EASL LCS2022 Design of Clinical Trials for Adjuvant and Locoregional Strategies

TRANSCRIPT

00:00 --> 00:30 – Lorenza Rimassa
Hello everyone, my name is Lorenza Rimassa. I'm associate professor of medical oncology at Humanitas University and IRCCS Humanitas Research Hospital in Milan, Italy. Today I have the pleasure of being here with Pierre Nahon who is professor of hepathology at the University of Paris in France and we are going to have a discussion about the session entitled Design of Clinical Trials for adjuvant and locoregional strategies that we had the pleasure to co-chair at EASL Liver Cancer Summit 2022. During this session speakers and panelists

00:30 --> 00:40 - Lorenza Rimassa
discussed some of the most relevant hot topics in the field of adjuvant and locoregional strategies for liver cancer including HCC, hepatocellular carcinoma, and cholangiocarcinoma or CCA.

00:41 --> 01:10- Lorenza Rimassa
The first talk was an overview on latest adjuvant and locoregional studies in liver cancer with a focus on study design and lesson learned from cholangiocarcinoma given by Julien Edeline from the Eugène Marquis comprehensive Cancer Center in Rennes, France, and during the discussion we had also the pleasure to discuss this topic with Juan Valle from The Christie in Manchester UK. So Pierre would you like to comment on what has been presented and discussed on this topic?

01:11 --> 01:27 - Pierre Nahon
Yes, it was indeed very, very interesting session. When we design the planning for the Liver Cancer Summit, It appeared really important to start to talk about these adjuvant approaches because of course we do not have any

01:28 --> 01:50 - Pierre Nahon
clear and strong data right now, except from small pilot studies, but it will probably change the future arena, and this is this was the idea of starting with Julien Edeline's experience in adjuvant treatment for cholangiocarcinoma because for cholangiocarcinoma we already have data as compared with HCC.

01:51 --> 02:20 - PierreNahon
I found that Julien did a very, very interesting talk because the whole thing is a methodological standpoint about these trials, and he highlighted how much heterogeneity of cholangiocarcinoma may have impacted the results, because usually these trials included patients with intrahepatic cholangiocarcinoma, biliary carcinoma, etcetera.

02:21 --> 02:50 - Pierre Nahon
But it would be of course more interesting to have dedicated trials to intrahepatic or gallbladder, etc, but of course cholangiocarcinoma is a rare tumor, so this is the idea of mixing on this kind of tumors together. I don't know what you think, but do we have enough cholangiocarcinoma in Europe to run trials in each category? I'm not sure and I was quite convinced by

02:50 --> 02:58 - Pierre Nahon
the demonstration by Julien, that we have to do with what we have, although the results may be conflicting.

02:59 --> 03:07 - Pierre Nahon
In the end, we have quite strong data suggesting that adjuvant therapy for cholangiocarcinoma, whatever the localization,

03:08 --> 03:13 - Pierre Nahon
should be performed. What is your opinion? What is the standard of care for you? For example, in Italy.

03:14 --> 03:15 – Lorenza Rimassa
Yes Pierre, I I totally agree.

03:15 --> 03:46 – Lorenza Rimassa
It in theory, maybe it would be better to have adjuvant trials for the different types of cholangiocarcinoma, so intrahepatic, extrahepatic, gall bladder and so on. But we don't have so many data suggesting that the response to chemotherapy is so different. And also it's really important, as you mentioned, that we have to design and run feasible clinical trials, so maybe not the best design but a feasible trial. We know that,

03:46 --> 04:16 - Lorenza Rimassa
in the past, adjuvant trials required lots of years to be completed, so if we split in different subtypes I think that they are not feasible. So I totally agree that using chemotherapy in the adjuvant setting, it's correct to run trials including all types of biliary tract cancer. And another important point that Julien mentioned was the endpoint. So is the

04:16 --> 04:24 – Lorenza Rimassa
overall survival or the relapse free survival the best endpoint for a adjuvant trials. What do you think about this?

04:25 --> 04:38 - Pierre Nahon
My opinion is that this is something we really have to consider for liver cancer, for HCC. For cholangiocarcinoma, because the locoregional therapies are not

04:39 --> 04:54 - Pierre Nahon
as wide as for HCC because we did not really endorse in the guidelines, the ablation and the embolization and so on, I think that overall survival is a better endpoint in cholangiocarcinoma. Remember we saw this

04:54 --> 05:04 - Pierre Nahon
example that Julien gave to us with the the median survival, which was not the right, maybe the right endpoint clearly.

05:05 --> 05:07 - Pierre Nahon
Finally, the overall survival.

05:08 --> 05:18 - Pierre Nahon
I don't know if you remember this example, but we show that on the long term, overall survival should be the best endpoint for cholangiocarcinoma, including adjuvant trials.

05:18 --> 05:44 – Lorenza Rimassa
Yes and Julien mentioned very well and explained very well that is important not to look at the median. So he compared the BILCAP study with the GemOx study, his study, and it's not important to compare the medians but to look at the curves and to consider the hazard ratio because in the end there you have an idea of the

05:45 --> 06:14 – Lorenza Rimassa
complete results of the trials are not only the medians. So I mentioned the BILCAP and also I think, importantly at ASCO GI, also the ASCOT trial was presented. So now we have a trial showing the benefit of capecitabine in the adjuvant setting and another trial that is in Asia but with another fluoropyrimidine that confirmed the activity in the advanced setting. So I think that at least so far we have sufficient data to consider a fluoropyrimidine

06:14 --> 06:17 - Lorenza Rimassa
as a standard of care in the adjuvant setting.

06:18 --> 06:33 - Lorenza Rimassa
We know that there is the ACTICA trial ongoing, so maybe in the future we will have cisplatin gemcitabine but so far I think that capecitabine in Western countries is a standard care. And another important point I think,

06:33 --> 06:38 – Lorenza Rimassa
again at ASCO GI, the TOPAZ-1 trial was presented so in the

06:38 --> 06:54 – Lorenza Rimassa
advanced setting in the near future, in the next montha, the standard of care will be cisplatin, gemcitabine plus durvalumab. Do you think that these results may have an impact also in the adjuvant setting or not yet? Or maybe no?

06:56 --> 07:17 - Pierre Nahon
Well, clearly I think that it would be tempting to speculate that improving the regimen as a adjuvant therapy would increase for these patients with difficult to treat cancer. I mean, cholangiocarcinoma a is a very, very tricky one to manage.

07:17 --> 07:26 - Pierre Nahon
It will be tempting to go further and go beyond the classical chemotherapy and maybe start associating with

07:26 --> 07:56 - Pierre Nahon
durvalumab as in the TOPAZ study. Because clearly this study that was presented at the ASCO GI was groundbreaking, not only because it increases survival in advanced stages, but because the tolerance seems to be quite good. And this is what we're looking at. These are patients that are supposed to be free of tumor, so they should be in fair state, ECOG 0 or 1, so clearly these patients may benefit from association of

07:57 --> 08:28 - Pierre Nahon
immunotherapy and chemotherapy. Maybe, I think we will discuss the design of the trials. Would it be so long because you remember the TOPAZ trial it's a six-month course plus chemotherapy, then durvalumab alone, so because it's going to take time again, we are facing again pragmatic issues here of running very long trials for which we have the answers several years later. But we are eagerly waiting for these

08:28 --> 08:35 - Pierre Nahon
results for our patient, for our teams, so maybe it will be a mixed, in my opinion. So but clear this is on the way.

08:36 --> 09:06 - Lorenza Rimassa
Yes, totally agree again. So I I think the last point of this talk that was, you briefly touched on this, is about locoregional therapies for cholangiocarcinoma because we have some studies already presented or published, but probably most of them are low quality studies, we don't have so robust data. I think we have to define how to select the population, which is the best technique, TACE for instance or TARE or SIRT?

09:06 --> 09:09 – Lorenza Rimassa
It's difficult to standardize the technique.

09:09 --> 09:28 - Lorenza Rimassa
Another open issue is how to combine? Maybe locoregional therapies with systemic therapies? The accrual is difficult. Julien mentioned the SIRCCA trial. It was a very interesting trial radioembolization plus cisplatin and gemcitabine but the trial was stopped.

09:28 --> 09:40 - Lorenza Rimassa
It was early stopped due to lack of enrolment or too slow enrollment. What do you think about locoregional therapy and potential combination with systemic therapies?

09:41 --> 10:06 - Pierre Nahon
Well, I would say it depends finally on the centers where the patients are managed. For example, yes, management in hepathology centers where we have the habits of dealing with patient with cirrhosis, discussion of transplantation and so on, I think that we may have a wider range of proposals for patients,

10:06 --> 10:22 - Pierre Nahon
and clearly this is where, for example, in my center we are really into ablation therapy. So we have an experience in ablation therapy in cholangiocarcinoma or at least on mixed hepatocholangiocarcinoma, which is another issue here. But there is room for these,

10:22 --> 10:30 - Pierre Nahon
for the testing and dedicated trials for these, for example, ablative therapy for cholangiocarcinoma. Up to now these are more

10:30 --> 10:35 - Pierre Nahon
reported as local experiences.

10:35 --> 10:48 - Pierre Nahon
But again, we're facing as a pragmatic issue, the low number of cases. So do we have enough patients to randomize them into a surgery versus ablations, for example? I'm not sure about this.

10:49 --> 11:14 - Pierre Nahon
This is what you said, I think cholangiocarcinoma is still a disease where there is surgery versus ablation versus systemic therapy, and in between we don't have enough experience. I think it will come with the years and maybe randomized trials are not the gold standard for this evaluation, and maybe I think it's on a case by case basis clearly.

11:14 --> 11:37 - Lorenza Rimassa
Yes, I agree. So moving to the second talk there was on the rationale for combining therapy in HCC given by Bruno Sangro from the University of Navarra in Pamplona, Spain, and Bruno talk about the combination of locoregional therapies and systemic therapies, in the past with tyrosine kinase inhibitors and, more recently,

11:38 --> 11:54 - Lorenza Rimassa
about the positive results of immuno-oncology drugs in the advanced settings. So maybe we have to consider to combine locoregional therapy with immuno-oncology drugs, immune checkpoint inhibitors. So

11:55 -->12:26 - Lorenza Rimassa
for the combination of locoregional therapies plus tyrosine kinase inhibitors, we have only the TACTICS trial run in Japan that was positive with the new endpoint of unTACEable progression and so we have to think of combining locoregional therapy with immunotherapy. So what do you think about this? There are ongoing trials, there are some data already available, which is the future of locoregional therapies plus
immune checkpoint inhibitors?

12:27 --> 12:32 - Pierre Nahon
Well, the only thing I can say is that the future is very exciting.

12:33 --> 12:34 - Lorenza Rimassa
I agree, yes.

12:34 --> 13:05 - Pierre Nahon
The only reason or clearly blurring for HCC where we have a more I would say standardized approach because we have more patients, so we have been able to clearly say these patients should be treated with endoarterial treatment, or ablative therapy etc. So clearly it's more fixed. It's more fixed approach and clearly I think the main issue here is what is the clinical question. Because this is where we must

13:05 --> 13:35 - Pierre Nahon
clearly differentiate what we call the downstaging approaches where we will combine, for example, endoarterial treatments or even a large ablation, for example, for patient with BCLC B or BCLC B tumors that could be downstaged to come back to the curative setting. So this is what we would call the downstaging approach of combining treatment. Then we have the adjuvant which is

13:35 --> 14:06 - Pierre Nahon
when a patient has been cleared of the tumor. Can we prevent recurrences? So this is a different question, and this is basically, I would say, the kingdom of all industrial trials that have been run in the last few years, and hopefully we'll get some resource in the forthcoming months and years, and then I would say the for me the most interesting approach is the neoadjuvant approach which is basically you have a patient you know you can ablate or respect, but you want to,

00:14:06.430 --> 00:14:09.230 - Pierre Nahon
I would say, potentialize
00:14:10.730 --> 00:14:13.390 - Pierre Nahon
particularly for ablative therapy whether
14:14 --> 14:43 - Pierre Nahon
thermal ablation or electroporation you want to foster this effect of the ablative treatment and at the same time decrease recurrence because usually you combine neoadjuvant and adjuvant

approaches and we're getting now some new data we have now 2 pilot studies published this month, showing that the necrosis of the tumor may happen maybe 25 to 30% of patients, and in a patient that

14:430 --> 15:14 - Pierre Nahon
is a good candidate for a curative approach, this is a good sign because it seems that, beyond the curative approach, you also provide a benefit in terms of necrosis of the tumor. So clearly we can expect that on the longer term, the patient will ultimately benefit from this dual approaches, so clearly very, very exciting, lots of trials going on, both on the industry and academic setting and very exciting

15:14 --> 15:16 - Pierre Nahon
time for us in the forthcoming years I'm sure.

15:17 --> 15:50 - Lorenza Rimassa
Yeah yeah, I agree, and I think there is a strong rationale also for combining that, you mentioned the adjuvant and neoadjuvant setting that are really exciting but also in combination maybe with a TACE or other locoregional therapies, there is a strong rationale in combining immunotherapy with this treatment. In earlier stages we have a less immunosuppressive tumor microenvironment and we can have a a potential synergism with locoregional therapy. Locoregional therapy may increase the amount of

15:50 --> 16:20 - Lorenza Rimassa
the exposure of new antigens and so may increase T cell priming, may improve the tumor micro environment, so again there is really a strong rationale for the combination. What we don't know, it's maybe in terms of locoregional therapies, intra-arterial therapies, which is the best one? So would it be better to combine immune checkpoint inhibitors with a TACE or with a TARE or SIRT? We have some data from the NASIR-HCC

16:20 --> 16:39 - Lorenza Rimassa
trial, or maybe also there are data, not so many data in HCC but maybe in other cancer types, with stereotactic body radiotherapy. So do you think there is a better locoregional therapy to be combined with immune checkpoint inhibitors or we will have to see in the future?

16:40 --> 17:00 - Pierre Nahon
Clearly again for HCC maybe we have the ability to run different trials, TACE and immunotherapy, SIRT and immunotherapy, and radiation therapy with immunotherapy. But I have a better question,

17:02 --> 17:30 - Pierre Nahon
which is: are we really convinced that for some patients, the dual approach of endoarterial treatment plus immunotherapy will be better than immunotherapy alone? This is another point. Because all these, I'm quite surprised that most of the ongoing industrial trials that, for example, compare TACE plus immunotherapy versus TACE plus

17:31 --> 18:03 - Pierre Nahon
placebo did not include an arm of immunotherapy alone because in the end maybe immunotherapy alone, at least in some patients, may be enough and we do not need to combine immunotherapy and endoarterial treatment for some BCLC, even for some BCLC B patients because the risk of deteriorating the liver function is an issue here. So what is your thoughts about this and how do you see what we could do to improve the scientific proof of this?

18:03 --> 18:07 - Lorenza Rimassa
Yeah, I think it's a really important point. As you mentioned the

18:07 --> 18:20 - Lorenza Rimassa
industry-sponsored trials, at least to my knowledge, are locoregional therapy mostly TACE plus or minus immunotherapy, but there are ongoing academic trials, for instance, the ABC-HCC,

18:21 --> 18:52 -Lorenza Rimassa
that are exactly comparing the locoregional therapy versus immunotherapy because the question is there and you are perfectly right. We we don't know, we have results with the systemic therapy, with immunotherapy that are completely different compared to the results we had in the past with tyrosine kinase inhibitors. So it's possible that for patients with intermediate stage HCC maybe with a high tumor burden or we have to define the characteristics but maybe systemic therapy can be the best

18:52 --> 19:04 - Lorenza Rimassa
option without locoregional therapy. So for instance, the ABC-HCC, I think it's a really important trial and will give us some important answers in this field.

19:05 --> 19:21 - Lorenza Rimassa
So in the end I think we are living in exciting time for liver cancer, both considering advanced setting but also the adjuvant setting and the intermediate setting. We have a new options for patients with advanced HCC and we are trying to

19:21 --> 19:46 - Lorenza Rimassa
have new options also for patients with early and intermediate stage HCC and I'm sure we will have more options in the future, but as we discussed so far we have several open issues we have several questions so that we have to to address so really exciting time. Thank you, Pierre. Thank you all for listening and bye bye.

19:43 --> 19:47 - Pierre Nahon
Thank you. Bye bye.