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PERIODICALS

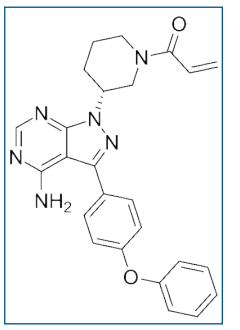
[ALSO]

ASH Annual Meeting

CLL: Ibrutinib Improves Therapeutic Responses in Elderly, Frail Patients

Results Also Encouraging for Previously Untreated and Relapsed Patients

BY MARK FUERST



"Up until now, chemotherapy combinations with antibodies have led to excellent remissions, but have not been curative… It's very exciting to now have an oral agent that patients tolerate easily to add to our armamentarium."

ATLANTA—The novel investigational therapeutic agent ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, may be a safe, effective targeted therapy for previously untreated, hard-to-treat, and relapsed patients with chronic lymphocytic leukemia (CLL). And when combined with rituximab, ibrutinib may be a better option than the current standard chemotherapy-based treatment regimen for patients with high-risk CLL. That was the conclusion of two studies reported here at the American Society of Hematology Annual Meeting.

"Both patients and clinicians are excited to hear about this oral, well-tolerated, non-chemotherapy agent that produces excellent responses for elderly, frail patients who are not candidates for chemotherapy regimens designed for younger, fitter patients," said Claire Dearden, MD, Consultant Hematologist and Head of the CLL Unit at the Royal Marsden NHS Foundation Trust in London, who moderated a media briefing at the meeting at which the researchers discussed the results.

"Chemotherapy does not work as well with high-risk cytogenetic CLL patients. Ibrutinib is an easily administered drug that may be slightly more effective and safer. These studies underscore the significant progress we are making in our quest to better understand and attack the specific cellular targets responsible for CLL, particularly in these vulnerable patient populations."

ASH 2012 President Armand Keating, MD, Professor of Medicine at the University of Toronto, added: "We have seen quite a lot of progress since we first heard about Phase I clinical trials with ibrutinib at [the 2011] ASH Annual Meeting. Now researchers have demonstrated that inhibition of BTK—part of a pathway that stimulates growth of lymphoid cells—seems to be selective in eliminating those cells. The results are really quite gratifying with this more targeted, less toxic therapy for a group of patients with hard-to-treat, aggressive disease and for those with disease that is resistant to current standard therapy."

American Society of Hematology

CLAIRE DEARDEN, MD: "These studies underscore the significant progress we are making in our quest to better understand and attack the specific cellular targets responsible for CLL, particularly in these vulnerable patients."

CLL, the most common type of leukemia in adults, is typically a disease of the elderly, with patients diagnosed at a median age of 72. "Current therapies for older patients are unacceptable because of low response rates, short remissions, and toxicities to chemotherapy," said the lead author of one of the studies (***Abstract 189***), John Byrd, MD, Director of the Division of Hematology at Ohio State University Comprehensive Cancer Center—James Cancer Hospital and Solove Research Institute.

BTK is essential to B-cell receptor signaling and is an important kinase for lymphoma cell survival and proliferation, he explained. The majority of B-cell tumors are dependent upon BTK for proliferation and survival. "Ibrutinib is the first in class irreversible inhibitor of BTK to enter clinical development. A once-daily dose of ibrutinib promotes apoptosis and CLL cell migration."

Currently, primary treatment for CLL includes a combination of a chemotherapy-based regimen with fludarabine and cyclophosphamide along with the immune therapy rituximab. The humanized monoclonal antibody rituximab is effective, but is generally not well tolerated among elderly patients, Byrd noted. Rituximab treatment compromises the immune system by attacking both cancerous and normal cells, putting patients at risk for a range of infections, and increasing their risk of developing treatment-related acute myeloid leukemia.

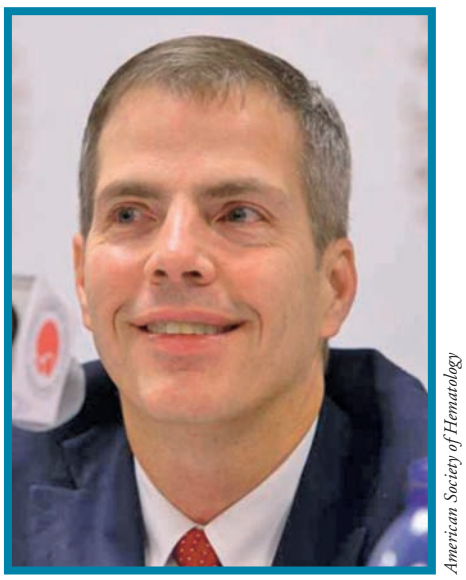
"Additionally, virtually all CLL patients eventually relapse after fludarabine-based chemo-immunotherapy, and effective salvage regimens that induce durable remissions are lacking," he said.

Single-agent Ibrutinib

To understand if ibrutinib may be effective for elderly CLL patients and to identify which patients might benefit most from the drug, Byrd and colleagues evaluated ibrutinib in a Phase IB/II study in patients with CLL or small lymphocytic leukemia (SLL). A total of 116 CLL patients were enrolled into several cohorts, evaluating oral ibrutinib at fixed doses of 420 or 840 mg daily until disease progression.

The treatment cohorts included patients who had never been treated (31 patients), those who had received two or more prior therapies (61 relapsed/refractory patients), and those who had relapsed within two years of treatment (24 high-risk patients).

The results showed a high response to therapy across all the cohorts, with largely manageable toxicities, Byrd reported. The overall response rate was 68 percent in the treatment-naïve group at 20.3 months of follow-up, which includes a complete response rate of 10 percent and a 71 percent response rate in a combination of the relapsed/refractory group at 22.1 months follow-up plus the high-risk group at 14.7 months follow-up.



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JOHN BYRD, MD: "Ibrutinib reduces a critical pathway in CLL, just as imatinib does in CML. It's important to reduce this pathway continuously. As long as ibrutinib works and patients tolerate it well, then we will continue to give the drug. If, as with imatinib, we see long-term remissions, then we may be able to discontinue it."

Among previously untreated patients, there was a 96 percent estimated rate of both progression-free survival (PFS) and overall survival (OS) at 22 months of follow-up. "These results are dramatic," Byrd said. "We would expect 50 percent or less survival."

For patients in the relapsed/refractory groups, there was a 76 percent estimated PFS rate and an 85 percent estimated OS rate at 22 months.

Well Tolerated

The treatment regimen was generally well-tolerated, with the majority of adverse events being Grade 2 or lower, including diarrhea (54%), fatigue (29%), upper respiratory tract infection (29%), rash (28%), nausea (26%), and arthralgias (25%). The incidence of hematologic

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toxicity of grade 3 or higher was relatively infrequent, he said. There was no evidence of cumulative toxicity or long-term safety concerns with a median follow-up of 16 months for treated patients.

"Adverse events were mostly mild to moderate. Diarrhea disappeared within the first few months. There was a very low incidence of cytopenias, with less than 25 percent in relapsed/refractory patients and less than 10 percent in treatment-naïve patients. With standard therapy, we see 70 to 80 percent grade 3/4 neutropenia. Grade 3/4 events were modest, except for infections—40 percent—in refractory patients. There are no long-term safety concerns," he said.

About 80 percent of patients had improved hemoglobin levels in all groups. Lymphocytosis, which was found in about 80 percent of patients who had and did not have mutations, is not a sign of progression, he added.

"Virtually all CLL patients eventually relapse after fludarabine-based chemo-immunotherapy, and effective salvage regimens that induce durable remissions are lacking."

In conclusion, "ibrutinib is a highly active targeted therapy for untreated and refractory CLL. Extended follow-up with ibrutinib monotherapy shows no safety issues with continued dosing beyond two years. Outcomes of high-risk patients are similar with the possible exception of del (17p), although PFS and OS of this group remain better than any other therapy explored to date and are more prolonged as compared with historical controls.

"The outcome in high-risk patients appears to be superior to currently available therapies. Ibrutinib offers great potential to significantly change the treatment landscape of CLL."

The Next Imatinib?

Byrd likened the pattern of drug development with ibrutinib to that of imatinib for the treatment of chronic myeloid leukemia (CML).

"Ibrutinib reduces a critical pathway in CLL, just as imatinib does in CML. It's important to reduce this pathway continuously. As long as ibrutinib works and patients tolerate it well, then we will continue to give the drug. If, as with imatinib, we see long-term remissions, then we may be able to discontinue it."

It will take extended follow-up with ibrutinib to see if responses are durable, which will be addressed in randomized clinical trials, he continued. "If we can replicate these high survival rates and good tolerability with ibrutinib through larger-scale Phase III studies, we may find it to be an extremely valuable new therapy for not just elderly patients with CLL but for all CLL patients."

'Treatment Landscape Changing'

"The treatment landscape is changing," Dearden said. "I have CLL patients coming from all over the country to get access to the drug, even if they have only a 50 percent chance of getting the drug in a clinical trial.

"I believe this will lead to a complete change in the way we treat this disease. Up until now, chemotherapy combinations with antibodies have led to excellent remissions, but are not curative. Patients continue to develop toxicities to chemotherapy combinations and become resistant. In a disease like CLL, it's very exciting to have an oral agent that patients tolerate easily to add to our armamentarium."

Ibrutinib+Rituximab for High-Risk CLL

In the second study, reported by Jan Burger, MD, PhD, Associate Professor of Medicine in the Department of Leukemia at the University of Texas MD Anderson Cancer Center, ibrutinib was given in combination with rituximab with the hope of accelerating and improving CLL patient responses (***Abstract 187***). A total of 40 high-risk CLL/SLL patients were treated with 420 mg of ibrutinib daily in combination with weekly rituximab at 375 mg/m^2 for four weeks, followed by ibrutinib given daily plus monthly rituximab until the sixth month, followed by single-agent ibrutinib.

The patients had the del17p/TP53 or del11q deletion, or had less than three years of remission after first-line chemo-immunotherapy. The patients' median age was 65, and about 60 percent had Stage III or IV disease.

At a median follow-up of 4.8 months, 38 of 40 patients continued on therapy without disease progression. One patient died from an unrelated infection, and one patient withdrew consent before starting therapy. "This is a dramatic response in patients who were refractory to standard treatment," Burger said.

The overall response rate was 83 percent, with one patient exhibiting a complete response and the others achieving partial responses. In addition, three patients had a partial response with lymphocytosis, two patients did not exhibit any response, and the results were too early to evaluate in two other patients.

He noted that the therapy induces transient lymphocytosis at the beginning of treatment, which peaked at one week with about a doubling of the lymphocyte count. But at 12 weeks, there was about a 50 percent reduction in lymphocyte count, and there was also continuous improvement in hemoglobin and platelet levels with treatment.

"Interestingly, on this combination trial, the re-distribution lymphocytosis peaked earlier and the duration was shorter than with single-agent ibrutinib, presumably due to the addition of rituximab," Burger said.

The treatment was well tolerated, with only 13 cases of Grade 3 or 4 toxicities, which were largely unrelated and transient,

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JAN BURGER, MD, PHD: "The combination of ibrutinib and rituximab has profound activity in high-risk CLL. There is a high overall response rate of more than 80 percent, and a favorable toxicity profile. The addition of rituximab accelerates responses compared with those of single-agent ibrutinib."

including neutropenia, fatigue, pneumonia, insomnia, and bone aches. "The majority of toxicities were consistent with those of single-agent ibrutinib, including 25 percent mild diarrhea in the first few weeks of treatment, with no intervention needed," he said. Patient health questionnaires also noted improvements in health and quality of life for all treated patients.

In summary, Burger said, "the combination of ibrutinib and rituximab has profound activity in high-risk CLL. There is a high overall response rate of more than 80 percent, and a favorable toxicity profile. The addition of rituximab accelerates responses compared with those of single-agent ibrutinib."

Open questions remain about the combination therapy, including the duration of remission and long-term side effects. "We need to continue to follow patients, but ibrutinib alone or in combination with rituximab should be rapidly developed for high-risk CLL. With the new combination, some negative prognostic factors may become less cumbersome," he said.

Further development of this drug combination includes an ongoing phase III trial in untreated and treated CLL patients. Other trials in the works include comparisons of ibrutinib with alemtuzumab and with chlorambucil and single-agent ibrutinib in high-risk patients, he said.

Burger also compared ibrutinib to imatinib. "As with imatinib, if we give single-agent ibrutinib, when we do bone marrow assessments, we can still detect residual cells. With more effective combinations, complete remission rates may improve. In some patients, it might be curative or can be discontinued safely."

Also elaborating in her role as moderator of the news briefing, Dearden said, "The combination of ibrutinib and rituximab appears to be a potent, safer, and more effective option than standard CLL agents currently used, and we could come to the same place as imatinib with the combination of ibrutinib and rituximab able to induce remissions that last off-therapy."

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