SPEAKER: One of the most relevant, frequent complications is graft versus host disease. And actually, graft versus host disease, both in its acute and chronic forms, is the most important complication that limits the success of allogeneic transplantation. Graft versus host disease has two forms, an acute form and a chronic form. They are very different diseases, and they usually happen at different times, although they can overlap to a certain extent. And I'm going to talk about both of them separately.

Acute graft versus host disease is a complication that occurs in approximately half of the allogeneic transplants that are matched, related, a little more than half in those that are matched and unrelated. So it's a very frequent complication, because this is in the setting of effective, or what we know as effective graft versus host disease prophylaxis. So basically, that prophylaxis does not work in half of the patients, roughly.

It is a reaction of the donor T cells that come with the graft against the patient's tissues. And the reason, that the pathophysiology of graft versus host disease has different components I would divide these components into groups. The first group is the cytokine component, what has been called the cytokine storm, that is triggered by the damage induced by the preparative regimen, that is, high-dose chemotherapy and/or radiation therapy. This damage results in inflammation, and this inflammation has pro-inflammatory cytokines that cause it. In addition to this inflammatory component, there is a donor T cell that encounters foreign antigens.

The three tissues that are affected by acute graft versus host disease include the skin, the GI tract, the gastrointestinal tract, and the liver. It can involve one or more organs. The more organs involved, the higher the degree of severity. And also, there are different grading systems that will stage each of these organs separately depending on the degree of damage and the severity of clinical manifestation.

So the staging of each individual organ will result in an overall grade of acute GVHD. Acute GVHD, as I said, is frequent. It happens usually in the first three months post-transplant although it can happen later. And some people call this late acute GVHD. That is when acute GVHD occurs between the third and the six month post-transplant.

Chronic graft versus host disease is defined through clinical manifestations. There are two syndromes, which I would say are the majority of the cases of chronic graft versus host disease. One of them is lichenoid chronic graft versus host disease, because it mimics lichen planus, another autoimmune disorder, and the other one is sclerodermatous chronic graft versus host disease because it mimics systemic sclerosis, another autoimmune disorder.

So the NIH consensus was the first effort to try to make sense of a lot of aspects of the disease that we did not understand. As I said, the consensus came up with the definition of what was chronic graft versus host disease. And the definition, as I said, was clinical. You may remember that up until this point, chronic graft versus host disease was defined chronologically-- that is, any graft versus host disease occurring after day 100. Well, there is nothing special about day 100 post-transplant. And then we all knew that we just needed to get together and define what clinical manifestations were typical of this disease and make those clinical manifestations the defining points of the disease.

As I said, there is a lichenoid subtype. There is a sclerodermatous subtype. Both of these types affect mostly skin, and also mucosa, including eyes and mouth. They can actually coexist in the same patient-- that is, a patient can start out having predominantly lichenoid features, and move on to having some sclerodermatous features as well. So it's not all black or white.

The NIH consensus has also worked on a staging system, where we can risk stratify chronic graft versus host disease into mild, moderate, severe, which as we will see, has implications for treatment. And also, it came up with a system to measure response to therapy. So I think a lot of advancement has been made in terms of categorizing and defining the disease.

Now, chronic graft versus host disease is the main long-term complication of allogeneic transplant. And actually, it affects a group of patients that is otherwise cured from their malignancy. And chronic graft versus host disease has been associated with a lower incidence of relapse. So these people usually change the problem of having cancer to a new problem, that when moderately severe to severe, it can impact not only their survivorship but very importantly, the quality of life in these people.

So as far as chronic GVHD, as I said, it's a different disease with a different pathophysiology, because we believe that it's more of an autoimmune pathophysiology. At this point, the host has, to put it simply, taken ownership over the graft, but the graft still does not tolerate the host. And I mean tolerance from an immunological perspective.

The pathophysiology of chronic graft versus host disease is a lot more obscure than the one of acute graft versus host disease. And this has different reasons. Mouse models in chronic graft versus host disease are a lot more complicated, and they may not replicate the disease that we see in humans in an accurate way, or just as accurate as a mouse model for acute GVHD might do. So there is very little that is known as far as its pathophysiology.

But recently, at the beginning of the 2000s, the NIH gathered a group of people that formed what we now know as the NIH consensus group for clinical trials in chronic graft versus host disease, that was charged with the mission of coming up with a better description of the disease, better staging systems, better ways of measuring response, better ways of defining what were adequate palliative therapies for chronic graft versus host disease, and also clinical trial design.