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Cover story

Acoustic Cluster Therapy for better treatment of solid tumors

For most drugs, systemic administration results in very inefficient delivery to solid tumors. Typically, less than 1% of the injected dose actually reaches the target tumors. The delivery is slightly increased with nanoparticle-based delivery systems, but the delivery is still limited to 2~3%. Researchers in the pharmaceutical field have spent vast resources in finding functional concepts for targeted drug delivery. Over the last decade, microbubbles in combination with ultrasound (US) have been extensively explored for this purpose. Microbubbles are usually co-injected with a drug followed by local US insonation of the target site. Bubbles that are insonated while confined in the vascular compartment exert a variety of biomechanical effects on the endothelial wall, which in turn induce improved extravasation, distribution and delivery of drugs to the targeted tissue. This concept has recently been explored for treatment of pancreatic cancer in humans with quite encouraging results [1]. Regular microbubbles intended for US contrast imaging (e.g., Sonazoid™ or Sonovue®) are widely used. These are, however, designed as diagnostic agents, and they carry several attributes that may limit their efficacy for improved drug delivery. Being small, free flowing and typically cleared from vascular compartments within 2-3 minutes, they display limited contact with the endothelial wall, reducing the level and range of the biomechanical effects.

Acoustic Cluster Therapy (ACT) [2] represents a novel and unique approach to ultrasound mediated, targeted delivery of drugs. While this concept explores biomechanical mechanisms similar to regular microbubbles, the formulation is carefully designed to enhance therapeutic efficacy. A dispersion of microbubble/microdroplet clusters is intravenously injected together with a drug followed by local, low power insonation with regular medical imaging US. This insonation produces an instant evaporation of the droplet component and the generation of large bubbles that transiently deposits in the local microvasculature. Further insonation of these large bubbles then induce the biomechanical effects. The unique attributes of the ACT bubbles, in comparison with regular contrast microbubbles, are their size and their close contact with the endothelial wall, which ensures an effective coupling and long-range effects.

In a series of articles, Drs. Sontum, Healey and van Wamel have earlier described the basic formulation concept/design behind ACT, demonstrated the generation and dynamics of the large bubbles in a dog model and demonstrated a proof of principle for tumor specific enhancement of the uptake of co-administered model molecules [2–4]. In the current issue, Dr. van Wamel and her team provide pre-clinical proof of concept, combining ACT with Abraxane® and paclitaxel for treatment of human prostate adenocarcinoma in mice [5]. Their results demonstrate a remarkable synergistic effect between ACT and the two formulations. Combined with sub-therapeutic dose of paclitaxel, ACT induced a 10-fold reduction in tumor growth rate, a doubling of median survival and stable, complete remission in > 40% of the animals. Administration of Abraxane® alone controlled the tumor growth, but only during the treatment period. Tumors started growing again when the treatment with Abraxane® ended. On the other hand, Abraxane® combined with ACT resulted in full, stable remission after 60 days, and 67% of animals were cancer free after 120 days. All animals were alive at the end of the study (120 days), while the median survival time of the Abraxane group was only 72 days.

The work by Dr. van Wamel demonstrates the potential of ACT for targeted therapy. In principle, the concept should be applicable for combination with a wide range of anticancer drugs and drug delivery systems. In this issue, Redouane Bouchaala et al. characterized lipid nanocarriers for cancer targeting [6], and the effect of such a delivery system can be significantly increased by combining with ACT. The work by the van Wamel team obviously requires further improvement for tumor-targeted therapy in clinical use, but it provides another positive step for conquering cancer. The recent Cancer Moonshot initiative of the U.S. will undoubtedly provide accelerated progress in prevention, diagnosis, and treatment of cancer. Such progress, however, occurs mainly as a result of cumulated, small improvements over time. Evolutionary advances occur faster with a large number of diverse scientists providing more fresh ideas.

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