Podcast Episode Title: The use of VEGFR-TKIs alone or in combination with immune checkpoint inhibitors in clinical practice for the treatment of HCC

Brought to you by:

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Peter Galle

Dear friends and colleagues a warm welcome to today's podcast on the topic of VEGF receptor tyrosine kinase inhibitors in the treatment of hepatocellular carcinoma alone, and in combination with PD1 inhibitors.

We will talk about dosing strategies, pre-habilitation of patients and we'll have a full spectrum covering efficacy and toxicity in clinical practice. I'm joined today by Dr Amit Singal from the US, a hepatologist and friend, and my name is Peter Galle, a hepatologist from Germany.

Amit Singal

Thanks for having me Peter, it's a pleasure to be here.

Peter Galle

The use of tyrosine kinase inhibitors tackling VEGF receptor signaling is, of course, not coming by chance. Here we have the hallmark of hepatocellular carcinoma hypervascularity and, naturally, this is coming also into consideration, and talking about therapy anything inhibiting this hypervascular feature of HCC might be of value.

Initially, we were hoping just to starve a tumour to stop the perfusion then we learned that anti-angiogenic agents are actually more potent. They normalise, in fact, the vasculature of tumour and later in addition to it, we were realising that there is a rather complex impact on the tumour micro-environment, and tyrosine kinase inhibitors have the function of an immune modulator, which is also very high relevance in terms of combination of partners, for example, checkpoint inhibitors.

Amit, what do you think is the relevant mode of action, what is the contribution of TKIs alone and in combination?

Amit Singal

You know, Peter it's a great question and, as you alluded to, our understanding of this has evolved over time. I think that in the beginning we thought that that VEGF inhibition was largely just anti-angiogenic, thereby, as you said, starving the tumour of its blood supply. But I think, as immune checkpoint inhibitors have come into the field of HCC, much like they've revolutionised the treatment for many cancers, we've started to really think through, the immune-modulatory effects so we've started to realise that VEGF inhibition can normalise tumour vasculature, increase T cell infiltration, it can decrease immunosuppressive cells, Tregs and myeloid derived suppressor cells and it can promote dendritic cell maturation. So it has a lot of immune-modulatory effects.

And this comes into, you know, play, particularly as you referenced when we start to combine, you know, VEGF inhibitors such as bevacizumab with immune checkpoint inhibitors, as well as ongoing trials combining TKIs, with immune checkpoint inhibitors.

When we take a look at this, I would argue that both mechanisms are probably important. Although arguably as we come into combination therapies, maybe the immune-modulatory effects may be greater than, or greater interest than, the anti-angiogenic effects directly.

Peter Galle

So we can assume we have different impact on the tumour and its micro environment and in simple words it might be tumouricidal, a tumouicidal effect on tumour cells and then be more complex impact on the tumour micro-environment described as immune modulation.

I would like to challenge you here, Amit in terms of dosing because this is a topic which we are referring to later on, and I'm a bit uncertain about the knowledge we have concerning the dosing strategy and it might actually be quite different in terms of which dose is required when you talk about a tumouricidal and immune modulatory impact. What are your thoughts here?

Amit Singal

Yeah I couldn't agree more Peter, so you know, when these tyrosine kinase inhibitors have been used alone, you had to have doses that actually work, achieving tumouricidal effects,

so, you know, really having a dose where you would have sufficient activity with monotherapy.

When you're using it with combination therapy its potential, I guess, we don't know for sure, that if you're relying on the immunomodulatory effects to be an add-on you may get away with lower doses, and so you may not need the same doses that you need when used as monotherapy. And this would be beneficial, because you could avoid some of the adverse events that you can see with tyrosine kinase inhibition and VEGF inhibition at the higher doses. So it's a very interesting question, something that I think needs to be evaluated, if we can use different combinations in combination then with monotherapy.

I think one of the many questions, we still have to answer in HCC. What are your thoughts?

Peter Galle

The different dosing strategies become apparent when you check the protocol of the COSMIC-312 trial.

Here cabozantinib, a TKI is used in combination with atezolizumab, and if this combination is used the dosing for cabozantinib is reduced to 40 milligrams compared to the mono arm cabozantinib, which is also used here, where 60 milligrams are recommended. So the assumption apparently is that for immune modulation, you need less, and I think there are some data exactly pointing out to this particular impact. If you want to kill a tumour cell, you might need more, if you want to immune modulate the tumour micro-environment, particularly in the setting of a combination, then you might need less. That needs to be further elaborate in the future.

Amit Singal

Yeah I couldn't agree more. I think, you know, the dosing of TKIs in general is something that requires a lot of art and, you know, isn't as simple as one may think just based on label.

Peter Galle

Absolutely.

Amit Singal

Even in monotherapy I think that, you know, we see the label with these recommended doses. But I think that, you know, many of us as we've used tyrosine kinase inhibitors in practice, we often will change that dosing strategy for an individual patient in front of us. And this is often done to try to avoid some of the adverse events that one knows can happen with tyrosine kinase inhibitors. I think all of us that have used these are well aware of adverse events, including hand foot skin reaction, hypertension, the anorexia. So I think these are all things that can be distressing to patients and sometimes cause dose discontinuation, if not complete cessation.

And so I think many of us have started to start with lower doses, this is our standard practice in our clinical practice: it is to start at lower doses, assess tolerability closely and then ramp up from there with continual dose escalation, to try to get them to their highest tolerable dose.

And, you know, this has actually been a tested strategy, I mean as you're aware, you know, for example in colon cancer, the ReDOS trial actually, looked at this. Like a dosing strategy will you start lower and dose escalate and compared it to a strategy where you start at the highest dose and patients did stay on therapy longer.

So, you know, the primary outcome of that colon cancer trial was patients getting to the third dose of therapy and a higher proportion achieved, you know, getting to that third dose in the dose escalation arm and I think many of us have applied similar techniques to our patients with HCC at least that's the practice in our setting. What do you do Peter with your patients?

Peter Galle

Yeah, we actually have changed our attitudes towards dosing. Initially we felt that the recommended strategy, the recommended dosing should be adhered to and naturally this is where most of the data comes from, and then we learned that individualisation of therapy is the way to keep patients on drug and to, in the end, get a better outcome because you are able, by down titrating the tolerated dose to a level where it can be, indeed tolerated by the patient and maintenance on drug is a very relevant aspect and achievement. Particularly though, because the correlation with adverse events and outcome is there, we know that actually those patients suffering in a way, a bit from side effects from TKI therapy actually are those where you could predict that the response rate is higher and the overall survival is longer. So, it's very, very relevant for these patients not to be stopped because of side effects, but to be maintained on drug and in fact that's precisely what we are doing today, and this is actually true for the large variety of different TKIs.

Initially we tried to have a high drug exposure early on, and then we learned this is not our goal, our goal is to have a patient, as long as possible on drug. And that may actually mean a dramatic reduction in the recommended dose and, in addition, if I may add Amit, there have been examples where this was actually, in a way, proven to be relevant. Take the linifanib trial. This trial did not allow dose adjustments and linifanib had to be dosed correctly, as recommended or stopped completely. What happened? In comparison to sorafenib, treatment with linifanib was shorter, so you could not maintain a patient on a recommended dose and if you're not allowed to downtitrate, then you just have to stop and that was a negative trial.

So, I think we have examples that the lower dose or the individualised adjustment is of high relevance. The interesting question is, of course, if it's better, as you were pointed out, to go up in the dose, start low and titrate to what is tolerable, or if you start with the recommended dose and pay attention to side effects. Your thoughts on that Amit?

Amit Singal

Yeah you know, Peter the reason why we start low and go up is simply to make sure that patients don't have a severe AE up front, you know, and then even if you as a provider, are able to titrate down and keep them on therapy the patient themselves becomes frustrated and, you know, doesn't want to go back on therapy or doesn't want to continue, even at a lower dose. And so, we have found just, over time, that patients are more accepting if they tolerate and you continue to escalate up.

And so, you know once again our current practice is to start low and titrate up, but you bring up a very important point. That if you're going to start low it's critical that you dose escalate up. You should not just start low and continue low out of fear for adverse events, because, as you raised these adverse events have been associated with longer survival, I mean, as you know the story started with sorafenib and regorafenib where the presence of hand foot skin reaction was associated with better outcomes and, you know, now this has been shown with some of the other TKIs.

I believe ramucirumab if you have, with treatment emergent hypertension, that's associated with better sort of outcomes and so I think these AEs, while can be you know quote unquote concerning when they happen or you know require some effort to manage, we should not under dose out of fear of them. I think we need to, I mean, if you're going to start low continue to escalate up to that tolerable dose and then, as you said, if you hit that AE talk to your patient, talk to them that this may be actually a good thing, although sort of odd to hear from a patient perspective, because of these associated improved outcomes and then to stay at that higher dose and manage that dose well.

But to get to your exact question, I mean our standard practice is to start low and then, as I said, escalate up to that higher tolerable dose.

Peter Galle

But it's probably relevant first of all for our patients and then for those in our audience today, the individualisation, the willingness to adjust to what is tolerated but to try to maintain a patient on drug is probably the most relevant recommendation here.

If you are not flexible enough, you might lose your patient. The patient, will no longer accept the side effect profile and, as we have learned over the years, it can be sometimes quite diffuse, just fatigue and the patient can't really explain what's going on. But there is an issue about tolerability.

So please, dear friends and colleagues, pay attention to the individual patient and dose adjust accordingly, it will result in longer treatment duration and in better outcome.

Amit Singal

Completely agree. So, Peter I think it's been an exciting time in the field of HCC as we've had more and more therapies come out so we now have multiple therapies available in the first line. And we have multiple therapies available in the second line, and I think one of the

things that becomes difficult with treatment options is how do we choose between them. And so, one of the ways that this could be done is by biomarkers. This is the holy grail of precision oncology is to have a biomarker that tells us, this is the best therapy for this individual patient.

And, as you know, there's been a lot of work in this field, although, unfortunately, some of it being quite negative to date. So, can you tell us how do you use biomarkers in your clinical practice if at all, and where does this stand in the field of HCC?

Peter Galle

This is a great point Amit and you can look at it differently. It has a lot of perspective, and it has been sort of disappointing in the past. If you think about it, it's now, more than two decades since we started to develop signature which initially were described to have clear prognostic potential and, of course, we were hoping that they would be able to stratify our patients according to response to a given therapy.

We as clinicians probably, were not good enough in using these strategies, integrating them into clinical trials and show their predictive potential, because the signatures are still there, but it has never in any way matured into prediction in terms of choices of therapy, that is disappointing.

The only biomarker and it's the oldest one we have, which we are currently using is alpha-fetoprotein, as it has been demonstrated by initially, the subgroup analysis of the REACH trial, and then by the REACH-2 trial that in patients with an alpha-fetoprotein above 400, ramucirumab, an antiangiogenic antibody, is effective.

So that is an option we have but, let's say fine tuning, the different signatures, we have, and particularly now, in times of immunotherapy where we would like to separate those hot and inflamed tumours from those who are not hot and we ask the question, how can we make this tumour hot. This is not existing, at present, and in that sense, we need to get better because, in simple words, not all patients respond and we would like to know better, who will respond to what.

Amit Singal

Yeah, it's been interesting. I mean AFP as you referenced has been around the longest and it continues to be the only biomarker that has withstood the test of time in HCC. And others have come and gone but haven't really born out in terms of having a prognostic or treatment response role in HCC.

I think the other one that's of course of interest as we move into immunotherapy is PD-L1. And unfortunately, the studies that have been done to date haven't shown PD-L1 status to be predictive in HCC. So although it's been of value in other tumour types, unfortunately, at least right now, isn't being used to select patients for one therapy or another. In short of having this biomarker we're forced to depend on other clinical characteristics that can help determine between patients, and our experience with these different therapies.

One of the studies that has caused a lot of hoopla, for lack of a better word, is this study that was recently raised in terms of differential effects of immune checkpoint inhibitors in viral etiologies versus non-viral etiologies.

So this is the study, as you know, that was recently published showing potential decreased efficacy of immune checkpoint inhibitors in subgroup analyses, when looking at the large Phase 3 studies. So taking a look at, you know, CheckMate 459, taking a look at the KEYNOTE study, the IMbrave 150 study essentially showing that the immune checkpoint inhibitors appeared to have decreased benefit in those patients with non-viral etiologies.

And this caused a lot of concern, and so I can tell you that my view on this is that the preclinical rationale there was elegantly done and I think it does bear further study, but right now, you know, given the fact that these studies weren't stratified on etiology and there could be inner group differences, you know, I think at least a clinical data that was included in that publication may be too premature to change clinical practice.

But I guess I'd like to hear Peter, what do you think of these data and what do you think about the maturity of these? Do you think that this bears further observation? Are you concerned? And have you changed your clinical practice at all?

Peter Galle

That's a great, great question and the relevance is absolutely there and it's a hot discussion. It goes actually back to the old SHARP days. In the SHARP trial, we saw a signal from subgroup analysis that hepatitis B and hepatitis C etiology resulted in the different outcomes in terms of response to sorafenib.

This is food for thoughts, this is hypothesis generating but not more that's the point. You need to then set up a clinical trial, where you really stratify for these, for example, etiologies. And then do a prospective trial and this has never happened, and the same is actually true for non-viral etiology.

And the signal as you were referencing to the Vander Heiden group and the Nature paper, well, it was nicely shown, and I would echo what you just said, in preclinical analysis that there is probably not as good a response to checkpoint inhibitors as to non-NAFLD, nonfatty liver disease etiologies, but the clinical aspects are just too weak and, if you, for example, take the IMBrave 150 trial, yes in the non-viral etiology, there is a crossing of the one in terms of poor hazard ratio in favour of atezolizumab/bevacizumab, but if you compare the data for these patients in non-viral etiology, with the general assessment, then you realise it's actually not a poor performance of atezolizumab/bevacizumab, it's rather a super performance of sorafenib.

So that needs to be further elaborated on, and at present, we certainly don't change our clinical practice and, in addition to what I just said the definition of these etiologies is sort of not very precise. I mean non-viral etiology is not exactly the same as NASH. And in many

parts of the world it's actually more ASH that NASH, and then we have a dilution and the signals become even less clear, so the future certainly worthwhile stratifying according to etiology and find out better who is responding and not but currently no change in clinical practice.

Amit Singal

Peter great points and I think this is of immense interest and particularly as we've seen a shift in epidemiology of cirrhosis in our HCC patients. I mean with hepatitis C therapies now becoming prevalent, I mean we're seeing less hepatitis C related HCC and cirrhosis and we're seeing more and more non-viral etiology, so this is an important question. I think one of the important questions that needs to be answered in the field of HCC and I think your point of this informing clinical trial design and the necessity to stratify based on etiology in clinical trials is critically important.

But I think short of that I completely agree that these data are too early for us to change clinical practice, and I think given the immense improvements in survival that we've seen with atezolizumab and bevacizumab, this combination of immune checkpoint inhibitors and VEGF inhibition compared to tyrosine kinase inhibitors, I think it would be a shame to withhold that therapy, based on the current strength of data in the clinical field. So I think interesting, but I think you know once again early in terms of clinical practice.

Peter, so I guess we're left in a world where we have some interesting data from a clinical perspective in terms of identifying which patients should be treated which therapy, we unfortunately are short on biomarkers outside of AFP as you referenced in terms of ramucirumab.

And so you know it really brings us to one of the last things that I think would be interesting to talk about is how do we make our patients optimal for any therapy that you may choose. You talked about the idea of precision oncology and individualising treatment regimens for our individual patient in front of us. And so, can you talk about some of the steps that you will take to make it so that patient comes in, as fit as possible or as optimal as possible to select a certain therapy and stay on a certain therapy once again with the idea that you raised of keeping patients on therapy for as long as possible to derive the greatest benefit.

Peter Galle

Yeah, thank you Amit, really glad to have you as sparring partner today because you are a hepatologist, and this question naturally comes from a hepatologist because we are aware that our patients are frail, they don't tolerate much toxicity and they need to be readjusted or pre-habilitation programs to be fit for therapy. Patients can be occasionally and intermittently, absolutely unfit for therapy. Particularly if there is complication of the underlying cirrhosis. If there is a bleed, if there is spontaneous bacterial peritonitis and encephalopathy these patients are no longer tolerating any sort of therapy and we have to push the reset button in a way and make them fit again. Pay attention to their needs, so

that is I mean it's in general, an important issue, help your patients with respect to nutrition, muscle status and so on, as fit as possible because it's very well described that the fitter the patient, the better tolerated the therapy, the better the outcome and in hepatological patients it's even more pronounced, because the liver, is the master of toxicity and if liver is not working the toxicity is very prevalent. So yeah, we have to pay attention and we might to do an interruption to stop treatment for a little while in order to get our patient into a shape to be fit for therapy, and this is extremely relevant.

Amit Singal

Yeah, I completely agree Peter, and I think it's great to hear that we both have the same perspective on this, not surprising, but great to hear.

I think that it's often difficult but important to talk to a patient that comes in, who is quote unquote unfit for therapy and to discuss, you know, the need to be patient upfront. Rushing into therapy can actually be disastrous, and so, taking the time, as you referenced to control the anxieties up front, to control the encephalopathy up front. So to make it so the liver function is as optimal as possible.

Now there are some components of liver disease that are reversible or at least addressable and there are other components that are not. I think one of the most common sort of questions I get is, what can I take to bring my bilirubin down, and I'm like, unfortunately, we don't have a medication that you know automatically reverses hyperbilirubinemia.

But I think that whatever you can address I think needs to be addressed, so addressing the SAEs, addressing the encephalopathy and outside of liver function, I think the other thing going into, you know, VEGF inhibition or TKI based therapy is to control some of the other comorbidities. So once again, we know that, you know, TKI therapy can cause hypertension, so to control the blood pressure, coming into therapy, to control the diabetes coming into the therapy, so you reduce the risk of you know diabetic neuropathy. These other sort of comorbidities that we often see in our patients with liver disease, particularly as we move into a field which is more and more driven by non-alcoholic fatty liver disease, so I think both of us have a very similar approach to making it so we discuss this up front and making sure that patients are fit coming into therapy.

I think, you know, one of the most common things that I talked to my patients about is having a battle plan. You know, a map of that battlefield before going into war and so that's the way that I think about this as a little bit of time of prep up front really helps us have the best outcomes long term.

Peter Galle

Yeah, I couldn't agree more, the willingness to check every time you see your patient performance status and liver function and to adjust the treatment accordingly is not only relevant upfront but also during therapy.

There's one last point which I would like to consider, and that is, those patients, where the tumour itself is contributing to poor liver function. So if you have a tumour sitting in the hilum interfering with a perfusion. Here, it can be actually quite beneficial for the patient, if you have an objective response, and we know that, for example, lenvatinib is creating more objective responses than other tyrosine kinase inhibitors and that actually might improve liver function, and you see that occasionally, not extremely often, but you see that occasionally that unlike in most patients who were over time of treatment liver function tends to get worse in that particular setting, liver function improves as a result of anti tumour treatment, and that also needs to be considered.

Pay attention, that's the simple message at the end of our podcast, pay attention to the individual needs, to liver function and performance status, upfront and during therapy.

Amit, we are at the end of our discussion, I enjoyed it tremendously, thank you very much, this was really covering the full spectrum, hope to have another podcast with you soon. Thank you so much, and to our audience, I hope you enjoyed this presentation and goodbye.

Amit Singal

Yeah Peter, always a joy, thanks so much and thanks again for the audience for joining.