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Letter to the Editor

Update to "Homologous Recombination Repair Defect May Predict Treatment Response to Peptide Receptor Radionuclide Therapy for Neuroendocrine Tumors"

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Last year, we reported successful treatment of a grade 3 pancreatic neuroendocrine tumor (PNET; Ki-67 index 40%) with ^{177}Lu-dotatate (4 treatments) in a patient with a pathogenic, heterozygous *BRCA1* germline mutation (c.68_69delAG).[1] This patient initially received capecitabine and temozolomide (CAPTEM) with at best mixed response. Given the presence of *BRCA1* mutation, ^{177}Lu-dotatate was administered as the next line of therapy, leading to resolution of bone pain and significant radiographic response in primary tumor and metastases in liver and bones that remained stable until new lesions revealed in liver and bones by a ^{68}Ga-dotatate PET/CT scan 15 months later. Patient restarted CAPTEM but had radiographic disease progression after 2 cycles of treatment. Rechallenge with 2 treatments of ^{177}Lu-dotatate were attempted 19 months after completion of the first course of peptide receptor radionuclide therapy (PRRT), and this again resulted in substantial improvement in the number and degree of uptake in the metastatic lesions with continued response on ^{68}Ga-dotatate PET/CT 5 months after completion of therapy (Figure 1). Patient tolerated PRRT rechallenge well without grades 3-4 toxicities based on Common Terminology Criteria for Adverse Events version 5.0.

This case report supports that rechallenging NET patients with PRRT can be considered in those with at least stable disease to the first course of PRRT which usually consists of 4 treatments.[2] In patients who were naïve to PRRT, grades 3-4 cytopenias occurred to about 10% of them during treatment[3] and the incidence of PRRT-induced myeloid neoplasms was estimated to be 2.6% with most diagnoses made 1 year after treatment.[4] The safety and efficacy of PRRT rechallenge have not been examined prospectively, but hematological toxicities did not appear increased based on retrospective studies[4-13]

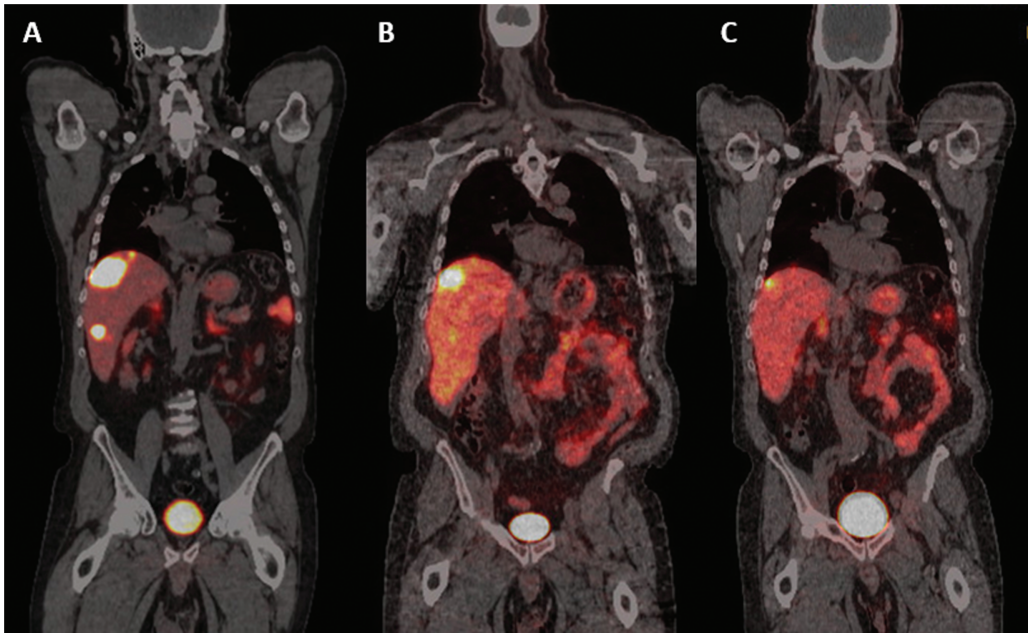

Figure 1. ^{68}Ga-Dotatate PET/CT of the patient: (**A**) before, (**B**) 1 month after, and (**C**) 5 months after PRRT rechallenge.

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and a disease control rate of about 70% was proposed by 2 meta-analyses despite significant between-study heterogeneity.[14,15] PRRT rechallenge is therefore feasible and represents a reasonable option in patients who have no alternative therapies that meaningfully prolong survival.

In our opinion, patient selection for PRRT remains a challenge in clinical practice. Similar to other agents such as poly ADP-ribose polymerase (PARP) inhibitors that target tumor cell DNA in patients with defective homologous recombination repair (HRR), PRRT may impact not only the therapeutic efficacy of subsequent anti-cancer therapies but also accumulative, treatment-related toxicities which can lead to irreversible hematological malignancies. Thus, clinical trials that evaluate the potential of HRR as a predictive biomarker for PRRT and examine the long-term toxicity of DNA-damaging agents in patients with HRR are prudent.

Conflict of interest

Tanios Bekaii-Saab: Boston Biomedical, Bayer, Amgen, Merck, Celgene, Eli Lilly and Company, Ipsen, Clovis, Seattle Genetics, Array Biopharma, Genentech, Abgenomics, Incyte, Bristol-Myers Squibb (RF [to institution]), Ipsen, Array Biopharma, Bayer, Genentech, Incyte, Merck (C/A [to institution]), AstraZeneca, Exelixis, Eli Lilly and Company, PanCan, 1Globe (IDMC/DSMB), Imugene, Immuneering, Sun Biopharma (SAB). **Mojun Zhu**: indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

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