Podcast: Optimising outcomes with late-line treatment of mCRC

Brought to you by:

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This GI CONNECT programme is supported through an independent educational grant from Bayer is an initiative of COR2ED.

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Transcript

Tonke de Jong:

Metastatic colorectal cancer (mCRC) patients can still achieve disease control and gain a survival benefit with treatments in the later line setting but maintaining quality of life is an important factor.

Keep listening to explore the considerations for treatment selection and sequencing, and strategies for adverse event management to help achieve optimal outcomes for your patients. Thanks for listening to this podcast episode from COR2ED independent medical education. This episode is supported by an independent educational grant from Bayer. Today's topic is all about how we can optimise outcomes with late-line treatment of metastatic CRC. I'm honoured to introduce to you two expert Medical Oncologists in the field of GI oncology: Associate Professor Gerald Prager from Austria and Dr Victor Hugo Fonseca de Jesus from Brazil. We're very excited to listen to your discussion.

Assoc. Prof. Gerald Prager:

Hello and welcome to today's podcast, where we are going to discuss how we can optimise outcomes with late-line treatments in metastatic colorectal cancer (mCRC). My name is Gerald Prager. I'm a medical oncologist who specialises in the treatment of gastrointestinal (GI) cancer. I work at the Medical University of Vienna in Austria. Today I'm looking forward to discussing the topic of late-line treatment of mCRC with my colleague, Victor Hugo Fonseca de Jesus. Victor, I'm very happy that you join us here today. Please could you introduce yourself?

Dr Victor Hugo Fonseca de Jesus:

Hi Gerald. It's a great pleasure to be with you here today. So, as you mentioned, my name is Victor. I'm a medical oncologist living in southern Brazil and I'm dedicated to the treatment of patients with GI tumours and I'm really looking forward to this discussion with you, Gerald.

Assoc. Prof. Gerald Prager:

So, Victor, if you think about late-line treatment. We have patients who have been through many lines of treatments before and so they might have faced some challenges, such as adverse events. We have to consider tumour heterogeneity, resistance to its previous treatment and maybe also ongoing adverse events. Then of course we have to consider other comorbidities of these patients. However, over recent years, we have seen a lot of new developments in the later line treatment of mCRC. Some new treatment options have been introduced into the clinic and it might become a little bit confusing for some of our colleagues deciding which would be the best option for the individual patient.

So, Victor, thinking of late-line therapy, how do you decide the best treatment for the individual patient? What different parameters do you consider? What tumour biology? What do you take into consideration when you make your treatment decision?

Dr Victor Hugo Fonseca de Jesus:

This is a very important issue. First of all, I would like to define what we mean by later line. Many authors define later line as patients who have had progressive disease after using oxaliplatin, irinotecan, 5-fluorouracil, anti-EGFR agents (in the case of RAS and BRAF wild type tumours), and bevacizumab or any other anti-VEGF agents. So these are the patients we are talking about.

Second, as we have started to understand more about the molecular biology of CRC, we have started to identify that some subgroups of patients might benefit from targeted therapies such as anti-HER2 therapies for patients with hyper expression of HER2 and tumours as identified by immunochemistry or by FISH. Also, patients with a microsatellite instability as identified by immunochemistry, PCR (polymerase chain reaction) or NGS (next generation sequencing), also have a great deal of a benefit after using immunotherapy with anti-PD-1 plus or minus anti-CTLA-4 agents. In the past year data were published from a randomised trial using KRAS G12C inhibitors,the combination of sotorasib plus panitumumab from the CodeBreaK 300 trial showed that these patients might benefit from using targeted therapies. Another subgroup of patients with targetable alterations includes those with fusions such as NTRK and RET where we have targeted agents that work very well. This is a very small group and they derive a lot of benefit from these drugs. For patients without any targetable alterations what we have currently is a combination of TAS-102 (trifluridine-tipiracil) plus or minus bevacizumab, regorafenib and recently fruquintinib.

Assoc. Prof. Gerald Prager:

I think it is extremely important that you were discussing the potential molecular targets. But when we talk about later lines of treatment, most of our patients should have already had this druggable target treated in the first or second line and not in the later line. Especially when we think about microsatellite instability, I think immunotherapy has its place in first-line treatment. Even if you think about the BRAF V600 mutation, I think we need to know up front, as soon as possible, since these tumours are more aggressive. We should think about treatment to specifically target the BRAF mutation in second line, although it's also approved in third line. So earlier lines of treatment.

When it comes to third-line and later-line treatment, in my opinion, of course we should appreciate the molecular profile of the individual tumour but there are other factors to consider. Patients have

been through prior lines of treatment and might have faced toxicities like skin toxicity or hematotoxicity, so when selecting the third-line treatment we can choose an option which takes into account these previous toxicities. I can give you an example: sometimes I have patients with high grade hematotoxicities where they need G-CSF (Granulocyte-colony-stimulating factor) support because they have neutropenia, for these patients I would consider in the third line that they have a chemotherapy-free treatment. I could choose a tyrosine kinase inhibitor (TKI) like regorafenib or in some countries fruquintinib is available. These would be the options for those patients. Then I have patients, who went through skin toxicities due to anti-EGFR receptor antibodies and they would prefer not to face another skin toxicity potential treatment in the later line. In particular, there are differences between seasons: in summer skin toxicity might be a bigger burden for some patients than in the colder winter months. So, these are aspects, we consider in later lines of treatment, because I think quality of life is key for patients. It's not just about prolonging the prognosis by increasing the overall survival but maintaining quality of life for these patients. Also, it's extremely interesting that we have seen data from clinical phase three trials that if you choose treatment which is active and compare it to placebo or less active treatment, the more active treatment maintains the good performance status of patients, more likely longer than if you just do best supportive care. It sounds paradoxical, but it's not. An active treatment is indeed keeping our patients, in a better performance status for a longer time.

So, these are different aspects I consider in my patients. I don't know, Victor, whether you have different experiences or additional opinions on this topic?

Dr Victor Hugo Fonseca de Jesus:

No, I couldn't agree more. I think the things you mentioned about previous hematological toxicity and patients' expectations are very important - some of these patients do not want to cope with a skin side effect. Many of these issues we have to understand, given the non-curable intent of treatment. These might be very important issues for the patient. I think this is a very important thing.

One thing I think we forgot to mention was about rechallenge with chemotherapy and with anti-EGFR agents. Maybe we could just explore this right now. What are your thoughts about rechallenge, Gerald?

Assoc. Prof. Gerald Prager:

I think with reintroduction and rechallenge we have to be a bit cautious as we have more active options in later line of treatment. First, we have to know the definitions. Reintroduction means that a patient has a treatment in first line and never gets resistant, so you might reintroduce the same treatment later. So, you stop first-line treatment because the patient wants to have a treatment break and after a few months, if there is a need to reintroduce the same treatment, you can do so. This can work and might also be reflected in some guidelines. However, when we talk about rechallenge we mean the patient is treated until progression of the disease. You eventually switch the treatment to another line of treatment and then rechallenge the first line of treatment again upon second progression of the disease. This rechallenging approach has attracted some attention recently and we have seen some intriguing and interesting trials when it comes to anti-EGFR rechallenging in patients with RAS wild type who had a good response in first-line treatment. However, Victor, we have to be aware that these trials were all clinical phase two trials, non-randomised with a low level of evidence. For most trials, we haven't seen overall survival data – there are a limited number of patients within these trials. This is a very highly selected subgroup of patients where we might consider rechallenging of anti-EGFR receptor treatment. So I hesitate to do this rechallenging approach in most of my patients in third line - I might do it in later lines, except when tumour shrinkage is needed, since rechallenging might cause tumour shrinkage in these patients but the chance is low. When we look at the guidelines with regard to rechallenging with

chemotherapy, there is a very low level of evidence. I looked this up in the ESMO guidelines, for instance, and reintroduction / rechallenging has a level of evidence of 3B or 3C which is much lower than we have for other options in third line derived from clinical phase three trials as you were mentioning such as regorafenib, trifluridine/tipiracil plus bevacizumab or fruquintinib, where in all these three options we have level 1 evidence. So we have better options at third line to select a different agent treatment rather than using the rechallenging approach. This is my opinion about rechallenging.

Dr Victor Hugo Fonseca de Jesus:

This is great that you mentioned this Gerald, because very often we find people are trying to do chemotherapy rechallenging. I think that given the amount of active drugs that we have now in later lines we should stick with the level of evidence that we have, and the best evidence we have is for the TKIs and for trifluridine/tipiracil, TAS-102 plus or minus bevacizumab. So it's very important that you mentioned that this is probably best left for later lines after we have exhausted all our options in terms of things that have been tried in phase three clinical trials.

Assoc. Prof. Gerald Prager:

Yes, I think also if we talk about tolerability, we have learned to handle the treatment, to manage the potential adverse events of the TKIs over the years. So now we have had TKIs for the treatment of solid tumours for almost 20 years and when we talk about mCRC, we have also learned that, for instance, when we treat patients with regorafenib, we can rapidly escalate the dosage to find the individual dosage for the patient. If you remember the ReDOS trial, which was an randomised trial, showed that if you start in week one with 80mg of regorafenib and in week 2 increase to 120mg and then eventually escalate to the full dosage of 160mg per day in week three, before taking one week off in week four, you find very rapidly the individual dose for your patient, which is tolerated. Then if you look at the data of the ReDOS study, the primary endpoint was the number of patients going to cycle three. This was a positive trial with this escalation design, the ReDOS design. More patients went to more cycles of treatment and the outcome was a secondary endpoint when it comes to overall survival where there was a clear trend towards the escalation design. This is now reflected in the NCCN guidelines that you can do this escalation of the dosage for the individual patient according to the ReDOS study and this works very well. We do this in our centres. We start with the two pills in week one, escalating to three, and then eventually to four pills per day so we don't see high grade toxicities anymore or very rarely.

I think the second point is that we focus on the informed consent of our patients when it comes to the management of potential adverse events. Talking again about TKIs, we talk to our patients about hand-foot skin reactions, we advise what they can do about potential diarrhoea (loperamide intake and so on). So I think, as it stands today, the management of TKIs is not a big problem anymore. They are well-tolerated in most of our patients. So, Victor, what is your experience? And can you tell us a little bit about toxicity of trifluridine/tipiracil, TAS 102, plus or minus bevacizumab.

Dr Victor Hugo Fonseca de Jesus:

Yes Gerald, I totally agree with you regarding the toxicity of regorafenib. I think that over the years we just learned how to better deliver this treatment for our patients. I think that we very rarely see severe toxicities nowadays, especially after the data from the ReDOS trial. We were very comfortable with the idea of increasing the dose of the medication. I think we're very comfortable nowadays with this approach.

Regarding trifluridine/tipiracil, I think that the toxicity profile is completely different, we mainly deal with hematologic toxicities and some nausea and diarrhoea. I think that also, over the years we have learned how to manage these toxicities. Many people at the beginning were very afraid of

proceeding with treatment because of neutropenia but I think that when we stick to the guidelines from the package insert and recommendations from the industry, we will find it very, very easy to continue with medication. When we add bevacizumab, we have some increase in terms of toxicity for neutropenia, for nausea and hypertension but I think these side effects are still very manageable and we have learned to deal with hypertension, and also from TKIs. Also because we developed the capability of dealing with neutropenia in many ways by postponing treatment and eventually decreasing the dose. So, I think it is very, very safe, the rates of febrile neutropenia for trifluridine/tipiracil are very, very low. So I think this is manageable.

One thing that I think is very important is to take a multi-disciplinary approach to patient care, because I think other specialists can be a big help in this setting. This is particularly important for patients with hand-foot skin reaction, which I think is maybe one of the most challenging side effects from TKIs, Gerald.

Assoc. Prof. Gerald Prager:

Yes, absolutely. What we have in our centre is oncology nurses who take care of adverse events and, they are very much involved. They see the patients on a regular basis. I think it is key that we detect and can react to potentially high-grade adverse events on time before they emerge and if they high-grade adverse events emerge, we can do a treatment break or dose de-escalation, so step down the dosage so that the patient has good tolerability. I think this is indeed key.

So Victor, short answer please: who would be the ideal patient in third line after they have had oxaliplatin, irinotecan, 5-FU plus antibody treatments by IV, to whom would you give regorafenib and which patient would you give trifluridine/tipiracil plus bevacizumab to?

Dr Victor Hugo Fonseca de Jesus:

I think as we don't have head-to-head comparisons, this is a difficult question to answer, since we don’t have a very high level of evidence. But I would say that the benefit we have from trifluridine/tipiracil plus bevacizumab is somewhat interesting, especially when we realise it was compared to trifluridine/tipiracil alone. So I think this might be considered as a standard for patients with a very good performance status or for patients with no contraindication to any other medication. For patients with a low volume of disease, especially pulmonary disease, with good performance status, I think these might be ideal patients to undergo treatment with regorafenib. I'm not saying that any other patient could not, but I think that these patients might benefit the most. Perhaps patients with a higher volume of disease, or those patients who do not want to have any kind of skin toxicity, maybe they are not going to be the patients that should undergo treatment with regorafenib. I don't know. What are your thoughts on this?

Assoc. Prof. Gerald Prager:

I completely agree with you. This is a very good approach to whom you would give regorafenib or a TKI. Then of course you might consider also the toxicity profile of the previous treatment and how the patient tolerated the previous treatments. Right? We discussed this before.

So what will the future bring us, Victor? What is in the pipeline that excites you most?

Dr Victor Hugo Fonseca de Jesus:

I think over the past ten years, we have started to understand the molecular biology of CRC to a greater extent. I think one of the big issues that we have in colon cancer is going to be addressed by one of the next developments - the development of anti-KRAS agents. We have seen this with G12C, but now we know that inhibitors against G12D are coming into the clinic and I think the

combinations of these G12D inhibitors with other medications to block MAP kinase pathway might be very, very important. I mean, this is the single most important genetic alteration in CRC that we see in the clinic. So, if we have something that is, particularly active against this kind of mutation, I think this is going to completely change the landscape of treatment for patients with mCRC. I don't know, what are your thoughts?

Assoc. Prof. Gerald Prager:

Yes, I absolutely agree. But at the same time, we have to study the resistance to these new drugs. We have seen this with G12C where there is disease control for a few months and then the patients become resistant to this treatment. So we have to learn what are their resistance mechanisms to be more efficient in the future. But I totally agree, the RAS story is interesting.

So I think it's time to sum up. We have a lot of novel treatment options in third and later lines of treatment of mCRC. Of course we need a molecular profile, but we should have the molecular profile up front before we start systemic treatment of metastatic or non-resectable CRC. Then in the third line and later lines, I think most patients have already had targeted treatment based upon the molecular profile or there is no option for a targeted treatment in the later line. For these patients, we have good options. We have TKIs like regorafenib and in some countries fruquintinib. Then we have the option of oral chemotherapy, which is trifluridine/tipiracil plus or minus bevacizumab where the combination is preferred. Then for those patients who went through all these options, we might consider rechallenging of an earlier line of treatment.

On saying this, I want to thank you, Victor, for this very interesting discussion. I enjoyed it very much and I hope we can do a podcast again very soon. Thank you.

Dr Victor Hugo Fonseca de Jesus:

Yes, thank you Gerald for the invitation. It was a pleasure for me and it was very fruitful for me to discuss these topics with you. Thank you.

Tonke de Jong:

Thank you so much for sharing your insights Dr. Prager and Dr Fonseca de Jesus. We've learned a lot from your discussion on optimising outcomes with late-line treatment of mCRC. If you liked this episode and want to find out more on GI oncology, then look on the 'Oncology Medical Conversation Podcast' under the account of COR2ED medical education for other interesting episodes. Also don't forget to rate this episode, subscribe to our channel or inform your colleagues about it. Thank you for listening and see you next time.