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Unlocking the CSF1R Code: Targeted Pathways and Tailored Choices

Announcer:
Welcome to CE on ReachMD. This activity is provided by AGILE and is part of our MinuteCE curriculum.

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Dr. Gelderblom:
This is CE on ReachMD, and I'm Dr. Hans Gelderblom. Today I'll review the rationale for targeting CSF1R in tenosynovial giant cell tumors, or TGCT.

TGCT is a CSF1R-driven tumor. CSF1 is fused to COL6A3, and these translocations result in overexpression of CSF1. The proposed mechanism of tumor growth is an autocrine loop with CSF1R leading to CSF1 upregulation and a paracrine loop leading to recruitment of neoplastic inflammatory cells.

So after this description of the mechanism of disease, it was only a matter of time that oncologists following this field would start using the available CSF1R inhibitors to treat these patients as a proof of concept.

This is a French patient published by Jean-Yves Blay in 2008 that was given the, albeit weaker, CSF1R inhibitor imatinib, but that was just the drug that was available for patients. And as you can see, these patients had a quite nice response to CSF1R inhibition.

So after the nice report of the index patient published by Dr. Blay, several medical oncologists in sarcoma centers started treating patients with recurrent or extensive TGCT with imatinib. Overall, 58 patients were treated, and of these, 38 discontinued imatinib after a median of 7 months. The response rate was only 31%, but after all, imatinib is a weak CSF1R inhibitor. That's the story about imatinib, which is important to know in the background of the newer drugs that are coming.

Another drug that is available is nilotinib. Nilotinib is also a weak CSF1R inhibitor, and this was studied in a formal phase 2 study, and presumably with less edema as toxicity, but still a lot of patients stopped early because of a lack of benefit.

On the waterfall plot, you can see that there are few partial responses, but both drugs are sometimes used when other treatments are not available.

Then the new generation of specific CSF1R inhibitors. In the beginning, monoclonals were studied, so by infusion, cabiralizumab—there's only an ASCO abstract from 2017—and also intra-articular administration of AMB-05X that was recently published, a phase 1 study.

Emactuzumab was studied in a phase 1 study a while ago, and recently, a randomized study called the TANGENT study was performed. Results are not available yet.

Several tyrosine kinase inhibitors were studied in this disease. The first one was pexidartinib in the registrational study, ENLIVEN. And this drug was FDA-approved in 2019 but not available in many other areas. And it is available through a REMS program in the US.

Vimseltinib was approved this year in 2025. This was based on the registration randomized MOTION study. And the newest drug is pimicotinib, studied in the MANEUVER study, and this is under review at several authorities in several continents.

For now, my time is up, and I hope you found this overview helpful, and thanks for listening.

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