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The Future of Targeted Alpha Therapy is Bright but Rigorous Studies are Necessary to Advance the Field

Commentary on
Survival Outcomes in Metastatic Gastroenteropancreatic Neuroendocrine Tumor Patients receiving Concomitant ^{225}Ac-DOTATATE Targeted Alpha Therapy and Capecitabine: A Real-world Scenario Management Based Long-term Outcome Study (jnumed.122.264043)

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Among advances in radiopharmaceutical therapy, few innovations show more promise than targeted alpha therapy (TAT). By inducing double-strand DNA breaks, high linear energy transfer (LET) isotopes such as ^{213}Bi, ^{212}Pb, and ^{225}Ac have the potential to produce substantially higher cytotoxicity than existing beta-emitters (e.g. ^{177}Lu). Indeed, since approval of ^{223}Ra for metastatic castrate resistant prostate cancer to bone, there has been a 6-fold increase in number of prospective trials of alpha-emitters.

Dr. Ballal and colleagues have accumulated the largest real-world experience using TAT in neuroendocrine tumor (NET) patients by radiolabeling of DOTATATE with ^{225}Ac in house and treating patients with multiple cycles (up to 10) at a dose of 100-120 KBq/Kg per cycle.[1] At the time of the most recent data analysis (cutoff February 2022), 91 patients at the All India Institute of Medical Sciences had been treated with this therapy: a mixed population of patients which included peptide receptor radionuclide therapy (PRRT) naïve individuals (n=34) as well as patients refractory to ^{177}Lu-PRRT (n=57); patients with progressive disease as well as those with stable disease but presumably treated due to symptom burden or tumor volume.

The results reported have been encouraging. At the time of analysis, median PFS had not been reached in the overall patient population and was reported to be 30 months in patients who had received prior ^{177}Lu-PRRT, who frequently do not exhibit long PFS intervals at the retreatment. Objective response rates were also impressive: reportedly 44% both in patients who had received prior PRRT (25/57) and those who were PRRT naïve (15/34). No cases of myelodysplastic syndrome or acute leukemia have been reported as of yet, and treatment was described overall as tolerable.

Nevertheless, there are reasons to interpret these data with caution. The authors have, on occasion, described their work as a prospective phase II study.[2] However, the term 'phase II study' implies certain prerequisites including a predetermined sample size, strict eligibility criteria, a clear prospective treatment protocol, and strict criteria for interpretation of response. These criteria do not apply to this analysis, which is best described as a retrospective study of real-world experience. The eligibility criteria seem to have shifted between the initial analysis of 32 patients in 2019[3] and the current analysis. For example, the exclusion of patients with European Cooperative Oncology Group (ECOG) status >2[3] seems to have been unheeded (31% of patients were described as having ECOG status 3 or 4 which is, in itself, remarkable). Disease response and progression were reportedly evaluated using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) despite the fact that many patients lacked contrasted anatomic imaging and were evaluated for response based on PET findings.

A notable revelation in this manuscript is the fact that patients received concurrent capecitabine along with ^{225}Ac-DOTATATE. To our knowledge, this component of therapy was not reported in prior published analyses of the same patient cohort.[2,3] While the contribution of radiosensitizing doses of capecitabine may have been minor, the display of this critical information is of utmost importance to allow for reproducibility of the results.

While many advances in nuclear medicine have begun with compassionate administration of in-house radiolabeled drugs, drug approvals depend on prospective trials that are strictly followed. It is therefore fortunate that such trials are rapidly proliferating, including studies of TAT for patients with NETs. Examples are a phase II study of ^{212}Pb-DOTAMTATE in PRRT naïve and refractory patients

(NCT05153772) and a phase I/III study of ^{225}Ac-DOTATATE in patients who have received prior PRRT (NCT05477576). If outcomes are nearly as favorable as those described by Dr. Ballal et al, the future of TAT in NETs is promising.

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Disclosure
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