

ADVANCES IN LLM

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

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New Agents in Chronic Lymphocytic Leukemia

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H&O Can a standard of care be said to exist in chronic lymphocytic leukemia?

JG In chronic lymphocytic leukemia (CLL), there is no established algorithm for the treatment approach. This disease is very heterogeneous, even in its requirement for treatment. Many clinicians therefore feel that it would be difficult to establish a standard of care that could be used in all patients with CLL. The disease's characteristics, the patient's age, and the treatment's goals all vary and must be taken into account when planning the therapeutic approach. However, there are some suggestions of what the frontline therapy should be. In many cases, fludarabine, cyclophosphamide, and rituximab (Rituxan, Genentech/Biogen Idec; FCR) would be considered established frontline therapy. However, FCR has not been shown to be the optimal standard therapy in a randomized phase III trial. Results from a recent German study are anticipated to help the community judge whether FCR should be considered the standard of care. Though this regimen is becoming the established frontline therapy, many clinicians feel it is too myelotoxic for a large proportion of elderly patients. In these patients, the combination of fludarabine and rituximab (FR) is considered a less toxic alternative. There are no randomized clinical trial data comparing the outcome of FR to that of fludarabine and cyclophosphamide (FC) or FCR.

H&O What are the goals of therapy in patients with CLL?

JG In treating patients with CLL, we are today moving beyond thinking of treatment as purely palliative. Cer-

tainly, 10 years ago, the goals of therapy for CLL were never more than palliative because palliation was what the best treatments could offer. We cannot yet consider our treatment approaches to be curative, but complete remission is now a viable goal of therapy. Clinicians are, moreover, beginning to consider eradication of minimal residual disease a goal of therapy. In my opinion, today, complete remission should be the goal of therapy and, in the future, eradicating minimal residual disease should become the goal.

H&O What trials are the important ongoing trials in patients with CLL?

JG In the frontline setting, the phase III German CLL-8 study is examining FC versus FCR in a randomized design, and it may confirm data from The University of Texas M. D. Anderson Cancer Center (MDACC) showing FCR to produce a very high response rate. These data also suggest an advantage for FCR in terms of progression-free and, potentially, overall survival. To date, there has never been a trial in CLL that has demonstrated an improvement in overall survival. Typically, improvements are in progression-free survival. It is important for patients to have an improvement in progression-free survival, but because patients want to live longer, researchers are hoping to demonstrate an advantage in terms of overall survival. In CLL, however, to demonstrate an advantage in terms of overall survival, a very long follow-up period will be necessary. The CLL-8 study has finished accruing and the results may be available this year. I believe these results will establish the optimal frontline therapy in eligible patients with CLL. Researchers will then be able to build upon these results by evaluating ways to improve survival. In looking for a curative approach, consolidation therapy or the use of other drugs in addition to the backbone of FCR will be evaluated in clinical trials.

H&O What agents are under consideration for addition to the FCR backbone?

JG Alemtuzumab (Campath, Genzyme/Bayer) is the most obvious candidate for addition to the FCR regimen. Researchers from MDACC presented data on the regimen of FCR plus alemtuzumab (CFAR) at the annual meeting of the American Society of Hematology in 2007. At first glance, it did not appear that this regimen offered a major advantage over FCR. Therefore, it has been postulated that a better use of alemtuzumab would be as a consolidation therapy after FCR, with the goal of eradicating minimal residual disease. There have been some promising phase II results in the use of alemtuzumab as consolidation therapy following FCR, suggesting that this approach could be useful; it thus merits further investigation.

H&O What have been the results of research with immunomodulatory agents in CLL?

JG Lenalidomide (Revlimid, Celgene) is one of the most exciting drugs already available in the marketplace. There are two relatively small phase II studies that have evaluated lenalidomide in CLL, which produced promising results. Several phase II multicenter studies now ongoing around the world are further evaluating lenalidomide in this setting. Although this agent is considered the second generation of drugs based on thalidomide, the next generation of thalidomide analogs is now under development. These drugs appear to be extremely interesting in CLL. We do not yet have sufficient data to determine what the role of lenalidomide in this setting should be, whether it should be used in combination, instead of chemotherapy, or as consolidation.

H&O What have been the results of research with Bcl-2 antisense?

JG Whereas cancer cells are often thought of as overproliferating, the major defect that characterizes the CLL cell appears to be that it does not die. The cell is programmed to overexpress the Bcl-2 family of proteins. Oblimersen sodium (Gentasense, Genta) targets that pathway and attempts to switch it off. There are interesting data showing that when used in combination with chemotherapy, oblimersen is beneficial. Whether oblimersen reaches its target with enough intensity has yet to be determined, in my opinion, though clinical trial data seem to support the postulation that in fact it does. Many other drugs in earlier stages of clinical development also target this pathway in different ways; these agents may be easier to administer than oblimersen. The problem with this class of drugs—a class worth further

investigation—is that each agent is highly unlikely to achieve a therapeutic effect as monotherapy. These agents are expected to be much more effective in combination with chemotherapy. However, it remains necessary for early research to be conducted as monotherapy before multidrug combinations can be investigated. Therefore, the community of researchers and investors must recognize that it may take many years of clinical development before these agents are available in the marketplace if they prove effective at each stage of research.

H&O What new monoclonal antibodies are under investigation in this setting?

JG Many monoclonal antibodies have been investigated in this setting, including antibodies that target CD20 other than rituximab, such as ofatumumab (HuMax-CD20, Genmab/GlaxoSmithKline). Rituximab monotherapy does not have much of a clinical effect in CLL, unlike in the other B-cell malignancies. In combination with chemotherapy, however, rituximab is effective in CLL, as discussed. Whether ofatumumab will show efficacy in phase II or III trials in CLL is not yet known. Researchers are eager to learn whether the next generation of anti-CD20 antibodies will achieve increased efficacy against the CLL cell in combination with chemotherapy. Additionally, lumiliximab (Biogen Idec) is a monoclonal antibody that targets CD23. There is an ongoing clinical trial comparing FCR to FCR plus lumiliximab to determine whether this addition to the FCR backbone improves outcomes. Anti-CD40 antibodies also appear promising in early-stage research in this setting.

H&O How does stem cell transplantation fit into the treatment algorithm in CLL?

JG The only curative treatment option for patients with CLL is allogeneic stem cell transplantation. (Autologous stem cell transplantation is currently considered noncurative and purely experimental in this setting.) In CLL, most patients who are offered stem cell transplantation receive reduced-intensity conditioning. The problem with stem cell transplantation is that although it offers the potential for cure, the risk of morbidity and mortality is high. It is imperative to weigh the potential benefit of the procedure with the risks on a patient-by-patient basis. Therefore, this option tends to be offered to end-stage patients. It is likely that in patients with CLL, as with patients with other hematologic malignancies, better results would be achieved if transplantation were offered earlier in the clinical course of the disease. Ongoing trials are trying to determine the subgroup of patients most likely to merit

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transplantation early in their clinical course based on risk parameters that are still to be established. It would be ideal to have the ability to identify a patient who would need a transplant and know this need early in the clinical course before the disease has become resistant to therapy. Such a patient could thus be offered transplantation at an earlier stage, likely improving the clinical outcome.

Even in the setting of highly refractory CLL, encouraging results have been seen in a number of phase II trials of stem cell transplantation. There has not been a trial comparing transplantation to an alternative treatment method, largely because transplantation tends to be offered to patients in whom there is no alternative available. In many other disease settings, randomized trials have shown that transplantation is superior to a given alternative therapy. This type of trial will require a great amount of planning, as clinicians must carefully decide which patients to randomize. I believe planning this trial and achieving consensus will be difficult even though the community needs confirmatory data as to whether transplantation is superior, in terms of outcome, to an alternative therapy. The Cancer and Leukemia Group B is planning a multicenter trial evaluating reduced-intensity conditioning transplantation administered to high-risk patients early in their clinical course. This study should open to accrual by the end of 2008.

H&O What have been the findings with consolidation after stem cell transplantation?

JG Further donor lymphocyte infusions are the typical consolidation therapy. The clinician is attempting to use the immune system of the donor to eradicate the disease. Immunomodulatory drugs may be quite interesting in the posttransplant setting. At present, there are no data on the use of these agents as consolidation therapy. The concern arises that these agents would modulate the immune response, leading to graft-versus-host disease (GVHD). However, a drug that could augment an immune response and have direct anticancer effects would be of great interest in the posttransplant setting. Some data from MDACC show that giving rituximab at the time of and after allogeneic transplantation confers surprisingly beneficial responses in terms of overall survival and decreasing GVHD. We know that GVHD is caused by T cells, but rituximab targets B cells. There is thus potentially an interaction between T and B cells effected by rituximab, which warrants further investigation. These findings could turn out to be quite useful in the future.

H&O How are fludarabine-refractory patients treated?

JG Some patients either do not respond to fludarabine-based therapy or relapse very soon thereafter. This patient population has a very poor prognosis. Several types of drugs are under investigation in this setting, including flavopiridol, which may be particularly effective in p53-mutated patients. Alemtuzumab is already approved in this setting. If an agent shows efficacy in this setting, it is believed that it would be fast-tracked for approval. Therefore, there may be more trials available to this population than there are patients whose disease is refractory to fludarabine. Of course, the hope would be that once a drug enters the marketplace, it could be investigated at earlier stages of the disease.

H&O What will be the next step once the debate of frontline FC versus FCR is settled?

JG Even when the question of whether the standard frontline therapy for patients with CLL should be FC or FCR is settled, the community will still need to seek an approach for patients who are not cured and relapse. If the most efficacious drug combination is used upfront, what combination should then be used in the relapsed setting? I believe there is plenty of room for new drugs to be developed for use in the relapsed setting. It is difficult to see how a new agent could be used in the frontline setting until the question of FC versus FCR is settled, but after the backbone is determined, other agents can be added to try to improve upon its results. I believe some such studies could begin in the next year or so, but results will not be available for another 5–6 years.

Suggested Readings

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