ADVANCES IN LLM

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Venetoclax, the First BCL-2 Inhibitor for Use in Patients With Chronic Lymphocytic Leukemia

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H&O What is the mechanism of action for venetoclax, and why is it suited for chronic lymphocytic leukemia (CLL)?

JS Venetoclax (Venclexta, AbbVie/Genentech) has a unique mechanism of action. It is the first drug in a novel class called BH3 mimetics. Venetoclax binds with high avidity to a particular protein, B-cell lymphoma 2 (BCL-2), within the family of proteins inside a cell that regulate apoptosis. Venetoclax has an exquisite selectivity for BCL-2. By binding to BCL-2 and inhibiting its normal function, venetoclax frees the proteins that would normally be bound to BCL-2 to initiate the apoptotic cascade.

Venetoclax has been studied in several diseases. It has the greatest clinical activity in CLL. Overexpression of BCL-2 is a near-universal feature of CLL and intrinsic to the pathophysiology of this disease. A deletion on chromosome 13q that is very common in CLL removes a regulatory element, a microRNA, that normally functions to suppress the expression of BCL-2.

H&O How did your institution contribute to the development of venetoclax?

JS I work clinically at the Peter MacCallum Cancer Centre and the Royal Melbourne Hospital in Melbourne, Australia. The seminal discovery of the cellular function of BCL-2 was made in the late 1980s by Dr David Vaux at the Walter and Eliza Hall Institute, a nearby medical research institute. Since that time, researchers at the Royal Melbourne Hospital and the Peter MacCallum Cancer Center have explored ways to target BCL-2 and other family members as a therapeutic maneuver in malignancies. Research began with BCL-2–targeted proteins, such as the antisense oligonucleotide oblimersen sodium. This agent was found to have minimal activity. In 2008, the center began research into the early-generation, less-selective BH3 mimetic navitoclax. In a phase 1 study, navitoclax showed significant activity, but it was associated with on-target thrombocytopenia through inhibition of the related BCL-2 family member BCL-XL.

Venetoclax is a second-generation agent and targets only BCL-2. Dr Andrew Roberts and I were involved in the development of the first-in-human phase 1 trial of venetoclax. In fact, the first 3 patients to receive venetoclax worldwide were treated here in Melbourne in July 2011. Institutions in Melbourne were therefore involved with the discovery of the function of the molecule, as well as treatment of the first patients. A very large team of scientists and clinical researchers have contributed to the preclinical and clinical development of this therapy.

H&O What data support the use of venetoclax as monotherapy in CLL?

JS Venetoclax is highly active as a single agent. My colleague Dr Andrew Roberts was the first author of a phase 1 trial of venetoclax in relapsed CLL published in 2016 in the *New England Journal of Medicine*. In the

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dose-escalation phase, 56 patients received daily doses ranging from 150 mg to 1200 mg. In the expansion cohort, 60 additional patients were treated with doses that reached 1200 mg per day, with 400 mg identified as the recommended dose. In these heavily pretreated, multiply-relapsed patients, venetoclax had a very high response, with an overall response rate of nearly 80% and a complete remission rate of approximately 20%. At the time, it was extraordinary to see patients in a phase 1 trial with remissions so deep that minimal residual disease (MRD) was not detectable with high-sensitivity flow cytometry. The median progression-free survival with single-agent venetoclax was approximately 2 years, depending on the patient's biologic features.

Venetoclax is generally well tolerated, once the initial graduated-dose ramp-up phase is overcome. The single-agent phase 1 trial identified a significant risk of tumor lysis syndrome with an initial dose of 200 mg. We have modified the dosing schedule so that it now begins at 20 mg for the first dose and incorporates a weekly, step-wise dose ramp-up throughout 5 weeks to reach the target dose of 400 mg.

H&O What prompted the exploration of venetoclax in combination with other agents?

JS Single-agent venetoclax has substantial activity, but the complete remission rate remains relatively low. Preclinically, there is marked synergy between venetoclax and a range of other agents that are active in CLL, including the anti-CD20 antibodies as well as conventional chemotherapeutics. Potential issues with the chemotherapy agents include impact on normal tissues, as well as possible additive myelosuppression. Therefore, the first combination studies began with the anti-CD20 antibodies. The addition of rituximab (Rituxan, Genentech/Biogen) to navitoclax, the precursor BCL-2 compound, improved rates of complete remission in follicular lymphoma and CLL. This strategy was the model for venetoclax. We conducted a single-arm, phase 1 study of venetoclax plus rituximab in CLL. Both agents were administered at their optimal single-agent dose in this setting. Venetoclax was given at 400 mg, and rituximab was given at the recommended dose of 500 mg/m^2, after a first infusion of 375 mg/m^2. This study showed a marked improvement in the complete remission rate, from 20% with single-agent venetoclax to 50% with the combination therapy. More than 60% of patients achieved bone marrow MRD negativity. These data provided the basis for moving ahead with randomized studies comparing venetoclax combination regimens vs conventional chemoimmunotherapy.

H&O Did the phase 1 trial provide any other insights?

JS The phase 1 trial of venetoclax plus rituximab allowed us to explore the feasibility of stopping treatment in patients with a deep response. For all of the targeted agents used as monotherapy in CLL to date, the paradigm is to administer continuous treatment until disease progression. Continuous treatment raises concerns regarding toxicity, quality of life, and expense. It can also lead to the development and selection of resistant clones owing to mutations in the target. This has been seen with the BTK inhibitors, and also very recently recognized with venetoclax.

The preferred model would be to achieve deep remissions that allow for drug withdrawal. The combination of venetoclax plus rituximab leads to such deep remissions, and in the trial, 18 patients elected to cease treatment with the drug. Fifteen of these patients remained free of disease progression nearly 3 years after the treatment ended. This study established the paradigm of combination treatment, optimizing MRD negativity and allowing for drug withdrawal.

H&O What did the randomized trials show?

JS The phase 3 MURANO trial (A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia [CLL]) randomly assigned patients with relapsed or refractory CLL to the combination of venetoclax plus rituximab given in a time-limited design or to standard chemoimmunotherapy with bendamustine plus rituximab. This trial, which was published in the *New England Journal of Medicine* in 2018, showed marked improvement in progression-free survival with venetoclax plus rituximab. Data on the outcome after treatment withdrawal were presented at the 2018 American Society of Hematology meeting and published in early 2019 in the *Journal of Clinical Oncology*. Among patients who received treatment for the full 2-year period, 85% were free of disease progression nearly 1 year after withdrawal of venetoclax. The outcomes for the patients treated with venetoclax plus rituximab were

substantially superior to those seen with bendamustine plus rituximab. The 3-year progression-free survival rates were 71% vs 15%, respectively. This benefit was consistent across all biologic subsets. Rates of 3-year overall survival were 88% vs 80%.

H&O What data led to the recent approval of venetoclax plus obinutuzumab in the first-line setting?

JS In May 2019, the US Food and Drug Administration approved the combination of venetoclax and obinutuzumab (Gazyva, Genentech) for the frontline treatment of patients with CLL or small lymphocytic lymphoma. This approval was based on findings from the phase 3 CLL14 trial, which enrolled patients with previously untreated CLL and coexisting medical conditions. Data presented at the 2019 American Society of Clinical Oncology Annual Meeting showed that progression-free survival at 24 months was 88% with venetoclax plus obinutuzumab vs 64% with chlorambucil plus obinutuzumab.

H&O What is known about the synergy between venetoclax and other treatments?

JS We are just beginning to explore and exploit the potential synergy. Preclinically, venetoclax has shown marked synergy with a range of conventional chemotherapeutic agents, as well as other targeted agents such as the BTK inhibitors, including ibrutinib (Imbruvica, Pharmacyclics/Janssen). Further exploration in the clinical trial context will be needed to determine whether it is possible to utilize synergy to safely improve long-term outcomes. It may permit treatment of a shorter duration and lower intensity than chemotherapy, while still preserving the disease-control benefits.

H&O What toxicities are associated with venetoclax?

JS With the gradual weekly, stepwise dose ramp-up of venetoclax, the rate of clinical tumor lysis syndrome is now less than 1%. However, clinicians must be vigilant about prophylaxis of tumor lysis syndrome, ensuring that patients maintain uric acid control, receive optimal hydration, and undergo careful biochemical monitoring.

Approximately 50% of patients will develop grade 3 or 4 neutropenia, predominantly during the first 1 to 2 months of the dose ramp-up. Later-onset neutropenia, occurring after the disease is controlled and marrow function improves, is infrequent. Even in the context of neutropenia, infection is infrequent. The rate of febrile neutropenia or serious infections, such as pneumonia, is less than 15%. Most cytopenias are asymptomatic. There is mild gastrointestinal toxicity. Grade 1 or 2 nausea and grade 1 diarrhea are not uncommon, but they are normally well tolerated by the patient and respond to symptom-directed supportive care.

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H&O Is venetoclax better or worse for certain patient subgroups?

JS Studies are evaluating biologic and molecular predictors and prognostic factors for novel agents. The high-risk subsets, particularly patients with the deletion 17p or *TP53* mutation, respond poorly to conventional chemoimmunotherapy but have much better responses to targeted agents, such as venetoclax. It remains unclear whether the presence of deletion 17p or the *TP53* mutation will impact response to targeted agents. To date, studies of venetoclax combinations have shown similar outcomes in patients with or without deletion 17p.

Disease bulk predicts for a lower probability of a complete remission. Based on relatively small numbers of patients, it appears that a complex karyotype may still be associated with an inferior outcome in the era of targeted therapies, including ibrutinib and venetoclax. Future research will likely identify particular molecular subsets with different sensitivities to the various classes of targeted agents.

H&O What are the treatment goals for patients with CLL, and how does venetoclax contribute to these goals?

JS This area is in a state of flux. Currently, the primary use of venetoclax in CLL is for relapsed or refractory disease. In these patients, the goal is to safely achieve a very deep remission that allows for drug withdrawal and prolongs progression-free survival and overall survival, with excellent quality of life. However, venetoclax combinations are undergoing investigation as frontline treatment. In this setting, based on the potency and frequency of very deep responses, it is possible that a cure may be achievable,

even with time-limited therapy. Longer follow-up and the results of ongoing randomized trials will be needed to see whether these hopes come to fruition.

H&O Do you have any suggestions on the best use of venetoclax in CLL?

JS Venetoclax is a highly effective, generally well-tolerated treatment. Administration does, however, require significant attention to detail and a degree of familiarity with the particular manifestations of biochemical changes in tumor lysis. Venetoclax should be administered by prescribers who are well informed about the treatment paradigm and who have the staffing, resources, and experience to carefully monitor and respond to any biochemical changes during the dose ramp-up. Venetoclax is most effective when used before patients develop very bulky disease. The risk-benefit ratio is optimized when venetoclax is used relatively early in the disease course of patients who have relapsed after their first treatment.

H&O Are there any other promising therapies in CLL?

JS The success of BCL-2 targeting in CLL has encouraged the development of other agents in this area. Ongoing clinical trials are evaluating inhibitors of other apoptotic regulatory family members, such as myeloid cell leukemia 1 (MCL-1). Like BCL-2, MCL-1 inhibits apoptosis, but it is a more prominent cellular biologic factor in diseases such as acute myeloid leukemia, multiple myeloma, and diffuse large B-cell lymphoma. MCL-1 inhibitors are undergoing active exploration in these diseases.

Venetoclax was the first drug to show that the BH3 pathway is a promising target in hematologic malignancies, as well as some solid tumors. I expect to see further expansion of the range of agents within this class. There may be other apoptotic regulatory proteins that can be targeted and clinically inhibited. Development of venetoclax represents the beginning of work in this domain, rather than the end.

Disclosure

Dr Seymour has received research funding from AbbVie and Genentech. He is a consultant and advisory board member of Roche and Genentech.

Suggested Readings

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