

# ADVANCES IN LLM

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

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## Expert Perspectives on Advances in Hematologic Malignancies

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### **H&O** How did you become interested in treating leukemia?

**SO** I became interested in oncology because my mother died at only 50 years old of metastatic lung cancer. I was an intern at the time, and her death had a great impact on me, particularly because of her young age, making it seem like the field needed advancement. When I started at The University of Texas M. D. Anderson Cancer Center, I did not know enough about cancer to know what subspecialty I would choose. My first rotation happened to be as a Fellow in leukemia. One might say that I liked it best because I worked in this field first, but the truth is that leukemia was a very interesting disease for me intellectually and my mentors in the department were very dynamic, thought outside the box, and constantly challenged Fellows on any dogma, pushing us to show why it was true or not true and to think of new ideas and approaches.

### **H&O** While you've been working as a hematologist, what have been the most exciting advances?

**SO** Since I entered the field, there have been dramatic strides in the treatment of chronic lymphocytic leukemia (CLL). When I was a Fellow, fludarabine was under investigation. The only drug for the treatment of CLL then was the alkylating agent chlorambucil, which was a reasonable palliative agent in that partial remissions were

possible to achieve in a number of patients. Complete remissions or durable remissions, however, were out of reach. The treatment picture changed with the introduction of fludarabine, and it has been further refined with the availability of chemoimmunotherapy with the combination of the anti-CD20 monoclonal antibody rituximab (Rituxan, Genentech/Biogen Idec) and fludarabine. Rituximab has been one of the most dramatic new agents in the treatment of lymphomas, but it has also changed the treatment of CLL. Today, regimens combining rituximab and nucleoside analogs are producing 5- and 6-year remissions. Neither nucleoside analogs or rituximab were available when I began treating patients with CLL.

The most dramatic change in treatment and expected outcomes I have experienced was with the introduction of imatinib (Gleevec, Novartis) for the treatment of chronic myelogenous leukemia (CML). The treatment of choice for CML when I started was either allogeneic stem cell transplantation, which could be successful but was associated with significant rates of morbidity and mortality, or interferon, which had a low mortality rate but a very high morbidity rate because the ideal dose for the treatment of CML was 5 million U/m<sup>2</sup> daily. With such doses of interferon, 20–25% of patients achieved complete remissions that were fairly durable. Today, over 80% of patients achieve a complete cytogenetic remission with imatinib, which is an oral agent with minimal toxicity. Although the data for this drug are relatively new in the frontline setting (approximately 5–6 years of follow-up), most of the patients who have achieved complete remission remain in remission at present. Historically, the average survival for patients with CML was 5–6 years. CML patients all

have the same cytogenetic/molecular abnormality (Philadelphia chromosome), which meant that this treatment, which interfered with the aberrant protein, became the prototype for the development of targeted therapy.

### **H&O** What are the most exciting directions of ongoing research in hematologic malignancies?

**SO** The more that is known about the biology of the cell, the more proteins and pathways we will have available to develop specific interventions that interfere with them. This concept is exciting, but it must be said that this approach remains in its infancy. A number of agents in clinical trials inhibit specific proteins or pathways, such as mammalian target of rapamycin (mTOR). Yet we find that inhibitors of such pathways are effective in only one disease or not in all diseases and the outcomes do not include complete remission. I believe that by the time malignant cells develop in most of the hematologic malignancies other than CML, there are most likely several aberrant pathways in the cell. Therefore, targeting only one pathway is not sufficient to induce complete remission. Thus, chemotherapy remains relevant for the treatment of most hematologic malignancies, and the ideal targeted therapy remains to be discovered. Nowadays, clinicians shy away from the word chemotherapy, but the fact remains that most of the diseases that are being cured, or in which great advances in survival have been achieved, are treated with chemotherapy. There is an enormous potential benefit to be accrued from interfering with targeted biologic pathways because of decreased toxicity, but it may be that in most diseases, more than one targeted treatment will be needed. The future changes in the way diseases are treated are not likely to be as dramatic as what we have witnessed with CML. There is no question in my opinion, though, that the explosion in learning about the biology of diseases and abnormal or constitutively upregulated pathways—and the attempt to target these pathways—will be a successful long-term strategy.

### **H&O** What is the status of research in the elderly with hematologic malignancies?

**SO** Currently, there is great attention focused on hematologic malignancies in the elderly, who, even if not by design, have not been included in a good deal of research on new agents. Researchers from The University of Texas M. D. Anderson Cancer Center and others have published data on very good response rates with chemoimmunotherapy in the setting of CLL, but the median age of patients enrolled in these trials ranges from approximately 55 to 61 years. In contrast, the Surveillance, Epidemiology, and End Results database has recorded the average

age of patients with CLL at nearly 70 years. Even though older patients have not been specifically excluded from the trials of chemoimmunotherapy for CLL at my institution, the reality is that it is unlikely an 80-year-old patient will be referred to a tertiary center for a clinical trial for a variety of reasons. At least half the leukemia patients in the United States are in their 70s or 80s, but they simply are not being enrolled in clinical trials. There is a growing realization that even the very good data available in hematologic malignancies may not be applicable to patients over 75 years old. In the frontline trial of rituximab, fludarabine, and cyclophosphamide for CLL by my institution, patients over age 70 experience significantly more myelosuppression and infection and are much less likely to complete the planned six cycles than younger patients (90% of patients <70 years old completed 6 cycles).

Hematologists are becoming more aware of the need to develop therapies that can be tolerated by an older population. With some of the biologic agents under development, one of the major hopes is that these agents may be particularly relevant to an older population that is underrepresented on trials. Although, as I said, complete remission may be impossible with an agent that targets only one pathway, an 80-year-old with several comorbidities does not need to achieve a 10-year complete remission. It would be fair in such a patient to use a palliative approach because aiming for a polymerase chain reaction–negative complete remission might not be feasible due to toxicities and comorbidities. A milder, gentler therapy with a relatively low complete response rate could be relevant to this patient population.

### **H&O** What is the status of the assessment of prognosis in hematologic malignancies?

**SO** There is a great deal of interest in developing new methods of assessing prognosis in patients with hematologic malignancies, but not much of what is known is ready for clinical use. There is a good deal of data being published on genomics, proteomics, and gene array profiles, and these developments are exciting. The application of this science to patients, though, will require more work in order to find the most practical methods and to delineate what is most relevant to a specific patient as opposed to a patient population as a whole. Even within a specific subtype of leukemia or lymphoma, there can be enormous heterogeneity in the patient outcomes because although patients are grouped by disease, within that disease state, there is variability. For example, in acute myeloid leukemia (AML), it has been known for 20 years that the most important indicator of outcome other than age is chromosomal abnormalities. Patients with AML who are known to do well based on chromosomal abnormalities

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receive a different treatment approach from those known to do poorly; moreover, clinicians can advocate investigational approaches upfront for poor-prognosis patients. Prognostic factors are thus very important because it is best not to approach the therapy of all patients with a given disease in the same way due to the heterogeneity within each disease state. Furthermore, it is important to remember that prognostic factors are strongly correlated with treatment; if a treatment could cure 100% of patients, there would be no way to assess prognosis. One slightly complicating factor is thus that as treatments evolve, prognostic factors too will need to evolve. What might predict for poor outcome with one treatment may not have the same predictive value for another treatment. As our treatments change, I think it would be fair to say that prognostic factors should be tested prospectively.

### **H&O** In what other areas does room for improvement exist?

**SO** There is room for improvement in every aspect of hematologic malignancies. Until we can cure 100% of patients, there will be room for improvement. And even if we could cure 100% of patients, toxic therapy that can lead to secondary malignancies would still not be an ideal

approach. For example, patients with lymphoma can be cured, but secondary myelodysplastic syndromes or AML arise later on. The disease for which we are able to offer patients the best therapy is likely CML due to imatinib's effect on the course of the disease. However, as I mentioned, only 5 years of follow-up data are available, and it is possible that its success will be tempered as more data become available with longer follow-up. There may still be room for improvement in CML too, and there is certainly a need for a better approach for the 10–20% of patients who have inadequate responses to imatinib. There is no hematologic malignancy with an outcome so positive that researchers should think their work is finished.

### **Suggested Readings**

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