[MUSIC PLAYING]

RENUKA IYER, MD: It's great to be here, and it's great to be among friends, collaborators. I've worked with [INAUDIBLE], with [INAUDIBLE], with many of you. And it's really a tough act to follow the previous speaker, but I'm going to try.

These are all my disclosures. They're also in your handout. And another disclosure. I don't have as many cool pictures as Dr. [INAUDIBLE].

So I would like to just go over what I want to cover in this 30 or so minutes. Just tell you where we are right now in biliary cancer care and talk a little bit about what you can expect coming up in the next few years. And especially talk about the collaborations.

We've spoken a lot already-- Dr. [INAUDIBLE] covered beautifully the state of currently the union, if you will, in targeted therapies. But I wanted to talk a little bit about immunotherapy, the hot topic that everyone's talking about. And then sort of end with supportive care, a big part of what you just heard the previous speaker talk about. Getting through this journey is not easy. And the nursing advisory board that I've had the privilege of working with has been doing some work to try to help lessen that burden on patients.

So the background, most of the people in this audience know this already, but the ABC-02 trial done in the UK, the Advanced Biliary Cancer Group, has made-- this is another example of a collaboration where they made the decision as a country that they would have patients with biliary cancer cared for in major cancer centers, major centers. And this has allowed them to complete a large number of studies and really set the stage and allowed us to have what is currently our standard of care because of their work. And this ABC-02 trial established that gemcitabine and cisplatin, when compared to gemcitabine alone was superior, with a median survival of about 11 and 1/2 months compared to eight months, and about a three-month improvement or delay in progression-free survival. And this continues to stand in all the work that has been done since.

But after that, really what to do has been a challenge. And even today, up until today, we didn't really have a clear standard of care for second-line therapy. 5-FU-based regimens for the majority of patients have been standard.

And looking at a number of different retrospective studies, it showed that about a third or so of patients actually are eligible to get second-line therapies. And when they do, on an average they work for about three months, which is not very encouraging. Clearly, a lot of work to be done. And the Cholangiocarcinoma Foundation tried to get some of the bigger centers to get together and look at their experience with FOLFOX, and three centers got together and looked. And their results with FOLFOX were pretty similar to that.

So this has been the landscape. This has been what has happened so far. ABC-02 was published 2009 and for a long period of time, with all the efforts of the Cholangiocarcinoma Foundation, collaborations happened, things happened, came together. And phase III trials have now become somewhat of a normal in biliary cancer, something that had not happened until ABC-02. And where we came in 2017, was we got pembrolizumab, one of our first few-- two drugs now approved that are not disease specific and mutation specific. Pembrolizumab for MSI-high patients and [INAUDIBLE] for enteric fusion patients.

And here we are in 2019 looking to see what is coming ahead. And what lies ahead is second-line therapy with FOLFOX is now something that we really believe should be what we consider. Recently, earlier this year, we heard from [INAUDIBLE] that the IDH-1 versus placebo, second-line study-- second-line and beyond study was positive. Results are expected at the end of the year.

And over the coming years we expect readouts from seven different FGFR inhibitor studies that are expected to come, BRAF/MEK inhibitor trials. And over time, we hope that our frontline-- Gem-Cis is not exactly a frontline that we're very happy with. We clearly have work we need to do. We'd like to see whether we can take some of these data from the targeted therapies and bring them up front and a little bit early.

So I'm going to talk for a moment about the second-line FOLFOX data that Angela Lamarca was very kind to share her slides and presented beautifully at ASCO this year, the ABC-06 study, which looked at in multiple centers FOLFOX versus best supportive care in the second-line setting after patients had progressed on Gem-Cis. These were the key inclusion criteria. They took patients with good performance status and gave them really active symptom control as their control arm. The primary endpoint was overall survival.

These were the stratification factors. They wanted to know if the patient had responded or not responded to platinums before they went on, because the question about the non-cross resistance because cisplatin is a platinum, oxaliplatin is a platinum, and how did they respond based on what they responded to platinum before.

And they accrued very well. 162 patients were randomized. These are the distribution of the patients and what happened to them from 20 sites over a 3-and-1/2, four-year period. And the data was mature enough for them to present this year at ASCO.

And the study was positive. It met its primary endpoint. The hazard ratio was 0.69.

And for the patients and caregivers in the room, this means about a 30% risk reduction in chance of dying from cancer by taking this chemotherapy. And this is very comparable, even though it's a small patient sample, this number 0.69 is very comparable to the benefit that you get from bevacizumab in colorectal cancer, Tarceva in lung cancer, and sorafenib in liver cancer. So really a clearly positive trial.

And the takeaways from this trial were that for the first time we have a second-line study, phase III, that has been done in biliary cancer. And this was a clinically meaningful reduction in risk of death, as well as a clinically meaningful increase in six-month and 12-month survival rate where 15% more patients were likely to make it further out. They're continuing to do further analyses and look at quality of life and the health economics and the impact of this care-- of this therapy on their care.

So let's look forward and see what else is coming. We start in a lab where we start with the patient's tumors and we try to learn from the patient's tumors to see where we need to go. And at the Mayo Clinic Lewis Roberts has been doing an amazing job looking at this GWAS project, widespread screening and testing, to see the genes associated with the different types and subsets of biliary cancers with the hope to have appropriate controls and allow us to know where we need to be thinking, focusing, and moving the field forward.

These are all the participating sites. And if you would like, if there are pathologists in the room or as a center you'd like to have samples sent and participate, by all means, please reach out. I'm sure Lewis would be thrilled.

There also is led by Dr. Lipika Goyle a group of individuals throughout the country that are trying to understand why cholangiocarcinoma occurs in the young. And this is the CITY Working Group. And these are all the key sites and collaborators.

And what they're trying to understand is in patients who have an initial diagnosis very young like you saw just a few minutes ago, what happens? Why did this happen? We know about primary sclerosing cholangitis as being one of the risk factors. Well, what else is it that might be driving disease in some of these young patients is something that they're trying to understand and compare to patients that were diagnosed when they were more than 50.

Other studies going on-- I'm from this side of you, and on the other side of you in Michigan Dr. Sahai is trying to understand whether adding something other than cisplatin or gemcitabine can be of benefit. And this is a multi-center single-arm, two-stage phase II that he's trying to do and try to get a different option for us to treat biliary cancer patients. This is his preliminary efficacy data. And it looks like for some of these patients triplet therapy would be too much, and maybe doublets, different doublets is a way to treat our patients. So these are all the sites that are participating, and we expect to have results over the coming years.

The last couple of years, there have been a lot of exciting presentations done by Dr. Shroff telling us that Gem-Cis is good but maybe in the good performance status patients, like we've learned in pancreatic cancer, using FOLFIRINOX can really push survival further ahead adding Abraxane. We tend to learn from pancreatic cancer. Things that work there, we try in biliary cancer. And she added Abraxane and tweaked and found the right dose.

And so a pretty high 40% radiographic response. Very impressive. And this has now turned into the SWOG 1815 phase III trial looking in early, newly diagnosed patients, good performance Gem-Cis or Gem-Cis/Abraxane.

The study is open at Roswell. And it's something that we hope to-- it's accruing really well, rapidly. And hopefully in the next couple of years we'll have results. This is the design of the study. Pre-specified stratification factors were pretty much most patients with reasonable liver function and good performance are eligible.

And the NCTN Champions and Timelines that, you know, activated last year, accrual is going really well. And if you need to reach out to anyone, depending on the cooperative groups in the area, please reach out to Dr. Goff, [INAUDIBLE], or anyone else. These are all the sites close by from here.

And then you've been hearing Stacy talking about looking at targeted therapies on a more global scale. So this is the BATCH study. For those in the room that aren't familiar, there was a match study in which they looked at patients, all solid tumors, and looked for mutations that had multiple different arms with targeted options.

And it turned out that about 20, 25% of these patients were actually biliary patients. It turns out of all the solid tumors, there's a lot of mutations amongst our patients. And that sort of led to, you know, some of these other early data that came that led to this initiative that perhaps we should all be getting together and having a biliary cancer specific match trial called the BATCH.

And these are really the main driving factors. One, that the mutations are present. And when they are present, the response rates are really, really high, as high as 40%.

So this is the proposed structure of the BATCH study. You know how it is when you newly are diagnosed, there's a rush to get started and get treatment going. And the thought is that sometimes that mutation testing, the profiling results are not back yet.

Sometimes there's not enough tissue, you have to re-biopsy. So start the patient on first-line chemotherapy. Have the BATCH screening. Have the molecular profiling done. And then at progression, look and see what you have, whether it's an FGFR fusion, a 90H mutation, or any additional alterations for which they hope to have arms and have options available.

It's also possible that there won't be alterations, which is going to be probably the majority of patients. And for them, there are also options they would like to encourage patients to participate, like immunotherapy or other things. And all of these arms we hope, as more trials read out, that this might be something that we add arms to over the coming years.

So this is one way for multiple companies to bring their drugs to one place, and really to have a readout of multiple arms and one goal. And I think the infrastructure it takes to get something like this is large. But the readout and the benefits for the patient, which we all want quick results and we want them to come from a wide variety of patients across the country, and that's what this really is set up to achieve.

Further, my mentor, Milind Javle, who is at MD Anderson now has been, along with Mitesh Borad, really leading an International Cholangiocarcinoma Research Network that has come so far in just the few years that I have been involved with the Cholangiocarcinoma Foundation. Every week we have phone calls, we talk to different companies that bring drugs and say, how can we get them into patients? Would this be right? Should this be adjuvants? Should this be studied in the metastatic setting?

And these are all the cancer centers that are involved. And it's really international. There are patients and trials going on all over the country, all over the world. And last year, the third Asia-Pacific conference for the cholangiocarcinoma awareness and education, similar to what we run here in Salt Lake City, occurred. And it was just a great meeting, great collaborators from all over Asia, all over the world.

So let's move ahead and talk a little bit about immunotherapy. So what's the rationale? Why would we even think that immunotherapy could work in patients with biliary cancer?

Well, cholangiocarcinoma, as you've heard earlier, is a heterogeneous family of cancers. They're not all just one disease. And there are subsets of cholangios.

For example, in Asia when patients get cholangio, a lot of times it's associated with liver fluke infection or viral hepatitis. In the US, we think that the increase in intrahepatic cholangio might be from fatty liver disease. So a lot of inflammation. And we know in inflammation-associated cancers, the chances that immunotherapy is going to work is a little bit higher.

Overall, as a disease the mutational burden is low. But there are some subsets of cholangio where the mutational burden is high. And we know that when there are mutations, the immunotherapies, checkpoint inhibitors have a little bit higher chance of working. And in addition, just looking at PD-1/PDL1 expression, several studies have shown that the expression is higher than in the tumor compared to the healthy cells.

So early phase studies have been done, multiple studies looking at checkpoint inhibitors as single therapy. And this is not a disease I would say that you see exceptional responses or very durable responses. If you look at overall response rates, give or take, it's in the 17, 19-ish percent range. But when you look at the toxicities, like I said, the duration of response is not that high, or it's not reported in some of these studies.

Well, when you look and see who are the patients who actually benefited and was it worth it, were the toxicities worth it, it doesn't look like these patients, you know, had excessive liver toxicities or something that would warrant us to be cautious. Certainly something you should look at, even though these patients do start off with elevated liver functions to begin with. There does not seem to be a predilection for response in one type of cholangio or another, but a slight preponderance towards intrahepatic cholangios getting a little bit better response.

So what other studies have been done with immunotherapy so far? We've looked at checkpoint inhibitor plus chemotherapy in this one trial with nivolumab and Gem-Cis reported in a series of Japanese centers. And they did see more toxicity. The toxicity rates were significantly higher.

And there were confirmed partial responses that were a little bit higher as well. But given the toxicity rate, I would be a little cautious about whether this is something we really want to study extensively. More work needs to be done.

Then the question, looking at melanoma and other diseases where combinations of checkpoint inhibitors have been active, there has been a study of durvalumab and tremelimumab, looking at CTLA-4 and PD-1 targeting. And what they see, again, is toxicities are a little bit higher, not too much higher considering they're adding CTLA-4. But in terms of responses, we haven't seen a huge bump in the responses that you would expect.

Moving ahead, what other immunotherapy targets do we have? So there's this one drug, M7824. It's a bispecific monoclonal antibody that sequesters TGF beta and inhibits PD-L1.

And in this Asian study, just a phase I study, they did see about 30, 35% of patients getting toxicities. But response rates were also pretty impressive. It was quite high in the intrahepatic cholangio subgroup. And that's something we should be looking for and maybe studying a little bit more.

And then just a couple more. Katie Kelley has been pioneering this work, looking at GM-CSF for cytokine growth factor and trying to see whether promoting CD8 T-cell infiltration, if the cell is-- if the tumor is not already inflammatory, would that make the cells, make the tumor cells respond a little bit better to checkpoint inhibition? And this study has been going on. And she's reported it in a couple of places, the Cholangiocarcinoma Foundation meeting. And so far response rates look more or less similar to what you would expect with immunotherapy alone.

Next, rationally we think of other approaches. And one other one is to use VEGF inhibitors. So far in biliary cancers, we haven't been as successful with VEGF inhibitors across the board as single agent. But here, combining it with immunotherapy, a small basket study looked in about 26 biliary cancer patients, and our response rates were, unfortunately, a little disappointing. And it was tolerable, but not as effective as we would have liked it to be to see an early signal.

And then the last combination, MEK. What is the rationale? MEK is a very critical signaling component for both the Ras-pathway-mutated tumors, as well as for normal T-cells. And in preclinical studies, they've shown that MEK inhibition increases class 1 MHC expression. And also, persistent stimulation of the T-cells causes exhaustion.

And, therefore, the rationale is that the combination may work. And this study is going on right now. And Nilo Assad is the principal investigator looking for a signal with atezolizumab in combination with the MEK inhibitor cobimetinib.

So beyond immunotherapy, where are we going? What are we expecting to see over the next few years? On cellular therapies that Melinda is probably the most qualified in this room to talk about, CAR T-cells and engineered T-cells are something that are being looked at. Vaccine therapies, very exciting.

Lots of options being studied still, but none that are really ready for prime time that we expect to report out anytime soon. And you've seen some examples of cases presented earlier in Dr. Stefan's talk, where using liver-directed therapies and combining things such as radiation have been beneficial to some patients. And we are looking now to see whether we can add to that some immunotherapy and sustain the benefit that they can help bring.

One of the things that I want to end this immunotherapy section of the talk with is that, although in the BATCH study we're looking at it as, do patients have a mutation? Can we target it? If they have no mutation, shall we go to immunotherapy? Down the road, a lot of patients will have, unfortunately, progression, and we're looking at immunotherapy down the road.

And something that we may want to look at more carefully is, do these driver mutations impact the response to checkpoint inhibitors? And it turns out that in lung cancer, responses to checkpoint inhibitors are lower in patients with EGFR mutations or ALK fusions. So will that pan out, you know, in biliary cancer is something we need to be looking at.

And in the future, as we continue to develop immunotherapies, we really have to be thinking about each patient on an individual basis and trying to personalize therapy for each of them. In various different cancers, one thing we've learned about immunotherapies, there's no one way to predict who's going to respond. And if there is, it's very disease specific.

So what will that be for cholangiocarcinoma? So far, we're not seeing a signal associated with PD-L1 expression that helps predict who's going to respond. And so there might be other signatures or other innovative ways to know who's going to benefit. And that's something we need to be looking at.

And with that, I'd like to move from the trials on to the how to keep patients on study, how to keep patients feeling well while they're going through treatment. So one of the problems that our patients face, unfortunately, is that the bile duct is obstructed in many of our patients. In fact, in the ABC-02 study 45 percent of patients in each arm had stents. In fact, also in the FOLFIRINOX pancreas trial, about 25% of them had stents, which means these are patients who are at high risk to get cholangitis and biliary obstruction.

And when you look at all the different toxicities that patients got when they were on gemcitamine and cisplatin, although we report out very well, and in the protocol there are guidelines on how to manage toxicities, I think for the nurses, nurse practitioners and advanced care providers in the room, you already know this, you already manage this very well. But sometimes helping, taking that little extra time to educate the urgent care or other members of the team on how to adjust those for toxicity and talking to the patients to know what they're feeling while they're going through therapy, is something we all need to be thinking about.

Fatigue is something that really bothers patients a lot. And at ASCO they reported a couple of years back that rather than pharmacology, therapeutics, you know, Ritalin or Decadron or something, exercise and family support, psychological support and other things actually help patients' fatigue a little bit more than even medications do. So some of these small things, tweaking the nausea meds and making sure the patients go home with prophylaxis are things that we all should be looking at for patients to have good support as they go through the chemotherapy.

And from retention to biliary obstruction is another thing that has been a focus and of interest to the Cholangiocarcinoma Foundation, as well as the nursing advisory board. So what am I referring to here? If you look the ABC-02 study, in the Gem-Cis arm there was actually less likelihood of patients having an elevated LFT problem compared to the Gem arm.

And they try to explain why that is. They think that even though the radiographic response was only about 20%, there wasn't much radiographic shrinkage, even just a little bit of shrinkage in the constriction around the stent, you know, in the bile duct allowed the bile to flow better. And those were patients that did not have these LFT problems, that did not then result in chemotherapy delays, infections, et cetera. And that might be one of the reasons why the patients benefited from the chemotherapy, was that improvement in the biliary flow.

So the Cholangiocarcinoma Foundation worked on putting together this Biliary Emergency card that you can download and have your patients fill up. And basically what it has is information for the patient to know, I'm at risk to get ascending cholangitis. I need to seek care. And if they fill out the information and have the card with them, if they go to an emergency room somewhere in Akron or far away from here, they would get the same care as they would if they came to see you.

And these are all the symptoms, you know, the patients present with, fever, chills, a change-- if they already have a drain, a change in the consistency, things are leaking around the tube or something else, worsening LFTs, leukocytosis. And for all of these things we want them to get care, get a scan, get antibiotics, fluids, and for communication to happen between you and the provider seeing the patient. Unfortunately, there aren't really guidelines around what you should do. When you look at HER2 inhibitors that can cause cardiac toxicity, there are guidelines, multiple guidelines, even though the likelihood of cardiac toxicity is like in the order of 2% to 5%. And here we're talking about anywhere from 19 to 40% of patients getting biliary tract obstruction in emergencies and really not much in terms of guidance on what you should do.

So we got together, the Cholangiocarcinoma Foundation got a group of us together, and we sat down and used this Delphi process where you take different situations and allow a group of experts from all over the country, and here also from the UK, to sit down and decide what would you do if this patient came in with biliary obstruction, and come up with some consensus guidelines. And these were presented at a couple of different meetings. And these were the things, the variables that we all agreed on, elevated liver functions. The bilirubin we gave a lot of weight to whether the white count was elevated or not, whether the patient was neutropenic.

And these were the conclusions, the takeaways, the guidelines that we came up with. We all agreed that it would be very appropriate to have the stent changed, or the tube changed if the patient has an elevated bilirubin and comes to the hospital. Would you admit the patient or not? There was a difference of opinion. And a large part of the decision was based on what the neutrophil count was and whether the patient was febrile or not.

So for example, the patient is afebrile and the counts are normal, it would be OK to send them home on Levaquin, and so on. And some of this work that we've done with the Delphi panel under the leadership of [INAUDIBLE], the chair of the nursing advisory board, they've tried to put together different guidelines for nurses, caretakers, caregivers. And this is the group of wonderful nurses and nurse practitioners that have been involved in putting this work together.

And so for all the nurses and advanced practitioners in the room, I encourage you to apply to come to the Cholangiocarcinoma Foundation meeting. There is a scholarship available every year, a few scholarships. So please come if you can. And we would love to have more of you involved in the advisory board. And when you're at the meeting, we would love for you to sit down with us and come up with any ideas you might have from what you've seen your patients need.

And one of the things that the projects that we've worked on this past year has been to look at-- we call this project To Flush Or Not To Flush, because when patients go home with their biliary tubes sometimes they get instructions to flush it, and sometimes they get instructions to not do anything with it. And we wanted to talk to all the NCCN cancer centers and find out what are your discharge instructions. And how can we maybe come to something that's more unified, more organized, more standardized.

And it has not been very easy, I'll tell you. There's been a wide variation in different centers. But this is something we want to work on and study further. We spoke about managing fatigue.

A couple of more things. You're in a room full of doctors that take care of cholangiocarcinoma patients. But there are several others that perhaps aren't here right now, like palliative care physicians, psychologists, nutrition experts. You have a lot of these services available right here at the Cleveland Clinic.

Well, one of the things that we all sometimes rush over or don't spend enough time doing is to improve communication. And I think a lot of what Lisa does and the Foundation does is to help you communicate, ask the right questions of your caretakers and providers. And at the University of Rochester there was this VOICE study where they trained doctors, and they trained patients to ask the right questions.

And sometimes we think we've told you the prognosis. We think we've told you what to expect. But we actually haven't. And asking us the same question a little bit differently perhaps would give you the answer you were really looking for.

There also was a big ASCO plenary presentation a couple of years ago that told us that just web-based symptom reporting can extend survival. This came as a surprise. Many of us sitting in the audience were like, really? But actually it matters, because you can get sick very quickly. Knowing when to report and what to report is very, very key.

And you can ask Stacy and Melinda, a lot of patients are on the Cholangiocarcinoma Foundation's various blogs, asking each other, what do I do? What do I do? And we're happy that they have someone to ask. But it would be great if you incorporated some of this in your care.

And of course, always, always encourage trial participation. Last year ASCO also puts out every year, what were the biggest discoveries? What were the biggest achievements of the year for 2018?

And in there there was only one patient's picture, and it was Melinda's. And they wanted us to know that, you know, many times when we think we know everything and everything is not good enough, just trying something new and doing it thoughtfully can make a difference. And she's proof that that can happen.

So I will end here and conclude with-- summarize a couple of things. Chemo still is the backbone, unfortunately, in advanced biliary cancer. And it will be, for the next few years at least.

But as you can see between Dr. Sohal and some of the conversations that you've been hearing, talks that you've been hearing all afternoon, more combinations are really on the horizon, especially targeted agents and immunotherapy. But a lot of this depends on us knowing your tumor.

And so if there's one thing you remember from what I'm saying right now it's sequence, sequence, sequence. And then if your sequencing of your tumor has been done a few years ago and, you know, you're doing OK, consider talking to your doctor and having the sequencing done again, because looking at some of these circulating [INAUDIBLE] assays, other circulating DNA assays, we're finding that even though you've put pressure and gotten rid of one clone, other clones are now developing and starting to grow. And this kind of work is something-- especially, for example, if you do have a mutation, you've been on an FGFR inhibitor and now there's disease progression. Now what?

Turns out maybe you can go on a different FGFR inhibitor. And understanding what kind of mechanism of resistance you have is something Dr. Goyle has been studying extensively and has published. And so bring that back, ask your doctor. And if you need to talk to someone through the Foundation that's really leading this effort, reach out. Just reach out.

Of course, education and so forth to recognize and manage side effects is key. Getting through the treatment is very important. And for you and your caregivers, having that conversation with your nurse, with your doctor and saying, what else is out there? This is hard, I need a break-- is important. You need to speak up and do that.

And other things that we're trying to do is a lot of what we're telling you right now, as an academic doctor, is what I see in my practice. But in the real world, what is happening? If you're getting your care somewhere in a smaller city or in a smaller group practice, how is your care? Maybe it's a little different.

And through working with a claims-based database that Stacy's has been working very closely with, we're learning that two out of every three biliary cancer patients actually do come to a major center. So we do have a chance to meet you. But are we meeting you at the right time? Are we able to make a difference in your care is something we want to measure.

What is the cost of care? I heard a couple of people talking about earlier, it's not covered. Mutation testing is sometimes not covered. But most of these companies that are doing the testing won't come back and sort of chase you down and ask you to, you know, pay. They have support programs.

So I think we just have to look at the cost of care overall as well as we move forward. And just always, always collaborate for this rare disease. We can't-- like Stacy said, we can't do this alone. We need each other.

And with that, I'll stop and thank all the investigators. This is a lot of work done by a lot of people. And several of them were very kind and shared their slides.

I want to congratulate Stacy and the Cholangiocarcinoma Foundation for putting this program together with the Cleveland Clinic, and all the work they're doing. I feel fortunate to work with the wonderful nurses on the nursing advisory board, my mentors and collaborators that are some in the room actually. And all of you. I think the biggest difference happens when we talk to you and you tell us what's important to you. And that's really how we've come this far. Thank you.

[MUSIC PLAYING]