensitive than routine x-rays, which were used in previous studies exploring interventions for SMM. A 2015 trial in Spain demonstrated that the combination of lenalidomide and dexamethasone lengthened the time before people with SMM developed multiple myeloma and extended survival.

In both the phase II and phase III trials, lenalidomide led to improved outcomes for patents with moderate and high-risk SMM.

- Progression-free survival: In phase II, after 3 years on the trial, 87% of the enrollees were alive without SMM progressing to multiple myeloma (progression-free survival). In phase III, after 1, 2, and 3 years on the trial, respective progression-free survival rates were 98%, 93%, and 91% for those who received lenalidomide and 89%, 76%, and 66%, respectively, for those who did not receive the treatment and were just observed.
- Toxicity: The proportion of people who could not tolerate lenalidomide was concerning, with 80% of people in phase II and 51% of people in phase III discontinuing the medicine due to toxicity. The most common side effects, seen in 28% of patients, included fatigue and non-blood or bone related side-effects. High-grade neutropenia was seen in about 5% of people. There was no patient-reported difference in quality of life between those who took lenalidomide and those who did not.

According to the researchers, the combined positive results of this trial and the 2015 Spanish trial may support a change in clinical practice.

"Living with the uncertainty of whether cancer will develop is very difficult, so it's exciting to be able to tell patients at high risk of multiple myeloma that they can take a pill to prevent or delay cancer. This approach is not for everyone, however, because it comes with potentially heavy side effects and costs, so watching and waiting still has clear advantages that every patient should discuss with their doctor," said ASCO President Monica M. Bertagnolli, MD, FACS, FASCO.

The investigators are currently performing an analysis of people who stopped taking lenalidomide due to toxicity to see if even limited doses of the medicine may have delayed progression to multiple myeloma. Dr. Lonial noted that a major hallmark of this trial is that it shows that intervening early can prevent patients from developing organ damage, the current criteria by which patients are defined as having myeloma.

This study received funding from the National Institutes of Health.

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