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The Bloodline with Blood Cancer United Podcast

A podcast for patients and caregivers

Episode: 'Myelodysplastic Syndromes (MDS): Progress, Possibility, and What's Next'

Description:

You cannot have progress without research.

In our latest episode, Dr. Jay Yang of the Karmanos Cancer Institute in Detroit, MI, breaks down the essentials of MDS care, from risk-based treatment plans to managing fatigue and exploring promising new therapies. Tune in to find out why the future of MDS treatment is brighter than ever.

Transcript:

Elissa: Welcome to *The Bloodline* with Blood Cancer United. I'm Elissa.

Lizette: And I'm Lizette. Thank you so much for joining us on this episode.

Elissa: Today, we'll be speaking with Dr. Jay Yang, a professor at the Wayne State University School of Medicine and hematologist/oncologist at the Karmanos Cancer Institute in Detroit, Michigan. He currently serves as the Leader of the Hematologic Malignancy's Multidisciplinary Team, President of the medical staff, Chairperson of the Pharmacy & Therapeutics Committee, and Director of the Hematology course for

medical students. He specializes in the management of patients with leukemias and myelodysplastic syndromes or MDS, and his research interests are focused on finding better therapies for these conditions. Welcome Dr. Yang.

Jay Yang, MD: Good morning. Thank you for the invitation. Happy to be here.

Elissa: Thank you for being here with us. So, our episode today is on myelodysplastic syndromes, or MDS. Could you tell our listeners what that is?

Dr. Yang: Yeah, MDS is a bone marrow cancer. You can think of it as a cancer of the bone marrow stem cells. Technically, we would call them hematopoietic stem cells. And these are the cells that are responsible for making the blood cells that show up in our blood. And so, this is a cancer of those stem cells. And as a result, people who have MDS usually present with low blood counts. MDS is considered a cancer. It does carry an inherent risk of progressing to something called acute myeloid leukemia (AML).

Elissa: Okay. So, why is the syndromes plural? Are there multiple subtypes or diseases under the MDS umbrella?

Dr. Yang: Yeah, that's exactly right; and it kind of goes back to the 1970s when they first came up with this name of myelodysplastic syndromes. And I think they first used the word syndromes because, they just didn't have a very clear or precise understanding of what MDS actually was back in the day. There was some debate,

back then about whether it was truly, indeed, a cancer or not. Of course, we now know that we do consider this a cancer. That's become much more clear with time.

But the use of the word syndromes was a way to sort of be a general umbrella term. And, yes, it is plural because there are multiple different subtypes of MDS. Some of them are based on different type of genetic abnormalities that are found in the MDS cells. Some of them are based on the way the MDS cells look under the microscope. So, there are different subtypes. Some of them, for example, MDS with low blasts or MDS with increased blasts, or MDS with 5q deletion.

Elissa: Now, you mentioned those gene mutations. And when you also talked about it potentially turning into AML, does it have any of the same gene mutations as somebody with AML?

Dr. Yang: Yeah, AML and MDS are, I would say, similar diseases. But there are a lot of overlap between the two. And sometimes I think of it, or I try to explain it to patients like a spectrum. AML is similar to MDS, but it's much more aggressive; and you need to treat it much more aggressively and much more quickly.

But getting back to the gene mutations, yes, there is considerable overlap between the gene mutations and abnormalities that you will find in MDS and what you will find in AML. Having said that, they are distinct, and there are some gene mutations that are

much more commonly found in MDS. And there are other gene mutations that are much more commonly found in AML, but there's definitely an overlap there.

Lizette: Now, I know we've heard from patients that they're sometimes told that MDS is referred to as like a pre-leukemia or a pre-acute myeloid leukemia, AML. Is it still thought of as this way?

Dr. Yang: Yeah, I mean that's one way to think about it, I think. And MDS, many people actually referred it to as a pre-leukemia many years ago; and we don't necessarily use that term anymore. But as I mentioned, anybody with MDS, there is this inherent chance or predisposition for the MDS to eventually turn into acute myeloid leukemia. So, it wouldn't be wrong to consider it a pre-leukemia. This risk of progression to AML is something that we have to think about, we have to prepare for, we have to educate patients about. And part of our treatments is to try to prevent that from happening, if possible. Part of our treatment plan takes into account what exactly is the risk of AML in any one particular patient.

Lizette: I know that you mentioned that there is a distinction between MDS and AML, and not every MDS patient does it turn into AML, correct?

Dr. Yang: Correct, yeah. I suppose if someone lived with MDS long enough, it would probably eventually turn into AML. But the fact is that your risk of AML really depends

on the type of MDS that you have and what we call the risk classification in that particular patient.

But, in general, I think of MDS, especially in terms of the prognosis, as a big spectrum from one end to another end. And on one end, you have patients who we say have lower-risk MDS; and these patients may have mildly decreased blood counts. Hopefully, they're not very symptomatic; and these patients have a very low risk of turning into AML, at least in the short term, at least maybe in the first five years. Their risk of turning into AML may be less than 5 to 10%. And their overall survival is quite good and may be up to ten years or so.

On the other end of the spectrum, you have patients who have higher-risk MDS; and these are patients whose blood counts may be very, very low. It may not just be the hemoglobin; but it may also be the neutrophil count or the platelet count. These patients tend to have more blasts in their bone marrow, tend to have poorer cytogenetic features. But these patients, in a one- to two-year follow-up, they may have a risk of developing AML at something like 75 to 80%. So, it's very, very high. And because of their prognosis and their life expectancy is expected to be much shorter, particularly if we don't have good therapies for those patients.

Lizette: So, once somebody is diagnosed, you do have a conversation with them in regards to letting them know about their risk category then?

Dr. Yang: Yeah, I think in some respects, once you establish the diagnosis, explaining to somebody or defining what their risk stratification is, perhaps the most important thing that we do in the clinic. And we do spend a lot of time talking to our patients about this. Because the risk stratification, the risk classification really affects, number one, what your prognosis is. And I think that's very helpful for patients to know, to help them plan for the short term, as well as the long term. But it also helps us to decide what's the best therapy for any particular patient. So, it's really, really useful.

Elissa: So, let's get into the current treatments for MDS. You are using then that risk category to determine what the treatment is; and are the treatments different for the different risk levels?

Dr. Yang: Yeah, for sure. There's a couple of different things to keep in mind when we talk about different treatments for patients; but, broadly speaking, if we divide patients into lower risk versus higher risk, in the lower-risk population, their short-term prognosis is much better than the higher-risk patients. Again, these patients may not be very symptomatic. These patients may have low blood counts, and the severity of those low blood counts will matter in terms of what treatments we recommend.

The type of low blood counts also matters. Most patients with MDS will have low hemoglobin values, so they're anemic. But some patients will have a low white blood cell count and a low platelet count, and how we manage those patients takes all of that into consideration.

One thing to remember about the lower-risk patients is that, unfortunately, even though there are good treatments that are available for many of these patients, we don't have a treatment that is known to really affect the disease progression, meaning we don't have a therapy that's been shown to improve the survival for these patients. And their survival is felt to be good anyway.

So, what that means, first of all, is that for some of these patients, if they have low-risk disease and if they're asymptomatic and their blood counts are safe, and we don't think that they're very symptomatic from the low blood counts, then oftentimes we will not recommend any treatment whatsoever. And that's a great thing for patients. They don't need treatment. They don't have to come to the clinic as often. They don't have to worry about any potential side effects of treatment. So, that's one scenario.

And then there are a host of other therapies that are available for lower-risk patients, particularly if they are very anemic. And anemic to the point that they're symptomatic from their anemia. That could be excessively fatigued; a lot of shortness of breath, particularly when they move around, something that limits their ability to enjoy life.

In terms of cut-offs, once you start needing transfusions, then, we definitely need to start some sort of therapy. Or, if you're not at that transfusion level yet, but you're pretty symptomatic, then we will start treatments.

So, yeah, we've got several therapies that are available for these type of patients. This is the one area of MDS where we have seen a lot of improvement over the past five years or so. Some of the therapies that we use include something called erythropoietin-stimulating agents. These are drugs like Procrit®, or sometimes it's called Retacrit® or darbepoetin. There are other drugs such as luspatercept, which was approved, five or six years ago. And then a more recent drug called imetelstat, which was approved a couple years ago. And these are all therapies that we can use for our lower-risk MDS patients who have anemia. So, it's nice that we have some choices there.

The other thing to keep in mind is that sometimes our choices of treatment depend on the subtype of MDS. So, for those patients who have a particular subtype called MDS with deletion 5q, there is a particular drug that's very effective. It's called lenalidomide or Revlimid®. And then for patients who have an MDS with ring-sideroblasts or SF3B1 mutation, the luspatercept therapy is a good treatment for those patients. So, sometimes we can match particular therapies, targeted therapies for specific subtypes of MDS.

So, the higher risk, these are patients again, tend to have lower blood counts across the spectrum. They tend to have what's called higher blast counts in the bone marrow, and they tend to have more abnormal genetic findings. But these are patients who, their life expectancy is expected to be shorter, so it's a much more serious situation.

And so, we would love to provide a therapy that could improve their symptoms; number two, improve their blood counts; number three, improve their survival. And the main medical therapy that we have available is a class of drugs called hypomethylating agents; and for short, we often call that HMAs.

And now, there are three of these that are available. One is called azacitidine. The second is called decitabine, and the third one is called decitabine-cedazuridine, which we can also call INQOVI®. And these are all essentially kissing cousins. They're all sort of the same class of drugs. In my mind, they all work equally well.

They're each administered a little bit differently. The azacitidine is given subcutaneous or IV. The decitabine is IV. The INQOVI medication is given as a pill, so that's much more convenient for some of our patients. But, these class of drugs are standard of care for our higher-risk MDS patients. They have been shown to help patients to live longer. They are not a cure for MDS, but they can help patients to live longer, they can help patients to delay the progression to acute myeloid leukemia, and they can improve patients' blood counts as well. So, one of these three drugs would be considered standard for higher-risk patients.

Elissa: What about stem cell transplant? Are any patients getting a stem cell transplant?

Dr. Yang: Yeah, exactly. So, that's very, very important to talk about; and that is always mentioned in one way, shape, or form, whether we recommend it or not for all of our patients when we see them. And that's because a stem cell transplant is a potential cure for MDS, and it is the only potential cure for MDS. So, it's important to consider. As I said, MDS is a cancer of your bone marrow stem cells; and so, the idea with doing a stem cell transplant is trying to replace a patient's cancerous or abnormal stem cells with somebody else's, a donor's healthy stem cells.

And so, it is something we have to consider. Of course, a stem cell transplant has inherent risks. There can be serious complications from a transplant, and patients can actually die from these complications itself. So, that's the risk, but the reward is that it can be a potential cure. Not necessarily for all patients with MDS; but, if we get somebody to a transplant, then, we typically quote like a 40 to 50% cure rate with MDS. So, that's certainly better than the alternatives for some of our patients.

Elissa: Okay.

Dr. Yang: Whether we recommend the transplant depends on a lot of different factors, of course. They need to have good social support and family support. We need to find a good donor for them. But really, the important thing is, is it really worth the risk for an MDS patient-

Elissa: Right.

Dr. Yang: -at any particular time? And so, if patients have lower-risk disease, their survival is going to be fairly good. So, we don't recommend the transplant in those patients because we're likely to actually make their life shorter by doing a transplant. But in our higher-risk patients, where their natural survival is expected to be shorter, those are the patients where we usually or seriously recommend a transplant because we can improve how long they live and hopefully result in a cure, as well. However, we also have to remember that a lot of our patients with MDS are older.

Elissa: Yes.

Dr. Yang: And, the average age for an MDS patient at the time of diagnosis is 70. And many of these patients, particularly if they're over 70 to 75 or if they have other medical problems, will not be considered candidates for transplantation. So, all of those things have to be considered.

To summarize, the lower-risk patients, we will probably say that transplant does not really benefit you; but that is something that we will readdress down the road if and when the disease progresses to something more higher risk. And then for the higher-risk patients, if we think that they may be a transplant candidate, that is something that we discuss seriously from the get-go.

Lizette: Now, I know that many patients have heard about newer treatments like CAR T-cell therapy and bispecifics. Are those used for MDS?

Dr. Yang: Yeah, I wish. Those fall in a class of therapies that broadly fall into the immunotherapy class of drugs; and immunotherapies have been broadly excellent novel therapies for people with many different types of cancers.

In the world of blood cancers, yeah, CAR T and bispecifics are excellent therapies for some of these patients, particularly with patients who have B-cell lymphomas and for patients who have multiple myeloma. For those diagnoses, these therapies have really revolutionized how we treat those patients and the prognosis for those patients.

Unfortunately, neither of those therapies are something that we can use right now in patients who have MDS or AML. It's been a lot more difficult to take that type of treatment and technology and apply it for patients with MDS. It's not like it hasn't been tried. There have been several products, several clinical trials using bispecific therapies and CAR T for patients with MDS. But right now, they have not been effective enough for it to be approved or for it to be routinely available for MDS patients. I think there's still a lot of hope that different types of immunotherapies, including CAR T or bispecifics, can still somehow be effective for patients with MDS; but we still have a lot of work in the research community to get there.

Elissa: Yeah. So, you've now mentioned several different treatments for MDS. What side effects may patients have from these treatments, and are they manageable?

Dr. Yang: Yeah. I mean broadly speaking, they are manageable. I think, again, going back to the lower-risk patients, when we're giving therapies to improve their anemia, for example, the good thing about these therapies are that they tend not to have a lot of side effects, which is great for our patients.

Elissa: Yeah.

Dr. Yang: So, the erythropoietin-stimulating agents, like darbepoetin or Procrit, very few, if any, side effects, to be honest with you, which is nice. Luspatercept can have some side effects, but there's not a specific side effect profile that is very common, actually. Some patients may have a little fatigue. Some patients, some side effects here and there have been seen. But by and large, it's well-tolerated by our patients. And then the other drug that I mentioned, imetelstat, it can lower your blood counts after you give them treatment. And so, we have to watch out for that and monitor that. But overall, at least in my experience, it's pretty well tolerated.

So, again, the lower-risk patients, the treatments tend to be very well-tolerated. Now when you get to the higher-risk patients, and we're talking about the use of hypomethylating agents, I would say still tolerated by our patients. The good thing about these drugs is that doesn't cause any specific organ toxicity. It's not inherently damaging to kidneys or lungs or heart or brain or anything like that. So, that's great. Can cause some nausea, which can usually be very well-controlled with nausea medications. Some patients have some diarrhea too which we can usually manage.

And then fatigue is something that can be seen. It tends to be mild. It tends to be manageable.

The main side effect with the HMAs that we do have to worry about is that they will lower your blood counts, and you have to be prepared for that. So, you're talking about patients who already have low blood counts; and then you start them on a HMA therapy. And often or typically for the first two to three weeks after you administer the chemotherapy, the blood counts will decrease. And then they tend to recover, after three or four weeks. So, you have this sort of roller coaster effect; and you have to manage that, and you have to treat through that. Sometimes, patients will require more transfusions immediately after starting therapy. In the end, we're hoping that the therapy improves their blood counts so that they may not need transfusions. That is the hope.

And then the other risk that we worry about when we lower these blood counts, particularly the white blood cell count and the neutrophil count, is that it will put them at an increased risk of infections. And so, if you have a very low white blood cell or neutrophil count, then you've lost one of your host defense mechanisms against bacterial infections. And so, sometimes these infections can be serious. Sometimes it can result in sepsis. It can even be life-threatening. So, we have to warn patients that if there's any sign of an infection or if they develop any fevers, particularly if they're neutropenic, then, we have to act on that immediately. I will often tell those patients

to go directly to the Emergency Room for an immediate evaluation and sometimes a hospitalization.

Elissa: Now, what about with a stem cell transplant? Could you talk about the side effects with that?

Dr. Yang: Yes, a stem cell transplant is a big deal. It's a big deal because it's a potential cure. But it's a big deal because it can have a host of different side effects.

I guess the first side effect to realize is that you're going to have to be hospitalized for approximately a month with the transplant. And that's, sometimes, difficult for patients to handle. You're getting a large dose of chemotherapy right before your transplant. That will knock down your blood counts to very low levels. So, again, risks of infections, potential life-threatening type of infections. They tend to have nausea. They tend to have mucositis, which is sores in the mouth. And then after a couple weeks after the transplant, then their blood counts start getting better, and some of those side effects get better. But the risk of infection is real.

And then the other risk that we worry about is something called graft-versus-host disease. And one of the reasons why we do a transplant is not only to replace those abnormal stem cells with healthy stem cells, but we're also replacing the patient with a whole new immune system. And that whole new immune system that comes with those stem cells is important because that donor immune system finds the patient's

MDS as foreign and attacks it. So, helps to keep in remission but can also find the patient's organs, different organs as foreign as well and can sort of attack those organs.

So, people can have like skin toxicities like rashes. It can affect the liver. It can affect the lungs. And it could affect the GI system, so, it can cause diarrhea and nausea. So, there are a lot of potential side effects from transplant. They can be very serious. There are medications that will be given to patients to try to prevent graft-versus-host disease. They are usually pretty effective, but they're not 100% effective. And then there are also different, transplantation techniques that can be done to lower the risk of graft-versus-host disease.

Overall, the risk of serious graft-versus-host disease has declined through the years, which is great. But it can still affect patients in a serious way.

Lizette: And I know that top of mind, I know from a lot of the MDS patients that I've spoken to, as well as the ones that are on our MDS online chats: fatigue. Do you have any practical tips of how we can manage fatigue for patients?

Dr. Yang: Yeah, that I would say consistently, that's the most common symptom that our patients have. And I would say that it's multifactorial, meaning that there are a lot of different reasons to have fatigue in an MDS patient.

Usually, the most important thing that we look at is the hemoglobin level. So, if we think that they're very fatigued due to their low hemoglobin, that could be a very good reason to start treatment for our MDS patients. And hopefully with treatment, if we improve the hemoglobin, then that will improve. Also, transfusions. If our treatments are not effective but patients are still very anemic, then transfusions can be helpful improving their fatigue.

The cutoffs for transfusion, we take it sort of individually from person to person. But oftentimes, we'll try to keep the hemoglobin greater than 8 or so.

But the problem with transfusions is that it's not a permanent fix. Transfusions may help patients immediately after the transfusion. Sometimes, it may help patients with their symptoms, one or two weeks or three weeks after the transfusion. But then if you don't have a good treatment for the MDS, then the hemoglobin comes back down again; and they may become symptomatic again. But, I guess a judicious use of blood transfusions can be helpful for patients.

Besides that, we encourage patients to try to stay as active as possible. Performance status and muscle mass is sort of a, you know, use it or lose it phenomenon. So, we like patients to be active. They have to listen to their bodies because if they're very anemic, then it actually may be dangerous to be too strenuous with your exercise activity. But to try to stay active is important, to maintain your nutrition. Probably the

most common question that I get is, "What can I do or what can I eat to help improve my blood counts or help me to improve the MDS or help me to feel better?"

And usually, unless you're deficient in any specific type of vitamin, there's not a specific diet that we can really recommend or shown to be proven to help patients with MDS. But, we ask patients to eat healthfully, as you might expect, and to make sure you get your basic food groups in.

Lizette: Thanks, yeah. And I know that we'd really love to hear about the future of MDS treatments. Are there any emerging therapies or those on the horizon that you're particularly excited about?

Dr. Yang: Yeah, that's a good question. I would say that compared to some other types of cancers like we talked about, like B-cell lymphomas or multiple myeloma, for example, there hasn't been as much progress in MDS as what we would like to have seen. But that doesn't mean that progress and breakthroughs aren't around the corner, but they very well could be.

So, there's a lot of research that's going on. There's a lot of different clinical trials that are ongoing. It's a little bit difficult right now to point to one particular area that we think is going to be the breakthrough. I don't think we know what the next breakthrough is going to be, but it's going to happen. And so, what that means is that we need to look at all these different avenues to try to find the next big thing.

Immunotherapy, we talked about a little bit. There's still a lot of interest in trying to develop immunotherapies for MDS. Targeted drugs targeting certain proteins and certain gene mutations are another avenue. For example, some patients with MDS may have something called an IDH1 or IDH2 mutations. We have drugs that can target these mutations, and there's still more research going on to how to optimize for that type of targeted therapy.

There is a lot of thought that inflammation is a unique part of MDS, meaning inflammation can lead to the development and progression of MDS. And inflammation can cause your blood counts to be lower. So, there's work in trying to come up with anti-inflammatory type of therapies to try to improve the prognosis of MDS and to try to improve blood counts.

There are a class of drugs called protein degraders that are of interest in actually all types of cancers nowadays. It's one of the next big things in cancer medicine. There are protein degraders targeting MDS proteins as well that are under investigation.

TP53 mutation is aa mutation that's found in about 10 to 20% of patients with MDS; and it is typically associated with a disease that's very resistant to therapy. But there's always interest in finding targeted therapy specifically targeting TP53. And so, there's research ongoing there.

So, there's a lot going on; and we just never know when the next one is going to work. It has been a little bit discouraging in terms of research for MDS because it's been a while since we had a new therapy, especially for higher-risk MDS. But I would also draw encouragement from other cancers that have had the same issue, that haven't had a breakthrough in a long time. But then they're seeing breakthroughs.

For example, there was a drug for pancreatic cancer that recently showed incredible activity, unseen activity up to this time. And that was a cancer and a protein called KRAS that was previously felt to be quote/unquote "undruggable," impossible to target that protein. But they found a way. And so, these things will happen in MDS. We just have to keep trying. We have to encourage patients to participate in clinical trials if they're available and if they're suitable for a particular patient and at a particular time.

We have to encourage increased and continued funding for research because that, of course, has been an issue recently. So, all of these things are critically important.

Elissa: Yes. And I do want to point out that if patients are looking for clinical trials at any point after diagnosis, they can contact our Clinical Trial Support Center and be connected with trials around the country. So, we love having patients look into clinical trials at any point because it is important to have that participation there. That's how we get the new drugs. And, so I'm glad that you mentioned that.

I do have a question. We've seen a lot through the blood cancer space about more and more combinations of different drugs. Is that something that's also happening in the MDS space?

Dr. Yang: Yeah, absolutely, absolutely. Combinations are important because, unfortunately, these cancer cells are very smart. So, if you treat them with one drug, they will eventually become resistant to that drug. They will find a way to become resistant. The other point is for example, the HMA therapy that we talked about as the standard for higher-risk patients, not everybody responds to HMA therapy.

Elissa: Yeah.

Dr. Yang: Maybe 30 to 50% of patients will have what we consider a reasonable response. So, combinations are a way of, number one, trying to improve the response rates, so that more patients can benefit from these therapies and, also, benefit longer so that we can prevent resistance to these therapies.

In the higher-risk setting, there has been a lot of interest in adding another drug to the HMA backbone, if you will, to try to improve the response rates and the duration of response for our higher-risk MDS patients; and that work is still ongoing. So, a lot of trials are designed like that. Take an HMA and add an investigational drug because we know that HMA can be effective; and we're just trying to improve the efficacy with adding investigational drugs.

And then even in the lower-risk space, there are combinations being explored. Like, can you combine ESAs with luspatercept, for example, or combine ESAs with imetelstat? So, there are different combinations that are being explored there as well. Combinations are a major theme in research in general and including research for MDS.

Elissa: Very good to know. So, our final question today, on our patient podcast home page, we have a quote that says, "After diagnosis comes hope." What would you say to patients and caregivers to give them hope after a diagnosis of MDS?

Dr. Yang: Yeah, so, it's important to have hope, you know, hope for the best. But, prepare sometimes for the worst. I think that's something to think about. Again, going back to the risk stratification, you kind of have to know where you are on that spectrum. That helps prepare you. But in any situation, there are patients that always do much, much, much better than expected.

And so, I have patients for example, the worst case of TP53-mutated MDS that your expectations long term are not very good for those patients. But we treated them on a clinical trial. That drug never got approved, but somehow it was effective for this particular patient. Then they had a transplant, and they're still alive five years later; and that's not something that you can really expect. But that's something you can hope for. So, I think that's one thing.

And then the second thing is that research. With research, as time goes on, there's always progress. You cannot have progress without research. You cannot have progress without clinical trials. But we would expect better and better treatments that come with time, and so I think that provides a real hope for myself and hopefully for our patients as well.

Elissa: Absolutely. Well, thank you so much, Dr. Yang, for joining us today and telling us all about MDS, the current and emerging therapies. It is all very exciting, and we do hope that the research is continuing on and you never know when that great new drug will come about and work really well for a particular patient. That is very, very exciting; and so, again, thank you for joining us today.

Dr. Yang: Thank you.

Elissa: And thank you to everyone listening today. *The Bloodline with Blood Cancer United* is one part of our mission to improve the quality of lives of patients and their families.

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