Treatment Selection in a Patient with Decompensated Cirrhosis

CMEO Podcast Transcript

Nancy Reau:

Hello, and welcome. On behalf of CME Outfitters. Thank you for joining us for today's CMEO BriefCase titled "Treatment Selection in a Patient with Decompensated Cirrhosis." Today's program is supported by an educational grant from Gilead Sciences. I'm Dr. Nancy Reau, Professor of Medicine at Rush University Medical Center in Chicago, Illinois. I'll be the moderator for today's BriefCase.

Paul Kwo:

Hi, and I'm Dr. Paul Kwo from Stanford University, and I'm pleased to be joining Dr. Reau today.

Nancy Reau:

Paul, I think you're going to be presenting our case today. I'm really excited about this interaction. This is a great case. The goal of this educational activity is to empower clinicians to integrate routine surveillance for liver cancer or hepatocellular carcinoma into clinical follow-up for patients with hepatitis C. Let's get started with our patient case.

Paul Kwo:

Hi Jonathan. My name is Dr. Kwo. It's nice to meet you. How are you doing?

Jonathan:

Hi, Dr. Kwo. So, I found out I have hepatitis C virus (HCV) last month and they say I have masses in my liver. I'm really scared. I had pain when I went to the emergency room (ER). It was really bad, but the pills they gave me are helping.

Paul Kwo:

That's really unfortunate. I'm sorry to hear this. Tell me a little bit about the pain that you had. How bad was it on a scale of 1 to 10?

Jonathan:

It was really bad. Like 9, almost 10. But it's better now and I can breathe better.

Paul Kwo:

Jonathan, I completely understand that, and that's the medicines working. I know you're concerned, but we're going to help you. I'm looking at your labs and imaging reports and I understand that you're worried.

Jonathan:

Yeah, I am worried. I've been sober for 20 years now, but I wish I could “drink away” how worried I am about this right now. I never want to have that kind of pain or bloating again.

Paul Kwo:

Can you tell me how you've been feeling lately, since you started the medicines? And what do you think caused this?

Jonathan:

Well, I was having trouble breathing for the last month and my stomach was sticking out so much. But that part has gone away now. What did I do? Well, I haven't done anything since 2000. I've been dry for over 20 years. I haven't touched drugs since I graduated from high school. I injected some drugs, doc.

Paul Kwo:

Jonathan, your story is not different than many other people who come to this clinic. I'm going to do some additional blood work on you. I'm going to order a different type of imaging study for your liver. But based on these findings, we should be able to create a plan that's going to help you and get you feeling better.

Jonathan:

Thank you, sir. Thank you so much.

Nancy Reau:

So, Jonathan was diagnosed with chronic hepatitis C infection after presenting to the emergency department (ED) with severe abdominal pain, protrusion and bloating. What symptomatic indicator of advanced hepatitis C infection was he likely experiencing?

Paul Kwo:

So, let's talk about Jonathan. He's a 68-year-old gentleman who had developed epigastric pain. He had not been engaged much in care and went to his local emergency department for this. When he presented, he was found to have significant ascites. They did a variety of serologies and he turned out to have an anti HCV antibody that ultimately turned out to reflect chronic hepatitis C.

When we look at his social history, there was a remote history of injection drug use in the 1970s.

There's also a remote history of alcohol use disorder, though he's been sober for two decades. On his exam when we saw him, he had some hepatomegaly and a palpable spleen, but because he had been initiated on diuretics, there wasn't really much in the way of obvious ascites.

His mental status was also unremarkable. He didn't have asterixis. He did in the emergency department, as part of the evaluation, have an ultrasound and they detected a 3-centimeter mass in the right lobe of the liver. When I reviewed his laboratory testing, it showed that he had elevated liver tests and that his albumin was a bit down at three grams per deciliter.

Moreover, there was some evidence of portal hypertension. His platelet count was 90,000 and also some evidence of synthetic dysfunction with an elevated international normalized ratio (INR) of 1.5. There was also serologies done for hepatitis B as well. And his surface antigen core antibody and surface antibody were all unremarkable or negative. And alpha-fetoprotein, a tumor marker was elevated, and his creatinine was marginally elevated at 1.4 with a sodium of 132.

Nancy Reau:

All right. Paul, there's a strong association between hepatitis C and liver cancer, as well as decompensated liver disease. Can you tell me a little bit about why this is an interaction? Is it because of the injection drug use or is it maybe comorbid conditions that our patients with hepatitis C have?

Paul Kwo:

Indeed, hepatitis C still, in the United States, causes the most liver cancer. Worldwide it's hepatitis B and non-alcoholic fatty liver disease related hepatocellular carcinoma is clearly rising. But, hepatitis C is still the dominant cause of liver cancer in the US. And what are the reasons for this? Well, hepatitis C infection in the liver causes ongoing necro-inflammatory activity that leads to impaired DNA repair mechanisms. There's increased oxidative stress. All of these inflammatory cascades result in a progressive fibrosis activation of our stellate cells, proliferation of hepatocytes in response to the injury, and it's this chronic ongoing inflammatory process that leads to precancerous changes and ultimately hepatocellular carcinoma. As I said globally, 20%-30% of hepatitis C infections over 10-30 years are going to progress to cirrhosis; and once you develop cirrhosis, each year annually, the risk of hepatocellular carcinoma is anywhere from 1%-4%. This is largely influenced by a variety of other co-factors in addition to having the chronic hepatitis C.

In addition, once you develop cirrhosis, there is a very well-established literature out there that shows that the rate of decompensation as happened in Jonathan, our patient here, this risk each year is anywhere from 2%-5%, with the most common presenting symptom being ascites, just as it was in Jonathan. What are some of these factors that are associated with accelerated hepatitis C progression that allow higher rates of decompensation and maybe a greater risk of hepatocellular carcinoma?

Unfortunately, the COVID pandemic has worsened some of these. We know that concomitant alcohol use, and obesity are clearly co-factors which can alter and accelerate the natural history. But there are many other factors as well, including other viruses (such as HIV or hepatitis B), in addition to alcohol and tobacco use. We talked about metabolic syndrome; age, the older age at which you're infected, you have a more accelerated course; male gender; and very interestingly genotype 3 is also the one virus which seems to have, for a variety of reasons, an accelerated natural history towards developing decompensation or hepatocellular cancer.

When we look at some of the real-world outcomes of hepatitis C progression, this too has been well studied. In this large study, there was almost 2,800 patients who had a qualifying liver biopsy. What you can see here is that over a 5-year period, the cumulative instance of hepatocellular carcinoma was above 30%, about 35%, and there was a comparable rate of decompensated cirrhosis, and those who had baseline liver biopsies of F4 fibrosis or cirrhotic stage disease.

Now, if you have F3 fibrosis, which is the next step prior to cirrhosis, you can see here in the turquoise color, that there are still risks of progression. Some of these people probably did have early cirrhosis to start with, but you can see here that there is still this linear progression of both hepatocellular carcinoma development, as well as decompensated cirrhosis. And again, this reflects the importance of finding these individuals, such as our patient Jonathan, in order to provide effective therapy where we can alter this natural history.

Nancy Reau:

So, Paul, this is really reassuring because I think that, especially in liver clinic, which is arguably not the real world, we see a lot of liver cancer. So, these rates really suggest that if you identify and cure a person at an earlier stage, their risk of progression and risk of liver cancer is much lower. We don't do many liver biopsies anymore, so I think it's important to emphasize that liver biopsy is not necessarily part of the standard care cascade. Would you say that this translates as well to those noninvasive technologies that we're using more now?

Paul Kwo:

So, even liver biopsy isn't perfect. Our noninvasive tests which is, as you said, is what we rely on, a FibroScan shows a very high level of liver stiffness then I think we can confidently say they have cirrhosis. It's certainly true that in the gray zones between F3and F4, that it sometimes is more problematic to distinguish who has cirrhosis and who has F3 fibrosis. We tend to lump these individuals into those who have advanced fibrosis. What we do is we rely on other features of the presentation to help guide us. So, for instance, if you have somebody who has a noninvasive test, or F4 says, "Well, this may not be quite cirrhosis, but the platelet count is 120,000. The liver is nodular." Well, that is somebody who has cirrhosis. My own approach in these particular cases is that, because we're not relying on liver biopsy as much, that I make sure all the noninvasive tests are pointing in a similar direction before I confidently tell individuals that the noninvasive testing has accurately staged them.

Nancy Reau:

So, let's poll the audience again. How often should patients with hepatic cirrhosis of any stage receive liver cancer screening? So Paul, we did not identify Jonathan's hepatitis C at an ideal time point, right? He presented with decompensation in the emergency room with ascites and was found to have liver cancer, all of which are likely avoidable. What would you tell individuals? What are our current screening recommendations and why did we miss Jonathan?

Paul Kwo:

The screening for hepatitis C has evolved over time. We used to screen based on risk factors or risk- based screening. And for a while, it was those who had a history of injection drug use. And again, if one is not engaged in care, or if one does not have a physician who takes a sufficient history, an anti HCV antibody may not be ordered.

We now have evolved though, and the US Preventive Services Taskforce has now recommended above the age of 18 the universal anti HCV antibody screening for hepatitis C. Nowadays, if Jonathan presents to a primary care physician, this is somebody who should be screened for hepatitis C and ideally it should have been caught much earlier, prior to him having to present, as you well know, with a decompensation episode. Somebody who has been then subsequently diagnosed with hepatitis C, it's very important to assess their level of fibrosis and make sure that they have compensated liver disease, because these are the criteria that will help inform our treatment strategies, as well as whether or not we need to monitor these individuals for other complications. This means further decompensation if you have cirrhosis; this means development of hepatocellular carcinoma.

And again, when you diagnose somebody with hepatitis C, it's important that you sit down and discuss other factors that could accelerate fibrosis, and make sure that these individuals, in addition to treating the hepatitis C, Nancy, also adopt a lifestyle of good liver health. This could include things such as screening for hepatitis B and HIV, which all patients with hepatitis C would be screened for, but it also means counseling about alcohol use, as well as reducing any metabolic-syndrome- type risk factors.

Once you identify advanced fibrosis or cirrhosis of any etiology, these individuals are typically screened every six months with an ultrasound. They need to also be routinely assessed for longitudinal changes in their hepatic function, looking for some evidence of decompensation while you address the hepatitis C and treat it. With regard to the hepatocellular carcinoma surveillance methods, what we typically use is an ultrasound, and this is recommended by all societies across the world. This is typically done in most areas of the country, an ultrasound every six months, in parts of Asia, a bit more intensive and high-risk individuals. An ultrasound has quite reasonable specificity but lacks early-stage sensitivity for hepatocellular carcinoma. We can add alpha-fetoprotein, but adding alpha-fetoprotein certainly improves early-stage sensitivity, but reduces the specificity. And particularly it's interesting with hepatitis C because hepatitis C, for whatever reason, in the untreated group does seem to sometimes have pretty impressive alpha-fetoprotein levels. And I know, Nancy, you remember the era of transplant, where a very high alpha-fetoprotein (AFP) could actually get you priority points for liver transplantation. We learned later on that that was not actually a prudent policy, but that took some time. In addition, when making sure that your individuals are enrolled in surveillance programs, if you do find a nodule less than 1centimeter, these are individuals that you should be bringing back seriously every 3 months. Or you should be referring to Dr. Reau or some other of your hepatology colleagues to make sure that they follow these individuals to make sure these nodules are completely and accurately characterized.

The good news is, is that the majority of these small nodules do not turn out to be cancer. But nonetheless, they all, in the setting of advanced liver disease, need to be followed. Again, if a nodule is greater than a centimeter, then we actually have very good diagnostic criteria, both using a multiphasic computed tomography (CT) scan with arterial portal venous phase and delayed images or magnetic resonance imaging (MRI)

as well. And liver cancer or hepatocellular carcinoma happens to be one of the few malignancies that does not require a liver biopsy for diagnosis.

Nancy Reau:

Thank you. And I think that that's really an important distinction because unlike most oncologic issues where you don't get any treatment unless you can confirm it by histology, liver cancer, at this time, still does not require that histologic confirmation.

So, I'd like to turn a little bit now to assessing cirrhosis. We suggested in the audience poll question that there are stages of cirrhosis. I have patients that come in and say, "Oh, doc, someone told me only 80% of my liver works," which always frustrates me because I don't have that measure of how much of your liver works. But we do have some ways of helping an individual understand their morbidity or mortality in front of them. Do you want to outline some of those scoring systems?

Paul Kwo:

Yes, Nancy. So, we have two historical scoring systems that we use to assess severity of cirrhosis. The one and the earliest one is the Child-Turcotte-Pugh (CPT) classification for the severity of cirrhosis. The components of a Child-Turcotte-Pugh classification are 5, of which 3 are laboratory values: the bilirubin, the albumin and the prothrombin time. There are also two physical exam findings that manifest themselves as decompensation: ascites, encephalopathy.

This has been somewhat of a drawback for the Child-Turcotte-Pugh (CTP) score, because these are somewhat subjective. So, if somebody has mild encephalopathy, a slight tremor, they may be... a few of their words or their syntax isn't quite accurate. Is that really encephalopathy? Once you get to asterixis, it's a little bit clearer. The same thing with ascites. We typically try to grade this as well. But this can be somewhat problematic, particularly in the era of non-alcoholic fatty liver disease. Someone has a descended abdomen; you'll need some imaging for this. Also, what is diuretic responsive or refractory, somewhat similar to hepatic encephalopathy, does introduce some level of subjectivity to this. Nonetheless, this is a score that has stood the test of time, and if you're a compensated person with cirrhosis, that is, a Child-Turcotte-Pugh Class A, then your prognosis is quite good.

We use this to risk stratify, and sometimes for people who need surgical procedures. Once you decompensate though, and have had a decompensation episode, your prognosis declines. We have learned this with the prescription of certain medicines, and in many other ways, that once you have presented, such as our patient Jonathan did with a decompensation episode, these are individuals that you need to follow longitudinally even if you successfully treat them and they clinically improve markedly.

The other tool that we use to assess severity of cirrhosis is the Model for End-Stage Liver Disease (MELD) score, and it includes only objective variables. The original MELD score was creatinine, bilirubin and INR. These were utilized in a multivariate model; later, sodium was added. Of course, we account for and cap the creatinine if you're on dialysis. But the MELD score is a continuous scale, whereas, the Child- Turcotte-Pugh was just "A", "B",

or “C.” And so if you're, for instance, a patient who has a bilirubin of 5, then your severity of cirrhosis score on the Child-Turcotte-Pugh would be the same as if your bilirubin was 40.

The good news is the MELD score is different. It's a linear model and the higher the bilirubin, the more you're going to reflect a worse prognosis. You can see here that the 3-month mortality rates are shown here if the MELD is 40, your three-month mortality rate is extremely high; well over 70%. And MELD scores above 30 are associated also with significant 3month mortality. We've been able to utilize this as a way to more equitably allocate livers and liver transplantation in the United States.

Nancy Reau:

I do think that there is still a push to better fine tune the MELD score, so everyone should stay tuned, but until then, we do strongly emphasize the use of the MELD sodium. So, let's turn back to Jonathan, Paul, and maybe you could walk us through the assessment of Jonathan and how these scoring systems might be applicable and helped you make your decision path for Jonathan.

Paul Kwo:

Yes, so let's talk about this. Jonathan comes to us and he's better, Nancy. I want to emphasize that he's responded to diuretics. But, he's still presented with decompensation, which may have been related to his mass in his liver. We have to come up with a treatment plan for him, not only to address his viral hepatitis, but the decompensated cirrhosis. And again, a mass in somebody with hepatitis C is extremely worrisome for hepatocellular carcinoma.

His exam is now showing features of ortho hypertension with a palpable spleen, but actually he's responded beautifully to diuretics. He doesn't seem have any encephalopathy when we saw him. But as we talked about with the Child-Turcotte-Pugh score, though his bilirubin is normal (and bilirubin of 1.6, Nancy, isn't really normal), and an albumin level is down and his INR, again within the Child- Turcotte-Pugh A range, but an INR of 1.5 is also not normal.

Moreover, because of his diuretic therapy his creatinine has increased just slightly. Creatinine is

1.4. Sodium is down just a bit, again because of the natriuresis from the diuretics. And thus, this gives him a Child-Turcotte-Pugh score right now of 7, but his MELD score is 20. And we’re not going to change any of his medicines right now. He does have diuretic therapy and he does also have some blood pressure medicine. If he truly has significant gastro esophageal reflux Nancy, then we should keep a protein pump inhibitor (PPI) going for that reason.

But, in general, it's always an opportunity in somewhat decompensated cirrhosis, because PPI, protein pump inhibitors are associated with a variety of deleterious effects in cirrhosis. If they don't really need it. I use this always as an opportunity to try and withdraw that medicine.

Nancy Reau:

Absolutely. I think there's a strong push to try to deescalate proton pump inhibitors across the board. Not just in our patients with cirrhosis, but our patients with cirrhosis are especially prone. So, let's turn now to his ultrasound. I think that in the earlier discussion, you already outlined that an individual with a mass by an ultrasound cannot stop there, and you need some degree of cross-sectional imaging. What would you recommend for Jonathan and how are you going to use this then to make his next steps in his course?

Paul Kwo:

That's exactly correct. He needs dynamic imaging, which can be MR or CT scan. Even though his estimated glomerular filtration rate (eGFR) is not particularly reduced, it is still something where I'm more interested in trying to preserve renal function and limit the exposure to iodinated contrast. I would tend to order an MRI. My own belief and literature really reflect that a well-done MRI probably is still slightly superior to a CT scan as far as diagnosing hepatocellular carcinoma, 7but really both are quite good.

And what we show here is that the mass in his liver that was demonstrated indeed is very worrisome for hepatocellular carcinoma. I show you at the top here, the hepatic arterial phases, and you can see there are actually two masses here. They light up in the arterial phase and you can tell, this is the arterial phase, Nancy, because the liver is dark, and the masses are bright. Then on the delayed phase where, because liver cancers generally get their blood supply from the hepatic artery and they enhance quickly, (and that's how we detect them in the late arterial phase), in the delayed phases, they tend to wash out and they can appear as darker areas.

This is shown very nicely in the delayed phases here, and as we were discussing earlier, hepatocellular carcinoma is one of the few malignancies that we have radiologic criteria where we don't require biopsy to move forward with definitive treatment options.

Nancy Reau:

You've outlined that these characteristics are consistent with a Liver Imaging Reporting and Data System (LI-RADS) 5 lesion. Do you want to talk a little bit about why we use LI-RADS and what that means when you're reading these reports?

Paul Kwo:

Yes. So, LI-RADS is a classification that allows radiologists to have uniform standards for how we diagnose hepatocellular carcinoma. LI-RADS goes from 1, 2, 3, 4, and 5. There are subcategories as well. In this particular case, we were able to confidently make a diagnosis of hepatocellular carcinoma. Given that our patient Jonathan has had decompensated cirrhosis, this certainly affects his treatment options and how we are going to approach this gentleman.

Nancy Reau:

Excellent. So, let's ask the audience, before we break down Jonathan's situation, which of the following interventions is the first line of priority when managing a patient with chronic hepatitis C, hepatic cirrhosis and early-stage liver cancer?

All right, Paul, I'm going to turn back to you. I think that it's not the "Wild, Wild West" when we're talking about managing a patient with liver cancer. We have some very nice algorithms that help us match appropriate treatment to a patient, their stage of disease. Do you want to kind of go through some of the most commonly used?

Paul Kwo:

Yes. Thank you so much. So, we typically approach hepatocellular carcinoma using the Barcelona Center Liver Clinic (BCLC) algorithm. Which was actually recently updated earlier this year. And what the BCLC staging strategy and treatment approach does, is it takes the stage of the liver cancer, in this particular case, this is an early-stage cancer. That is, he has two lesions: one 3 centimeters, one 1 centimeter.

The most important thing when presenting hepatocellular carcinoma and hepatitis C is whether or not this person is a transplant candidate. And the reason that's important is because transplantation for liver cancer is the definitive therapy. You are getting rid of the precancerous organ. So in him, with his episode of decompensation, the Barcelona Liver Clinic algorithm would tell you that some of the other approaches where you have these earlier stage cancers won't be applicable for him.

If you catch somebody who has a very early-stage cancer, say you have an ultrasound that shows a 1 centimeter lesion, you do a triple phase CT scan, and it shows that you have a classically enhancing, washing-out small cancer, then these are individuals that you can ablate or resect. This is a bit geographically depended on the liver because if it's near the surface then ablation is fine. I'm actually, in some of these individuals, a little bit more partial to resection if feasible, but this depends also on the degree of portal hypertension and the bilirubin level as well. But the expected survival for all of these is quite excellent.

The more decompensated you get, then the calculus here changes. There are a variety of options. We call these bridging therapies. We'd like to bridge to transplantation. You can still downsize some of these and bring them within transplant consideration criteria, and still others won't be able to be transplant candidates because of vascular invasion or an infiltrative cancer.

And there we confine ourselves to other loco-regional therapies with our interventional radiology colleagues for the more advanced stage diseases where you have extra hepatic spread. We tend to rely more on systemic therapies, and indeed some of the more recent data here shows that we actually have better systemic options now. Hopefully our options here will also continue to improve.

Those who present, unfortunately with really advanced liver disease and advanced hepatocellular carcinoma, this again is a failure of not being able to adequately screen for hepatocellular carcinoma. These

individuals generally are offered best supportive care and goals of care are typically finalized with our patients in clinic.

Nancy Reau:

So, Jonathan is not as simple as looking at him as just a patient with cirrhosis and cancer. He also has untreated hepatitis C. When would you treat his hepatitis C, or would you even treat his hepatitis C?

Paul Kwo:

Thank you, Nancy, that's a tough question. I think this a little bit depends upon the geography of where you are, what your transplant centers are doing, and in addition this requires a discussion with the patient as well. If we go forward with transplantation, you can choose to treat the person now and we'll go over some of the data here. If you do choose to not treat, you can take advantage of a donor who is positive for hepatitis C. The opiate epidemic has led to, in different parts of the country, a fairly large number of individuals who pass away from opiate overdose, who are HCV ribonucleic acid (RNA) positive. In those particular cases, if you're in an area such as that, you can choose not to treat the hepatitis C and wait for an HCV RNA positive donor as well. These are all options you have to sit down and discuss with the patient.

The target registry actually had a very valuable publication where they looked at decompensated individuals. And what they found was that you have a reasonable chance, 90% chance of sustained virologic response. However, what you find is that in the entire cohort, that you did have factors that they could reliably use to predict whether or not you were going to respond and have this level of decompensation and alanine aminotransferase (ALT) less than 60, Child-Turcotte-Pugh and a MELD score greater than 16 were all factors that predicted that you would not improve.

There was also a very elegant study that was done that looked at various factors for improvement after direct-acting antiviral (DAA) therapy in patients with decompensated cirrhosis. This score called the BE3a score was created. What was found was that if your body mass index (BMI) pretreatment was less than 25, if you had no ascites, no encephalopathy, ALT greater than 60 (which reflects fairly significant inflammation), and the albumin is greater than 3.5, that your chance of compensating to a Child-Turcotte-Pugh A state was actually quite high.

Our gentleman here, unfortunately, presented with several factors that suggested he's not going to be in this group with a lower albumin, significant ascites and an elevated BMI, so this requires a discussion with the patient, as well as working closely with your transplant center to see what resources are available to you and what the transplant center typically does in these cases as well.

Nancy Reau:

So, Paul, before we move on a little bit to treatment and the outcomes of therapy before and after transplant, there has been historical discussion about DAA therapy actually making cancers worse. So, there have been moving targets at what point after stabilizing a cancer, you would be brave enough to consider DAA treatment. Do you have an opinion there?

Paul Kwo:

Yes. When DAA therapies were first introduced (and this was back in 2014/2015), there were several early and really quite alarming reports that suggested, Nancy, that DAA therapy somehow changed the biologic behavior of these hepatocellular carcinomas. There were initial reports of people, individuals with hepatitis C and hepatocellular carcinoma developing significant multinodular disease.

Essentially one wondered if in some way the DAA therapy was affecting dramatically the natural history of the hepatocellular carcinoma in these individuals. These were early reports and likely several factors were involved in this. One, was that many of these hepatocellular carcinomas where people had presumed were adequately treated, probably were not. Some of the reports had AFP levels and people who had no radiologic evidence of disease still had very high AFP levels. In addition, because DAA therapies can be administered to people with more significantly decompensated disease than we could ever do with interferon, there was also a bit of a selection bias as well.

I know you and I did attempt to treat some of these decompensated people with interferon and found out that this was something that really should not be done. That wasn't the case with DAA therapy, but the patient population that we were treating with hepatitis C and hepatocellular carcinoma was markedly different than the patient population that we previously treated, where we did not see these types of aggressive changes purportedly in biologic behavior.

What we learned was that when you do larger, well controlled studies, controlling for all of these factors, that actually DAA therapy in general is not deleterious, and actually in some studies has actually been shown to improve survival. We have two studies here where they looked at hepatocellular carcinoma death and liver transplantation in patients who presented with a decompensated episode.

And what they were able to show was that if you treated individuals with DAA therapy that you actually had a significant improvement in survival in patients who were treated with DAA therapies. DAA therapy did not really change the risk of hepatocellular carcinoma, and it didn't really affect the outcome of liver transplantation as well.

In addition, in those who you do consider transplant, we have now evolved to the point where I think it is now the de facto standard of care that most centers use HCV RNA, nucleic acid, positive donors, if available, and can treat these individuals post-transplant. So, in our individual Jonathan here, if he's in a region of the country where there are HCV RNA positive donors waiting, and not treating the hepatitis C, and waiting till after he's transplanted is certainly an extremely reasonable option for him.

This was actually looked at in a consortium between 2015 and 2019, where patients with hepatitis C related hepatocellular carcinoma underwent deceased donor liver transplant and received DAA therapy. And what was very helpful about this was that they stratified this analysis for three different time periods: One time period was DAA therapy prior to liver transplantation; one time period was DAA therapy between 0 and 3months post-liver transplant; and the other one was waiting until the patient was safely transplanted and recovered, giving DAA therapy for hepatitis C greater than three months post-transplant. What they found was that the best

outcomes with recurrence-free survival turned out to be an initiation of DAA therapy within three months of transplantation.

Here in the state of California, we have just removed, Nancy, the restriction for preauthorization so that we can, if we do treat somebody and they have Medical, that they can automatically now receive DAA therapy, which has always been a concern of ours when we offer a nucleic acid positive donor, in that you can usually get these individuals reimbursed. But sometimes there are delays, and what this data showed was that in delaying in some individuals, that you can actually develop significant complications that can affect the surgical outcome as well.

Now, what about those individuals who have complete radiologic response after curative resection or ablation? There is also here a very nice study that shows that if you initiate DAA therapy, that your survival rate is markedly improved compared to those individuals who are not subsequently treated. Now, the well-controlled studies have really helped point to the fact that DAA therapy is in no way deleterious and likely does have benefits, recognizing the sustained response rates are actually a bit lower in the presence of hepatocellular cancer.

Nancy Reau:

So, let's now turn to the audience. We recognize that Jonathan is going to need to have hepatitis C therapy at some point, whether it's before transplantation or after transplantation. If you were going to treat him before transplant, which of the following DAA regimens is recommended by the American Association for the Study of Liver Disease/Infectious Diseases Society of America (AASLD/IDSA) guidelines for patients with all hepatitis C genotypes and decompensated cirrhosis.

All right, Dr. Kwo, I'm going to ask you, because we have come to believe that treating hepatitis C is, "Easy peasy, lemon squeezy," and that really all the therapies are safe and effective and we don't have to think about that, but that's probably not true. We still need to put thought into our therapy and especially in a patient like Jonathan. Why don't you remind us as to why a decompensated patient with cirrhosis needs to be a little more carefully approached than someone who has compensated cirrhosis or no cirrhosis at all?

Paul Kwo:

Yes, it is great that we actually have pretty darn effective therapies for those who have decompensated cirrhosis. We have one option for decompensated cirrhosis, which is a pangenotypic option, and this is sofosbuvir/velpatasvir with weight-based ribavirin. This is given for 12 weeks, and you get very consistent, sustained virologic response rates above 85%.

There are other regimens that we can use. Ledipasvir/sofosbuvir is another one. It's not quite pangenotypic, typically it doesn't get genotypes two and three. But again, is quite an excellent option for those who have decompensated cirrhosis. Adding the ribavirin in the setting of cirrhosis does require some additional management. So, our patient Jonathan, fortunately isn't very anemic, but some of these individuals do come and they are anemic, and trying to introduce ribavirin can actually be quite problematic. When ribavirin was first

introduced with interferon, we may not have had quite the appreciation for its side-effect profile because the interferon side effects were so magnified compared to ribavirin.

But as we have now transitioned to really excellently tolerated, direct acting antiviral agents, what we found is that the ribavirin also is a medicine because of its anemia, its cough and some other side effects that really can make it somewhat problematic for those with decompensated liver disease to tolerate. Nonetheless, the majority of people can do that.

If you are ribavirin intolerant, you can extend the sofosbuvir/velpatasvir without ribavirin for 24 weeks, and actually, you get quite good sustained virologic response (SVR) rates. It falls down a little bit in genotype three, but is another reasonable option for people who have significant ascites. Clearly these are individuals that the hemoglobin drop with ribavirin is not well tolerated. There's also sofosbuvir/ledipasvir as well.

In Jonathan's case, you actually have two options. I personally would just write sofosbuvir/velpatasvir and weight-based ribavirin. In his particular case, you always have to look at the drug-to-drug interactions, and we did not discuss his medicines earlier. And fortunately, there are no meaningful drug interactions except for his proton pump inhibitor, omeprazole. This is a case again, that we discussed earlier, where we would go back and find out, does he really need the omeprazole? You can certainly give and time the omeprazole with the sofosbuvir, making sure the sofosbuvir is taken with food at least four hours prior to the proton pump inhibitor if you're going to continue it. But again, we always look for an opportunity to simplify regimens and find out if they truly need the proton pump inhibitor. Really that's the only interaction that we would have to be assessing in Jonathan's particular case.

Nancy Reau:

Thank you, and I think it's reasonable to point out that if you have a belly full of ascites, that you might have some reflux. And remember, he did go to the emergency room with abdominal pain. and now that that is better controlled, he may no longer have that same risk for reflux. Although, Jonathan was a little chubby, and so, that is also a risk factor for gastroesophageal reflux disease (GERD).

All right, I want to really thank you, Dr. Kwo, for walking us through Jonathan's case and sharing your insight today. We do see patients like this, and we hope that Jonathan nicely transitions to liver transplantation.

Let's pull it all together with our smart goals to apply in practice. After today, we hope participants will: perform guideline recommended liver cancer monitoring every 6 months in patients with a history of advanced fibrosis and cirrhosis; evaluate severity of hepatic cirrhosis, liver cancer progression, and/or liver transplant eligibility to inform optimal management of patients with advanced hepatitis C infection; use validated DAA regimens determined to be safe and effective for use in decompensated cirrhosis when treating patients with hepatitis C infection and a past or present history of decompensated cirrhosis.

Be sure to check out the first two activities in the CMEO Briefcase series: “Treatment Decisions for Patients with Hepatitis C and Chronic Kidney Disease” and “Mitigating Progression of Liver Fibrosis and HIV, Hepatitis C Coinfection.” These activities as well as many other educational resources for clinicians and patients can be found online at the CME Outfitters infectious disease and virtual education hubs. To receive continuing

education credit, and a printable certificate for completing today's activity, participants must complete the post test and evaluation online. Thank you all for participating and providing the best care for your patients. Take care.