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Cancer-related fatigue

Dr Vaz-Luis: Good morning, good afternoon. It's my pleasure to be here today to speak about cancer-related fatigue in the particular subset of breast cancer survivors. These are my disclosures. So, putting the topic into context. So, we know that a cancer survivor is anyone with a history of cancer from the time of diagnosis for the reminder of their life. Currently, we have over 18 million individuals living with a history of cancer, and these numbers are expected to increase. It's expected by 2040 that we have over 26-millions of cancer survivors. A substantial proportion of cancer survivors are breast cancer survivors. And the truth is that with the corresponding improvement in survival and the corresponding increasing of these numbers, there are an increased awareness of survivorship care challenges, new research priorities, and new needs. It's very clear now that we need to focus on minimizing the physical, the psychological and the social burden of surviving after breast cancer. In this setting, very recently, the CANTO cohort published these data that looked since the moment at diagnosis until two years after diagnosis at the different dimensions of quality of life in over 4,000 patients. Basically, in this slide, we have a very simple analysis where we can see the proportion of patients reporting poor quality of life in the different domains that are recognized as quality of life domains by scales as the EORTC C30 and EORTC BR23, sorry. And what you can see here is that we have a substantial proportion of patients that report poor quality of life, and that this number increases over time. So, in dark blue, you have the proportion of patients with poor quality of life at diagnosis, and then, in a little bit lighter blue, at one year after diagnosis and then, at two years of after diagnosis. And for most of the domains of quality life, this number increases. So, I think this slide shows very well that there are variety of treatment-related sequelae and severe deterioration of quality of life among breast cancer survivors that are dramatic and persistent downstream impact of treatments in several domains of quality of life. And we know that there is substantial under-diagnosis and inadequate management. Among the domains that are listed in the quality of life, we have fatigue, and it's very striking to see that from the 23% of patients reporting severe fatigue of diagnosis, this number increased to 35% at one and at two years after diagnosis. So, what is the...so it's a prevalent issue, and what is this? What is cancer-related fatigue? So, cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional and cognitive tiredness or exhaustion related to cancer or to cancer treatment that is not proportional to a recent activity and that interferes with usual functioning. It's a symptom that is more intense, distressing, and less responsive to rest and regular fatigue. So, it's not the same type of fatigue that non-cancer patients have. It's extremely common and it's persistent. During treatment, it can reach up to 90% and as we saw in the last slide, following treatment, we have around 40% of patients that can have this symptom and this persists over time. So, we have reports that up to 20% of patients, 10 years afterwards, still have persistent severe cancer-related fatigue. So, in the first figure I show, several studies that looked at overtime evolution of cancer-related fatigue. So, these are several series and you can see that over time, we have these consistent figures that show that we have an important

proportion of patients reporting severe cancer-related fatigue over time. And I showed before in the very contemporary cohort the CANTO cohort, we also can see that this is true. So, we have at baseline, and then at one year, two years and four years after diagnosis, almost one third of the patients that after the diagnosis have severe fatigue. Fatigue now we know, it's a very complex and multidimensional symptom. So, traditionally we'll looked at fatigue a lot from the physical sense, but now we know that fatigue is combined with different dimensions: physical, emotional, and cognitive dimensions. And we now are able with specific metrics, specific questionnaires, including the EORTC FA12 to measure these dimensions, and to be able to better understand the granularity and the differences between the different types of fatigue. So, we did this in CANTO, and, as you can see here, so, the physical fatigue reports more or less the same prevalence that we had seen in global fatigue. So, we have about one third of the patients that after diagnosis endure this persistent fatigue. When it comes to emotional fatigue, the trajectory is a little bit different. So, we have about 20% of patients that have severe emotional fatigue over time but it's interesting to see that the fatigue decreases from diagnosis to after treatments showing that the emotional fatigue at diagnosis is very important. Interesting, the cognitive fatigue slightly increased over time but it's very stable from diagnosis until four years after treatment. It's interesting to see the prevalence over time in different time-points; but it's also interesting to understand if patients can have specific trajectories of their symptoms. Meaning can we define what is going to be the trajectory of descent? Can we cluster patients? Can we use longitudinal techniques, Class Latent Analysis, for example, and be able to recognize what are the patients that are going to have one evolution of deterioration or one evolution more of recovery. So, there were some investigators that tried to do this. So, there is a team of UCLA that did amazing job, amazing work focus on cancer-related fatigue, and they use trajectory analysis exactly to try to understand if patients are clustering, if we can identify subtypes, subgroups of patients, that we then will be able to predict their behavior. So, in one first study that was published in 2008 in Health Psychology, you can see that we had a group of patients that since the diagnosis, they always endured very severe fatigue. We had a group of patients that interesting at diagnosis, they had severe fatigue and then their fatigue, there's almost this trend to recover. And then, we had another group of patients that it seems that the fatigue starts to pick-up later after the diagnosis. So, what they call a light fatigue. And then, they have two groups of patients that always had low or very low fatigue. So, these groups of patients low or very low, meaning groups of patients that probably will not be concerned by this symptom. These here, they replicate the kinds same set of analysis to look at the trajectories of a different cohort and they kind of found the same symptoms. So, they found a very reassuring group of patients that they called stable-low, that they always have... that they don't have fatigue over time and then, interesting, they have patients with this propensity to increase fatigue over time, deteriorate their trajectory, the ones that they will ameliorate that trajectory, the ones that have more reactive pattern. So, they don't have fatigue in the beginning that they will get fatigue over time and they will recover. And then, the ones that are stable-high over time. So, this is interesting because this kind allow us to cluster patients in classes and eventually in the future will allow us to tell the patients who are they in this clusters. We did the same exercise in the CANTO cohort. And we did this exercise looking at the global fatigue, but we also look at the different dimensions of fatigue. So, we kind of thought maybe the dynamics that we saw, that we are seeing in the trajectories that the group of power saw, they are very associated with the dimensions. So, what you can see here, so what we found here, here we did trajectory analysis doing Latent Class Analysis, where we try to cluster patients by the risk of a severe fatigue over time. So, we had evaluations at diagnosis year one, year two, and four. And what we could found looking at severe global fatigue is that the vast majority of patients will cluster in this group that they will never have severe fatigue over time. That is the low. Then, we have a group of patients that it's about 20% of patients that they have very severe fatigue at diagnosis and the risk continues to be very high over time. And interestingly, we have this group that has about 20% also of patients, that the risk increases over time. So, it's really a deteriorating group. Then, we took a look by dimension and what we found for physical fatigue? We found more granular information that we found for global fatigue. So, we have a high-risk group, a low-risk group and then, we have these two groups, one that in fact deteriorates over time, but another one that the risk of fatigue it's high in the

beginning, but recovers over time replicating what the group of power shows. In the same one, we found these four trajectories also for emotional fatigue. Interestingly, when we look at cognitive fatigue, we only found two groups of trajectories, the patients with low-risk of cognitive fatigue, and then, a much more small proportion of patients that seems to be always at risk of severe fatigue. So, fatigue is a prevalent subject. It's, as we see, a lot of patients can endure it. As we see by these trajectory analyses, patients are heterogenous and not everyone is going to have the same trajectory. And the other important thing is to know that it can really interfere with normal function and greatly deteriorate quality of life. So, we have studies for a long time that show these. There is these data that comes from 1997 that clearly show that for some patients, they consider fatigue the most distressing symptom, worse than pain that is usually what oncology is considered to be the worst distressing symptom. In addition, so, this old paper showed us that a substantial proportion of patients consider that fatigue was impacting their ability to work, their ability to care for family and it kind of was associated with concerns about survival, hope of fighting, and for them, for a small proportion of them, they were even so dramatic to see that treating fatigue was as important as treating fungus. So, really this paper highlights the importance that this had for patients. We kind of also look at this question using data from the CANTO cohort. And as this is very new data that was recently published. And what we can see here is that clearly fatigue is associated with a decrease adherence to treatment. So, it interferes so much in the quality of life that impacts the ability to take the treatment. And on the other side, we showed in another paper that there is an association and a trend towards the association of reduced probability of return to work. So, it can have an impact on social functions as a return to work. So, clear prevalent, clearly heterogenous, clearly with impact, so, what drives fatigue? What are the associations of fatigue? So, we have several studies that were done and there is this nice review published in 2016 with associations that shows that several factors impact the probability of having persistent fatigue over time. So, classically demographic factors, such as age, income, marital status, they play a role in the development of persistence of fatigue, comorbidity in medical conditions as cardiovascular disease and obesity. It's very important, the role of psychological factors, depression, but also there is a lot of literature about the impact of catastrophizing coping style, comorbid symptoms seem to play an important role. So, the fact that there is pain, menopausal symptoms, insomnia, these play a role in fatigue. When we look at persistence of fatigue, the fact that upfront at diagnosis, we already have fatigue this plays a role. And then, also health behaviors. So, active patients tend to have less fatigue. So, there's bunch of literature that looked at these symptoms, there is also literature about the impact of treatment that is not always consistent. So, my colleague Antonio Di Meglio try to using this concept of associations to build prediction models, to really try to understand who are the patients that...can we predict the patients that are going to develop fatigue? So, he built prediction models at one year after diagnosis, two years, four years, and he kind of found more or less the predictive factors that are consistent with these associations that I spoke. So, health behaviors like tobacco, obesity, he actually found the role of chemotherapy in the year one, and then, hormonal therapy later on. He found an important role of emotional distress and an important role of symptoms, including fatigue of diagnosis. And these models are not perfect, so, they have AUCs that are around 070, 075, but they already are able to do reasonable, good prediction value. So, with this he was able to build equations that allow us to, when we put the characteristics of the patient, have an idea what is the probability of having severe fatigue at two years after diagnosis? So, in fact, for example, for a patient 55, 28 BMI, current smoker, low-income, that is going to receive endocrine therapy, that has anxiety, that has pain, insomnia, hot flashes, and fatigue at diagnosis. So, this patient with these characteristics at diagnosis, we can say that he has a 93% probability to being suffering of severe fatigue at two years after diagnosis. We did the same exercise looking at associations with the different trajectories. And for example, we found, we were able to also build models that we found that, so, risk factors for belonging to the deteriorating group include the younger, heavier, being a smoker, single, higher income, in chemo and hormonal therapy-treated and have more symptoms at diagnosis. So, there is a parallel between the prediction at different time points, and then, the factors that we found in the trajectories analysis. So, what drives fatigue? And so, I think there is a lot of science that is being explored in terms of what can really drive fatigue. There are psychological and behavioral processes. There is probably

neuroendocrine dysregulation, alterations in cellular immunity. There are consistent data that show that cancer survivors with persistent fatigue have elevated markers of inflammatory activity. What we don't really know is if this may affect an increase activity of pro-inflammatory cytokines signaling the brain to produce symptoms of fatigue, or maybe, it's because individuals who are prone to produce more pro-inflammatory cytokines may be at higher risk of cancer-related fatigue. So, there is this association of inflammation and fatigue. There are a lot of studies that look at this association and that seem to validate it. It's not really clear what is the longitudinal track of these two phenomenon, fatigue and inflammation. Once again, the group of UCLA did several studies about this, what you can see in the first slide, it's the evolution of fatigue and the evolution of CRP over time. And it's interesting to know that in these two patients that they studied, they kind of track very well. They did another study that they looked at an inflammatory marker among patients that were treated with no chemotherapy and chemotherapy. And it looked that the among patients treated with chemotherapy, there was more a correlation between the inflammatory marker and the fatigue severity, calling into the question that there's maybe a role of treatment and blocking this pro-inflammatory state and things associated with fatigue. The same group also looked at the expression of alleles, genes that are associated with inflammation. And so, what they did was, they created a score using the at-risk alleles and what they can confined was creating like a score that has a genetic component, that seems to indicate that some patients with this genetic background are associated, will have a higher likelihood to have fatigue. And what you can see in this second figure it's exactly this. So, you have associations between three individual snips on these three inflammatory genes and the phenotype of fatigue. So, these three are only three examples of studies that were done, that kind of linked to this phenotype with inflammation. What is important now is to put this in the context of a longitudinal study. So, we know this is an important symptom. We know that has an impact for patients, that it can be flagged by clinical variables, that they're probably a biological subtract. How can we manage fatigue? So, the first thing important to say is that we have data that shows that it's often untreated and unaddressed. So, something that we all have to be aware of to do a better job. And there are guidelines in different societies, ASCO, ESMO, NCCN, that now can help us, the medical community, to better treat fatigue. So, what I show here, it's some tips that ASCO guideline gives us that are very consistent with what happens with other guidelines. So, one important thing is to screen. So, one important screen is consistently ask your patients if you have fatigue or not. Then, if they had fatigue, it's important to do a comprehensive and focused approach. And one important thing is to rule out, identify and treat any underlying conditions. So, there are medical situations that can be the factor of this state. So, endocrinological situations, for example, hypothyroidism, lung disease, cardiovascular disease, So, it's important, even the relapse of the cancer really. So, it's important to identify and treat the underlying contributing factors. When we do this evaluation and we cannot identify underlying and contributive factors, non-specific interventions may be useful. And we have more and more data calling into the benefit of these non-specific interventions. So, these are the guidelines of the NCCN that are replicated a little bit in the other guidelines. So, the first thing is a physical activity. We have several data that were already aggregated in different meta-analyses that show that patients that are able to maintain a physical activity, they will benefit in terms of their fatigue. So, fatigue will decrease in patients that are able to maintain an optimal level of physical activity. The recommendation is to do at least 115 minutes of moderate, aerobic activity, and two or three sessions per week, it's per week, two or three sections per week of strengthening. Then, we also have good data about the value of psychosocial interventions. And here we have different types of psychosocial interventions. We have, for example, data on education interventions. Several years ago, they have studied that showed that only a 30-minute video of education about how to cope with after-cancer could have a good impact on fatigue. We have other studies, other randomized trials that show that more focus, 12-week sessions focus on different subjects around fatigue can be helpful to cope with the symptom. And there are even, and in addition to these, education therapies, there are a lot of evidence showing that cognitive behavioral therapy can be helpful to treat this symptom. We have some other data that suggest the benefit or mindful-based stress education, of strategies like yoga. We have less consistent data, but some data about the effect of acupuncture on fatigue. It's important to say that when we speak about fatigue after-

cancer, we don't have any pharmacological option with evidence that can be helpful to treat fatigue. So, are we doing a good job in managing fatigue? Are our patients up-taking, you know, physical activity or psychotherapy to treat their fatigue? So, my colleague, Antonio Di Meglio tried to look at these in the CANTO cohort. And so, the first thing he did was try to look at the utilization of physical activity and then, the utilization of psychology, psychiatric, acupuncture, consultations, but also, about complimentary medicine that we know that is not useful to treat fatigue in the population. The utilization between the end of the treatment and one year after the end of the treatment. And the first thing we can see is that, although, we have a substantial proportion of patients that are active, we have more than 30% of patients that have persistent insufficient activity and some that had reduced activity. So, we have one third of the patients that can improve the uptake of physical activity. And then, what we found is that we have a very small proportion of patients that either saw a psychologist, a psychiatrist, a very small proportion of patients that saw acupuncture. That is even smaller than the ones that report to do complimentary, oral medicine. The other thing that he saw was try to tease out among the patients that had or not fatigued after treatment, is there a difference in the uptake of these types of activities? And what you can see here is that, if anything, the fact that you have fatigue decreases the odds of being physically active. When it comes to the consultations with other healthcare providers, again, very small numbers overall across the board. So, it's not something that we are using a lot in our patients, but here, the fact that you have fatigue increases the probability of reaching to a psychologist or a psychiatrist, to acupuncture. We have the sense with these data, that there is a room to better management fatigue. And so, we...there are several researchers that try to explore the preferences and barriers to the management of fatigue. So, Dr Charles, she runs key-informative interviews with patients exactly to explore, like, what are the preferences and barriers to the management of this symptom. So, she looked at this in a very few patients with deep interviews, and in this population of patients, most of them were doing physical activity. And then, you have a very few patients that were doing mindfulness and none were doing, actually, had help. They had done, like psychological or psychiatric consultations. It's interesting to say that all patients were not physical active, declared that they should move more. And although, no one had a defined project, so, patients know that they should know more. What are the barriers that they identify? They identify physical barriers. So, the fact that I'm fatigued, it's itself a barrier. They also identify psychological and social barriers, lack of motivation, lack of social support, environmental barriers. It's difficult to go to places where I can do these. The winter also can be a barrier and that they also identify levers. So, they say that the fact... if we have a friend that can do physical activity, it can be helpful and overall, they all had a very positive representation of physical activity. It's something that they identify, it's something that feels good, that can in fact help, it's just a question of getting there. We did the same exercise when it comes to providers. So, we asked providers, this was my colleague, Elise Martin. So, what are the barriers to manage fatigue? So, most of the providers, they say that they recommend physical activity. All the other things, the psychosocial interventions, mind-body interventions, they are much more refractory and they all are unanimous to say, I understand that I don't care as I should about cancer-related fatigue. The barriers were resources of barriers, so, they felt that they were not, that in terms of the resources in the hospital and outside the hospital, they were not available to allow them to address this symptom and refer patients. Also, a question of time and priority. If I have a 15-minute consultation, I will not address fatigue. I will address other subjects, a question of social representation and stereotypes. When it comes with psychosocial interventions and mind-body interventions, there are colleagues that were not so comfortable, given stereotypes to address these issues. And most of them said there was in fact, a lack of knowledge and need of training and the need of more information to give to the patient an evidence-based approach. It's important that we try to overcome the barriers and try to give, you know, all these resources, physical activity, but also, psychosocial help in innovative ways. So, there are several studies that look at the use of physical activity, digital tools to help to treat fatigue and other symptoms. This is just an example of a study that was done that use digital gamification to promote physical activity, and that the patients were very open to these strategies. My colleague, Dr Cecile Charles is also trying to put together a digital approach to give psychosocial approach to patients with fatigue. We did a personalized cleaning focus on fatigue in our

institution, was a very small pilot experience. And so, we're basically a multidisciplinary team of people. We're addressing patients with severe fatigue that were referred by the oncologist. This is very small experience, but overall, this shows us that the patients, when they were addressed and they saw their fatigue complain to be addressed, and they were really satisfied with this experience. And even if only in half they really saw their fatigue improved, overall, they would recommend this clinic to be implemented in a more broad way. So, what I hope is that we are able to merge the knowledge about fatigue and the knowledge about how to take care of patients, and move to more a comprehensive way to address these symptoms that can arise since diagnosis. So, ideally what we should be able to do is to screen patients and to upfront offer them the ability to be treated and managed by these symptoms. So, in conclusion, cancer-related fatigue is a highly distressed and prevalent symptom. We have some ability to predict fatigue, but it's still not optimal. We probably will have to understand more about biology of this symptom and about treating cancer-related fatigue, we have a substantial number of evidence that are some strategies that can help, but we need to optimize the implementation of the available strategies to treat cancer-related fatigue. I would like to acknowledge all my collaborators and my funding agencies, and I will open this discussion.

Prof Joly: So, I have a couple of questions, as you can imagine, just to have your point of view, if we have a look of your data, we have the feeling that in fact, persistent fatigue is mainly driven by physical fatigue. And so, what do you think if is this part of fatigue, we should work on it?

Dr Vaz-Luis: I think it's true that you have, so, this idea of deterioration after-cancer and cancer experience, it's more preeminent when you look at the physical dimension of fatigue. I think there's probably in the emotional fatigue, you still have a substantial proportion of patients that endure, but the trajectory is almost the opposite way. So, inverse the scheme. So, I think it's true that it seems that for most of the... then there is a lot of overlap between the dimensions. So, when we split the dimensions, we don't see the overlap, but it's true that, I agree with you, that you have this perception of an important prevalence of this dimension of physical fatigue. Saying this, when we look, when we forget fatigue, and we look at the domain, like the emotional distress and cognitive distress, these are different concepts that are not to be neglected. But when it comes to the dimension of the fatigue, it's true that I think, although all are important, probably, all have a different management. You have a substantial proportion of patients that endure physical.

Prof Joly: My question is just to stress on the potential action we could start very early during the treatment, because, maybe, it's easier to try to develop some program, to help the patient to have physical activities. And maybe, to give them a new way of life. And probably, it's a point we could work on it easier than other actions. So, that's why my question, to say, should we stress on the importance of physical activity during treatment, not waiting for the end of the treatment, because, maybe, it's too late to prevent the long-term increase of physical fatigue?

Dr Vaz-Luis: So, I think that there are two important things is...we focus a lot on management. So, we focus a lot on being reactive to something. And I think you are right. We have to start to be more proactive and we probably have to have these trials that show that if you are able to flag patients and to be proactive since diagnosis, that you are able to decrease these numbers. About the physical activity, I think another thing is because all our studies mixed physical, emotional, cognitive, fatigue, we really don't know which of the interventions, the physical activity, the psychosocial help each of the dimensions. So, I agree with you that we have this idea that physical activity will be something that will fit very well the physical fatigue, but there may be also this other, as you said, actually, this other component of more psychosocial programs that can also help that component. I think you're right. I think patients that suffer from physical fatigue, they may be a subset of patients that if we work earlier in a comprehensive way, we are able to recover.

Prof Joly: Yeah, actually, I agree with you. If we work on physical fatigue, we will work on the other dimensions of fatigue. It's all on the same packet in fact. So, that was my first question. I have another

question. So, you showed that chemotherapy is one of the parameters of fatigue. And what about with hormonal therapy? Because there's less evidence. What is your opinion?

Dr Vaz-Luis: We know our models. You have...so you have this time-impact. So, you have in the first time-points the chemotherapy shows up, but then, you have an impact of hormonal therapy over time. So, when you arrive to the lighter segments, you have an impact of hormonal therapy that calls to this question, that, in fact, we have to continue to care about patients over time. And then, even if we have this belief that oh hormonal therapy is easier, it's not. And in fact, when we look at the adherence data, fatigue is one of the determinants of non-adherence to treatment, so, showing like this triangle of associations.

Prof Joly: Yeah, but the question that is difficult is to know, is the patients are tired because they have hormone therapy or if because they are tired, they stop hormone therapy because they think it's a link with.

Dr Vaz-Luis: The casualties, is always difficult. But independently, there is this association that you see in later time-points of the persistent fatigue with the treatment of hormonal therapy.

Prof Joly: It's particularly important to prevent the patient, to explain to the patient that she could have some fatigue during the period of hormone treatment, because it's during a couple of years after chemo and it's not a fatality.

Dr Vaz-Luis: And I think that's, this is interesting that you say, because, maybe, what we have to get better, it's communicating the risks of side effects. You know, it's true. It's not the fatality, we have a huge proportion of patients that don't have it, and we can do things for to help the ones that develop. But we have to get better in communicating. When we speak about hormonal therapy, we often speak about hot flashes, vaginal dryness, are challenges we often don't tell the patient that fatigue can go in the package and we are not even able to quantify how this increases the risks. So, we have a work to do on there.

Prof Joly: Oh yes, I think it's particularly important because I realized during my clinic, if I have well explained to the patient the risk, they better accept the symptoms. Another question, very interesting question about the link between inflammation and fatigue. What do you think about the role of cancer per se and the generation of fatigue?

Dr Vaz-Luis: So, I think that's the one-million-dollar question. What comes first, you know, what is the causality? I think that there is probably a role between cancer itself and also, the treatments and this generation of pro-inflammatory status that can contribute to the development and persistence of all of these symptoms as fatigue. So, they're probably, and this, we cannot show with these data because we have data only at the diagnosis. So, the patient already has his tumor, and I think that's what we are missing in all these stories. So, there is this association, but what starts first? You know, what is the line of the longitudinal track of events? And that, I don't know the answer. Maybe you know better than me.

Prof Joly: No, no, no, I don't know. I think both, in fact. I think the concept can induce some inflammation and induce some fatigue, but on the other end, we have already shown that treatment itself can modify the inflammatory environment and induce inflammation as well. So, probably, it's a mixture of different causes. That's why it's so complicated. And it's particularly complicated when you have metastatic disease. Maybe, it's less complicated for localized cancer, but when we have some patients who complains about fatigue in the metastatic setting, it's difficult to do who is responsible. So, another question, I see there is a lot of initiative for information by internet. But what about the interest of group of patients with therapeutic education? Is it something we have to push and to develop?

Dr Vaz-Luis: We actually, in all this like-focus groups and key-informant interviews, you realize that patients are very different and there are patients that want the digital, there are patients that want the in-person and there are a lot of patients demanding like this group-experiences, this in-person group-experience. So, I think there's probably a role in the pathway of the patient of integrating all these modalities. You've kind to pursue

and try to personalize what will fit best each patient. But definitely, what we found out in a lot of focus-groups is that there are some patients that really ask for this type of group educational- based approaches in-person.

Prof Joly: It's very complicated because we focused today on the topic of fatigue, but usually, there is some other symptom as well. So, it's very difficult to organize management who can take account all the symptoms for one patient. And this is the complexity of the type of intervention in fact.

Dr Vaz-Luis: Yeah, for sure.

Prof Joly: I think I asked all my questions. Thank you so much for this excellent work you do with CANTO and it's really important for the community because we improve the care of the patient with all these data. Thank you so much.

Dr Vaz-Luis: Thank you. Thank you so much.