

ASTATINE-211-LABELED TARGETED RADIOTHERAPEUTICS: AN UPDATE

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The heavy halogen ^{211}At was first proposed for use in α -particle targeted radiotherapy more than 30 years ago and continues to be one of the most promising radionuclides for this purpose. Although its 7.2-h half life is not ideal for intravenously administered whole antibodies, it is compatible with the pharmacokinetics of antibody fragments, peptides, aptamers and organic molecules. Its diverse chemistry allows its incorporation into a wide array of targeting vehicles, relying on its chemical similarity to iodine to provide a useful point of departure. On the other hand, the relatively low carbon-astatine bond strength is challenging. In common with the other α -emitters being discussed at this symposium, lack of reliable availability is one of the biggest hurdles in the use of ^{211}At for targeted radiotherapy. However, in the case of ^{211}At , it is not a question of production cost or availability of target material, because ^{211}At can be produced in reasonable yield from natural bismuth targets. Rather, the difficulty is the lack of cyclotrons equipped with the medium energy α -particle beams required for its production. If the infrastructure for producing ^{211}At is to be improved to the stage where ^{211}At -labeled radiopharmaceuticals can have a meaningful impact, several developments must occur. First, the ability to produce clinically relevant levels of ^{211}At that can be shipped to remote locations in chemically tractable form must be demonstrated. Approaches under consideration include compensating for radiolysis-mediated effects and the consideration of alternative chemistries. Second, strategies for compensating for heterogeneities in dose deposition must be developed, hopefully in a way that is compatible with approval for human use. And third, it is essential that more clinical trials be performed with ^{211}At -labeled therapeutics, particularly in settings of minimum residual disease where the radiobiological advantages of α -particles can be best exploited. Our own efforts in that regard will be to acquire the remaining data needed to initiate clinical evaluation of meta- ^{211}At astatobenzylguanidine and ^{211}At -labeled trastuzumab in patients with neuroblastoma and breast cancer neoplastic meningitis, respectively. In conclusion, the major barrier in moving ^{211}At -labeled targeted radiotherapeutics from appealing concept to practical treatment is the limited availability of the radionuclide. Hopefully, advances in radiochemistry and the results clinical trials at multiple institutions will provide a compelling rationale for the construction of more cyclotrons capable of producing ^{211}At .