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Overcoming sAML Therapeutic and Clinical Challenges

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Jazz Pharmaceuticals. Here's your host, Dr. Charles Turck.

Dr. Turck
Welcome to *Project Oncology* on ReachMD, I'm Dr. Charles Turk, and joining me to examine the current therapeutic landscape and challenges in the management of secondary acute myeloid leukemia, or secondary AML for short, are Dr. Sanam Loghavi and Dr. Curtis Lachowiez. Dr. Loghavi is an Assistant Professor in the Department of Hematopathology in the Division of Pathology Lab Medicine at the University of Texas MD Anderson Cancer Center. Dr. Loghavi, thanks for being here today.

Dr. Loghavi:
Thank you very much for having me. It's a pleasure.

Dr. Turck:
And Dr. Curtis Lachowiez is an Assistant Professor of Medicine in the Division of Hematology and Medical Oncology at the Oregon Health and Science University. Dr. Lachowiez, glad to have you with us.

Dr. Lachowiez
Thanks for having me. It's great to be here.

Dr. Turck
Well, to get us started, Dr. Loghavi, would you talk about the clinical challenges associated with secondary AML as compared to de novo AML?

Dr. Loghavi
Of course. So putting my pathology hat on, I just want to make in the very beginning a distinction between because I think the term secondary AML is used for both patients that develop acute myeloid leukemia arising from a chronic condition like myelodysplastic syndrome or myelodysplastic neoplasm or other myeloproliferative neoplasms or more chronic myeloid conditions. But it's also used for patients that develop myeloid neoplasms post-chemotherapy for other solid tumors.

But I think what we're referring here to in this program is specifically secondary myeloid neoplasms that arise from chronic myeloid neoplasms. So just to clarify that, and of course, there are a lot of challenges that are associated with this because these patients are often older, they have other preexisting conditions, namely, they've been probably heavily treated for their preexisting chronic myeloid condition. And also usually the molecular or genetic landscape of secondary acute myeloid leukemias much more complex and it's associated with worse genetic features compared to de novo AML. So those are really predominantly the challenges that are associated with this disease.

Dr. Turck:
And with that information in mind, Dr. Lachowiez, what therapies are currently available for secondary AML?

Dr. Lachowiez:
So when we think about the treatment landscape for secondary AML, I think it's important to first think about patient fitness and whether or not the patient is fit enough, or a better term is to say that they do not have comorbidities that would preclude the use of intensive induction chemotherapy, so anthracycline and site therapy based chemotherapy. And if a patient is fit and able to receive induction

intensive induction therapy, then the preferred use in patients with secondary AML would be the combination of liposomal daunorubicin and cytarabine, which has been shown to improve survival compared to standard seven plus three-based intensive induction therapy in the randomized phase three setting. In patients that were older, patients over age 65, with secondary AML that were fit enough to receive intensive induction-based therapy, particularly the outcomes in this patient population were improved in the subset of patients that proceeded to allogeneic stem cell transplant, which is and remains a pivotal component of consolidation therapy for patients of any AML type that attain a remission as it is the only curative therapy that we have.

Dr. Turck
As a follow-up to that, Dr. Lachowiez, when it comes to using these therapies, what sorts of limitations or challenges do practitioners run into?

Dr. Lachowiez
Well, I think specifically within a patient population of individuals that have secondary AML as Dr. Loghavi pointed out, these patients are usually older to begin with. That's usually, we don't see as many secondary AML cases in a younger, more fit patient population. And so being older, many of these patients will have medical comorbidities that limit the use of intensive chemotherapy, as I just alluded to. But even more so and important for practitioners to remember is that a lot of these patients may have received months, if not years, worth of therapy directed at their preceding malignancy. So in the case of a patient may be with MDS, myelodysplastic syndrome, also known as myelodysplastic neoplasms or CMML, they may have received hypomethylating agent therapy before we see them for the main focus of secondary AML.

And so this limits us in some fashions; one, patients that have what we would now term treated secondary AML tend to have even more dismal prognosis or inferior outcomes and suboptimal responses to therapy compared to patients that have secondary AML from an antecedent hematologic disorder that has not received prior therapy. So maybe somebody had mild MDS that was monitored, and they received growth factor support. And then at some point in time during routine surveillance, as we typically do for these lower-risk patients, they've evolved into a higher-risk myeloid neoplasm or frank AML. Those patients tend to have a more robust response because they have not seen therapy. And in that setting, so if someone has received treatment and then they also on top of that are poised to have a suboptimal response or more likely to have a suboptimal response, they also are more likely to have prolonged cytopenia as the effect of our therapy because these are aggressive malignancies that have arisen from a marrow that already has a dysplastic process underneath it. And so the normal count recovery that we would expect to see following chemotherapy can be more delayed and more prolonged and with a deeper Nader. So their counts can stay lower longer than maybe a patient that has previously untreated secondary AML or de novo AML. And so these are very challenging cases to treat. And I think it's also important to recognize that allogeneic stem cell transplant is still the only curative therapy that we have for patients with acute myeloid leukemia of any subtype. And particularly in these patients. These are individuals that we want to obtain a remission quickly and then move them onto transplant as soon as possible.

Dr. Turck
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turk, and I'm speaking with Dr. Sanam Loghavi and Curtis Lachowiez about clinical challenges in the management of secondary acute myeloid leukemia.

Dr. Turck
Looking a little bit at other potential solutions to the challenges we just discussed, and sticking with you for a moment longer, Dr. Lachowiez, what novel therapies are on the horizon for this malignancy?

Dr. Lachowiez:
So I think patients with secondary AML have really benefited from the addition of venetoclax-based therapies. It may not be as novel as some of the other splicing modulators that are coming down the drug development pipeline. So Dr. Loghavi alluded to there are a handful of mutations that essentially have a molecular footprint that indicate a patient may have secondary AML, and some of these mutations are in genes that are involved in RNA splicing. And so there's a lot of active research being done with different targeted agents that impact splicing factors on a variety of levels. So I think that's where the future is going, and I think that's going to actually enable us to really individualize treatment for patient's AML based on their genetic signature. And I think not to derail the conversation too much, but just to throw in a plug that every newly diagnosed patient with AML should have comprehensive genomic profiling performed with cytogenetic and molecular analysis because it does inform prognosis.

And historically, that's been the main reason for doing it because we had limited options of therapies, but more so we really can tailor therapy based on mutational profiles now. And so that's particularly important to do. And so we have splicing modulators that are in the drug development pipeline. And then I think, as I mentioned before, venetoclax-based therapies, if I have a patient that has secondary AML type mutations in splicing factor genes or chromatin or cohesion complex pathways, I'm more excited about reaching for a ven-

based regimen in these patients because I think that it negates the negative prognosis associated with these mutations.

Dr. Turck:
Now turning to you, Dr. Loghavi, how else do you think these treatments might help address unmet needs when it comes to managing patients with secondary AML?

Dr. Loghavi:
I think that what Dr. Lachowiez touched upon is very important in terms of the molecular specifics of the disease. So I just want to highlight that before we touch upon the therapy a little bit more, is that secondary AML is a broad group of disease. There are ones that are associated with the splicing factor mutations. There are ones that are related to the expansion of a preexisting TP 53 mutated clone going, let's say from a TP 53 mutated MDS to a pure erythroid leukemia, and I think one of the challenges that we face as pathologists, traditionally, the way we monitor AML and patients with AML is really through three means. It's morphologic evaluation of their bone marrow to look for reduction in the blast count. It is molecular evaluation for measurable residual disease, and it's also flow cytometric evaluation for measurable residual disease.

The problem with patients with secondary AML is that oftentimes their preexisting MDS clone or the clone with the secondary type mutations actually exist throughout therapy unless they get a hematopoietic stem cell transplant. So our routine ways of measuring residual AML really does not translate into a perfect way of looking for residual AML clones the way we do it right now because we're really unable to tell the morphology of their bone marrow, even in remission oftentimes looks very abnormal. The molecular mutations persist throughout therapy and even by immunophenotype, they really almost never revert back to a completely normal phenotype. So surveillance is difficult and therefore tailoring therapy becomes difficult as well because venetoclax itself, like Dr. Lachowiez was saying, is a myelosuppressive therapy. So where do you draw the line between eliminating the leukemia clone versus recovering the patient's normal marrow or normal hematopoiesis? So I think that's one of the main challenges. But again, looking at it from a more optimistic view I think, again, as Dr. Lachowiez was alluding to, having molecularly tailored therapies is going to be the future for, hopefully, the future for this disease. Because if we can aim at eliminating the guilty clones and without really suppressing the marrow as much as more than necessary, I would say that is probably how we can bridge these patients to transplant, which is ultimately going to be the curative option for them.

Dr. Lachowiez:
But even to emphasize the importance of molecular characterization even more, it's something that should be repeated longitudinally throughout a patient's disease evolution. And so I would hate for someone to take away from this conversation that, well, somebody had their disease comprehensively evaluated at the time of their MDS or MPN diagnosis, and then not have it repeated at the time of evolution to secondary AML. And the reason that that's important is because we do see new mutations that are either required or expanded over the course of someone's disease evolution, so to speak. And this can identify new genes that we have targeted therapies for. So the first thing that comes to mind is patients that are notoriously difficult to treat and do not respond mainly to venetoclax-based therapies or patients with blast phase or accelerated phase myeloproliferative neoplasms. However, these patients do have a higher incidence of harboring IDH one or IDH two mutations at the time of progression. And we have clinically available FDA-approved IDH two inhibitors that are fortunately not particularly myelosuppressive that are active agents single agents who are in combination with hypomethylating agents who are in the clinical trial setting as triplet therapies with venetoclax as well. And so it really is important that we perform this comprehensive sequencing at defined time points throughout disease evolution.

Dr. Turck:
And with those helpful thoughts in mind, I want to thank my guests, Dr. Sanam Loghavi and Curtis Lachowiez, for joining me to share their insights on the therapeutic landscape for secondary acute myeloid leukemia. Dr. Loghavi, Dr. Lachowiez, it was great having you both on the program.

Dr. Loghavi:
Thank you very much for having us.

Dr. Lachowiez:
Yeah, thanks for having us.

Announcer:
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