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Pharmacogenomics in Radionuclide Therapy: Impact on Response to Theranostics

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The intrinsic variability in response and toxicity of patients to treatment is a crucial issue in modern medicine, and may be due to a range of pharmacologic, metabolic and genomic factors (1). Through deeper understanding of the impact of genetic differences between patients, in has become clear that predisposition to developing cancer, and response to drugs and other therapies including radiation, may be explained in many patients by underlying changes in germline DNA (1). In some circumstances, somatic mutations or alterations in gene expression may be present in tumor cells that impact on target expression, drug sensitivity, and also response to radiation (2,3). Tumor pharmacogenomics is the study of how the genome influences a patient's response to different cancer drug treatments. These genomic changes may also impact on successful radionuclide therapy, and understanding the role of pharmacogenomics in selecting patients for treatment is essential in developing new radiopharmaceutical therapies in cancer patients.

GERMLINE AND SOMATIC MUTATIONS IN CANCER

Pharmacogenomics in cancer involves two genomes, the germline and the tumor. The germline genome involves inherited genetic variations, and the tumor genome considers any somatic mutations that accumulate as a cancer evolves. There are a number of well established germline variants that may influence drug metabolism and pharmacokinetics in cancer patients, particularly *UGT1A1* (irinotecan), *CYP2D6* (tamoxifen) and *TPMT* (mercaptopurine) (1). Some germline mutations are associated with predisposition to cancer, such as *BRCA1/BRCA2* (breast and ovarian cancer), and *MLH1* (colon cancer). Somatic mutations are frequently found in cancers, may drive the phenotype of tumors, and also influence response to therapy. For example, mutations in *EGFR* may impact on sensitivity to tyrosine kinase inhibitors, and variants of androgen and oestrogen receptors may influence hormonal therapy in prostate and breast cancer patients (1). Specific somatic mutations may be preferentially targeted by purposed drugs, such as *BRAFV600E* mutations in malignant melanoma (1). In this context, knowledge of the role of germline and somatic mutations can have major implications on the selection of therapy and prediction of potential toxicity in individual patients. Thus, mutation testing is increasingly important in standard of care, and also in cancer drug development.

GENOMIC MUTATIONS AND RADIATION

Radiation therapy is associated with induction of DNA single-strand breaks, double-strand breaks, DNA base damage, and indirect damage from oxygenated free radicals, leading to cell death (2). Mutations in DNA repair genes may therefore play an important role in both the development of cancer, and also response to radiotherapy. It has been well established that germline variants may be associated with toxicity to radiotherapy, particularly DNA damage response genes such as *ATM* (2). Germline mutations in both *ATM* and *MRE11* have been shown to be linked to increased responsiveness to radiotherapy.

PHARMACOGENOMICS IN RADIONUCLIDE THERAPY

The use of beta and alpha emitting radionuclide therapies has been a key component in nuclear medicine practice for decades, and in the last 20 years by the development of peptide-receptor radionuclide therapy (PRRT) and recently prostate specific membrane antigen (PSMA) radioligand therapy (PRLT). The development of these therapeutic approaches has mainly focused on patient selection for treatment based on the expression of target in tumor, namely a surrogate for the absorbed dose, but has, so far, neglected the tumor and tissue radiosensitivity, which is the other term of the radiation effect equation. Despite these improved techniques for effective

delivery of radionuclide to cancer cells, and strategies for reducing toxicity, there are still many patients who do not respond to treatment. The role of germline variants and somatic mutations in tumor in therapeutic response to radionuclide therapy is an area of increasing relevance for patient selection and monitoring of response. How can we use pharmacogenomics to improve our approaches to treatment of cancer patients with radionuclides?

THYROID CANCER

The treatment of well differentiated thyroid cancer with surgery, and in appropriate patients ^{131}I therapy, has been the mainstay of patient management for over 40 years. However, there are some patients in whom ^{131}I therapy is not successful, or where radioiodine uptake is not evident in some metastatic lesions, and in these patients downregulation of the NaI symporter in tumor cells may be responsible for reduced efficacy. Redifferentiation therapy may induce NaI expression and restore responsiveness to ^{131}I therapy, and recent studies have shown that tyrosine kinase inhibitors against *NRAS* and *BRAFV600E* mutations in tumor can be successfully used to allow effective ^{131}I treatment to be given in such patients (4).

NEUROENDOCRINE TUMORS

Well differentiated neuroendocrine tumors (NETs) generally exhibit low mutation burdens. Mutations are infrequent in small intestinal types, mainly involving *CDKN1B* (< 10%), while other mutations, e.g. *BRAF*, *KRAS*, *TP53*, are even rarer. Germline mutations of *MUTYH* and *IPMK* are sporadic. Pancreatic NET mutations are more common, mainly of *MEN1* (35-50%), *DAXX* (20%), and *ATRX* (10%), although other genes, such as DNA damage repair or negative regulators may be involved. Bronchopulmonary NETs exhibit mutations of histone modifiers in about 40% of cases, including *MEN1* and *TP53*. Many of these mutations (e.g. *MEN1*, *TP53*, *DAXX*, *ATM*) have prognostic significance and none so far has been specifically associated with response to PRRT.

Tumor gene expression profiling has revealed that NET subtypes have characteristic features. Down-regulation of *TTF1* was the only demonstrated association with poor response to PRRT in bronchopulmonary NETs (3), although this is likely a prognostic characteristic, namely independent from the treatment applied. Multigene signature analyses of circulating mRNA have been introduced as liquid biopsies. High expression of growth-factor signaling and metabolism genes were noted to be associated to absence of progression on PRRT. Integration of gene expression with Ki67 grading forms the basis for a PRRT- prediction quotient (PPQ) which functions as a predictive biomarker with 95% accuracy in 3 independent prospective cohorts. Notably, PPQ could not predict the effect of other therapies, therefore representing a specific radiation sensitivity signature for PRRT. Despite several SNPs and gene expression profiles have been associated with radiation injury, no specific tool exists for PRRT toxicity yet (5).

PROSTATE CANCER

There are inherited germline mutations in DNA-repair genes that are linked to more aggressive prostate cancer, including *BRCA2*, *CHEK2* and *ATM*, although the frequency of these mutations is low. Germline mutations are also associated with responsiveness to anti-androgen therapy (eg *SLCO2B1*) (1). Somatic mutations in AR (including splice variants) and p53 are the most commen seen in prostate cancer, although mutations in DNA-repair genes may also be found in up to 23% of metastatic castrate resistant prostate cancer.

There are emerging reports of the impact of germline and somatic mutations in patients with metastatic castrate-resistant prostate cancer treated with PRLT. In one study, germline mutations in *CHEK2* but not in other radiosensitiser genes (eg *FANCA, BRCA1, ATR*) was associated with PSA response to ^{177}Lu-PSMA (6). In a study of patients treated with ^{225}Ac-PSMA, somatic mutations (eg *TP53, CHEK2, ATM*) were identified in biopsies of metastatic lesions which did not respond to therapy despite high PSMA uptake on screeening PSMA PET, suggestion a mechanism of resistance to therapy (7). A case report of a patient who had a poor response to ^{177}Lu-PSMA therapy despite high uptake on PSMA PET, but who was found to have a germline *BRCA2* mutation present, and who subsequently responded to PARP inhibitor therapy, confirms the importance of mutation testing of patients with poor response to PRLT (8). Recent data evaluating plasma androgen receptor gene expression in mCRPC revealed that high gene levels identified resistance to ^{177}Lu-PSMA-617, which is likely a prognostic feature (9).

The role of DNA-repair somatic mutations in prostate cancer has also been exploited by the use of poly ADP ribose polymerase (PARP) inhibitors, which inhibit DNA repair. The PARP inhibitors Olaparib and Rucaparib were recently been approved for treating patients with metastatic castration-resistant prostate cancer where germline or somatic DNA repair mutations are present. Multiple clinical trials of PARP inhibitors with radiotherapy have commenced across a range of cancers, and the combination of PARP inhibitors and PRLT have also entered clinical trials (NCT03874884). In this context, combination studies of radionuclide therapy with inhibitors of DNA repair may provide enhanced therapeutic response, particularly where germline or somatic mutations of DNA repair genes are present.

In summary, pharmacogenomics may play a vital role in assessing patients who undergo radionuclide therapy, and prospective studies exploring germline and somatic mutations as well as gene expression profiling and their relationship to response are urgently required for prediction of efficacy and toxicity. We propose systematic inclusion of pharmacogenomics in prospective trials as a key strategy to inform future treatment strategies in patients undergoing radionuclide therapy.

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