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When Will Circulating Tumor DNA Be Ready for Prime Time in Lymphoma?

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H&O What are the potential uses of circulating tumor DNA (ctDNA) in lymphoma?

MR The most impactful potential uses of ctDNA would be to improve outcomes and/or reduce toxicity. We have 2 big problems in lymphoma right now. The first problem is that our ability to measure the disease is imperfect. The only way to know whether lymphoma is gone is to know where it was before treatment began, and the best way to determine that in recent years has been through anatomic imaging with positron emission tomography plus computed tomography (PET/CT). These techniques allow us to detect lymphoma that cannot be felt on a physical examination. The fundamental limitation of these techniques is that no matter how much we improve imaging, it is unable to measure disease at the molecular level. A tumor must be approximately 1 cm across before it can be detected on PET/CT, and a 1-cm tumor represents approximately 1 billion cancer cells.

The second problem in lymphoma is that different patients have different types of tumors. Unlike PET/CT, which simply detects whether tumors are present, ctDNA can detect immunologic characteristics of the tumor, including genetic characteristics. Knowing these characteristics can give us insights into the best way to treat an individual patient. It is clear that blood tests that detect and quantify ctDNA are better than imaging, and that they can be used as a surrogate for tissue biopsy.

H&O What is the status of ctDNA in lymphoma?

MR We are already using ctDNA in clinical practice to measure molecular residual disease (MRD) status in certain subtypes of lymphoma.

When the treatment goal for a patient with aggressive lymphoma is cure, I conduct PET/CT after treatment. Even if the scan shows no evidence of disease, relapse will occur in approximately 15% to 20% of patients in that situation. However, if I conduct a ctDNA test confirming that the patient is in remission, the chance of progression goes down to approximately 1% to 2%. This is useful prognostic information because otherwise, we would need to wait for 5 years to see whether the patient's chance of a relapse is that low. Patients can live their life in a different way if they think they have a 1% to 2% chance of relapse rather than a 15% chance.

Another potential use of ctDNA, which will probably take approximately 5 years to establish, is to establish clinical utility. In other words, can we act on the information from ctDNA in a way that improves outcomes or reduces toxicity? The results may be able to help us choose a therapy, know how long to give treatment, and identify which patients' disease has been cured. Just knowing that a patient has high-risk features or has not had an adequate response may not be enough; we also want to know the best way to alter therapy. Right now, we are focused on improving the cure rate. An ongoing randomized

study called ALPHA3 is looking at whether the use of ctDNA can help us improve the cure rate; results should be available in the next 2 to 3 years (NCT06500273). If the results are positive, this study will serve as a proof of principle that will lead to an avalanche of more studies.

H&O Could you describe the ALPHA3 study?

MR ALPHA3 is an open-label phase 2 trial of patients with large B-cell lymphoma (LBCL) who have achieved a complete or partial response to standard first-line therapy but still have MRD detected by an investigational ctDNA-based assay. Approximately 250 patients will be randomized in a 1:1 ratio to consolidation treatment with the experimental allogeneic CD19 chimeric antigen receptor T-cell product cemacabtagene ansegedleucel or to standard-of-care observation.

> Circulating tumor DNA testing has the potential to completely replace imaging, which itself is very useful—which is to say just how high the bar is.

H&O What other studies of interest have been conducted?

MR Several important studies published online in the *Journal of Oncology* at the end of 2025 looked at the validity of ctDNA testing to provide prognostic information in lymphoma. In our study, we examined MRD by ctDNA in 137 patients with LBCL by monitoring 409 plasma specimens over time. We found that MRD status with ctDNA after frontline LBCL therapy was more prognostic than conventional radiographic response criteria.[1]

A study by Wang and colleagues of 136 patients with LBCL found that MRD positivity on ctDNA testing was strongly associated with inferior outcomes.[2]

Finally, DIRECT, the study by Krupka and colleagues of 155 patients with LBCL, found that MRD positivity on ctDNA testing at the end of first-line therapy provided a clinically meaningful assessment of response.[3]

The first 2 studies used the PhasED-Seq ctDNA test from Foresight Diagnostics, and the third study used an open-source ctDNA assay that was customized for lymphoma. All these studies showed the prognostic value of MRD by ctDNA in LBCL. Relapse occurred in most of the patients who had detectable disease at the end of therapy, which was not a big surprise, but MRD by ctDNA did a better job than PET/CT at identifying who was at risk for relapse.

What we do not have at this point is MRD eraser studies, meaning studies to determine whether treating patients with detectable MRD improves the cure rate. We have evidence that we can skip further treatment in patients with leukemia, myeloma, or even mantle cell lymphoma, but we lack that evidence for aggressive lymphoma. That is why the results of ALPHA3 are expected to be so important.

H&O What other potential uses of ctDNA measurement exist?

MR One alternative to using it at the end of first-line therapy would be to use it after just 2 cycles of therapy. A study is currently being developed to look at this approach. Tests of ctDNA are so simple to perform that we can order them frequently, and they provide up-to-date information because the level of cancerous DNA in the blood responds very quickly to changes in the tumors. If a patient has millions of cancerous fragments in the blood and the level does not drop sharply after treatment begins, that patient probably has relatively resistant tumor cells. This information might allow the physician to adjust treatment before it has been completed. We call this response-adapted treatment. If we intensify treatment, we may be able to improve outcomes, and if we shorten treatment, we should be able to reduce toxicity.

H&O What are the current technical limitations or challenges regarding ctDNA detection of lymphoma?

MR First, ctDNA is not part of our normal workflow. We have been doing PET/CT for 15 to 20 years, which means we know how to order the scans, read them, interpret them, and report them. The imaging units are also widely available. Introducing ctDNA means introducing a new paradigm. Now we need to get a blood test at the beginning of therapy so that we have a baseline value for comparison; then we need to have the sample tested at the Foresight Diagnostics laboratory in Aurora, Colorado, and wait as long as 10 days to get the results. That is not a practical approach, at least not in the care of aggressive lymphoma, in which we want to have the results in less than a week. Another practical issue is that drawing blood for ctDNA testing requires that a specific blood tube be used to stabilize the DNA and make sure it does not

become damaged. Any time we introduce a new process, it takes a little bit of time to implement it.

For now, it is up to individual doctors to decide whether they want to add this extra step. As soon as the data show that this approach is necessary to improve cure rates, however, we will see a much greater effort to implement it.

H&O In what situations are you currently using ctDNA testing?

MR I reserve the use of ctDNA testing for when I have some level of uncertainty and want to get additional information to help me make decisions. We are still unable to cure the disease of approximately 20% to 25% of patients with aggressive lymphomas, which is a lot of challenging cases. One question I dislike regarding ctDNA testing is, "Does this test change your management?" I think that is too reductionist because it is very uncommon to use one piece of information to make a major decision. Usually, we are using multiple pieces of information.

Because it is early days, I recognize that progression will not occur in everyone who has detectable MRD on ctDNA testing. Approximately 15% of patients still have detectable MRD after therapy, but at least in our data set, the disease of these patients has not yet progressed. Either it will never progress, or it will progress later. We do not necessarily need to act on a positive MRD test result at this point because of the potential risk of overtreatment, but we do know we need to monitor such patients more closely. A finding of undetectable MRD also can be very helpful.

H&O How does ctDNA testing differ among different lymphoma subtypes?

MR Hodgkin lymphoma is an example of a subtype in which ctDNA testing is going to be very important because, just as in large cell lymphoma, cancerous cells are not in the blood but we can find the DNA. In fact, the levels of ctDNA in patients with Hodgkin lymphoma are much higher than they are in patients who have non-Hodgkin lymphoma. So our approach to the use of ctDNA testing will be the same in Hodgkin lymphoma as in large cell lymphoma.

The paradigm will be a bit different in indolent non-Hodgkin lymphomas, in which the treatment is not designed to cure the disease. As a result, we are not convinced that we might need to intensify therapy; we may be able to just watch these patients.

H&O When do you envision that ctDNA testing will be ready for prime time in lymphoma, and for what specific purposes?

MR I think that we will see it being used more commonly in the next 2 to 3 years to improve outcomes and reduce toxicity, and that it will be in widespread use across all lymphomas in the next 5 to 10 years. It has the potential to completely replace imaging, which itself is very useful—which is to say just how high the bar is. Another potential use of ctDNA testing is as a surrogate endpoint to facilitate drug development. Efforts are ongoing to achieve this goal, as we have seen this approach be successful in other hematologic malignancies.

Disclosures

Dr Roschewski has no disclosures.

References

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