Podcast: Role of immunotherapy beyond advanced HCC

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Transcript

Neil Mehta

Hi there. Welcome to our HCC CONNECT podcast. I'm Neil Mehta an Associate Professor at UCSF in Transplant Hepatology and I'm joined by Amit Singal, who I'll throw it over to in a moment, but today we're going to be discussing highlights from three major GI and oncology congresses as well as recent publications and we'll be trying to discuss advances in the management of HCC including both systemic therapies and locoregional therapies data.

So Amit, I'd love it if you could introduce yourself, but I was really wanting to get your opinion to start on. What are some of the advances in systemic therapies at these congresses and in recent publications. Really what's caught your eye?

Amit Singal

Thanks Neil, I'm super excited to do this with you and welcome to the audience. As Neil said, my name is Amit Singal, Professor of Medicine and Director of the Liver Cancer Program at UT Southwestern Medical Center in Dallas.

So, Neil, I completely agree with you - very exciting time in HCC - we've seen tremendous advances in the systemic therapy landscape.

As you and our listeners probably know, we've gone from a field where we had one systemic therapy available in 2007. Then we had other tyrosine kinase inhibitors come in first-line and second-line.

And now, like many cancers we've seen immune checkpoint inhibitors completely revolutionise our approach to HCC management, not only in the systemic therapy space, but as you and I will discuss over the next 20 minutes or so, also in this earlier stages of disease, where we see a lot of exciting trials go on.

As you referenced, I think the trials that we've seen drop recently include IMbrave150 - so a large randomised controlled trial, sorafenib versus the combination of atezolizumab and bevacizumab. Recently we saw an update published in *Journal of Hepatology*, and we finally saw the overall survival estimate for this combination and so now we know that this combination of a atezo and bev provide a median survival of approximately 19 months, so you know, we've surpassed that one and a half year benchmark for survival in the advanced stage setting. Huge advance for systemic therapy.

We've also seen the HIMALAYA trial report. So this was, a large randomised controlled trial comparing durvalumab and tremelimumab. So this combination of two immune checkpoint inhibitors compared to sorafenib. And once again very exciting data, so we see objective responses in approximately 20% of

people. We see a median survival estimate surpassing 16 months and, most notably, this is a trial, where we see a landmark reporting at three years and we see a three year survival estimate over 30%. Which is super exciting once again in the advanced stage setting to know that you can achieve long survivals of three years or greater in over 30% of your patients.

And finally, we saw the COSMIC-312 trial report, this was published in *Lancet Oncology* looking at the combination of cabozantinib and atezolizumab. I think this was a mixed trial, and I think all of us are trying to figure out how we will use this in our clinical practice. We saw significant improvements in progression-free survival, but unfortunately the trial failed to show an improvement in overall survival and I can tell you I personally was surprised about this. There was a lot of interest in cabozantinib as an agent, which hits c-Met and AXL and they potentiate immune checkpoint inhibitors, more so than other TKI agents. But unfortunately, this is why we wait for the actual phase 3 data because we unfortunately did not see improvements in survival.

So I think, in short, super exciting time, a lot of promise once again in the systemic therapy space.

Neil Mehta

I echo your thoughts, especially for COSMIC-312 - super surprising that progression-free survival was improved, but then overall survival was quite similar.

So I agree that story is not finished yet. I'm sure we'll be eagerly awaiting more data as to what the role of cabo atezo is.

But I think, from a clinical perspective Amit, this is a great new problem to have, but it is a problem, you know. How do you think about these different first-line options in terms of, are you recommending one over the other now that we have multiple options or is it kind of like dealer's choice? Where were you thinking we are right now?

Amit Singal

Yeah you know, Neil I think it's funny - in HCC there's some simplicity about only having one therapy, right? Life is simple, life is easy. And once again it's great - all of us wanted to have multiple therapy options for our patients. But, as you have more agents come to market you sort of have to make decisions between these different treatments. And you have to make sequencing decisions and the issue here is that we don't have biomarkers, so there's no biomarker that I can say this therapy is the best therapy for this patient versus another.

And so there is a little bit of the Wild West that's forming and I think that it's only going to get worse over time, as we see other trials also report. We're looking for the combination of lenvatinib and pembrolizumab which should report soon. Ipi nivo's being evaluated in the frontline setting so there's all these other therapies that are being evaluated. I mean at this point we shouldn't be doing to cross trial comparisons, as we know that can be quite dangerous to do.

But I have to say that both atezo and bev, and durva treme are good therapies for us to have available for our patients. Very good exciting survival estimates. As you know, atezo bev requires an EGD to screen for varices. Those at higher risk of bleeding are not eligible to go on bev. So durva treme's a good option for those patients. But I think atezo bev, in many people's books is a good, preferred first line therapy to start.

Neil Mehta

Perfect, yeah no that's kind of how we approach it as well and it does seem like the kind of grade three and four adverse events are fairly similar in terms of percentages and severity across some of these combination options, so as we said it's a good problem to have to have multiple good options in this space.

But more and more we're hearing okay well let's push the envelope, now we have a couple of different first-line regimens well that's, for BCLC stage C advanced HCC. What about earlier stages? What are you seeing from these conferences or recent publications or even in your clinical practice? Are you seeing more and more earlier intermediate stage HCC patients being offered some of these therapies? Is there any data for that?

Amit Singal

So yeah, you know, Neil, I think, of course, as we start to see advances in the systemic therapy landscape, the question is can you apply this to earlier stages of disease? I guess briefly let's lay the landscape.

So even when sorafenib came around you saw that same excitement. So sorafenib came around and then immediately thereafter STORM, looking at this in the adjuvant setting in high-risk with surgical resection and ablation patients, as well as SPACE, looking at this in the combination with TACE. And once again let's go back in time to when sorafenib came to market, I mean there's a revisionist history that's like 'oh sorafenib - we do better now'.

But there was a lot of excitement. Sorafenib was a first therapy for HCC at the time, and everyone expected STORM and SPACE would also have significant improvements in the early and intermediate stage. And as we both know those trials both ended up being negative.

So this is now being completely reassessed with the introduction of the immune checkpoint inhibitors. So data ongoing in the early stage setting and as we'll talk about also in the intermediate stage setting.

However, we're going to be talking about how exciting these data are and how interesting these data are. I have to say, we don't do this as part of routine clinical practice and I think that's important. These data do not mean we should start doing it right now. These data highlight that trials are important and we need to evaluate this and to enroll patients into trials so we know if these combinations work.

But right now, so let's review this, where do we stand in terms of early stage disease? And so let's start with surgical resection. So Ahmed Kaseb and colleagues looked at the combination of ipilimumab and nivolumab, so once again two immune checkpoint inhibitors, prior to surgical resection. So phase two study looking at nivo with or without ipi, prior to liver resection in 27 patients. Actually the randomised control trial looking at this in this phase two setting. These grade three and four AEs we're seeing in some patients so somewhere between 25 and 45% of patients, depending on if you use nivo alone or use the combination. Once again combination, not surprisingly, higher treatment related to AEs.

Good news, no patients had to delay in surgery due to the treatment related AEs, so it doesn't look like that this is going to inhibit or delay surgery. And, interestingly major pathologic responses were seen in approximately 30% of patients in both groups and medium progression free survival was over nine months in both groups. So early data suggesting efficacy in this early stage setting.

Now, this was further advanced when we saw an abstract published at ASCO this year. We saw data from the phase 1b PRIME-HCC trial. 17 patients, once again, with ipi nivo prior to resection. Primary endpoint of this phase 1b trial being safety. So once again therapy was well tolerated, only one patient had a grade three treatment-related AE and that was AST and ALT elevation. Notably, responses were seen in over 20% of patients. Disease control rate over 90%. So once again exciting data, albeit early.

And finally, we saw data looking at the neo adjuvant therapy using cabo and nivo. And this was done by Mark Yarchoan and investigators from Hopkins and I think the twist here is that these were not patients that were resectable at baseline. These were what they were terming borderline resectable. And I have to say, Neil, I think this is a case where beauty is in the eye of the beholder. Borderline resectable - I think that's where the surgeons will debate what is borderline resectable. But that being said, that is the caveat for this trial. They looked at 15 patients and 12 of those patients who they deemed borderline resectable were able to undergo margin negative resection. So that by itself is a win and then of those patients who underwent resection over 40% had a major pathological response.

So now I just went through a bunch of data, what does this even mean? My takeaway is that immune checkpoint inhibitors appear safe. But it looks like you can give these immune checkpoint inhibitors, you have some degree of AEs but it doesn't look like this delays surgery, and further, there appears to be an efficacy signal. You're seeing responses in 20 to 30% of patients.

Now that being said, nobody really cares about a response because that patient is going to have a surgery, they're going to have that completely taken out. The question is, does this improve recurrence-free survival and most notably does this improve overall survival?

And those ones we needed to wait for the data, so that's where the phase three data are going to come in and understanding, I think, particularly assessing overall survival is going to be difficult because of subsequent lines of therapy. But I think that's what we need to see, we need to see improvements in recurrence-free survival and you know, plus minus OS before we start to use these routinely in clinical practice.

Good thing for those people who are itching to use these, and a bit impatient and saying they want to do it. The data aren't that far away. These phase three studies have already launched and honestly I anticipate that we're going to see our first one, I think IMbrave050, I guess we'll see if that's true or not, but I think we're going to see data from that in the next year, if not in the next few months. So for those that are like super excited and want to do this, it's not that far away. I think we're going to see the data, but I anticipate we'll know the answer soon.

Neil Mehta

That's a really nice summary of these recent studies that are in this new adjuvant space. The IMbrave050 trial that you mentioned, I think, is super exciting. It, hopefully, will give us this answer and just to discuss it a bit more, I think the goal is over 600 patients. They're enrolling both patients in the adjuvant setting after resection or ablation with atezo bev versus active surveillance, which I think is a great study design. I think it's 25 countries, 170 sites is the goal, this is all super exciting and what I'm most excited about, and we've kind of seen this a little bit in the transplant space, it's been really hard to design a really good adjuvant trial to look at HCC recurrence but, what the IMbrave050 authors have done is they're actually doing the stratification based on how many high-risk features that patients have once you examine other section specimens. So looking at things like tumour size and number, looking at vascular invasion, looking at tumour differentiation and highlighting the poorly differentiated tumours. Because we've gotten into trouble in the transplant space. If you look at a group of patients with a really low risk of post-transplant recurrence, well then it's going to be really hard to find a signal or say anything useful.

But fortunately in the resection space or in the ablation space where there's a 70% or so risk of recurrence, I think, we'll be able to get our answer with the way they've designed this trial and, of course, their key endpoint is, as you mentioned, the primary is recurrence-free survival. So as you mentioned, this is exciting I think we'll get the data hopefully soon and you know, this could be a game changer and in this highly relevant population of patients when we're trying for cure.

Amit Singal

Yeah, I completely agree Neil, and I think that right now the trials are primarily evaluating adjuvant therapy. And then, of course, you see some of these early studies in neoadjuvant and then the question will be, should this be used as adjuvant or neoadjuvant? And you know we'll see this.

So Neil you mentioned transplant as you were discussing this and putting this in a frame here. And I think, surgery, surgical resection is easier. Transplant, of course, you have to worry about this, risk of graft loss, etc. But we've seen some of the data so, can you talk about some of the early data we've seen in terms of immune checkpoint inhibitors as bridging therapy and what should be our thought here? Should this be used, should it not? What's the idea?

Neil Mehta

Yeah sure. This is giving us, in the transplant space, a lot of headaches trying to figure out what is the role of the immune checkpoint inhibitors in these patients who are trying to get to transplant?

So just to kind of lay the land a little bit, so Amit earlier, you talked about some of the immune related adverse events that we're commonly seeing, and one signal is that potentially if you combine two together, such as in the HIMALAYA trial where serious immune related adverse events were almost twice as common as in the durva mono therapy arm in the HIMALAYA trial, for example. So that gives us a little bit of concern when we're talking about, usually patients listed for transplant with HCC often are decompensated and so now if you're thinking about throwing a combination of ICI there, now you're worried about are we going to be causing further liver failure taking someone from a Child Pugh patient A to B or C, for example?

So that is a concern that we don't have much data, but the bigger concern really I think is the one that's gotten the most publicity is what about when you give immunotherapy to a patient who's about to undergo a liver transplant? Is there a risk of post-transplant acute rejection and graft failure? Really that's the question, are we kind of co-inhibiting tumour and donor antigens?

There's been a couple studies, they're all relatively small, but one of the first studies to come out with by the UCSD group and they had five patients, five HCC patients who received pre-transplant immunotherapy and they found that both of the patients who received immunotherapy within three months of transplant actually developed acute cellular rejection and severe hepatic necrosis and one of them actually required repeat transplant, so that's quite concerning.

On the other hand, and again a small sample size, but none of the three patients who underwent transplant more than three months from the last dose of immunotherapy developed rejection or graft loss.

So that was an interesting study and then there's also been a report from Parissa Tabrizian from Mount Sinai that described nine HCC patients who underwent transplant after receiving nivolumab monotherapy, as an element of pre-transplant tumour treatment. Almost all of those patients actually received their last dose of nivo within a month of transplant. Some of them were being used for down staging, some were always within Milan and most of them received concurrent locoregional therapy. So a good example of a common approach to transplant with these elements. And what they found is after over a year of post transplant follow up they didn't see any severe allograft rejections or graft loss, there was no post transplant deaths reported.

So obviously we'd like to get longer term follow up data from both of those studies and neither of them are really kind of trying to answer the question should we be giving this therapy? They're really trying to tell us is it safe.

From the way I look at these is that, we don't have a great washout period number. Given the half lives of some of these commonly used immunotherapies like atezo for example, of nearly four weeks, I think it is reasonable to consider a washout period of two to three months. So that you're not getting your last dose of ICI right before transplant and then running into this risk that we saw from the UCSD group. So I think that's a reasonable approach in terms of safety, but I think we still need to get more efficacy data as well.

Amit Singal

And Neil, can you tell me your thought of using immune checkpoint inhibitors as bridging therapy? Do you think that this is mainly to decrease risk of drop out from the waitlist? Or do you think that this is to improve recurrence-free survival after transplant? What's the goal here?

Neil Mehta

That is the question. Why are we even bothering doing that? So from my perspective, I think most patients with HCC within Milan, who are listed for transplant with a for example, relatively low AFP likely are going to have a relatively successful journey down the transplant pathway. We have relatively high rates of getting these patients to transplant and they typically do really well after transplant.

So I don't really think that there's going to be a main role for checkpoint therapy for example, in most patients with HCC listed for transplant. But I think what we've seen is that we're really trying to push the envelope and in certain high risk patients such as those who exceed the Milan criteria, who are beyond even downstaging criteria. Or patients with multifocal disease or who aren't really responding to locoregional therapy, there is a certain subset of these patients who have inferior outcomes, they have higher risk of waitlist dropout and they also have higher risk of post-transplant recurrence. I think these are the patients that I think we really need to highlight, so you know when I think about it, I think the ones that I think we should start to consider for trials like this, are patients who are what we would call all comers are patients who are beyond downstaging. These are the patients we think have the highest risk of waitlist drop out and may not do as well post transplant.

And so, these are the ones that we're starting to think about maybe, including in a protocol, where you might combine locoregional therapy and systemic therapy, to try to improve transplant-related outcomes.

Amit Singal

Yeah I completely agree, I mean Neil you and your group, have done a lot of this work in terms of those patients who are highest risk and so I think those would be some of the features that we can maybe use once again assuming we have better data to target this so it's not like an all comer sort of approach, but really a targeted approach.

So, Neil you primarily focused there on the bridging aspect, and I know that's sort of what we were planning to talk about. But it's so frustrating when you transplant somebody and you're thinking this is a cure, and then they reccur and they typically reccur badly. The tumour biologies are just different when you're immunosuppressed even mildly post transplant.

I have to say I've been at least considering IOs in some of these patients, but I haven't pulled the trigger. And so can you just discuss how safe is it to consider immune checkpoint inhibitors in those patients post transplant?

Neil Mehta

That's the other big question of this space, is it something that we can even offer? And I think that the issue here is, as you mentioned at the top of this podcast, most of these combination therapies have at least one if not both immune checkpoint inhibitors but, again, this risk of using these therapies after transplant is high on the minds of most transplant providers.

It's not just the risk of acute cellular rejection, graft loss and the potential need for re transplant. But also there's other kind of immune-related adverse events that happen quite commonly in this patient population who are on immunosuppression after their liver transplant, and so even at UCSF we've seen a couple of patients with really severe colitis, for example. Or other really bad reactions, I guess, we could say, to trying to use some of these therapies after transplant.

So I will say the data is sparce. There are some smaller case series that have looked at this and, you know, obviously, most of them are retrospective and 'here's how many patients we looked at' and 'here's how many had problems'. So it's really hard to really trust data like that, just because it's so sensitive to what you're seeing. If you have eight patients who have done it and none of them had any problems, you may not publish that but, if you have three who did it and two had bad problems that's something that you're going to put out there.

So I think we're still waiting for more data, but at this time I think most of the community is still extremely nervous about the risks of using these agents after transplant. So I think outside of a clinical trial it's probably not recommended, especially because there's so many nuances like 'What do you do with their steroids doses?' We've seen some of this data that's come out talking about trying to get them on stable doses, making sure they haven't had any recent rejection. Adjust their steroid dose and so kind of tailoring their immunosuppression while you maybe add one of these therapies, is something that probably should be done in the clinical trial setting and we're still waiting more data, I think.

One thing I also wanted to chat about, I know we've been talking about this use of maybe systemic therapy prior to transplant. But we've seen a lot of excitement about this and we've talked about who might be targeted for this, but I think one of the nice things about this space Amit is just the how many clinical trials are currently going on about combining systemic therapy and liver-directed therapy for intermediate stage BCLC B HCC. Maybe 10, if not more, large trials currently trying to understand this issue that we were talking about a lot has been for many years - okay here's your one therapy, you are in the TACE arm. Or you are in the systemic therapy arm. So I've been really excited about this. Obviously we're still awaiting data, but any of these phase two and three studies that are combining systemic therapy liver directed therapy, what are you looking out for? Is it TACE versus TARE one of the highlights, or is there a certain kind of combination that you think is likely to become something that we can really provide some benefit for these patients?

Amit Singal

Yeah I think that's exactly right Neil. We've seen this early stage explode with trials looking at the role of systemic therapies we've seen also a lot of studies ongoing in the intermediate stage setting.

And so I think it starts with increasing recognition of heterogeneity within the BCLC stage B. So we've now been like this is not just one group of patients, this is really a group of patients that have different prognoses and different treatment strategies. So you can see this, for example, within downstaging. We often think about these patients if they're otherwise eligible should be thought of as downstaging to transplant.

Those patients who have a little bit beyond that, probably LRT is their destination therapy, so these patients will get TACE/TARE as their destination therapy.

And those patients who are on the larger side of BCLC stage B may be better for systemic therapy or combination therapies. This idea of 'TACE unsuitable'. One again this is like beauty in the eye of the beholder, where everyone has their own definition for this - different thresholds.

Some people are thinking beyond downstaging, some people use the six and 12 prognostic score, some people say greater than 50% liver involvement and nobody really knows the answer of where locoregional therapy by itself is insufficient.

For example, the BCLC update uses this diffuse extensive bilobar disease or infiltrated disease in their 2020 update and so that's where they say these patients should be considered for something else. And independent of that exact threshold, I think that there's recognition that once again we need to do better than LRT alone, whether that's systemic therapy alone or whether that's combinations as you brought up.

And I think this concept is best supported, in my opinion, by this study by Kudo and colleagues. So Kudo basically did a retrospective propensity match analysis - patients treated with locoregional therapy versus lenvatinib upfront. And, in short, lenvatinib had better survival primarily driven by preservation of liver function, and now the thought is that this may be true for IOs as well.

And so, as you say you know there's lots of data going on, so there's actual studies comparing IO versus LRT.

So the ABC trial was a global phase three randomized controlled trial comparing atezo bev versus TACE in those patients with intermediate stage HCC. Primary endpoint: time to treatment failure.

We are launching a phase two study comparing atezo bev versus local regional therapy in patients beyond Milan criteria in the United States. And the spin here is that we're also incorporating radio embolization as a potential local regional therapy, and this is important because, as you know, this has become in many centers that preferred locoregional approach whenever possible.

Now, as you mentioned, I think that it's not just necessarily locoregional or systemic. There's a lot of interesting combinations which I agree with you are very interesting. We don't have any of those data currently although there's many studies ongoing, and I think those are very promising and I think we're going to have to then determine, is it combination? Is it LRT alone? Is a systemic therapy alone?

Once again, this whole idea of the Wild Wild West. It's going to be pretty bad in intermediate stage HCC. What's your thoughts on these trials and the studies ongoing there?

Neil Mehta

Especially thinking of it from a transplant lens, always trying to get patients, if possible, to cure, you know, often we think about transplant, and when I some of these studies, like the one by Kudo that you referenced earlier, I really start to think okay well, we've been doing things a certain way and should we be using more systemic therapy to even downstage patients to transplant? You look at these numbers from Kudo and you're like 'wow that's pretty impressive'. 73% objective response rate - that's a much longer progression-free survival. I still think TACE and radio embolization are going to be the backbone of downstaging and we haven't really found any difference in probability of downstaging between those two options. But you know, for example, if we do have a patient, beyond downstaging, for example, that we're trying to get downstaged and maybe we started with TACE or radio embolization and I think within this kind of prospective trial space, I think we're going to be seeing a lot of these studies coming out that suggest well if you can add atezo bev or durva or there's a lot of different combinations out. Maybe these are patients that are going to have much higher response rates overall, much more likely to be able to maintain within Milan. And then therefore much more likely to be able to get to transplant.

So I think it's a super exciting space again. Not necessarily just for the standard 80% of patients who are listed for transplant with HCC but more for those that we're a little bit trying to push the envelope. We don't want to do anything too crazy. We don't want patients with rising AFP or just keep popping up tumours. Maybe those aren't you know the right patients to transplant, but there is that subset I think that currently have a higher risk waitlist dropout that probably are potentially if we can start adding systemic therapy to these patients, maybe we're going to be able to get out larger percentage to get disease stability within Milan and get a higher percentage to transplant.

Amit Singal

I think Neil that's a really great approach and a great way to think about this. I think the take homes that I think both of us are saying - really exciting time in HCC. We've seen tremendous advances in systemic therapy. We're starting to see data that are applying these to earlier stages of disease, however, too early to do this as part of clinical practice, but a lot of excitement.

And I think the next stage, as you referenced here is who do we apply these combinations in to optimize outcomes? Which are the patients, you should consider this in?

The nice thing is, as we have advances there's more clinical questions that come up, more work to do, and I think this is where the next few years are going to be very, very exciting.

But the simple days of drawing a line down and saying this is a TACE patient, this is a resection patient, those days are done. Those algorithms, unfortunately, are going to become much more complicated and it's going to be combinations, it's going to be transitions back and forth.

The key thing here: multidisciplinary care. These things can no longer be decided by a hepatologist alone or an interventional radiologist alone or a medical oncologist alone, as you have combinations lwhich are going to be the future, you need to do these things in a multidisciplinary fashion to optimize patient outcomes.

I think it was really fun to talk to you about this. It's the type of thing where talking about it just reminds me how exciting everything is and I guess we'll sort of see what comes out from these data over the next several years.

Thanks again for the listeners for listening, for the last 20 to 30 minutes and hopefully you're as excited as Neil and I about all the advances to come.