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Treatment: The Right Royal for the Castle?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

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Dr. Casper:
This is CME on ReachMD, and I'm Dr. Corey Casper. Here with me today is Dr. Sudipto Mukherjee.

Let's get right into today's topic, Dr. Mukherjee. What can you tell us about treatment guidelines that are in place for treating idiopathic multicentric Castleman's disease, or iMCD?

Dr. Mukherjee:
Most of the evidence in support of trading iMCD comes from the international evidence-based consensus treatment guidelines for iMCD that was just recently published in Blood in 2017 [Blood. 2017; 129(12):1646-1657.]. And based on those treatment guidelines, all patients diagnosed with iMCD are recommended to start treatment on anti-IL-6 monoclonal antibody therapy with siltuximab. Siltuximab, in fact, is the only FDA-approved drug for managing iMCD in the US and is also recommended as a first-line therapy by National Comprehensive Cancer Network. It is administered as an intravenous infusion once every 3 weeks.

However, initiating therapy and what is the right therapy for each patient depends upon the underlying clinical condition of the disease and the availability of the drugs. Up to 10% to 20% of iMCD patients can present with severe iMCD, which is marked by multi-organ failure and requiring life support such as dialysis, intubation, vasopressor support. And in such cases, where there's a cytokine storm with a very high circulating levels of IL-6, a more aggressive approach might be needed for a quick disease control. And in most such cases, high-dose steroids with siltuximab as the initial combination regimen might be a reasonable approach. If the patient declines on this initial combination regimen or we do not see any improvement within a week, then in those cases, it may be reasonable to employ multi-agent chemotherapy based on lymphoma or myeloma-based regimens.

Additionally, siltuximab is not available in all countries around the globe. Where siltuximab is not available or is not approved by the regulatory agencies, it is reasonable to use tocilizumab. For example, tocilizumab is the primary IL-6 monoclonal antibody used in Japan. And in some countries where neither of these drugs are available or approved, it is reasonable to start with rituximab, which has been reported in several case series.

With rituximab there is published data showing a role for rituximab, but it seems like it is most effective in patients with iMCD who do not have any marked cytokine symptomatology or marked organ dysfunction or lab abnormalities. However, the caveat is rituximab has never been rigorously tested in clinical trial like siltuximab, and wherever possible, siltuximab should always be the preferred first-line therapy. In most of these patients, they do end up getting on steroids, and steroids are useful adjunctive therapy for initial disease control, but should be quickly discontinued because of their long-term side effects.

Importantly, in all iMCD patients treated with IL-6-directed therapy, about 50% would at some point fail to respond to these therapies. And for these patients, currently, there are no standard of care. A variety of agents being tested in clinical trials are considered

candidate targets. One of the best evidence-based data suggests a role for mTOR inhibitors such as sirolimus that is currently being tested in a clinical trial. Other candidate targets include CXCL4 inhibitors or targeting the JAK/STAT pathway. There are various other agents that have been used to manage these patients. And there are case reports in the literature, but none of them have been rigorously tested or validated.

Dr. Casper:
Thank you, Dr. Mukherjee. You did a wonderful job summarizing very complicated treatments and options for Castleman's disease. Just to sort of amplify what you said, so first and foremost, this is a disease that is mediated by making too much interleukin-6. So by international guidelines, the first line of therapy is an anti-IL-6 inhibitor. Siltuximab is the medication that has been tested in randomized controlled trials and licensed by the FDA for this purpose. There are other IL-6 inhibitors that have been less rigorously studied but are more widely available in other parts of the world, like tocilizumab. These are options as well. The majority of patients will respond to siltuximab, but among those who don't, there are other options in the future.

So this has been a great initial bite-sized discussion. Unfortunately, our time is up. Thank you for listening.

Announcer:
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