European Journal of Cancer (2014) **50**, 2360–2363

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Current Perspective

Radiopharmaceutical therapy in the era of precision medicine

George Sgouros [a,*], David M. Goldenberg [b]

[a] *Division of Nuclear Medicine, Dept. of Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, United States*
[b] *Garden State Cancer Center, Center for Molecular Medicine and Immunology, Morris Plains, NJ, United States*

Received 21 April 2014; received in revised form 26 April 2014; accepted 26 April 2014
Available online 19 June 2014

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.

KEYWORDS
Radiopharmaceutical therapy
Treatment planning
Dosimetry
Patient-specific radionuclide therapy

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 signalling 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 tumours 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 customise RPT by imaging and deriving individual patient tumour 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 tumour dosimetry. This is the essence of precision medicine.

Despite ongoing promising efforts with new chemotherapeutics and molecular signalling pathway inhibitors, systemic cancer therapy continues to fall short, with few exceptions, of the efficacy required to control

* *Corresponding author:* Tel.: +1 4106140116; fax: +1 4134873753.
E-mail address: gsgouros@jhmi.edu (G. Sgouros).

http://dx.doi.org/10.1016/j.ejca.2014.04.025
0959-8049/

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 (signalling) pathway characteristics that identify tumours which are more responsive to the therapeutic agent under study, a 'personalised' or 'precision medicine' based on genomics and other 'omics' [1]. The value of accounting for such individual patient and tumour characteristics has been recognised, and biomarker-based stratification is being introduced in clinical trials of novel therapeutics [2]. The imperative of customising treatment to individual patients or populations of patients (i.e. of adopting such precision medicine techniques) has been demonstrated recently [3,4].

Molecular signalling pathway inhibitors generally operate by inhibiting a metabolic or signalling pathway to which cancer cells are addicted. This approach has led to remarkable successes (e.g. imatinib in leukaemia and GI stromal tumours, trastuzumab in breast cancer and erlotinib in lung cancer). Continued use of these agents, however, has highlighted the ability of tumour 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, tumours 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 tumour 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 radiopharmaceutical therapy (RPT), a cytotoxic treatment that is also targeted. Radiopharmaceutical therapy exploits pharmaceuticals that either bind specifically to tumours 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 United States 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 recognised 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, labelled with ^{90}Y, in combination with low-dose gemcitabine used as a radiosensitiser [15]. In Europe, RPT using radiolabelled peptides has demonstrated efficacy in patients with late-stage, refractory, neuroendocrine tumours, which are substantially more radioresistant than lymphomas and leukaemias. Although no randomised, multicenter trial of radiopeptide-based RPT has been conducted, thousands of patients have benefitted from this treatment modality, with approximately 25% showing objective tumour responses in the near absence of serious side-effects [16]. In patients whose cancers express catecholamine receptors (e.g. neuroendocrine tumours such as neuroblastoma and pheochromocytoma), metaiodobenzylguanidine (MIBG), labelled with ^{131}I has reduced tumour 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 localised therapy of cancer [19]. A century later, the first modern-day clinical trial of alpha-emitter RPT was reported [20]. Recently, the Food and Drug Administration (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 leukaemia 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 have even received RPT. The toxicity of most RPT is usually haematopoietic, 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 tumour cells while sparing normal