EDITORIAL

Opportunities and potential challenges of using terbium-161 for targeted radionuclide therapy in clinics

Cristina Müller[1,2] · Nicholas P. van der Meulen[1,3] · Roger Schibli[1,2]

The selection of appropriate radiometals to improve the outcome of tumor-targeted radionuclide therapy in cancer patients requires careful consideration. It is primarily the radiometal's physical decay characteristics that determine its suitability to treat a particular tumor type and/or stage. The practicality of the radiometal's application in combination with existing tumor-targeting agents, as well as potential production opportunities to make the radionuclide available in high activities, is also to be considered. Terbium-161 has recently been highlighted as a promising candidate for clinical translation. Herein, we summarize the relevant aspects to be taken into consideration in this regard.

Terbium-161 decays with a half-life of 6.95 days [1] and emits β^--particles ($E\beta^-_{mean}$ 154 keV) and γ-radiation ($E\gamma$ = 48.9 keV (17.0%); 74.6 keV (10.2%)) similar to the decay properties of lutetium-177 [2]. It is believed, however, that the co-emission of conversion and Auger electrons make terbium-161 superior. These short-ranged electrons may effectively eliminate microscopic metastases that are not even visible on a PET image, but responsible for relapse and metastatic spread [3]. This hypothesis is based on dose calculations, of which several exist in literature [3–6]. Champion et al. found that the absorbed dose to spheres in the cellular or subcellular range is increased several-fold when using terbium-161 as compared to lutetium-177; hence, it was concluded that terbium-161 would be the preferred candidate to treat minimal residual disease in a clinical setting [7].

The question arises, however, whether there is preclinical evidence for the superior therapeutic efficacy of terbium-161 over lutetium-177. Indeed, in vitro studies revealed an increased efficacy of a [^{161}Tb]Tb-DOTA-folate conjugate as compared to its ^{177}Lu-based counterpart using folate receptor-positive cervical (KB) and ovarian (IGROV-1) tumor cell lines [8]. The same observation was made for [^{161}Tb]Tb-PSMA-617, which reduced the viability and survival of PSMA-expressing PC-3 PIP tumor cells more than twice as effectively as [^{177}Lu]Lu-PSMA-617 [9]. In line with dose calculations that predicted the superiority of terbium-161 over lutetium-177, irrespective of its subcellular localization [6], it was experimentally demonstrated that [^{161}Tb]Tb-DOTA-LM3 was many-fold more effective in reducing the viability of AR42J tumor cells than its ^{177}Lu-labeled counterpart — despite the fact that more than 90% of this somatostatin receptor antagonist are localized at the cellular membrane [10]. Further experiments are ongoing to elucidate whether high radiation doses to the cell membrane induced by cell surface localization of short-ranged electrons [11] would also induce cell damage through bystander effects, as previously proposed [12]. The development of a cell-nuclear-localizing peptide to be used in combination with terbium-161 would be of interest to deliver high radiation doses to the cell nucleus [6, 11] and benefit from the direct effects of the emitted Auger electrons that are to induce DNA-double-strand breaks due to their high linear energy transfer (LET: 1–23 keV/μm) [13].

The more effective tumor growth delay achieved with ^{161}Tb-based radioligands as compared to that of ^{177}Lu-labeled counterparts was demonstrated several-fold in preclinical therapy studies using tumor-bearing mice. It was initially exemplified with a DOTA-folate conjugate [8, 14] and a L1CAM-targeting antibody [15], later confirmed with tumor cell internalizing and non-internalizing somatostatin analogues [10] and finally demonstrated with PSMA-I&T and the albumin-binding SibuDAB [16]. It has to be critically acknowledged, however, that mouse models of

✉ Cristina Müller
cristina.mueller@psi.ch

1 Center for Radiopharmaceutical Sciences ETH-PSI, Paul Scherrer Institute, Forschungsstrasse 111, Villigen-PSI, Switzerland

2 Department of Chemistry and Applied Biosciences, ETH Zurich, Vladimir-Prelog-Weg 1-5/10, Zurich, Switzerland

3 Laboratory of Radiochemistry, Paul Scherrer Institute, Forschungsstrasse 111, Villigen-PSI, Switzerland

metastasized disease have not been used in this context, although such models would be essential to conclusively determine the benefit of terbium-161 to eliminate microscopic tumors or even single-cancer cells in vivo.

Undoubtedly, the experimental data obtained with terbium-161 are promising. Only few preclinical studies were, however, conducted to address the question of potential side effects to normal tissue [16, 17] and conclusive statements are not possible at this stage. Terbium-161 and lutetium-177 both decay to stable isotopes (dysprosium-161 and hafnium-177, respectively). This means that, in contrast to other recently proposed therapy radionuclides such as actinium-225 and lead-212, there are no additional risks to be feared from particle-emitting daughter radionuclides. Long-term investigations in mice after application of a ^{161}Tb-labeled DOTA-folate conjugate, known to accumulate in the kidneys, did not show enhanced renal toxicity as compared to equal activities of the ^{177}Lu-based counterpart [17]. Short-ranged electrons emitted by terbium-161 are unlikely to cause radionephropathy in patients treated with radiopharmaceuticals, in which lutetium-177 is replaced by terbium-161, provided that the renal radiation dose does not exceed the safe limit of 23 Gy. Auger electron therapy, initially applied to patients through the use of $[^{111}$In]In-octreotide, resulted in kidney doses up to 30 Gy without causing significant renal damage [18]. Bone marrow toxicity is, however, a well-known risk of radioligand therapy that may occur, depending on multiple factors of patient characteristics and pre-treatments [19]. Only the understanding of the distribution of a particular radiopharmaceutical in the bone marrow would enable an accurate risk evaluation of active marrow irradiation by low-energy electrons such as those emitted by terbium-161 [20]. More realistically, the introduction of ^{161}Tb-based radiopharmaceuticals in a clinical setting will be performed in carefully designed dose escalation studies for each individual targeting agent.

Overall, the existing preclinical data, along with previous clinical experience with Auger electron emitters, suggest that terbium-161 would be a powerful and safe alternative to the currently used lutetium-177 in order to treat patients with known or suspected micrometastases. The question arises, however, whether a widespread clinical translation of terbium-161 will be feasible and realistic in the near future. As this will depend on how easily terbium-161 will be made available and on the practicality of using terbium-161 for radiopharmaceutical preparation and application, the most important points are summarized below.

Production and availability: The production of no-carrier-added (n.c.a.) terbium-161 requires irradiation of gadolinium-160 targets in a reactor to obtain gadolinium-161 which, subsequently, decays to the desired terbium-161 using the ^{160}Gd(n,γ)^{161}Gd →^{161}Tb nuclear reaction. The production principle is, thus, the same as for the production of n.c.a. lutetium-177 using the ^{176}Yb(n,γ)^{177}Yb →^{177}Lu nuclear reaction. Any issues with reactors that affect the world supply of lutetium-177 would, thus, also affect the production of terbium-161 as the same type of facilities will be used for target irradiation. The chemical separation of lanthanides is challenging, but the process of isolating terbium from the target material has been demonstrated [2] and established over the last decade [21]. It is feasible using cation exchange chromatographic methods, followed by extraction chromatography, to provide $[^{161}$Tb]TbCl$_3$ in dilute hydrochloric acid solution, enabling its direct use for radiolabeling of biomolecules at high molar activities (up to 180 MBq/nmol) as demonstrated by Gracheva et al. [21]. Of note is the need to use enriched gadolinium-160 target material $[^{160}$Ga]Gd$_2$O$_3$] to ensure the highest possible radionuclidic purity and minimizing the co-produced terbium-160, as it may affect the waste management due to its long half-life (T$_{1/2}$: 72.3 days). Upscaling the production of terbium-161 is feasible, in analogy to the large-scale production of lutetium-177, by commercial units. Although widespread availability of terbium-161 has not yet been achieved, the situation is likely to change in the coming years when the demand increases following the publication of initial clinical therapy data.

Measurability: Both terbium-161 and lutetium-177 decay with similar half-lives of approximately one week by the emission of medium-energy β⁻-particles. The co-emitted γ-radiation enables detection of both radionuclides using standard instrumentation such as germanium detectors, γ-counters, ionization chambers and medical equipment containing detectors. As the γ-rays emitted by terbium-161 are of considerably lower energy (Eγ = 48.9 keV (17.0 %); 74.6 keV (10.2%)) than those of lutetium-177 (Eγ = 113 (6.23%); 208 keV (10.4 %)), the volume of the solution to be measured and the geometry of the vial in question may have an impact on the determined activity [22]. Studies that involve terbium-161 in preclinical and clinical settings will, therefore, require calibrated ionization chambers for relevant geometries in order to avoid errors in exact activity measurements.

SPECT imaging: Imaging of terbium-161 based on its γ-ray emission is feasible, as demonstrated in several studies that made use of a dedicated small-animal SPECT/CT scanner [8, 9, 14, 23]. Due to the different γ-energies, terbium-161 and lutetium-177 can be detected simultaneously and, therefore, be used for dual-isotope SPECT imaging, as demonstrated in the preclinical setting [16, 23]. In-depth investigations with human phantoms on a clinical SPECT scanner suggest the use of low-energy-high resolution (LEHR) collimators to detect

terbium-161, which is in contrast to the commonly used medium-energy-general-purpose (MEGP) collimators for γ-ray detection of lutetium-177 [24]. The first clinical application of terbium-161 in two patients with neuroendocrine neoplasms confirmed the excellent SPECT image quality achievable with even low activities (600 MBq and 1300 MBq, respectively) of [161]Tb-DOTATOC [25].

Radioligand preparation: Terbium-161 and lutetium-177 are both radiolanthanides with chemical similarities, enabling chelation of both radionuclides with DOTA to form stable radiometal complexes [21]. This allows the use of terbium-161 with the same DOTA-functionalized biomolecules that are currently employed with lutetium-177. Importantly, as terbium-161 is commonly made available in dilute hydrochloric acid solution as is the case for commercial lutetium-177, identical labeling protocols can be employed for both radionuclides. The straightforward manufacturing of [161]Tb-based radiopharmaceuticals according to Good Manufacturing Practice (GMP) guidelines has been recently exemplified for [161]Tb-DOTATOC [26]. Initial studies also indicate comparable stability of radioligands, irrespective of whether they are labeled with terbium-161 or lutetium-177 [21].

Pharmacokinetics: Unlike the switch from one radiometal to another (indium/gallium [27] or lutetium/actinium [28]), which can alter the properties of the resultant radiopharmaceuticals in terms of receptor-binding affinity and, thus, tissue distribution profile including tumor uptake, this is not expected to occur when using terbium-161 instead of lutetium-177. In preclinical studies performed with small molecules, the distribution profile was similar, irrespective of whether the biomolecule was labeled with terbium-161 or lutetium-177 [8–10, 23]. Dual-isotope SPECT imaging ultimately confirmed that terbium-161 and lutetium-177 are interchangeable without affecting the tissue distribution profile, even at sub-organ distribution levels [23]. Importantly, first-in-human studies using [161]Tb-DOTATOC demonstrated a distribution profile that would have been expected for [177Lu]Lu-DOTATOC [25]. The same was also observed for [161]Tb-PSMA-617, which was recently used in a proof-of-concept study with a prostate cancer patient [29].

Due to the opportunities offered by the use of terbium-161, which clearly outweigh the challenges, several clinical trials have been initiated or are currently ongoing. In Switzerland, the investigation of [161]Tb-DOTA-LM3 in patients with neuroendocrine neoplasms, a collaboration between the Basel University Hospital and Paul Scherrer Institute (NCT05359146), has just begun. At the Peter McCallum Cancer Center in Melbourne, Australia, a clinical study is ongoing to evaluate the efficacy and safety of [161]Tb-PSMA-I&T in mCRPC patients (VIOLET trial:

NCT05521412) and another study with a similar aim is ongoing in Germany with [161]Tb-PSMA-617 (REALITY trial: NCT04833517) [30]. Meanwhile, there is a case study published that reports on initial evidence of the therapeutic potential of [161]Tb-PSMA-617 [31]. Extended efficacy data of 161Tb-based radioligand therapy are not yet available, but expected to be published in the near future.

It will likely take years to demonstrate the expected superiority of terbium-161 over lutetium-177 in eliminating microscopic tumors. In this context, new diagnostic methodologies beyond nuclear imaging may be necessary to enable the selection of patients who could benefit most from 161Tb-based radionuclide therapy and to quantitatively evaluate the therapeutic effect of short-ranged electrons. The detection of circulating tumor cells and their quantitative and qualitative analysis for specific markers that are potentially predictive for disease severity and treatment response may be a valuable means to reach this goal [32, 33].

Provided that initial clinical data confirm the expected safety profile of terbium-161 in patients, this radionuclide is likely to be further evaluated in various future clinical trials. The time needed until 161Tb-based radionuclide therapy can be implemented in daily routine treatment regimens in hospitals is difficult to predict, as it will critically depend on the efforts of researchers and clinicians to continue exploring terbium-161 in (pre)clinical studies. This, in turn, is only reasonably achievable if terbium-161 can be made available to the radiopharmaceutical and nuclear medicine community in large activities and sufficiently high quality.

Declarations

References

1. Duran MT, Juget F, Nedjadi Y, et al. Determination of 161Tb half-life by three measurement methods. Appl Radiat Isot. 2020;159: 109085. https://doi.org/10.1016/j.apradiso.2020.109085.
2. Lehenberger S, Barkhausen C, Cohrs S, et al. The low-energy beta⁻ and electron emitter 161Tb as an alternative to 177Lu for targeted radionuclide therapy. Nucl Med Biol. 2011;38:917–24. https://doi.org/10.1016/j.nucmedbio.2011.02.007.
3. Bernhardt P, Svensson J, Hemmingsson J, et al. Dosimetric analysis of the short-ranged particle emitter 161Tb for

radionuclide therapy of metastatic prostate cancer. Cancers (Basel). 2021;13:2011. https://doi.org/10.3390/cancers13092011.

4. Uusijärvi H, Bernhardt P, Ericsson T, Forssell-Aronsson E. Dosimetric characterization of radionuclides for systemic tumor therapy: influence of particle range, photon emission, and subcellular distribution. Med Phys. 2006;33:3260–9. https://doi.org/10.1118/1.2229428.

5. Hindié E, Zanotti-Fregonara P, Quinto MA, Morgat C, Champion C. Dose deposits from ^{90}Y, ^{177}Lu, ^{111}In, and ^{161}Tb in micrometastases of various Sizes: implications for radiopharmaceutical therapy. J Nucl Med. 2016;57:759–64. https://doi.org/10.2967/jnumed.115.170423.

6. Alcocer-Avila ME, Ferreira A, Quinto MA, Morgat C, Hindié E, Champion C. Radiation doses from ^{161}Tb and ^{177}Lu in single tumour cells and micrometastases. EJNMMI Phys. 2020;7:33. https://doi.org/10.1186/s40658-020-00301-2.

7. Champion C, Quinto MA, Morgat C, Zanotti-Fregonara P, Hindié E. Comparison between three promising β–emitting radionuclides, ^{67}Cu, ^{47}Sc and ^{161}Tb, with emphasis on doses delivered to minimal residual disease. Theranostics. 2016;6:1611–8. https://doi.org/10.7150/thno.15132.

8. Müller C, Reber J, Haller S, et al. Direct in vitro and in vivo comparison of ^{161}Tb and ^{177}Lu using a tumour-targeting folate conjugate. Eur J Nucl Med Mol Imaging. 2014;41:476–85. https://doi.org/10.1007/s00259-013-2563-z.

9. Müller C, Umbricht CA, Gracheva N, et al. Terbium-161 for PSMA-targeted radionuclide therapy of prostate cancer. Eur J Nucl Med Mol Imaging. 2019;46:1919–30. https://doi.org/10.1007/s00259-019-04345-0.

10. Borgna F, Haller S, Rodriguez JMM, et al. Combination of terbium-161 with somatostatin receptor antagonists-a potential paradigm shift for the treatment of neuroendocrine neoplasms. Eur J Nucl Med Mol Imaging. 2022;49:1113–26. https://doi.org/10.1007/s00259-021-05564-0.

11. Larouze A, Alcocer-Avila M, Morgat C, Champion C, Hindié E. Membrane and nuclear absorbed doses from ^{177}Lu and ^{161}Tb in umor clusters: effect of cellular heterogeneity and potential benefit of dual targeting-a Monte Carlo study. J Nucl Med. 2023;64(7). https://doi.org/10.2967/jnumed.123.265509.

12. Pouget JP, Santoro L, Raymond L, et al. Cell membrane is a more sensitive target than cytoplasm to dense ionization produced by auger electrons. Radiat Res. 2008;170:192–200. https://doi.org/10.1667/RR1359.1.

13. Ku A, Facca VJ, Cai Z, Reilly RM. Auger electrons for cancer therapy - a review. EJNMMI Radiopharm Chem. 2019;4:27. https://doi.org/10.1186/s41181-019-0075-2.

14. Müller C, Zhernosekov K, Köster U, et al. A unique matched quadruplet of terbium radioisotopes for PET and SPECT and for α- and β–radionuclide therapy: an in vivo proof-of-concept study with a new receptor-targeted folate derivative. J Nucl Med. 2012;53:1951–9. https://doi.org/10.2967/jnumed.112.107540.

15. Grünberg J, Lindenblatt D, Dorrer H, et al. Anti-L1CAM radioimmunotherapy is more effective with the radiolanthanide terbium-161 compared to lutetium-177 in an ovarian cancer model. Eur J Nucl Med Mol Imaging. 2014;41:1907–15. https://doi.org/10.1007/s00259-014-2798-3.

16. Tschan VJ, Busslinger SD, Bernard B, et al. Albumin-binding and conventional PSMA ligands in combination with terbium-161: biodistribution, dosimetry and preclinical therapy. J Nucl Med. 2023; in press. https://doi.org/10.2967/jnumed.123.265524

17. Haller S, Pellegrini G, Vermeulen C, et al. Contribution of Auger/conversion electrons to renal side effects after radionuclide therapy: preclinical comparison of ^{161}Tb-folate and ^{177}Lu-folate. EJNMMI Res. 2016;6:13. https://doi.org/10.1186/s13550-016-0171-1.

18. Valkema R, De Jong M, Bakker WH, et al. Phase I study of peptide receptor radionuclide therapy with [In-DTPA]octreotide: the Rotterdam experience. Semin Nucl Med. 2002;32:110–22. https://doi.org/10.1053/snuc/2002.31025.

19. Kesavan M, Turner JH. Myeloid toxicity of radionuclide cancer therapy. Cancer Biother Radiopharm. 2022;37:164–72. https://doi.org/10.1089/cbr.2021.0286.

20. Hemmingsson J, Svensson J, van der Meulen NP, Müller C, Bernhardt P. Active bone marrow S-values for the low-energy electron emitter terbium-161 compared to S-values for lutetium-177 and yttrium-90. EJNMMI Phys. 2022;9:65. https://doi.org/10.1186/s40658-022-00495-7.

21. Gracheva N, Müller C, Talip Z, et al. Production and characterization of no-carrier-added ^{161}Tb as an alternative to the clinically-applied ^{177}Lu for radionuclide therapy. EJNMMI Radiopharm Chem. 2019;4:12. https://doi.org/10.1186/s41181-019-0063-6.

22. Juget F, Talip Z, Nedjadi Y, et al. Precise activity measurements of medical radionuclides using an ionization chamber: a case study with terbium-161. EJNMMI Phys. 2022;9:19. https://doi.org/10.1186/s40658-022-00448-0.

23. Borgna F, Barritt P, Grundler PV, et al. Simultaneous visualization of ^{161}Tb- and ^{177}Lu-labeled somatostatin analogues using dual-isotope SPECT imaging. Pharmaceutics. 2021;13:536. https://doi.org/10.3390/pharmaceutics13040536.

24. Marin I, Ryden T, Van Essen M, et al. Establishment of a clinical SPECT/CT protocol for imaging of ^{161}Tb. EJNMMI Phys. 2020;7:45. https://doi.org/10.1186/s40658-020-00314-x.

25. Baum RP, Singh A, Kulkarni HR, et al. First-in-humans application of ^{161}Tb: a feasibility study using ^{161}Tb-DOTATOC. J Nucl Med. 2021;62:1391–7. https://doi.org/10.2967/jnumed.120.258376.

26. Favaretto C, Grundler PV, Talip Z, et al. ^{161}Tb-DOTATOC production using a fully automated disposable cassette system: a first step toward the introduction of ^{161}Tb into the clinic. J Nucl Med. 2023. https://doi.org/10.2967/jnumed.122.265268.

27. Decristoforo C, Hernandez Gonzalez I, Carlsen J, et al. ^{68}Ga- and ^{111}In-labelled DOTA-RGD peptides for imaging of alphavbeta3 integrin expression. Eur J Nucl Med Mol Imaging. 2008;35:1507–15. https://doi.org/10.1007/s00259-008-0757-6.

28. Busslinger SD, Tschan VJ, Richard OK, Talip Z, Schibli R, Müller C. [^{225}Ac]Ac-SibuDAB for targeted alpha therapy of prostate cancer: preclinical evaluation and comparison with [^{225}Ac]Ac-PSMA-617. Cancers (Basel). 2022;14:5651. https://doi.org/10.3390/cancers14225651.

29. Al-Ibraheem A, Doudeen RM, Juaidi D, Abufara A, Maus S. ^{161}Tb-PSMA radioligand therapy: first-in-human SPECT/CT imaging. J Nucl Med. 2023;122.265291. https://doi.org/10.2967/jnumed.122.265291.

30. Al-Ibraheem A, Scott AM. ^{161}Tb-PSMA unleashed: a promising new player in the theranostics of prostate cancer. Nucl Med Mol Imaging. 2023. https://doi.org/10.1007/s13139-023-00804-7.

31. Rosar F, Maus S, Schaefer-Schuler A, Burgard C, Khreish F, Ezziddin S. New horizons in radioligand therapy: ^{161}Tb-PSMA-617 in advanced mCRPC. Clin Nucl Med. 2023;48:433–4. https://doi.org/10.1097/RLU.0000000000004589.

32. Gupta S, Halabi S, Yang Q, et al. PSMA-positive circulating tumor cell detection and outcomes with abiraterone or enzalutamide treatment in men with metastatic castrate resistant prostate cancer. Clin Cancer Res. 2023;29:1929–37. https://doi.org/10.1158/1078-0432.CCR-22-3233.

33. Derlin T, Riethdorf S, Schumacher U, et al. PSMA-heterogeneity in metastatic castration-resistant prostate cancer: circulating tumor cells, metastatic tumor burden, and response to targeted radioligand therapy. Prostate. 2023;83:1076–88. https://doi.org/10.1002/pros.24549.