Potential of ^{188}Re as an Alternative to ^{177}Lu and Dosimetric Consequences

TO THE EDITOR: We read with interest the article "PSMA-GCK01: A Generator-Based ^{99m}Tc/^{188}Re Theranostic Ligand for the Prostate-Specific Membrane Antigen" in *The Journal of Nuclear Medicine* (*1*). It is noteworthy that kidney accumulation of ^{188}Re-PSMA-GCK01 in LNCaP tumor–bearing mice was found to be 14 times higher than tumor uptake 1 h after injection and 9 times higher 2 h after injection (*1*).

It is worthwhile to investigate ^{188}Re as an alternative to ^{177}Lu, because accredited ^{177}Lu radiopharmaceuticals are available and the amount of ^{177}Lu is limited. Further alternatives such as ^{161}Tb (*2*) or ^{67}Cu (*3*) are moving into the focus of clinical research and could have even better therapeutic properties because of the coemission of Auger–Meitner electrons.

However, the kidney geometry in small animals is not representative for humans regarding geometry and pathlengths of the β-emission. Recently, Vargas et al. presented a method to understand the heterogeneity of absorbed doses in the kidneys of mice (*4*). In humans, the heterogeneity of absorbed doses in, for example, kidneys is crucial for the application of therapeutic radiopharmaceuticals (*5*). Hence, studies in pigs (single kidney weight, 125 g for pig vs. 150 g for human) may be required. Further, most patients currently receive radionuclide therapy as the last line of treatment after previous hormone and chemotherapy, so that bone marrow and kidney function may already be predamaged. This effect, too, can neither be simulated nor reproduced in animal experiments but requires clinical testing.

In our own efforts on ^{188}Re-PSMA derivatives, we found that biokinetics must be considered in terms of the physical half-life of the applied isotopes: at 17 h (^{188}Re) versus 6.6 d (^{177}Lu), the initial phase is more significant for ^{188}Re, and this is the phase with the greatest renal accumulation or excretion. Dosimetric calculations for ^{177}Lu-PSMA by Kurth et al. revealed kidney doses between 2.9 and 3.7 Gy, depending on the therapeutic cycle (*6*). On the basis of the effective half-lives for the kidneys that were reported, we calculated the biologic half-life for PSMA in the kidneys. We identified the expected effective half-life for ^{188}Re-PSMA by assuming a biodistribution identical to that for ^{177}Lu-PSMA and using the physical half-life for ^{188}Re. The calculated number of ^{188}Re decay in the kidneys was found to be approximately 66% lower than that of ^{177}Lu-PSMA decay. Nevertheless, the *S* value, *S*(kidney←kidney), for ^{188}Re is 5 times higher than that for ^{177}Lu. This means that the dose to the kidney is expected to be 1.7 times higher when using the same activity for ^{188}Re-PSMA as for ^{177}Lu-PSMA. The dose would be even higher when the initial kidney biokinetic is considered more accurately by assuming a linear accumulation within the first 2 h (*6*).

Furthermore, radiation biology must be considered, as higher activity levels must be used to achieve the same dose because of the shorter half-life of ^{188}Re. The authors used the same activity of ^{188}Re-PSMA and ^{177}Lu-PSMA (3.7 GBq) (*1*). Assuming an identical tumor uptake in a lesion with a mass of 10 g, the absorbed dose of ^{188}Re will be only 51% of the absorbed dose of ^{177}Lu. Hence, in therapeutic applications, the activity of ^{188}Re must be twice the activity of ^{177}Lu to achieve the same tumor dose. Furthermore, the various effective half-lives must be considered with respect to cellular repair mechanisms. The biologically effective dose is expected to be about 25% higher from ^{188}Re than from ^{177}Lu for equal absorbed doses. In conclusion, it is necessary to consider the dosimetric consequences carefully when replacing ^{177}Lu with ^{188}Re as mentioned above.

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