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Magnetic vectoring for drug delivery to tumors: Past, present and is there a future?

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The concept of using external magnetic fields to drive drug-loaded, magnetically-responsive particulate carriers into tumors has been long-standing, first demonstrated in a pre-clinical, loco-regional administration setting by Widder and colleagues more than 30 years ago. Further, 15 years later, an initial clinical trial of magnetic drug targeting using nanoparticles loaded with chem-adsorbed epirubicin was conducted in 14 patients with carcinomas and sarcomas, and some objective clinical responses were observed. Nevertheless, further development of this strategy since then has been virtually non-existent in terms of clinical impact. We propose that the basis for this stagnation may reside in the complex dual and mutually interdependent arms of this technology: the carrier-drug complex itself and the external apparatus that creates a magnetic field gradient that enables directed extravasation via the EPR effect. Regarding the carrier-drug complex, a major challenge is optimizing the control of drug release from the carrier to occur predominantly at the tumor target site and minimizing drug release while in transit in the plasma or in non-target normal tissues. This may require the synthesis of prodrugs with tunable stability and release characteristics, an approach that has recently been validated in our laboratory and now also in others. Regarding the generation of the external magnetic field, scant progress has been made beyond single permanent magnets abutting the intended tumor target area. Without development of more powerful magnetic capability, this technology would appear incapable of progressing beyond treatment of anything more than superficial tumors, greatly limiting potential clinical utility. Applications to visceral tumors, such as inoperable pancreatic tumors, or to disseminated metastases--the overwhelmingly predominant cause of patient mortality would be largely infeasible. To address this need, we are developing prototype arrays of multiple permanent magnets that might provide the initial steps in the transition from superficial applications, such as locally advanced breast cancer, to visceral tumors and sites of frequent metastases: Bone, brain, lung and liver. Results to date in an orthotopic triple-negative human breast tumor xenograft model indeed reflect the ability of an experimental array to cause tumor accumulation of magnetite-based nanoparticles despite being placed a considerable distance from the tumor, but focused on it. Further development of this approach is viewed as a relevant transition to the ability to cause magnetic nanoparticle accumulation at deep aspects of superficial tumors, as well as at visceral and metastatic tumor sites.

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