ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Update on Ibrutinib

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H&O Please provide some background on ibrutinib. What is known about its mechanism of action?

SO Several agents are currently being evaluated in clinical trials whose mechanism of action is inhibition of the B-cell receptors (BCRs). A chronic lymphocytic leukemia (CLL) cell is a B cell, and when the B-cell receptor on either a normal B cell or a malignant B cell is ligated, that cell receives a very strong survival and proliferative signal. In B-cell malignancies, interference with that signaling could very well have a laudatory effect on the disease. As with other inhibitors of the BCR pathway, ibrutinib causes rapid nodal reduction and rapid increase in lymphocytosis, which returns to baseline over time. Ibrutinib is a first-in-class specific inhibitor of Bruton's tyrosine kinase (BTK), which is known to be expressed in CLL, small lymphocytic lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma.

In terms of the clinical relevance of BTK, people who are born with a mutation in BTK have the syndrome of X-linked agammaglobulinemia. Clearly, this is an important kinase in B-cell development.

H&O How does ibrutinib differ from conventional chemoimmunotherapy? What are some unique characteristics?

SO Ibrutinib is unique in its pattern of response, which is very different from that of chemotherapy and/or antibodies. A characteristic feature of ibrutinib is that it may transiently increase the peripheral lymphocyte count while the lymph nodes are shrinking and patients are improving. Some patients were taken off study very early in ibrutinib trials because their lymphocyte count began to go up and it was assumed that they were progressing. There has been a fair amount of preclinical work—a lot of which was done by Dr Jan Burger at MD Anderson, as well as by multiple drug companies—showing that you are markedly interfering with chemokines that cause the cells to both chemotax and adhere to the stroma. This transient lymphocytosis is now understood to be an effect of redistributing parts of the disease into the blood. It is not a sign of disease progression, and it has led to a reassessment of the standard response criteria. There is now a response criterion known as *partial response with lymphocytosis*, which refers to patients who have a greater than 50% shrinkage of nodal disease and who fulfill all criteria of partial response (PR) except for a persistent lymphocytosis. What is remarkable is that overall responses have been observed across all classic risk groups, including patients with high β2 microglobulin, patients with advanced disease, patients with 17p or 11q deletions, and patients with bulky disease.

H&O In which disease settings and/or patient populations has ibrutinib shown promise?

SO One group that we are very excited about is the older population. Older patients—particularly those with a lot of comorbidities—do not tolerate chemoimmunotherapy, so this is another group for whom we are looking for alternate treatment strategies.

H&O Please discuss the current reviews of ibrutinib by the US Food and Drug Administration (FDA).

SO In terms of the registration strategies, there are a couple of pivotal ibrutinib trials from Pharmacyclics and Janssen. They have filed for accelerated approval based on the phase 2 data involving a relapsed refractory population. There are trials in the relapsed setting that have reached accrual. One study was designed for patients who could tolerate chemotherapy but whose disease had relapsed after prior regimens. That protocol was bendamustine and rituximab (Rituxan, Genentech), which is a very commonly used salvage regimen, plus or minus ibrutinib.

At the same time, there was a protocol for relapse for patients who would not be considered good candidates for chemotherapy for a variety of reasons (eg, age, comorbidities, poor response to prior chemotherapies) who could be entered on this randomized trial of ibrutinib vs ofatumumab. Although these trials have reached full accrual, we have not seen any data from them yet.

The third relapsed registration trial to reach accrual is a single-arm study involving patients with 17p deletion. We have not yet seen any data from that trial. There is also a frontline pivotal trial, which is a randomized study of ibrutinib vs chlorambucil, and that is still accruing patients. The initial label will be in the relapse population.

H&O What are the potential implications for patients in need of treatment?

SO I think that there is a lot of optimism because of the breakthrough status ibrutinib has received. The whole review process is somewhat more expedited than it might be under normal circumstances, and there is a lot of hope that at the end of this year or, at worst, the beginning of next year, this drug will be available. We are talking about something that is truly right around the corner, which is very exciting.

H&O Are there any particular concerns regarding accessibility or cost if ibrutinib becomes approved?

SO Yes, there are certainly concerns. We fully expect that this drug is going to be very expensive, much like other tyrosine kinase inhibitors (TKIs) for CML. Unless the US government changes the way oral cancer drugs are reimbursed, and I do not foresee that changing soon, this poses a problem. Currently, most patients have co-pays on oral medications. If you are on an oral antihypertensive, particularly a generic, that co-pay may be $10 per month. However, if you are receiving very expensive drugs that may be more than $10,000 per month and your co-pay is 10%, that could be a major problem, particularly for patients who are older, on fixed incomes, or who only have Medicare. I think cost is going to be a very significant issue in CLL, just as it has been in chronic myeloid leukemia (CML).

Most drug companies that have TKIs have developed assistance programs for patients to try to make it easier for them to access the drug. A lot of those programs are directed at helping very poor people, and so those who are not destitute but cannot afford $1000 per month for a drug are left without alternatives. We know that this is an issue for CML patients, and I would expect that it is likely to be an issue for some patients with CLL, too.

H&O What are the biggest remaining challenges?

SO My own belief is that in the long run, the use of ibrutinib as a single agent is not going to be the best way to use this drug. The reason is that we would still like to get patients into complete remission. Our obvious long-term goal is to cure patients and to not have them on drugs that they have to take for the rest of their lives. Since most of the remissions that are seen with this agent are PRs, we would like to move forward and develop combinations, and that is already being done in clinical trials. There have been some small trials combining ibrutinib with monoclonal antibodies, such as rituximab or ofatumumab. The big advantage of this type of combination is that it avoids the need for chemotherapy and the complications associated with chemotherapy. On the other hand, monoclonal antibodies are fairly weak single agents in CLL. When they are administered with ibrutinib, another function that they serve is getting the lymphocyte count down very quickly; you abrogate the lymphocytosis that is seen with the TKIs and achieve faster responses. We do not know whether these responses will be deeper or more durable, because most of the trials that have been done combining an antibody with ibrutinib have had very short follow-up.

What about combining ibrutinib with chemotherapy? There have been some small trials investigating this approach, and they appear to show that response rates are increased compared with what one would see with chemotherapy alone. However, the downside of that type of combination is that the lack of toxicity that is seen with ibrutinib alone is lost, owing to the chemotherapy.

Ultimately, it would be ideal to see combinations of TKIs as a therapeutic approach. In fact, there is a recently opened trial by Gilead using a combination of their SYK inhibitor and their PI3K inhibitor, idelalisib; the latter agent is currently in pivotal FDA trials. This will be the first study to truly combine 2 inhibitors in the same BCR pathway, although they are targeting different kinases.

H&O What does the future hold?

SO I do not believe that chemotherapy is dead yet. I think that future efforts should aim to preserve the excellent

and very durable responses that can be achieved in some patients using chemotherapy and not be too quick to throw it away for drugs that only offer PRs. Although there is no doubt that these TKIs are very exciting, I do not believe that their best uses will be as single agents.

Suggested Readings

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