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Radiopharmaceutical Therapy in the Era of Precision Medicine*

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Abstract

Precision medicine is the selection of a treatment modality that is specifically tailored to the genetic and phenotypic characteristics of a particular patient's disease. In cancer, the objective is to treat with agents that inhibit cell signaling pathways that drive uncontrolled proliferation and dissemination of the disease. To overcome the eventual resistance to pathway inhibition therapy, this treatment modality has been combined with chemotherapy. We propose that pathway inhibition therapy is more rationally combined with radiopharmaceutical therapy (RPT), a cytotoxic treatment that is also targeted. RPT exploits pharmaceuticals that either bind specifically to tumors or accumulate by a broad array of physiological mechanisms indigenous to the neoplastic cells to deliver radiation specifically to these cells. Consistent with pathway inhibition therapy and in contrast to chemotherapy, RPT is well tolerated. However, the potential of RPT has not been fully exploited; for the most part, treatment has been implemented without using the ability to customize RPT by imaging and deriving individual patient tumor and normal organ radiation absorbed doses. These are more closely related to biological response and their determination should enable RPT treatment administration to maximum therapeutic benefit by treating to normal organ tolerance or demonstrating futility via tumor dosimetry. This is the essence of precision medicine.

Despite ongoing promising efforts with new chemotherapeutics and molecular signaling pathway inhibitors, systemic cancer therapy continues to fall short, with few exceptions, of the efficacy required to control cancer once patients are not eligible for curative therapy with surgery or external radiotherapy. Current basic research and clinical investigations in cancer therapy are focused on increasing the efficacy of chemotherapy and pathway inhibition therapy by identifying patients whose cancer exhibits genetic or metabolic (signaling)

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*Dedicated to the memory of Henry N. Wagner, Jr., MD, Professor of Nuclear Medicine, Radiology, and Allied Health Sciences, Johns Hopkins Medical Institutions, and pioneer in the development of nuclear medicine as an independent academic discipline on an international basis, as well as in the use of positron-emission tomography in brain imaging.

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pathway characteristics that identify tumors which are more responsive to the therapeutic agent under study, a “personalized” or “precision medicine” based on genomics and other ‘omics’ (1). The value of accounting for such individual patient and tumor characteristics has been recognized, and biomarker-based stratification is being introduced in clinical trials of novel therapeutics (2). The imperative of customizing treatment to individual patients or populations of patients (*i.e.*, of adopting such precision medicine techniques) has been demonstrated recently (3, 4).

Molecular signaling pathway inhibitors generally operate by inhibiting a metabolic or signaling pathway to which cancer cells are addicted. This approach has led to remarkable successes (*e.g.*, imatinib in leukemia and GI stromal tumors, trastuzumab in breast cancer, and erlotinib in lung cancer). Continued use of these agents, however, has highlighted the ability of tumor cells to escape by using alternative pathways leading to resistance (5–7) or, worse, active malignancy (8), or as in the case of some angiogenesis inhibitors, tumors exhibiting increased invasiveness and enhanced metastatic potential (9, 10). The heterogeneity in “driver” mutations and associated pathways also can limit the efficacy of this treatment modality (11). To address these limitations, pathway inhibition therapy has been combined with conventional cytotoxic chemotherapy. The combination of a tumor selective therapy with one that is cytotoxic to all proliferating cells is sub-optimal due to the potential for concomitant systemic toxicities. We propose that pathway inhibition therapy is more rationally combined with RPT, a cytotoxic treatment that is also targeted. Radiopharmaceutical therapy exploits pharmaceuticals that either bind specifically to tumors or accumulate by a broad array of physiological mechanisms indigenous to the neoplastic cells to deliver radiation specifically to the targeted cells. The potential advantage of combination RPT with precision biologic therapy has been presented recently for undifferentiated thyroid cancer (12).

In chemo-refractory and radiotherapy-ineligible patients, RPT offers viable treatment options. There are 134 open trials in the US that investigate RPT (ClinTrials.gov), making RPT an area of modest but on-going clinical (and basic/translational) research. In lymphoma patients, RPT has yielded durable responses in heavily pretreated, refractory patients (13) and, with the approval of Ibritumomab tiuxetan as first-line consolidation therapy, is recognized as competitive or superior to current early-stage treatments (14). Initial studies in pancreatic cancer have shown encouraging results with an anti-mucin antibody, clivatuzumab, labeled with ^{90}Y , in combination with low-dose gemcitabine used as a radiosensitizer (15). In Europe, RPT using radiolabeled peptides has demonstrated efficacy in patients with late-stage, refractory, neuroendocrine tumors, which are substantially more radioresistant than lymphomas and leukemias. Although no randomized, multicenter trial of radiopeptide-based RPT has been conducted, thousands of patients have benefitted from this treatment modality, with approximately 25% showing objective tumor responses in the near absence of serious side effects (16). In patients whose cancers express catecholamine receptors (*e.g.*, neuroendocrine tumors such as neuroblastoma and pheochromocytoma), metaiodobenzylguanidine (MIBG), labeled with ^{131}I has reduced tumor volumes and the symptoms associated with release of hormones (17). Finally, perhaps the most successful RPT and possibly the most successful systemic cancer therapeutic in general is radioiodine

treatment of differentiated thyroid cancer (18). The RPT agents described above used beta-particle (*i.e.*, electron) emitters. In 1903, Alexander Graham Bell suggested using radium for localized therapy of cancer (19). A century later, the first modern-day clinical trial of alpha-emitter RPT was reported (20). Recently, the FDA approved radium-223 dichloride (Xofigo™) for the treatment of castrate-resistant metastatic prostate cancer. This agent has yielded significantly increased survival in patients previously considered incurable (21). Similarly promising results have been observed in acute myelogenous leukemia patients treated with antibody-conjugated actinium-225 (22). These RPTs deliver a cascade of short-range (40–80 µm) alpha-particles (helium nuclei) that, because of their larger size, are 1000 times more likely to cause irreparable DNA damage than beta-particle emitters.

In a recent *Perspective*, Basch (23) proposed incorporating patient-reported outcomes in clinical trial design so that an answer to the “How will it make me feel?” (HWMMF) question is obtained during the drug approval process and included in the package insert. Information regarding potential toxicity and long-term sequelae has always been included in the form of an organ absorbed dose table in package inserts for radiopharmaceuticals. On the HWMMF question, radiopharmaceuticals are at a tremendous advantage over chemotherapy and most pathway inhibition therapy; the side-effects are typically so mild that the occasional patient will question whether they’ve even received RPT. The toxicity of most RPT is usually hematopoietic, which is manageable when the absorbed dose to the red marrow is considered.

The efficacy of RPT depends upon delivering a lethal level of radiation to tumor cells while sparing normal cells, and is thus less susceptible to the resistance mechanisms or inadvertent side-effects that have been observed with pathway inhibition therapy. However, the potential of RPT has not been fully exploited. For the most part, treatment has been implemented without using the innate potential advantage of RPT over other treatment modalities – the ability to perform longitudinal imaging and use this information to individualize treatment according to tumor and normal organ absorbed doses. This unique aspect of RPT has been seen as an unnecessary logistical and financial expense of this treatment. In the narrow scope of a particular individual patient treatment and in the absence of unequivocal evidence demonstrating patient benefit, this may seem to be the case. In the broader context of drug development and optimization, however, the ability to image and calculate normal organ and tumor absorbed doses provides a number of advantages. Because these variables are more closely related to biological response, such an approach enables maximal therapeutic benefit either by treating to tolerance via normal organ dosimetry or by demonstrating futility via tumor dosimetry, thus being the essence of precision medicine. Alternatively, if the pharmacokinetics of the agent in the patient population is shown to be largely invariant to patient-specific differences over a wide enough range of patient characteristics, then a justification for not implementing patient-specific dosimetry is provided.

The origins of RPT, especially antibody-mediated RPT, are multidisciplinary. This treatment arose from a collaboration of radiochemists, immunologists, endocrinologists, physicists, nuclear medicine physicians, oncologists, and radiation oncologists, and was born from the initial studies, over 35 years ago, showing the selective targeting of tumors using radiolabeled anti-cancer-marker antibodies by scintigraphy (24). This led to first-generation

immunoscintigraphic imaging agents, which were the precursors to radioimmunotherapy (25). Similarly, successful implementation of RPT will likewise require that multiple disciplines be involved in ongoing development and optimization of this treatment modality. The first step in making the transition to absorbed dose-based treatment planning is to conduct new Phase I trials using absorbed dose to the dose-limiting organ as the escalation variable (Fig. 1). In this context, absorbed dose calculations must be specific to the individual patient being treated. The Phase I stage in the development of new therapeutic agents provides the best opportunity for adopting this approach. Such studies typically also include secondary end-points (*e.g.*, tumor and normal organ absorbed doses, impact of prior therapy), and provide the opportunity to collect the imaging and pharmacokinetic data required to investigate the utility of treatment planning and possibly implement it in phase II and subsequent trials.

Although the multidisciplinary nature of RPT can be seen as a weakness, because the modality is not amenable to the simplicity and reimbursement advantages of solo practice, it is also a strength, in that advances in any of the related fields lead to advances in RPT. Examples of this abound. A highly abbreviated list includes: genetic engineering to reduce immunogenicity and design lower molecular weight yet highly reactive constructs (26), and advances in tumor biology and immunology to improve targeting (12), and identify an ever-expanding repertoire of tumor receptors and antigens (27), advances in imaging capabilities, including immunoPET (28) to enable patient-specific dosimetry (29), and, most recently, the use of highly potent alpha-particle-emitting radionuclides (30). The recent FDA approval of radium-223 dichloride has highlighted the potential of RPT in a clinical setting with few treatment options. The anticancer drug development pipeline is currently focused on antibody drug-conjugates (ADC) that are analogous to RPT but generally require internalization to achieve cell killing. We expect that as ADCs advance through the drug development pipeline, attention will return to investigating radiolabeled antibodies, especially in solid tumors. As this new RPT pipeline becomes established, it will be important to recognize that the ability to image and plan treatment for individual patients is an already available precision medicine technique.

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Figure 1.

A simplified approach to precision radiopharmaceutical therapy is illustrated.