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LDH and Evolving Treatment Success?

Announcer:
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Dr. de Castro:
Hi, my name is Carlos de Castro. I'm a professor of medicine at Duke University Medical Center in Durham, North Carolina. Today's talk is entitled, LDH and Evolving Treatment Success. And my goal is to talk about the role of LDH in the management of patients with paroxysmal nocturnal hemoglobinuria. What is lactate dehydrogenase or LDH? LDH is an enzyme that's found in nearly all living cells. It catalyzes the enzymatic change from lactate to pyruvate and back again, and as such, it converts NAD+ to NADH and back, and is important in anaerobic glycolysis. It can be a marker of tissue damage, but it's very nonspecific because it's found in all cells. The LDH enzyme itself is a tetramer consisting of four subunits, and it's different mixtures of these subunits that lead to five isoforms. As you can see here, LDH 1 through 5, and the tissue that they're associated with, but again fairly non-specific. Clinically, we rarely measure isoforms anymore as it just wasn't clinically that helpful. An elevated serum LDH reflects tissue damage. Because LDH has such a wide tissue distribution, however, it's very non-specific as a diagnostic tool and causes of elevated LDH, and this is just a partial list, can include things, such as hemolytic anemia, B12 deficiency anemia, a variety of infections, infarction of all sorts of tissues, such as bowel, myocardium, or lung, acute kidney disease, acute liver disease, rhabdomyolysis, pancreatitis, bone fractures, cancers, especially testicular cancer, and lymphoma, severe shock, and hypoxia.

LDH is not very useful diagnostically, but it certainly can be used as a biomarker. And we use it as a biomarker for prognosis in certain diseases. I know we already mentioned testicular cancer and lymphoma, but it can also be used to follow treatment effectiveness. So if you have a patient with lymphoma and you treat them with chemotherapy or immunochemotherapy, you can use the LDH to sort of measure how well they are responding.

LDH can also be used as a marker of hemolysis, but it has to be in the right context. And that's usually in somebody who's anemic with a decreased hemoglobin or an elevated reticulocyte count, and/or a low haptoglobin, and/or a elevated total or indirect bilirubins. So all of these are markers that we use to look for hemolysis and determine whether the hemolysis is intravascular or extravascular. In PNH, especially untreated PNH, LDH levels can be markedly elevated due to intravascular hemolysis. And it's not uncommon for us to see them in the 1000 to 2000 range. So 10 times normal levels. In PNH patients who are treated with a C5 inhibitor, LDH levels fall to near normal, but often not normal levels, and I'll show you that on the next slide, and this may reflect some ongoing extravascular hemolysis that occurs.

Here was the TRIUMPH study where eculizumab was randomized to placebo. And you can see what happens to LDH levels almost immediately after starting eculizumab the C5 inhibitor. LDH levels fall dramatically within the first or second week to near normal levels but not quite normal, which is represented by the dash line. Whereas patients who are on placebo continue to have ongoing intravascular hemolysis that leads to levels in the 2000 range. In the PEGASUS trial, we looked at pegcetacoplan and compared that to monotherapy with eculizumab. Pegcetacopian is a C3 inhibitor that should block not only intravascular hemolysis, but also extravascular

hemolysis that occurs. And you can see that when we did this, the LDH levels fell to normal range in patients on the pegcetacoplan in most cases, with just a very little variation there, indicating, again, that blocking extravascular hemolysis will lead to normalization of LDH levels, and this has been quite dramatic.

So in summary, I use LDH as a marker of hemolysis in PNH. I use it to monitor how well they are responding to therapy and in cases where the LDH may still be elevated, I may look to see if there's ongoing extravascular hemolysis and if the patient symptomatic we may consider switching them to a C3 inhibitor. Thank you for your attention.

Announcer:
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