ADVANCES IN LLM

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

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Monitoring Lymphoma Patients After Therapy

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H&O What methods are commonly used to monitor lymphoma patients after therapy?

MR Different methods are used for different types of lymphoma. It is important to distinguish between lymphomas that are treated with curative intent, such as diffuse large B-cell lymphoma (DLBCL); and indolent lymphomas that have a perpetual risk of relapse, such as follicular lymphoma (FL). In DLBCL, the risk of relapse is highest proximal to treatment and reduces over time. Most disease that fails to respond to therapy will relapse within 2 years of treatment completion. In FL, however, the risk of relapse continues to rise over time because most patients are not cured with initial therapy.

All patients are followed with regular clinic visits in which the provider assesses for signs and symptoms suggestive of lymphoma recurrence, such as lymph node swelling, pain, or constitutional symptoms. In addition, it is customary to test blood counts and lactate dehydrogenase (LDH) levels at each clinic visit.

The challenge is to identify evidence of recurrent disease while a patient remains asymptomatic. In this regard, the focus has been on medical imaging, such as computed tomography (CT) scans and—more recently—positron emission tomography (PET) scans, performed at regular intervals after therapy. In potentially curable lymphomas such as DLBCL, this is of particular interest as a strategy to improve the cure rate. Unfortunately, medical imaging scans have not been shown to affect clinical outcomes, probably because they lack the ability to detect disease at the molecular level. Thus, enthusiasm for performing routine surveillance imaging in patients with DLBCL is waning and some centers have abandoned the practice altogether.

H&O Could you describe some of the imaging methods to monitor lymphoma patients after therapy?

MR The imaging method used most commonly is contrasted CT scans of the chest, abdomen, and pelvis. The interval is typically shortest for the first 2 years after therapy and then extended out until 5 years. Because DLBCL does not commonly relapse after 5 years, it is customary to stop imaging then. Different protocols exist, but an example might be imaging every 3 months for the first 2 years, then every 6 months for years 2 to 5. However, national guidelines have been updated recently, and they suggest that having this many scans is unnecessary and potentially harmful to patients.

PET scans were developed to have better sensitivity for aggressive lymphomas than CT scans, and that appears to be true. However, the increased sensitivity comes at the cost of less specificity, and they also have been unable to affect clinical outcomes when used during or after therapy in patients with DLBCL.

H&O What are the pros and cons of these imaging methods?

MR The argument for surveillance imaging in DLBCL is that relapsed disease is potentially curable. However, in the current era of rituximab (Rituxan, Genentech/Biogen Idec)-containing therapy, fewer patients relapse after initial therapy. Thus, relapsed disease is more difficult to cure with standard approaches (eg, autologous stem cell transplantation) that were developed in the pre-rituximab era. The biology of the disease at relapse certainly plays a

role in this, but it is also likely related to tumor burden at the time of relapse. Thus, the hypothesis is that detecting disease recurrence earlier (ie, with more lead time) and at the lowest possible level has the potential to improve the cure rate. Liedtke and colleagues reported a retrospective study demonstrating that they could identify relapses earlier and at a lower international prognostic index (IPI) score with imaging. This study, however, did not demonstrate an improvement in survival for the patients.

The argument against surveillance imaging is that most evidence suggests that it only detects recurrence in a small minority of patients and, thus, will not benefit the group as a whole. The largest and most recent publication on this topic, a retrospective study by Thompson and coauthors, did not demonstrate any advantage in using imaging scans compared with clinical evaluations. Furthermore, there is no evidence that these imaging scans improve patient survival. Importantly, there are also concerns about the cost of scans and the potential for long-term health risks when patients—particularly young ones—are exposed to repeated doses of ionizing radiation from imaging scans.

My opinion is that some patients probably benefit from close monitoring, and we should not completely disregard monitoring altogether on the basis of retrospective studies and their inherent bias. The challenges of monitoring are similar to the challenges in therapy where we, as researchers, are trying to utilize new technologies to develop a more precise approach. The fundamental questions are focused on patient selection, modality, and timing.

H&O Could you describe the molecular methods used to monitor lymphoma patients after therapy?

MR We have recently published a correlative biomarker study in *The Lancet Oncology* that compares a molecular monitoring tool vs medical imaging in a large number of patients with untreated DLBCL. All patients had a CT scan done at the same time as their blood test, in this case a serum sample. We amplified small amounts of circulating tumor DNA (ctDNA) in a qualitative and quantitative fashion before, during, and after therapy. The primary challenge of such molecular monitoring tools is distinguishing between circulating DNA that comes from the tumor and DNA that comes from normal or inflamed cells. To resolve this problem, we focused on the DNA that encoded the gene sequence of the immunoglobulin receptor, which is a unique marker of clonality for B-cell lymphomas, such as DLBCL. A small region of that receptor known as the VDJ sequence was amplified and quantitated using next-generation sequencing via the LymphoSIGHT platform. The DNA sequence was determined from baseline tissue, and that same sequence—called the tumor clonotype—was followed in the patient's blood to determine risk of recurrence. The ctDNA assay we used is commercially available through Adaptive Biotechnologies.

When we compared the ctDNA method with CT imaging, we found that most patients who progressed had positive ctDNA test results before recurrence was recognized on a CT scan. The lead time in our study was more than 3 months for most patients, and even longer in the patients who relapsed late. We also tested the ability of the ctDNA to monitor tumor dynamics during therapy. We examined the ctDNA kinetics after the second cycle of therapy, and found that we could predict with rather high accuracy which patients would ultimately progress. Other methods and assays could also be used to monitor patients with DLBCL at the molecular level, but they will require some level of clinical validation.

H&O What are the pros and cons of these molecular methods?

MR One major benefit of molecular monitoring is that the test is noninvasive, because it uses peripheral blood. Not only does it avoid the long-term health risk of CT scans, but it could theoretically be employed as often as needed in order to monitor a patient. Thus, the ctDNA assay is a much better platform to measure tumor dynamics during therapy. The test also uses a very specific marker compared with CT scans, because the marker of interest comes from the tumor itself.

The intrinsic cons of molecular methods are limited compared with CT scans. Importantly, however, some patients relapse without the reappearance of ctDNA in the serum, so there is a chance one might miss disease recurrence if this test is used alone. In our study, however, we saw clear evidence of disease progression in imaging scans that was mainly localized in the mediastinal lymph nodes. Thus, in some cases, molecular methods may best be used as an adjunct to scans instead of completely replacing them. I think future studies will need to explore these questions with more detail.

H&O What is your suggestion for monitoring lymphoma patients after therapy?

MR I think this is the critical question, and many people will have different opinions. One piece of information that often gets lost in this discussion is the patient and his or her risk of relapse. A patient who will not be offered curative therapy at the time of relapse probably does not glean much benefit from close monitoring with molecular methods or CT scans. For that patient, I would probably focus only on clinical monitoring. For patients with DLBCL who are candidates for curative therapy, however, it is our

practice to follow them closely with CT scans every 3 to 4 months for the first 2 years, then every 6 to 12 months for the next 3 years. After 5 years, we follow patients clinically once a year, but do not perform routine imaging scans. For patients with incurable lymphomas such as FL, we do not perform routine surveillance imaging.

Many questions still exist regarding about the best applications of molecular monitoring methods in DLBCL at this time because the concept is in its infancy. On one hand, the assay that we used in our study is commercially available and the process is quite simple. We have demonstrated that this ctDNA assay is more effective than CT imaging in predicting DLBCL recurrence. However, the caveat is that we do not know whether identifying DLBCL earlier will result in improved outcomes. Personally, I would discuss this test with my patients and would have few reservations about ordering the test. If placed in the right context, I think the assay can successfully be used now, but more data will certainly make the results easier to interpret in the future.

H&O How do you think the way patients are monitored after therapy will change in the future?

MR The debate on surveillance after therapy for curable lymphomas is likely to continue for years. I think ctDNA assays and other noninvasive methods of molecularly monitoring patients are exciting, mainly because they add another potential weapon to the arsenal. I think these tools will ultimately be the way we monitor patients in the future once we better flesh-out the most effective ways to utilize them.

What is equally interesting, however, is the recognition that important data can be generated from the blood during therapy as well. The ctDNA test provides a level of detail not available with imaging scans, such as quantitative data and specific information about how immunoglobulin receptors mutate over time. I think these tests may have additional applications far beyond a surveillance tool; future studies should explore these potential applications.

I personally believe that the peripheral blood is such a rich source of information, and that molecular monitoring methods will likely replace imaging scans for monitoring most patients after therapy. However, I think there is still a lot to learn, and this should be the focus of future research.

H&O Is there anything you would like to add or emphasize?

MR I would like to emphasize that molecular monitoring of DLBCL is a very new concept, and it was only recently appreciated that ctDNA could be assayed in a disease that did not have tumor cells in circulation. Thus, the data are very new and we do not yet have a nuanced appreciation of the use of this technology.

Suggested Readings

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