Researchers shed light on new multiple myeloma therapy

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Researchers from John Theurer Cancer Center at HackensackUMC, one of the nation's 50 best hospitals for cancer, played leading roles in three separate multi-center studies with the new proteasome inhibitor carfilzomib published in *Blood*, a major peer-reviewed scientific journal.

Carfilzomib is a novel, highly selective proteasome inhibitor, a type of medication that blocks the actions of certain proteins (proteasomes) that cancer cells need to survive and multiply. Carfilzomib is also known by its branded name Kyprolis™.

On July 20th the U.S. Food and Drug Administration (FDA) approved Kyprolis (carfilzomib) as a new treatment for advanced multiple myeloma. The treatment was fast-tracked due to the unmet need in multiple myeloma.

The most recent *Blood* study, published online today, includes results from the open-label, single arm phase IIb 003-A1 study of single-agent carfilzomib for patients with relapsed and refractory multiple myeloma. Carfilzomib's New Drug Application (NDA) is based primarily on this study. This research, along with the two other *Blood* studies, may change the way multiple myeloma is managed for newly diagnosed and relapsed/refractory patients.

Phase IIb Clinical Trial Published in *Blood*

David S. Siegel, M.D., Ph.D., Chief, Multiple Myeloma was the lead

investigator of this pivotal multi-center, phase IIb study involving 30 cancer centers in the United States and Canada. The trial evaluated 266 heavily-pretreated patients with relapsed and refractory multiple myeloma who had received at least two prior therapies, including bortezomib and either thalidomide or lenalidomide.

"We found that carfilzomib produced clinically significant responses with an acceptable safety profile in heavily pretreated patients with relapsed and refractory multiple myeloma," said Dr. Siegel. "Given the limited number of treatment options available to patients with advanced-stage multiple myeloma and the diminished prospects for retreatment once an agent has been utilized, we believe there is a significant need in this patient population."

Two hundred and sixty-six patients received single agent carfilzomib twice weekly for 3 out of 4 weeks. The study's primary endpoint was overall response rate (ORR; ≥partial response) and secondary endpoints included clinical benefit response rate (≥minimal response), duration of response (DOR), time to progression, progression-free survival, overall survival (OS), and safety.

ORR was 23.7 percent with median DOR of 7.8 months. Median OS was 15.6 months. Adverse events (AEs) were manageable without cumulative toxicities. The researchers concluded that durable responses and an acceptable tolerability profile in this heavily-pretreated population demonstrate the potential of carfilzomib to offer meaningful clinical benefit.

Phase 1/2 Results for Frontline Therapy for Newly Diagnosed Multiple Myeloma Patients

David H. Vesole, M.D., Ph.D., F.A.C.P., Co-Chief and Director of

Research served as co-author of a study published on June 4th in *Blood*, which involved researchers from six leading cancer centers. The multi-center, open-label phase 1/2 study looked at carfilzomib in combination with lenalidomide and low-dose dexamethasone (CRd) as a frontline treatment for multiple myeloma.

"Triple-agent regimens with bortezomib, lenalidomide, and/or thalidomide are currently the preferred frontline strategy for newly diagnosed multiple myeloma. However, maintaining dose levels over time can be limited by the treatments' emerging toxicities," said Dr. Vesole. "This study demonstrated that the combination of carfilzomib, lenalidomide and dexamethasone is well tolerated and highly active for these patients."

The researchers enrolled 53 patients with newly-diagnosed multiple myeloma who had symptomatic disease. Patients received CRd induction therapy in 28-day cycles for up to eight cycles or until disease progression or unacceptable toxicity. After eight cycles, patients received maintenance CRd for up to 24 cycles and then moved to a single-agent lenalidomide.

During phase 1, the primary endpoints were safety and determination of the maximum tolerated dose of carfilzomib within the context of CRd combination therapy. Carfilzomib doses were escalated, while lenalidomide and dexamethasone were given at standard low-dose induction levels. Once the maximum tolerated dose of carfilzomib was reached, the researchers began Phase II with a primary endpoint of near complete response (nCR). Secondary endpoints were overall response rate, time on study, duration of response, progression-free survival (PFS), time to progression, overall survival and overall treatment toxicity.

Study results indicated that patients experienced a rapid and good initial

response to CRd, and their responses improved as the trial continued. Of the 49 patients who completed four treatment cycles, 67 percent achieved at least nCR, with 45 percent in stringent complete response (sCR), defined as no detectable tumor cells or myeloma protein in the blood or bone marrow. Of the 36 patients who completed eight or more treatment cycles, 78 percent achieved nCR with 61 percent in sCR. Overall, 62 percent of trial participants achieved at least nCR, with 42 percent achieving sCR. The investigators also found PFS rates were 97 percent at 12 months and 92 percent at 24 months. All patients who achieved sCR continued to respond to therapy for a median of nine months, demonstrating the durability of responses to this regimen. Importantly, these periods of extended treatment were well tolerated, including low rates of peripheral neuropathy, a treatment-limiting side effect of bortezomib, the first-generation proteasome inhibitor.

Bortezomib is currently FDA approved to treat advanced multiple myeloma, however, it has been shown to cause peripheral neuropathy in approximately 38 percent of treated patients with subcutaneous administration.

Phase II 004 Clinical Trial Results for Advanced Myeloma

Dr. Siegel and Dr. Vesole served as co-investigators on an 18-center, phase II open-label efficacy and safety clinical trial, also known as 004, of carfilzomib in combination with Bortezomib, another proteasome inhibitor. The study was published in the June 14th issue of *Blood*.

"We saw significant responses in patients considered more difficult to treat, including those with more advanced disease and poor prognoses," said Dr. Siegel, the senior author of the study. "Our results support the potential use of carfilzomib in this patient population."

The researchers enrolled 129 patients with multiple myeloma who had relapsed following one to three previous courses of treatment. Patients treated with bortezomib were excluded, as it is in the same drug class as carfilzomib and its use might make the effect of carfilzomib more difficult to determine. The study's primary endpoint was overall response rate. Researchers also measured patients' responses at various intervals as well as time to disease progression, and recorded reactions (adverse events) to treatment.

The most common adverse events in the study were fatigue (62 percent) and nausea (48.8 percent), while 17.1 percent of patients developed peripheral neuropathy, mostly Grades 1 and 2. Peripheral neuropathy, damage to nerves that fan out across the body from the brain and spinal cord, causes pain and other symptoms; lower grades have less severe symptoms. Peripheral neuropathy has been reported in 37-70 percent of myeloma patients receiving other commonly used drug therapies.

"Our myeloma team is leading the way in innovative research that makes promising therapies available to our patients, while also continually testing new ways to improve patients' quality of life," said Andrew L. Pecora, M.D., F.A.C.P., C.P.E., Chief Innovations Officer and Professor and Vice President of Cancer Services, John Theurer Cancer Center.

Provided by John Theurer Cancer Center