

BTK inhibitor ibrutinib in CLL and mantle cell lymphoma

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Bruton's tyrosine kinase (BTK) is a critical component of B-cell-receptor signaling that mediates interactions with the tumor microenvironment and promotes survival and proliferation of chronic lymphocytic leukemia (CLL) cells. Ibrutinib is a first-in-class oral covalent inhibitor of BTK designed for the treatment of B-cell cancers. In a phase 1b/2 study reported by Byrd and colleagues, ibrutinib treatment was found to produce high rates of durable responses in patients with relapsed or refractory CLL or small lymphocytic lymphoma.¹

In the multicenter study of 82 patients with relapsed or refractory CLL and 3 patients with small lymphocytic lymphoma, 51 patients received continuous ibrutinib once daily at 420 mg and 34 patients received 840 mg. Patients had a median age of 66 years and 76% were men. Patients had received a median of 4 prior therapies and the median time from last treatment was 3 months (range, 1-98 months). The most common prior treatments were rituximab (98%), nucleoside analogues (95%), and alkylators (89%). Most patients (65%) had high-risk disease (Rai stage III or IV) and unmutated immunoglobulin variable-region heavy-chain genes (81%). Bulky nodes of ≥ 5 mm and ≥ 10 mm in diameter were present in 52% and 15% of patients, respectively. High-risk cytogenetic abnormalities consisted of 17p13.1 deletion in 33% of patients and 11q22.3 deletion in 36%.

Response was observed in 36 of 51 patients (71%) in the 420-mg group (including 2 complete responses) and 24 of 34 (71%) in the 840-mg group (all partial responses). In addition, 10 patients (20%) in the 420-mg group and 5 (15%) in the 840-mg group had a partial response with persistent lymphocytosis. Response was independent of baseline clinical and genomic risk factors, including advanced-stage disease, number of previous therapies, and the 17p13.1 deletion. At 26 months, the estimated progression-free survival (PFS) rate was 75% and the overall survival (OS) rate was 83%. Among patients with 17p13.1 deletion, estimated 26-month PFS was 57% and OS was 70%. Disease progression occurred in 11 patients (13%) during follow-up, with 7 having progression by biologic transformation. The median time from diagnosis to transformation was 98 months (range,

What's new, what's important

Ibrutinib is a very exciting novel class of oral selective irreversible inhibitor of Bruton's tyrosine kinase (Btk), which is an important signaling kinase in the B-cell receptor pathway. It is being developed as a treatment for various B-cell malignancies. Based on the results of some very promising clinical trials, as described by Hamadani and Kanate on page 279, the Food and Drug Administration accepted the manufacturer's new drug application for previously treated mantle cell lymphoma and previously treated chronic lymphocytic leukemia and small lymphocytic lymphoma.

The B-cell antigen receptor has surface immunoglobulins that recognize foreign antigens and the downstream effector pathway, of which Btk is a central mediator. Btk phosphorylates and activates phospholipase-C λ and protein kinase C. The transcription factors such as NF- κ B, which are results of this activation, is critical to the survival, proliferation, and differentiation of B-cell lymphocytes.

The dose of ibrutinib used in clinical trial was 420 mg orally, daily until progression. The most common side effects were diarrhea (50% of patients), fatigue (41%), nausea (31%), peripheral edema (28%), and dyspnea (27%). The most common grade 3 or higher nonhematologic adverse events were diarrhea (6%), fatigue (5%), abdominal pain (5%), and dyspnea (5%). Grade 3 or higher hematologic adverse were also infrequent, consisting of neutropenia in 16% of patients, thrombocytopenia in 11%, and anemia in 10%.

In addition to mantle cell lymphoma and chronic lymphocytic leukemia, several studies are looking at the role of ibrutinib in other lymphoid malignancies such as diffuse large B-cell lymphomas. Some of the early results are very promising.

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How I treat patients with newly diagnosed CLL

CLL is the most commonly diagnosed leukemia. In suspected cases, I confirm diagnosis with peripheral blood flow cytometry alone ($\geq 5,000/\mu\text{L}$ B cells co-expressing CD19, dimCD20, CD23, and CD5). Bone marrow biopsy is not required. I estimate the extent of disease with blood counts and physical examination alone, to determine the Rai stage. CAT-scans are generally not needed, and PET-scanning is not appropriate in the absence of transformation. I use FISH on peripheral blood, β -2 microglobulin level and IgVH gene mutation testing for risk stratification. ZAP-70 assay from most laboratories is not reliable. In asymptomatic patients (including those with high-risk disease, for example, with -17p, -11q23, unmutated IgVH gene) watchful waiting remains the standard of care, however, I do evaluate patients with high-risk disease more frequently (every 3-6 months).

I try to enroll all symptomatic CLL patients requiring treatment (ie, those with nonimmune anemia or thrombocytopenia, B-symptoms, symptomatic adenopathy or hepatosplenomegaly, recurrent infections, and so on) on clinical trials. Rarely, if ever, I treat patients solely because of rapid lymphocyte doubling time. Off clinical trial, I approach young-fit patients differently than older-frail patients. In young-fit patients with normal renal function, first-line therapy with either fludarabine plus rituximab (FR) or FR plus cyclophosphamide (FCR) is reasonable. Although FCR is superior to

FC, there are no data available to prove its superiority over FR. Until data from the German CLL-10 trial are available, bendamustine plus rituximab should not be used. Because of the activity of cyclophosphamide in patients with 11q23 deletion, FCR is preferable in that setting. 17p deleted patients do poorly with both FR and FCR. In such young patients, I typically use single-agent campath or high-dose rituximab with solumedrol. I always consider allogeneic transplant after first-line therapy in patients with -17p and -11q23, especially if they fail to achieve clinical response (CR).

Rituximab maintenance is inappropriate in CLL patients. Off trial, I perform only physical examination to assess response, but always perform a bone marrow biopsy to confirm CR. The frail-elderly patients aged 65 years or older and those with impaired renal function should not be treated with fludarabine-based regimens, including FCR. In such patients, I favor either oral chlorambucil alone, or in combination with rituximab. Single agent bendamustine is also reasonable. In all CLL patients, I consider prophylaxis with acyclovir (or equivalent) and Bactrim (sulfamethoxazole and trimethoprim) during treatment. In patients responding to first-line therapy, I perform surveillance without imaging every 3-6 months. At relapse all patients are screened for available clinical trials.

– Mehdi Hamadani, MD

24-143], months). Among the 11 patients with progression, 10 had a 17p13.1 or 11q22.3 deletion and 1 had no high-risk cytogenetic abnormalities.

At a median follow-up of 20.9 months (range, 0.7-26.7 months), 64% of patients were still receiving ibrutinib treatment. Reasons for treatment discontinuation included disease progression in 11 patients (13%), patient or investigator decision in 13 (15%, with 5 of these 13 patients subsequently undergoing stem cell transplantation), and adverse events in 7 patients (8%), including 3 with pneumonia, 2 with sepsis, 1 with staphylococcal bacteremia without signs of sepsis, and 1 with gastrointestinal hemorrhage.

Blood lymphocytosis was observed by day 7 in 78% of the patients, peaked at a median of 4 weeks, and gradually declined. In 50 (79%) of 63 evaluated patients, the lymphocyte count was normalized or reduced by 50% from baseline. Lymphocytosis developed in similar proportions of patients with unmutated versus mutated immunoglobulin variable-region heavy-chain genes (77% vs 83%), although lymphocyte counts normalized more rapidly (median, 6.4 vs 14.8

months) and more frequently (85% vs 50%) in those with unmutated immunoglobulin genes. Lymphocytosis was associated with reductions in lymph node and spleen size and frequent improvement in cytopenias.

The most common adverse events of any grade were diarrhea (49%), upper respiratory tract infection (33%), fatigue (32%), and cough (31%). The most common grade 3 or 4 nonhematologic adverse events were pyrexia, hypertension, and sinusitis, each occurring in 5% of patients. Grade 3 or 4 hematologic toxic effects consisted of neutropenia in 15% of patients, anemia in 6%, and thrombocytopenia in 6%. Neutropenia did not require treatment discontinuation and was managed with growth factor treatment in 5 of 13 patients. Bleeding events of grade 3 or higher occurred in 4 patients. A total of 8 patients died within 30 days after the last dose of ibrutinib, 3 due to pneumonia, 1 from systemic inflammatory response, 1 from sarcoma, and 3 from disease progression.

The investigators noted that the favorable toxicity profile of ibrutinib may facilitate its use in combination treatment of CLL, but also suggested that the durable remissions thus far observed with ibrutinib alone might make monotherapy a suit-

able option in many patients. Randomized trials of ibrutinib in patients with CLL or small lymphocytic lymphoma are ongoing.

In relapsed or refractory mantle cell lymphoma

In another recently reported phase 2 study, Wang and colleagues found that ibrutinib monotherapy produced a high response rate and prolonged responses while exhibiting a favorable toxicity profile in patients with relapsed or refractory mantle cell lymphoma (MCL).²

In the study, 111 patients with relapsed or refractory MCL were treated with ibrutinib 560 mg/d. Patients were enrolled in 2 groups consisting of 48 patients who had received at least 2 cycles of bortezomib therapy and 63 patients who had received less than 2 complete cycles of bortezomib or no prior bortezomib (“no prior bortezomib” group). Patients had a median age of 68 years, 76% were men, 86% had intermediate- or high-risk disease based on simplified Mantle-Cell Lymphoma International Prognostic Index (MIPI) score, 86% had ECOG performance status of 0 or 1, 45% had refractory disease, 72% had advanced disease, and 39% had at least 1 lymph node \geq 5 cm in diameter. Patients had received a median of 3 prior therapies, including rituximab (89%), hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (30%), lenalidomide (24%), and stem cell transplantation (11%).

Response was observed in 75 patients (68%), including complete response (CR) in 21%. Response rates did not differ between patients with prior bortezomib therapy (67%, including CR in 23%) and those with no prior bortezomib therapy (68%, including CR in 19%). Response rates also did not vary according to other baseline characteristics or risk factors associated with chemotherapy failure. Response was observed in 63% of patients with lymph nodes \geq 5 cm and in 63% of those who received prior lenalidomide. The overall response rate and CR rate were found to improve over time with continued therapy.

After an estimated median follow-up of 15.3 months, the estimated median response duration was 17.5 months (95% CI, 15.8 months to not reached). Median time to response was 1.9 months (range, 1.4-13.7 months) and median time to CR was 5.5 months (range, 1.7-11.5 months). Estimated median progression-free survival (PFS) was 13.9 months (95% CI, 7.0 months to not reached) among all patients, 17.5 months among those with PR as best response, and not reached for those with CR. Median overall survival (OS) was not reached; estimated OS at 18 months was 58%. At the time of reporting, 46 patients (41%) were still receiving ibrutinib treatment.

The most common nonhematologic treatment-related adverse events of any grade were diarrhea (50%), fatigue (41%), nausea (31%), peripheral edema (28%), and dyspnea (27%). The most common grade 3 or higher nonhematologic adverse events were diarrhea (6%), fatigue (5%), abdominal pain (5%), and dyspnea (5%). Grade 3 or higher hematologic adverse events were also infrequent, consisting of neutropenia in 16% of patients, thrombocytopenia in 11%, and anemia in 10%. Grade 3 bleeding events occurred in 5 patients (5%). Subdural hematoma occurred in 4 patients, and in all cases was associated with falls or head trauma in patients who had also received aspirin or warfarin within 2 days of the event. Treatment was discontinued due to adverse events in 8 patients (7%, including 2 patients with subdural hematoma, and 1 each with pneumonia, elevated bilirubin, sepsis, metastatic adenocarcinoma, respiratory failure, and cardiac arrest). Four patients died due to an adverse event (2 from pneumonia, 1 from sepsis, and 1 from a cardiac arrest that was not considered drug-related).

References

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