

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## New Agents in Early Clinical Trials for CLL Therapy

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**H&O** What is the gold standard for chronic lymphocytic leukemia (CLL) therapy, and what are its shortcomings?

**RF** Whether or not there is a gold standard for CLL therapy is a debatable issue. If forced to choose, my pick would be FCR (fludarabine, cyclophosphamide, and rituximab [Rituxan, Genentech]) chemotherapy. The regimen is known to be effective, with response rates of approximately 90% and median progression-free survival rates ranging 35–60 months depending on the study. Although very efficacious, FCR is associated with toxicities, most worrisome of which are myelosuppression and immunosuppression. These shortcomings are manageable. What needs to be addressed the most is what to do when patients progress after they receive FCR chemotherapy. Although effective, FCR is not curative, and patients will progress.

An important question regarding the use of FCR as treatment for CLL is the goal of therapy. FCR achieves very deep remissions, including ones where CLL cells cannot be detected even by our most sensitive techniques. However, whether or not achieving such a deep remission with its associated toxicities is advantageous still has to be answered. Chemotherapy potentially depletes bone marrow stem cells. As we develop more therapies that enable patients to live longer, there becomes the possibility of patients developing bone marrow failure or myelodysplastic syndromes from the aggressive chemotherapies, or outcomes that are fatal. Patients may be better off with less aggressive therapies that they can remain on for longer periods of time. This change in treatment paradigm is only now being challenged with the new treatments available.

The treatment algorithm based on those agents approved by the US Food and Drug Administration (FDA) for patients with CLL includes either bendamustine (Treanda, Cephalon) or alemtuzumab (Campath, Genzyme) as first-line therapy for untreated patients. Once relapsed, approved therapies include FCR, chlorambucil (Leukeran, GlaxoSmithKline), and bendamustine (approved for all lines of therapy). Agents approved for subsequent use include alemtuzumab (for fludarabine-refractory patients) and ofatumumab (Arzerra, GlaxoSmithKline; for fludarabine- and alemtuzumab-refractory patients).

However, clinical practice varies greatly from the approved indications for agents. Approximately 75% of patients in the United States are treated with FCR as their first-line therapy and not at first relapse. Additionally, bendamustine use is increasing rapidly, and few patients receive alemtuzumab as initial therapy secondary to its risk of immunosuppression. It is likely that ofatumumab will gain a great deal of use as it is approved for CLL, as it is more effective than rituximab as a single agent and less immunosuppressive and myelosuppressive than other agents. Our current data for ofatumumab are in patients who are refractory to fludarabine and alemtuzumab, so how it will fare as treatment for less refractory patients is unclear.

**H&O** What are some new agents in early clinical trials that you take particular interest in? What sort of evidence are we seeing in phase I/II trials?

**RF** There are few new agents in early clinical development that are of particular interest to me and that I believe will change how we treat CLL patients.

The one furthest along in clinical development is lenalidomide (Revlimid, Celgene). Lenalidomide is approved for multiple myeloma and myelodysplastic syndrome and is known to have a great deal of activity in CLL. The greatest obstacles to its use are the complications of tumor lysis and tumor flare. Our current research

involving lenalidomide focuses on trying to identify means to make it safer and better tolerated. Various methods have been investigated, including: 1) combining lenalidomide with rituximab, using the rituximab to ameliorate some of the tumor lysis and tumor flare; 2) combining lenalidomide with thalidomide (Thalomid, Celgene), enabling both agents to be used at lower doses, hopefully achieving the same efficacy with reduced toxicity; 3) using lenalidomide as consolidation after fludarabine-based chemotherapy, when the tumor burden is sufficiently reduced so that there will be no tumor lysis or tumor flare and the lenalidomide could eliminate any CLL cells that were able to resist the chemotherapy.

The next agent furthest along is ABT-263, an oral small-molecule inhibitor of bcl-2. ABT-263 has shown efficacy as treatment for CLL patients, but its most predominant toxicity is thrombocytopenia. One strategy to deal with this complication is to start with low dosages of ABT-263 and increase as tolerated. Another option is to treat patient early in their disease, which is possible because of ABT-263 lacks other toxicities.

CAL-101 is a new agent for which I am particularly excited. CAL-101 is a highly specific inhibitor of the delta isoform of phosphatidylinositol-3-kinase (PI3 kinase). The delta isoform is expressed only in hematopoietic cells, generating an excellent safety profile. CAL-101 has demonstrated very dramatic reductions in lymphadenopathy in very refractory patients in its phase I study. More than 90% of the patients in this very refractory group of patients had greater than 50% reductions in their lymphadenopathy. CAL-101 seems to have far less efficacy on bone marrow disease, which has taught us a great deal about the molecular pathways involved in lymphocyte trafficking, including CXCR4 and CXCL12.

Another agent that is also showing excellent results in refractory patients is PCI-32765, an orally available, small-molecule inhibitor of Bruton's tyrosine kinase (Btk) and has just begun to enter phase II studies in CLL.

### **H&O** How are the new agents different, in terms of mechanism of action, from currently used agents?

**RF** Prior agents (FCR, bendamustine, chlorambucil) are chemotherapy agents that work relatively nonspecifically at inducing cell death by damaging DNA or DNA synthesis. They damage DNA not just in lymphocytes but in the normal bone marrow cells as well. This causes myelosuppression and makes long-term treatment not possible. Typically, when patients relapse after chemo-

therapy, the CLL cells have acquired additional genetic damage that results in a great deal of refractoriness.

Small-molecule inhibitors, such as those previously discussed, target a specific enzyme and not DNA integrity in general. Through the blockage of an individual enzyme, they target specific cell populations, leading to improved efficacy and less toxicity.

### **H&O** How do you see these agents progressing in the drug development process?

**RF** Phase III trials are relatively rare in CLL. They are likely to become more common as the FDA has recently suggested that they will start requiring more phase III trials for approval of novel agents. CAL-101 has begun a randomized phase II study, comparing rituximab, bendamustine, plus CAL-101, to bendamustine plus CAL-101, to rituximab plus CAL-101. This trial is in preparation for a phase III pivotal study, hopefully to lead to FDA approval for CAL-101. Additionally, investigator-initiated trials of combinations such as CAL-101 and ofatumumab are planned. Likewise, ABT-263 has begun phase II studies to be followed by its phase III trials. PCI-32765 is just entering its phase II trial, so this agent has a little ways to go before it is ready for pivotal phase III studies.

I think the most important idea to remember is that we are entering an age where the treatment paradigm for CLL will be altered. There is now the potential for patients with CLL to live much longer once they start receiving therapy. The most important therapeutic question then becomes: how are we going to treat these patients in a manner that is safe, and improve their overall survival and not just the response rates?

I believe the aim of achieving very deep remissions that are MRD-negative needs to be rethought. We know these chemoimmunotherapy regimens are not curative. How patients will fare after they relapse and whether associated toxicities or secondary genetic changes the CLL is resistant to subsequent therapy, are questions that will need to be considered. These new agents, because they are nontoxic, afford the possibility of controlling disease over a long period time without necessarily achieving a deep remission, as patients can remain on therapy for long periods of time. If someone can achieve a partial response and remain that way for 10 years just continuing on the drug, that would be far superior to what is currently available. These novel therapies can make CLL a truly chronic disease.