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The Safety Equation: Managing Adverse Events Associated With CSF1R Inhibitors in TGCT

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Dr. Gelderblom:
This is CE on ReachMD, and I'm Dr. Hans Gelderblom. Today, I'll discuss management strategies for adverse events associated with CSF1R inhibitors in TGCT.

So on this slide, you can see the Kupffer cell inhibition in the liver, which is temporary due to the CSF1R inhibition. And this is very important to realize because the enzyme elevations we see in the lab works of these patients—and this could be CK, liver enzymes, amylase, lipase, and others—are due to reduced clearance of enzymes due to Kupffer cell inhibition and are not indicative of organ failure.

That's important. And it's also important in your letter to other physicians so they understand when they do regular lab works elsewhere.

The duration of the side effects are shorter with TKIs as with monoclonal antibodies due to the longer half-life of monoclonal antibodies. And it could take up to a few months after stopping these monoclonal antibodies that you can still see these enzyme elevations.

Pexidartinib is available in the REMS program; I'll come back to that later. And so it's important to realize that this is a temporary, reversible thing.

So the REMS program of pexidartinib was installed because there was a rare but serious liver toxicity in a few patients in the registrational study. So in practice, the loading dose was skipped, and the prescription was only possible after physician and patient education. There were frequent liver labs in the first month because the liver side effects did occur in the first 2 months. There were 4.7% hepatic adverse events, and they were all reversible, and one patient restarted pexidartinib. So it's important—if you follow the rules of the REMS program, pexidartinib can be safely administered.

Edema is another thing. And you can see here on the picture, edema of the hands and also the dimpling of the skin due to edema. And edema is different from edema that you can see with heart failure. This is due to the increased MMP-2 and -3 and hyaluronan, and that's due to the CSF1R inhibition. So it's really a thing of the skin and not of cardiac decompensation or other reasons that we usually see with edema. So this edema does not respond to diuretics. It's important to know that. It's usually mild, but it can be up to 10% of body weight in some of these patients. So you have to follow the weight and listen and see your patient.

There may be a reason for dose interruptions or dose reductions because it's difficult to treat, but usually, it's not really bothering the patients. So again, with monoclonal antibodies, it can last for several months; with TKIs, it will be of shorter duration.

Skin itch and skin toxicity comparable with other TKIs but more than because of the specific CSF1R inhibition. The itch usually precedes skin toxicity and may respond to antihistamines in my practice. And skin tox is usually mostly seen in sun-exposed areas, so you have to explain to your patient that they should avoid too much sun exposure and use UV protection. In very rare cases, there might be lupus-like reactions, but very, very rarely. So involve your dermatologist when not under control, and it may be, again, a reason for dose reductions.

So other common side effects are the whitening of the hair—and this is only with pexidartinib—due to the off-target effect KIT blockade. And fatigue is a side effect that can be seen. Headache and hypertension, although this is also seen, of course, in the general population. And fertility probably is not a problem, but we need to have more data.

So this, again, is all the time I have today. I hope this brief review of toxicity was useful for your practice, and thanks for listening.

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