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tTF-NGR – A procoagulant fusion protein to induce tumor infarction

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Medical need

Anti-angiogenic agents, which inhibit the formation of new blood vessels in tumors, are well established in a number of neoplastic diseases. But what happens when such vessels are already present? Then anti-vascular agents that destroy the existing blood supply would be preferable. However, many attempts to develop such agents have failed.

Suggested solution

It has long been the goal of Wolfgang Berdel to induce coagulation and thus thrombotic occlusion in the vasculature of a tumor by activating tissue factor (TF). As a coagulation protein, TF normally adheres to the abluminal side of the endothelial membrane to become active after injury by initiating the formation of thrombin, a crucial step in blood clotting. At first glance, this goal may seem counterintuitive, since TF is usually systematically pro-tumorigenic. Berdel and his team circumvent this risk by targeting truncated TF (tTF) to the tumor-specific protein CD 13 on the luminal side of the endothelium via a small peptide linker containing the amino acids asparagine, glycine and arginine (NGR). Their lead compound, tTF-NGR, shows stable and specific anti-tumor activity.

Current Status

Due to the limited research time of the principal investigator, who was a university hospital director, insufficient funding and high regulatory hurdles, 20 years elapsed between the conceptualization of the tumor infarct approach in 1997 and the start of a Phase I trial with tTF-NGR in 2017. Convincing preclinical data were published as early as 2011, but it took another five years to obtain approval for GMP production of the recombinant drug in a clean room facility. The Phase I trial with tTF-NGR alone was successfully completed in December 2019, demonstrating safety and effective shutdown of tumor perfusion. Recruitment is currently underway for a randomized, multicenter Phase III trial in 126 patients with metastatic sarcoma. Half of the patients will receive standard therapy with trabectedin and half will receive standard therapy plus tTF-NGR. The primary endpoint is progression-free survival.

Translational Gap (ForTra Funding)

ForTra provided unbureaucratic support to Berdel and his team to move their project into Phase I by funding the establishment of the GMP manufacturing facility.

Perspective:

The Phase III study (called TRABTRAB) must be conducted with caution and in a clinical setting with specific hemostaseology expertise, also because trabectedin affects the pharmacokinetics of tTF-NGR. Results are expected in three years.

Reference

Berdel AF et al. Targeting Tissue Factor to Tumor Vasculature to Induce Tumor Infarction. Cancers (Basel). 2021 Jun 7;13(11):2841. http://doi.org/10.3390/cancers13112841.

Link to further information

https://www.ukm.de/kliniken/medizinische-klinik-a/forschung/ag-schwoeppe-peptid-basiertes-vaskulaeres-targeting