Science to Practice

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Science to Practice: Which Approaches to Combination Interventional Oncologic Therapy Hold the Greatest Promise of Obtaining Maximal Clinical Benefit?

Summary:

Soundararajan et al (1) were able to demonstrate that combination therapy of radiofrequency (RF) ablation with rhenium 186 (^{186}Re)-labeled liposomal doxorubicin resulted in better drug uptake and reduced tumor growth compared with other therapies tested in a rodent head and neck tumor model. In essence, this “triple” combination therapy of chemotherapy, radiation, and thermal ablation induced significantly smaller viable tumor volume compared with the therapies tested alone at histopathologic examination.

The Setting

As noted in my previous Science to Practice article regarding the use of high-intensity focused ultrasound to increase the uptake of the protease inhibitor bortezomib (2), image-guided strategies to enhance selective tumor drug

delivery, deposition, and retention have formed one of the mainstays of interventional oncology. Classic examples of this have included direct tumoral injection of ethanol and doxorubicin (3,4) in addition to selective intraarterial delivery of chemotherapy as is often practiced with chemoembolization of liver

RFA and ^{186}Re -Liposomal doxorubicin

^{186}Re -Liposomal doxorubicin

Baseline 4 h 20 h 72 h 116 h

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tumors (5,6). In addition, thermal energy sources such as RF and high-intensity focused ultrasound have been used to markedly increase the deposition of drugs such as doxorubicin into the tumor at the periphery to the zone of ablation, with demonstration of induction of larger zones of ablation (7–9). Thus, regardless of whether one wishes to approach the issue from the perspective of the chemotherapeutic (ie, that ablation improves drug delivery) or from the opposite side of the coin (ie, that adjuvant drugs can increase the size and completeness of the ablation), a proliferation of recent studies supports the contention that combination interventional oncology therapies will play an ever-important role in the future.

Interventional oncologic strategies are not the only approaches being explored to overcome the barriers of systemic drug delivery, most notably poor target tumor delivery and retention, which are often further limited by unfavorable drug toxicity profiles. Indeed, there has been a veritable explosion of nanotechnology in cancer, particularly with use of vehicles such as liposomes to deliver higher tissue doses of agents such as doxorubicin with lower side effect profiles (10). Fortunately, the advances of oncologic nanodrugs have shown to be complementary to the interests of interventional oncology. For example, the administration of a single dose of liposomal doxorubicin following RF ablation has been shown to increase tumor destruction in humans and survival in animal models (7).

The Science

By resorting to the use of multiple types of tumoricidal agents (^{186}Re , doxorubicin, and RF ablation), the current study continues the trend most recently noted by Yang et al (11), who combined both liposomal doxorubicin (the agent of the current study) and liposomal paclitaxel with RF ablation to achieve greater apoptosis and survival compared with RF combined with either liposomal chemotherapeutic alone. In essence, the concept of combination “combination interventional oncologic therapies” represents a

positive transformation in our thinking, namely using many weapons and strategies synergistically to win the war against cancer. This gets beyond the hubris of an idea entrenched in some quarters that a single therapy “magic bullet” (be it an ablative energy source or a drug targeted to a single protein) is likely to be maximally efficacious against a complex dynamic and adaptive process such as a metastatic tumor.

A key advance in the study by Soundararajan et al is that they elegantly added radiation to the mix of combination ablative therapy. This is fortuitous, as the use of ^{186}Re enabled the investigators to take advantage of even greater hyperthermic interactions between RF ablation and radiation than that seen for RF and chemotherapy (12). Although others have pioneered the interventional use of transcatheter delivery of radiation particles, particularly those based on yttrium 90 (^{90}Y) for liver tumors (13), it must be noted that chemo-radioliposomes can potentially be delivered in a less invasive manner (ie, intravenously) to a greater spectrum of tumors, including those outside of the liver. Regardless, given that three tumoricidal agents have been successfully combined to achieve the best outcomes, we have essentially been led to the expansion of interventional oncology to its natural conclusion—providing an ideal image-guided minimally invasive method for performing a one-stop version of the classic combined surgical–medical oncology–radiation oncology paradigm.

Another important facet of the study was its use of small-animal single photon emission computed tomography to demonstrate that rats treated with ^{186}Re -liposomal doxorubicin plus RF ablation had increased tumor accumulation compared with rats treated with only ^{186}Re -liposomal doxorubicin. In essence, by taking advantage of the imaging properties of the radioactive agent, these investigators went far beyond merely confirming the observations of Monsky et al (14) (ie, RF ablation can increase liposomal uptake) to demonstrate a potentially powerful tool for noninvasive determination of drug deposition and retention. This approach of creating

“theranostics” (ie, agents with dual properties that enable them to be both simultaneously diagnostic and therapeutic) is presently receiving substantial attention as a primary paradigm for the future of personalized medicine (15).

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The Practice

Clinical use: Clearly, confirmation of these results in animals with well-designed clinical studies is paramount before the widespread introduction of any specific combined therapy approach. The goal of these studies must be expanded to include not only seeing improved efficacy but also achieving satisfactory clinical results in the most minimally invasive and least toxic way possible. Such studies would help us to develop rational strategies for tailoring combination therapy on an indication-by-indication and patient-by-patient basis. Regardless, achieving reduced tumor growth while lowering the dose of potentially toxic chemotherapeutic approaches would literally be “a dream come true” for the treatment of the many cancers that respond quite poorly to current state-of-the-art chemotherapy. Likewise, creating larger, more complete ablation zones with any method would be met with substantial enthusiasm. Most readily translatable into potential daily practice are the insights gleaned by the demonstration of an increase in fluorine 18 fluorodeoxyglucose (FDG) uptake in all tumors not receiving liposomal doxorubicin drugs versus an almost constant

basal uptake of FDG in tumors receiving this therapy. Indeed, this finding highlights the potential greater use of physiologic and/or nuclear imaging in the assessment of current interventional oncologic therapies (16).

Future opportunities and challenges: For any given tumor type, selection of the ideal components in a combined regimen to obtain optimal synergistic results (including types of chemotherapy, radiation, and energy source) is simultaneously going to represent one of our greatest future opportunities and challenges. For example, although the selection of nanodelivery of the β emitter ^{186}Re radionuclide with a tissue penetration depth of 2–4 mm was not only a rational first choice for the described tumor model but was also efficacious, this may not always prove to be the case. Indeed, other more aggressive methods of radiation delivery or higher dosimetry values may be required or necessary to obtain better results for some tumor types and sites. Thus, comparison of this source and method of delivery of radiation with others such as the already clinically prevalent high-dose external stereotactic systems (17) and transcatheter ^{90}Y (13) may ultimately prove necessary. Similarly, the variable sensitivity of different tumors to different drugs and the wide range of different nanodelivery vehicles available suggest that a similar study will be needed for any chemotherapeutic component selected. To complicate matters further, beyond radiation and chemotherapy lies the issues of the proliferation of different methods of ablation, including not only RF but also microwave, cryotherapy, and irreversible electroporation (18). Although different tissue responses to these ablative therapies hold the potential for better matching of adjuvants with the specific mechanisms amplified by specific devices, sorting this out will require substantial investigation.

It must also be remembered that although in many cases combination interventional oncologic therapies will offer a better chance for improved outcomes, this will not always be invariably true. Thus, we will need to justify increased complexity and potential toxicity of any

compound regimen on an indication-by-indication basis. Clearly, rational selection ideally based on careful mechanistic study is in order. Yet, given the number of potential mechanisms it must also be acknowledged that the floodgates are about to open. Classic chemotherapy works on many different cellular pathways. As noted earlier, hitting two or more pathways with more than one agent is likely to be more efficacious than targeting just one. How the use of these agents will fare alone versus in combination with nanodrugs targeted to other mechanisms being actively studied, such as the heat shock protein family (using liposomal quercetin [19]), glycolysis with use of bromopyruvate (20), transcription factors using small interfering RNA (21), or protease inhibitors such as bortezomib (9), remains an open question. Thus, there is a real need not only for rational clinical trials on an organ-by-organ basis but also for quite a fair bit of further animal study. This can be best accomplished by concerted collaboration among the fortunately expanding collegial pool of researchers in this field.

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