Ask the AML Expert: What Do New Drugs Mean for My AML?

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Andrew Schorr:
And greetings for this Patient Power program, Ask the Expert program for those of you dealing with acute myeloid leukemia. I'm Andrew Schorr, down near San Diego, and I want to welcome you, and thanks to AbbVie for supporting this educational program, although, they have no editorial control, it's all what we say, and what our leading expert says. Now, I'd like to introduce him. Joining us from Denver, Colorado is Dr. Dan Pollyea. Dr. Pollyea is the head of the research for the Department of Leukemia. Am I right about that? Of leukemia research?

Dr. Pollyea:
Clinical Director of Leukemia Services, so I'm more on the clinical side, but yes, yes.

Andrew Schorr:
Okay, I want to get the title right. Thank you so much, and of course, he is a myeloid specialist. That means people dealing with myeloid conditions, and of course, acute myeloid leukemia, he often sees them, and has been dealing with research, as well. Dr. Pollyea, welcome. Let's just start with a couple questions for me, and I want to tell our audience, if you have a question, send it in to AML at patientpower.info. Many people have, and we'll be posing that to Dr. Pollyea.

And one other note before we begin, and that is, Dr. Pollyea is going to give you an overview and answer some questions, but he can't tell you and your doctor what to do, nor would that be appropriate on the Internet, right? So, from what you learn here, discuss it with a healthcare team that you trust, and see what's right for you.

Okay. Dr. Pollyea, I understand it's a whole new ball game in AML in the last year or two after many years where you didn't have, really, any new treatments, so am I right about that?

Dr. Pollyea:
Yeah, you're absolutely right, Andrew. I mean, it's just an incredible time right now for AML. We've had years and years of research that we've been building upon to get to this point where we've been able to understand enough about the biology of this disease so that we can have new and exciting therapies that really make an impact.

So, it's really this incredible time of a confluence between all the work that's been done on the research side for many years coming together with all the things we've been learning about and working with some of our pharmaceutical partners with new targeted therapies, and it's just everything's come together at the right time, it's very exciting.

Andrew Schorr:
Okay, but we're not done yet. And I know one of the questions we got in is, are there drugs in the pipeline where this evolution will continue?

Dr. Pollyea:
Well, absolutely, Andrew. So, I mean, I think we've had an explosion of drugs approved in AML. In the last two years, I think something like eight new drugs approved, only yesterday a drug that was recently approved was approved by the FDA for a new indication in AML. So, the pipeline is happening right now. I mean, that's the first message, but yes.

Even beyond the eight or so drugs that have been approved in the last two years, there are several that we think are on the launching pad, and then several more that are hopefully a little bit behind that. And then lots more that are several years out. So, it's really really an active pipeline between university academic leukemia doctors, community-based oncologists, and industry. So, a really nice partnership.

Andrew Schorr:
Okay, so for our viewers, family members, and patients, it sounds like if you're dealing with AML, it's crucial to have the right testing so that you and your doctor know of these different options, now, in ones that are investigational in clinical trials, what may line up with your personal situations, is that right?

Dr. Pollyea:
That's absolutely right. So, this disease is very complicated. And so different from person to person. So, AML is one disease, but everyone's case of AML is unique to them. It really is. So, for a long time, for many years, that was a barrier because of those that heterogeneity; the differences in the disease. But over time, we've become able to really identify some key features of individual disease, and everyone has a unique disease, but we're using sort of the same parts.

And so, we're able to identify commonalities between patient's diseases, and that has to be done at the time diagnosis. So, the only time—and here I'm really talking about gene mutation testing, almost every AML patient has at least one gene that is mutated that is responsible or contributing to their disease. And most patients have several. And we've developed mutation gene panels, you know, 50 different genes that we can test for, at the time diagnosis to determine what unique features a patient has.

Because if a person has a combination of three of the 50 genes, that's likely to be unique from another patient who has another three genes, and the prognosis, and even the treatment plans are gonna differ based on what constellation of gene mutations you have. The only time to get that information, is at the time of diagnosis. We also repeat it if people relapse, but really, the time to really understand a person's disease is that very first bone marrow biopsy. That's an important message we're trying to get out.

Andrew Schorr:
Okay, so some people may have gone to a community hospital because they were really sick and then suddenly, you're in a hospital, there may not be an AML program or a specialist there. So, let's acknowledge that people could be anywhere, not necessarily at the University of Colorado at your big medical center. So, what can patients and family members be asking so that this revolution in AML care can be brought to bear for them?

Dr. Pollyea:
Yeah, so that is a great point. And resources are not the same all over the country. I think all of us have a preference for patients at the time of diagnosis to be treated at a large academic medical center. I think there is some data that outcomes are probably better when that is a possibility. So, we often will take newly diagnosed patients as transfers to our center from all over the region. And sometimes that's appropriate.

And so, that's a question that could be asked if you're at a smaller community center, whether or not it would be appropriate to be transferred over to a larger regional center, if you're already inpatient. If you're outpatient and things are going at a pace at which it's not so much of an emergency, then seeking a second opinion at a large center where a lot of AML experience is had would be important.

Sometimes a person finds themselves, like you said, in a smaller regional hospital without much leukemia experience, and there really aren't options to go to a bigger place because there's limitations based on safety or maybe just insurance and things like that can be barriers. So, then you'd want to just nicely ask whether the treating physical, you know, if they don't have a lot of experience with this disease, which is understandable, it's a rare disease, only 30,000 new cases in the United States each year, whether they have a colleague at another institution who they feel comfortable talking to and sharing the case with, and getting some advice, or having a discussion about.

That's a very regular routine thing that most community-based oncologists are very amenable to. Most of them have that resource, that partner that they work with at a larger center. And so, just making sure that they're speaking to them in the early days of your diagnosis would be important.

Andrew Schorr:
Okay. Let's go on. So, first of all, if you have a question, folks, send it to AML at paitienpower.info. I have just a couple more because I've been around this for a long time and I'm a chronic leukemia patient myself. So, not everybody, but a lot of people who develop AML are older. And I had a cousin years ago, didn't live long with what was available then. Are treatments changing for older people in what you've said, and they're sort of—I don't want to say kinder, gentler, but maybe you're more frail when you're old, but even with this revolution can give older people, mom, dad, grandma, grandpa hope.

Dr. Pollyea:
You know, older people is really ground zero for AML. So, this standard of care for many years has been a newly diagnosed patient would receive intensive induction chemotherapy. Sometimes we call it the seven plus three regimen. People might—that might sound familiar to them. Now, that is the standard of care, but because like, you said, the average patient with AML is older, the standard of care can be very difficult to apply to older patients because older patients have a very difficult time with intensive chemotherapy.

So, for the last several years, decade at least, the population of AML that's really been the most intensely studies with respect to drug development and new clinical trials has been older patients, newly diagnosed, who can't tolerate intensive induction chemotherapy. And so, in fact, most of these advances that I've spoken about, the new drugs approved in the last two years, etcetera, most of them are specific to older newly diagnosed patients.

And so, yes, I would say the bulk of advances in drug development in the recent past have been for older AML patients because that's the bulk of who AML is. Yes, like you said, AML can happen in younger patients, but that's really rare. That's uncommon. This is mostly a disease of older patients.

Andrew Schorr:
Okay. One of the approaches has been, in blood cancers, generally, has been transplant, which is a big deal. Maybe not right for someone who's older. And so, now you have pills, as well. So, what kind of success are you seeing with these pills?

Dr. Pollyea:
Yeah, so a lot of these pills are dramatic. I mean, we have venetoclax (Venclexta) is the main one that comes to mind in terms of a newly diagnosed older AML patient, and just this past November, the FDA approved the use of venetoclax with a low intensity chemotherapy backbone treatment for this population, a newly diagnosed, older AML patient.

Prior to this, the standard of care had been using just low intensity chemotherapy treatments and the responses and the outcomes there have been quite disappointing. The response rates that we see with venetoclax, which is the pill that you mentioned in this setting are really really promising, unlike anything we've really seen. The duration of responses are very good. The patient's quality of life is quite good.

So, that's just one example. There are several other pills that play that are relevant here. Some are for patients in the relapse setting when they have particular gene mutations. We talked before that almost every patient has at least one if not several gene mutations. We've been able to target several of those gene mutations with pill therapies, and most of those have been approved in the relapse setting.

So, relapsed AML patients, usually older can now be candidates for these pill therapies that can work quite well and have a very tolerable side-effect profile for the most part if they carry a particular mutation; if their disease carries a particular mutation. So, that's a really promising new direction too.

Andrew Schorr:
We got a question, and people were asking, well, is there a venetoclax dose that is too low? So, how do you figure out the right dose so that it's effective and side effects are non-significant?

Dr. Pollyea:
Sure. Well, the FDA approval is for 400 milligrams of venetoclax. So, venetoclax comes in 100 milligram tablets, so four of those a day. There's scale up to get to that dose the first couple days of the first cycle we like to escalate up to 400 milligrams slowly for a variety of reasons. So, that is the standard accepted dose for venetoclax. There are some opportunities to reduce the dose of venetoclax depending on the situation.

Sometimes, if a patient needs to be on a certain class of medications that can interact with the venetoclax, we have to reduce the dose. Sometimes, if a person's blood counts are low and the treating physical believes that they are low because of the venetoclax, it may be appropriate to reduce the dose. But the standard dose of venetoclax after that initial scale up is four pills or 400 milligrams a day.

Andrew Schorr:
Now, we got a lot of questions, Dr. Pollyea about the effects of chemo in many people. We've talked about older people are often not strong enough to deal with it. So, are we moving away from chemo, or you mentioned even with venetoclax somebody might have a low dose of chemo, but people are concerned about the side effects, or whether they can withstand them?

Dr. Pollyea:
That is our greatest concern, as well. I think intensive chemotherapy regimens for older patients, I shudder at the thought of that. Even the healthiest older patients, when you expose them to these intensive chemotherapy regimens can have very poor outcomes. And I often will tell patients that depending on the situation, a person has upwards of a 20 percent chance of death from the treatment, not from their disease. We really, at our institution, I know others have varying degrees of thoughts on this, but at least at our institution, we really do our best to avoid that experience, for almost all older patients, to expose them to that intensive chemotherapy.

Now, in years past, there weren't many other viable options, and so you tolerated a great deal of risk because of the reality that there were few, if any, other treatment options. So, if you didn't expose your patient to this horrible intensive chemotherapy regimen, then they would die of their disease. So, you made that calculation. The landscape is really different now.

And so, we have two FDA approved therapies that are lower intensity for a newly diagnosed AML patient. One I already referred to is the venetoclax. A second is called glasdegib (Daurismo), that works a different way. And actually, as of yesterday, a third was—I alluded to this before, if you have an IDH1 mutation, and you're a newly diagnosed patient who's either older or can't tolerate intensive chemotherapy, then the FDA has said now that you can be prescribed an IDH5681 inhibitor, previously that drug has only be approved in the relapse setting, but now it's available in the untreated or newly diagnosed setting.

So, in the end, that's a long answer to the question, but the shorter answer is, yes, we need to get away from intensive chemotherapy, particularly for older patients. I would like if I could look at a crystal ball, I would like to see in five, seven, 10 years that the amount of intensive chemotherapy we're giving to any patient, younger or older is very limited, low. I would hope that that's the direction the field is going to.

Andrew Schorr:
What about transplant? Some people, particularly younger people may have had a transplant, or you have a discussion with them about it. Where does that fit in now?

Dr. Pollyea:
Right. So, a transplant is still today the only way that for almost all patients with AML that their disease can be cured. There are some caveats there. There are some patients who can't be cured with chemotherapy alone. That's unusually or uncommon. Most patients will need a transplant to be cured.

The landscape of transplant has changed dramatically. So, we're now successfully doing lower intensity transplant regimens in patients up to their late 70s really. And so, age is less of a factor in my opinion in transplant patients. And we're getting better and better at that. So, I believe that a transplant it still a reasonable consideration for a patient who may not be a candidate for intensive induction chemotherapy. So, it used to be that if you weren't a candidate for induction chemotherapy, then by extension, that would mean you couldn't get a transplant. I don't believe that's true anymore.

I think if you're an older patient who can get into a remission with a less intensive regimen, which now we are able to do quite frequently with some of these new weapons in the arsenal, if you can get into a remission, then I think a transplant is not unreasonable, even if you're doctor said, look, you're not a candidate for intensive chemotherapy. So, the pool for transplants in getting bigger and deeper. We're getting better and better at that. And so, I think that's a part of the conversation.

Personally, that's a discussion that I begin in people who could be eligible for a transplant on day one. The day they're diagnosed. That's part of the discussion that we start to have even that early on. Now, not everyone is a candidate. Some people are too old or too sick for a transplant. Some people hear about the risks of a transplant, and they say that's not for me. And that is a completely reasonable reaction or response to it.

And so, in those cases, the strategy is more, let's see what we can do to deepen and prolong your remission so that you can live as long as possible, we may not be able to cure your disease without a transplant, but we can still do a much better job now, I believe, than even a few short years ago.

Andrew Schorr:
So, Dr. Pollyea, whether it's younger patients, or a fitter older patient, everybody says, okay, if you can get me an effective treatment now, and get me into remission, how long is it going to last, or if I come out of remission, what do we do then? So, we're really talking about the uncertainty of this journey.

Dr. Pollyea:
Yeah. That's a big struggle for patients, families, and for us too. So, I think there's two questions there. You know, as far as how long could one expect a remission to last, the true answer is nobody knows. I mean, so anyone who tells a patient that your remission will last x months, or weeks, or whatever, that's an impossible thing that they are telling you. So, we have in our experience, statistics, large numbers of patients, we can come up with expectations, but we cannot apply any of that to an individual patient.

So, you have to be really careful…I know that's what everybody wants to know. That's the question everyone would want to know, but the truth is, nobody knows the answer to it, and you could push a person for an answer, and you might even get an answer, but that answer is not reliable. That would be akin to predicting the future, and of course, nobody can do that. What I would say is that the remission duration are very dependent on what treatment you're getting, and very dependent on the biology of a patient's disease.

So, those are the two things that really go in to trying to suss out what an expectation for a remission duration might be. But I will say that patients who I might predict would have a very brief duration of remission have been in remission in my experience for years. And the opposite is also true. I've had patients who relapsed very unexpectedly. The truth is is that this disease is still very poorly understood. As good as we are getting at understanding this disease, the truth is is that, it's difficult to make predictions in AML.

As far as what to do after a relapse, that is a huge challenge. Once this disease relapses from any therapy, be it chemotherapy, one of these novel new therapies, or transplants, it can be very difficult to get back under control. And historically, outcomes have been very poor in this situation. We do have no, like I alluded to before, there are some

targeted therapies, if your disease has a particular mutation that we can exploit with one of these pills, that would be a logical thing to do.

There are other chemotherapy regimens, probably drugs that the disease probably hasn't yet seen, if a person is still a candidate for an intensive induction chemotherapy type approach. We have a lot of tricks up our sleeve. We have a lot of things that we can do, but in general, that's a challenging situation.

Andrew Schorr:
Okay. But you referred to the pipeline earlier, which means there could be something in development, like in a clinical trial where you are, the University of Colorado, that could be part of the discussion, whether tomorrow's medicine could work for you today in a trial to try to get you a second remission.

Dr. Pollyea:
Absolutely. Clinical trials are—we have to continue to develop, design, and put patients on clinical trials if we are going to learn anything about this disease, and if we are to have any hope for the future. All of these exciting developments that have come to fruition just very recently are the result of clinical trials in patients who volunteered to participate in unknown situations, and doctors who are willing to go there with them. So, that's a really crucial part of all this.

And in fact, just to give you some semblance of how important this is, if you go to the National Comprehensive Cancer Network website, the NCCN, and you find the—they have treatment recommendations for every type of cancer, almost every situation for every type of cancer, and if you look up what's the number one recommendation for a relapsed AML patient, in some cases, even a newly diagnosed AML patient, but certainly for relapse, number one recommendation is to participate in a clinical trial.

So, that's an acknowledgement that this is not an area that we're currently very good at, but it's also indicative that we have hope, like you said, that some of these new therapies are going to be the future. And it's a gamble, it's an experiment that you're participating in, but we always hope that, like you said, that the patient is going to get a treatment right now, that if we could peer ahead five years into the future, that's how we're going to be treating everybody.

And that's what's happened in our experience running all these clinical trials the last couple years, we had the opportunity to be providing therapies of the future to people in the present. And that's why we do what we do. That's an exciting thing to do.

Andrew Schorr:
I bet, given the research that you've done, and people living longer, you get some hugs from people who didn't know whether they were originally gonna survive. And that must be very gratifying.

Dr. Pollyea:
It's an incredible privilege to be able to do this.

Andrew Schorr:
I wanna ask you about testing. You mentioned it earlier about how crucial it is, genomic testing at the beginning to find out what is your version of AML that you're dealing with, and then retesting along the way. So, I would imagine if somebody come out of remission, what are you dealing with then. But what tests are done, and I know in some fields of blood cancer, you do minimal residual disease testing, so what does a remission look like, and how do you know?

Dr. Pollyea:
Yeah. Okay, good. So, at the time of diagnosis, there are a couple of things that happened all of which pretty much have to happen off of that original bone marrow plasty. One, we have to get just some cells from the bone marrow that we can look at under a microscope and just look to see how many immature cells. That's number one, that's what we call morphology. That just means, what do the cells look like. Two, we do a fancy test called flow psychometry where we put the cells from the bone marrow through a special instrument, and it can tell us, and count for us how many really immature cells are there.

That is also a test to confirm is this acute myeloid leukemia; is this acute lymphoblastic leukemia, because those can look the same; is this another disease? So, that's a really important test, as well. Three, we look at the chromosomes. The chromosomes are the, sort of, houses of all of the genes, all the genetic material in each cell. Every cell in its nucleus has 23 chromosomes, two copies of 23 chromosomes, and we have learned over decades of working with AML about 50 percent of patients will have abnormalities in the chromosomes of their disease cell.

Sometimes there's a chromosome missing. Sometimes there's an extra copy of a chromosome. Sometimes two chromosomes have fused together. All of that is crucial information because what we've learned over the years is that some of those chromosomal abnormalities are associated with better than average outcomes; some of those chromosomes are associated with worse than average outcomes. So, that is a crucial piece of information.

The newest test that we do that is crucial, again, at the time diagnosis is genomic testing. Sometimes we call it next generation sequencing, or there's a couple different phrases for it. This is where we have the opportunity to look at about 50 different genes that may be mutated in a person's disease. And we need to know which 2, 3, 5, 10, whatever, genes each person has mutated in their disease because that is prognostic, it helps us understand how a person might do, how aggressive their disease may be, and it's also important for treatment decision making because now we have several treatments that are only applicable if you have a certain gene mutation associated with your disease.

So, that's all what we do at the time diagnosis, very important to get every single one of those tests. At the time of remission, so hopefully a person goes into a remission, that means when we look under the microscope, we don't see any leukemia cells, and it also technically means that the normal blood cells have recovered. The normal blood counts, not meaning transfusion. That's a remission. But what we know is if we peek a little bit deeper, under the surface, we might still see some residual disease.

And there are a couple different ways to look for residual disease. One is by looking for those chromosomal abnormalities, so that was an opportunity to compare, do we still see the chromosome abnormalities that we might have detected at the time diagnosis? The second is to look for evidence of gene mutations. Are they still present, and if they are, at what level?

So, those are what we call MRD, or minimal residual disease. Of course, it's in remission, bone marrow looks great under a microscope, cell counts have removed, they're not needing transfusion, they feel fine. But getting a sense of how deep the remission is and how much disease might still be present at a super low level is important because if it's still present, then that is a potential population that could relapse. And so, there's ways now that we might want to treat that residual disease population.

Or maybe that helps us make a decision. If you still have some residual disease, maybe you should go and get a transplant because that might be the only way that you can be cured. Alternatively, maybe you don't have any residual disease that we can detect at any level. Maybe we should just back off and watch you closely because maybe you've been cured. So, that's how the minimal residual disease helps us.

Andrew Schorr:
Okay. So, there's one other area, I wanna go just a few minutes longer if we could to discuss one other thing that a lot of people have asked about, and that is side effects. So, there's no free lunch in cancer care. These are very powerful medicine whether it's chemo which blast a lot or more targeted therapies, there's still side effects. So, for your patients who are undergoing care, I know it's going to vary by patient, but whether it's fatigue, constipation, low counts of this or that, let's talk about that, what you have for the side effect management.

Dr. Pollyea:
Yeah, so you're absolutely right. We have the potential for side effects with any of our therapies. And it goes the whole gamut from sever organ failure, toxicity, mostly with more intensive regimens to more nuisance type things, but those are quite dramatic on a day to day basis, like the fatigue that you mentioned, maybe nausea, constipation, et cetera.

We have gotten very good, the whole oncology community, I would say, at managing side effects. So, we have very good anti-nausea medicines; we have very good medicines to manage constipation or diarrhea. So, some of those, we can be very aggressive and typically are, such that we'll give anti-nausea medicine, et cetera, before we even give you a treatment, just

on the off chance you might have nausea or GI complications. So, being very aggressive with those types of side effects is really important.

Fatigue, unfortunately, is a nearly universal component of AML and related diseases, and many times, the treatments cause extra fatigue either directly or indirectly because maybe they make you more anemic. For some of those things, the best any only thing that we can do is just try to teach the underlying disease as effectively and quickly as possible because often that is the barrier to getting energy back. And that can be a difficult challenge.

Andrew Schorr:
Okay. We've talked about a lot; I would just want to sum up a few things for people. So, first of all, what I think you heard Dr. Pollyea say is, it's not just one disease, what is your personal AML situation, and the testing that he ticked off, it's so important, crucial is the word you used, and if you're in a community oncology center, can they consult with a specialist, like Dr. Pollyea; can you be transferred to a university hospital where they have a leukemia program, so that you for yourself, your loved one, get the care that's right.

Then it's a matter of what medicine lines up with that, based on the test results, and then managing side effects that we just spoke about, and then hopefully, you get into remission, and as we just talked about, minimal residual disease testing, how deep is that remission. And also considering a clinical trial, because so many of these medicines that we're talking about that are approved now, we have a lot of people to thank who are in those trials, but you might be a candidate for a trial, as well. Having been in two clinical trials myself for blood cancers, I believe I'm alive today because I was in a Phase II trial, which is a fairly early trial, so I hope you'll consider that.

Dr. Pollyea:
…wow, that's tremendous.

Andrew Schorr:
So, I hope you will consider that. So, Dr. Dan Pollyea, thank you so much for doing this program. We'll have you back, and thank you for your devotion. And I hope as you go to the exam rooms and up and down the hallways, and you meet patients that you've been treating successfully, you get a lot of hugs, okay?

Dr. Pollyea:
Definitely get a lot of hugs. Thank you, Andrew.

Andrew Schorr:
And for many years. Thanks for Dr. Pollyea from the University of Colorado, I want to thank our sponsor AbbVie for sponsoring this educational program, and I also want to remind you that there will be a replay coming soon, and then all kinds of video clips in future AML programs, and we want your questions, and we've been noting those along the way today.

So, be sure you're signed up with patientpower.info to get our AML e-alerts, tell others, tell your doctor, tell your nurse, and also, if you're dealing with side effects, speak up about it, right? Because you heard Dr. Pollyea say there is help. There are things they can do. Not in all cases, but in many. Hope you have a great weekend if you watched this live, and I'm Andrew Schorr down in sunny Southern California, I hope you have a great weekend. Remember, knowledge can be the best medicine of all.