

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Drugs for Chronic Lymphocytic Leukemia

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H&O Could you give a brief overview of the evolution of chemotherapy for chronic lymphocytic leukemia?

JB The alkylating agents, chlorambucil, and fludarabine have been the main chemotherapeutic agents evaluated for the treatment of chronic lymphocytic leukemia (CLL). Recent randomized phase III studies found fludarabine to be more effective than alkylator-based therapy in terms of both response and progression-free survival. Even more recently, a phase III study of fludarabine plus cyclophosphamide found this combination to result in improvements in response rates and progression-free survival compared with fludarabine alone.

However, in these phase III studies, a complete response has been observed in only approximately 25% of patients. The remaining 75% of patients experience a partial response with leukemia still detectable or do not respond at all. Only approximately 10–15% of patients do not respond, but both this group and partial responders have shorter remission times than complete responders. There is no curative chemotherapy-based approach for CLL.

H&O How have monoclonal antibodies improved patient outcomes?

JB Phase II trials of rituximab (Rituxan, Genentech) combined with either fludarabine or fludarabine and cyclophosphamide have found complete response rates in the range of 47–70%. Retrospective comparisons of these studies with older studies suggest that the inclusion of a

monoclonal antibody improves outcomes, but there are not yet any phase III studies confirming that rituximab is associated with a superior survival time; ongoing studies are evaluating whether outcomes are improved with the newer treatment regimens.

With regard to first-line therapy, even among patients who receive aggressive combination therapy, many still relapse. Patients with high-risk CLL—those with deletions of chromosome 11q or the 17p locus—tend to do very poorly when administered fludarabine plus cyclophosphamide or fludarabine plus rituximab. While no data exist to tell us if fludarabine/cyclophosphamide/rituximab will work in this group, it is unlikely that this will be very effective. Aside from transplantation, there is still no curative therapy for genetically high-risk CLL.

H&O Are purine nucleoside analogs being studied for the treatment of CLL?

JB There is an ongoing study comparing the combination of pentostatin, cyclophosphamide, and rituximab with fludarabine, cyclophosphamide, and rituximab in relapsed disease. The Polish CLL group is evaluating cladribine-based combinations, and newer nucleoside analogs, such as clofarabine, which was developed at the M. D. Anderson Cancer Center, are also being studied.

H&O What are some of the newer strategies employing rituximab?

JB There are several new strategies being evaluated. Investigators at the M. D. Anderson Cancer Center are evaluating rituximab in combination with agents that enhance antibody-dependent cellular cytotoxicity (ADCC). Rituximab in combination with granulocyte-macrophage colony-stimulating factor has shown promising results in the treatment of previously untreated and elderly patients with CLL. This approach may be of interest for elderly patients who are not appropriate candidates for aggressive chemotherapy-based approaches such as those discussed above.

Antibodies are also being combined with signal transduction inhibitors, such as heat shock protein 90 inhibitors or others relevant to CLL. Rituximab has a

very favorable side effect profile in CLL and other B-cell diseases, and thus there is much interest in combining other targeted agents with this antibody.

H&O How is alemtuzumab being studied in the treatment of CLL?

JB Ongoing studies are evaluating alemtuzumab (Campath-1H, Berlex) in the first-line setting in combination with fludarabine, fludarabine/rituximab, or fludarabine/rituximab/cyclophosphamide. These studies are focusing in particular on high-risk patients, mainly those with the 17p deletion; several groups have found that alemtuzumab is effective in this genetic subtype. Alemtuzumab is also being studied for its potential to eliminate minimal residual disease. This approach is being studied by the CLL Research Consortium and the Cancer and Leukemia Group B, which is conducting a study in which patients receive fludarabine/rituximab followed 3 months later by alemtuzumab as consolidation therapy.

Alemtuzumab is approved for the treatment of relapsed CLL, and in this setting it is often used as consolidation therapy. As a single agent, alemtuzumab is effective in approximately 33% of patients with relapsed CLL, a group composed mainly of patients with disease confined to the blood, bone marrow, and spleen. This antibody does not appear to be effective in patients with bulky lymph nodes. However, preliminary studies suggest that it might have significant clinical efficacy in patients with genetic high-risk CLL.

H&O What other approaches are being explored for alemtuzumab?

JB Alemtuzumab is associated with immunosuppression, and many groups have been seeking ways to diminish this side effect. For example, subcutaneous administration may decrease infusion toxicity. Dr. Dyer and colleagues in England have been evaluating the administration of alemtuzumab at higher doses than have previously been used. A pilot study presented at the 2005 annual meeting of the American Society of Hematology (ASH) showed good nodal responses when this agent was used at higher doses.

In addition, several biotechnology companies are exploring the possibility of modifying alemtuzumab to enhance ADCC. There is also broad interest in using alemtuzumab as an immunosuppressive agent as part of the conditioning regimen for mini nonmyeloablative stem cell transplantations.

H&O Could you discuss other antibodies being evaluated for the treatment of CLL?

JB Data were presented at the 2005 ASH meeting on the Genmab CD20 antibody (HuMax-CD20), which fixes complement more effectively than other antibodies; in vitro assays have found this agent to be potentially as effective as rituximab. Based on the data presented, it is not clear whether this antibody offers an advantage over single-agent rituximab. Studies of this agent are continuing.

The two most interesting targets for which agents are being studied in clinical trials are CD23 and CD40. CD23 is targeted by lumiliximab (Biogen Idec). Phase I studies of this monoclonal antibody showed a very good safety profile and minimal activity as a single agent. In a subsequent phase II study, lumiliximab was combined with fludarabine/cyclophosphamide/rituximab for the treatment of patients with relapsed CLL. The preliminary results showed a promising complete response rate. As a single agent, this antibody does not appear to be very active, but it may offer a significant advantage when administered in combination with other therapies.

There are two anti-CD40 antibodies currently being studied in clinical trials: CHIR-12.12 (Chiron) and SGN-40 (Seattle Genetics). Although these agents have the same target, they work quite differently. CHIR-12.12 blocks the CD40-CD40 ligand interaction, thereby making the cells more sensitive to apoptosis. SGN-40 mediates ADCC and may also activate CD40. Several studies have shown that activation of CD40 induces apoptosis in CLL. Both of these agents appear promising and clinical studies are ongoing.

H&O What small molecules are being studied for the treatment of CLL?

JB Currently, the two most promising small molecules are the cyclin-dependent kinase inhibitor flavopiridol (Sanofi-Aventis), which our group reported on at the 2005 ASH meeting and at this year's International Workshop on Chronic Lymphocytic Leukemia. In a phase I study of flavopiridol with a modified treatment schedule, we observed a response rate of 45% in patients with refractory CLL, including patients with high-risk genetic features. The dose-limiting side effect was acute tumor lysis syndrome. This drug appears to be very effective for the treatment of CLL.

Preliminary data from a phase II trial at Roswell Park show that lenolidomide (Revlimid, Celgene) is also active in treating relapsed CLL, with an observed response rate

of 45–50%. The main side effects were cytopenias and flair reaction. This small molecule appears promising and, together with flavopiridol, represents the most exciting agents in the small-molecule category for the treatment of CLL.

H&O How was the treatment schedule of flavopiridol modified? Why?

JB Several earlier studies giving flavopiridol on a 1-hour, 24-hour, and 72-hour administration schedule showed little activity of this agent in CLL. Our group showed that flavopiridol was highly protein-bound when incubated in human serum, but using laboratory conditions with fetal calf serum it was not. This finding led to previous underestimation of the dose that would be needed to effectively promote apoptosis. A novel pharmacokinetically derived schedule modeled to maintain a 1.5 μ M concentration of flavopiridol was designed. This schedule dramatically changed the response profile of flavopiridol, making it a highly effective agent for refractory CLL.

H&O How is gene therapy being applied in the treatment of CLL?

JB Several groups are evaluating gene therapy–based treatment of CLL. Dr. Tom Kipps's laboratory started this work and performed the initial phase I study with this approach. Dr. William Wierda and colleagues at the M. D. Anderson Cancer Center have continued studying CD154 gene therapy in collaboration with Dr. Kipps, his former mentor. A phase II study following a very promising phase I study is ongoing. Several vaccine-based approaches are beginning to be explored, and where such approaches will be applied in the treatment of CLL remains an open question.

H&O What new understandings have been gained by the successful development of new drugs for CLL?

JB The work with flavopiridol has confirmed the importance of protein binding in leukemia. By identifying this

factor in the development of leukemia and then modifying the treatment schedule of flavopiridol accordingly, a drug that initially showed very little activity has been found to be very active.

Another consideration that has been brought to light is the way in which preclinical assays are used to screen new drugs. Potential new agents need to be tested in conditions that are similar to in vivo environments, where there are stromal cells or cytokines that keep cells alive and thereby alter the strength and/or ability of drugs to kill cells. It is essential that effective assays are used and that only the most promising agents are selected for development.

Finally, an important step in the evolution of therapy for CLL has been the evaluation of combination regimens in the preclinical setting. Instead of identifying a single monotherapy that mediates cell killing and then moving that agent forward to the clinic, much bigger gains will be made from designing rational combination studies and testing such regimens in the preclinical setting. Most importantly, we are at a juncture in therapeutics for CLL where many major advances may be on the near horizon. The support of the National Cancer Institute and Leukemia and Lymphoma Society has greatly facilitated this process.

Suggested Reading

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