Tackling the Last Mile: A Major Component to Successfully Establish Radioligand Therapy

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The term *last mile* originates from the telecommunication industry and describes the difficulty of connecting the end customer to the main telecommunication networks (*1*). Successfully tackling the last mile is associated with economic success in several different industries in addition to telecommunications, in particular within the supply chain and logistics industry. Translating this concept to the anticipated expansion of radioligand therapy automatically shifts the focus to the delivery of the therapy to the patients. The first difficult 25 miles of the marathon have been run by discovering and developing new therapies, investigating them in well-designed clinical trials, and gaining government approval. To complete the last mile is to successfully deliver the therapy to patients.

With 2 promising radioligand therapies recently approved by the Food and Drug Administration—^{177}Lu-DOTATATE (Lutathera; Advanced Accelerator Applications) and ^{177}Lu-PSMA-617 (Pluvicto; Advanced Accelerator Applications)—the stage is set for a radioligand therapy renaissance, especially with the abundance of convincing clinical data in support of Pluvicto (*2–5*), leading to a huge buzz. However, early lessons were learned from Lutathera after the Food and Drug Administration approval in 2018. There was an initial steep rise in demand, but sales plateaued far earlier than expected, never fully reaching the anticipated revenue potential. One can infer why this occurred. First, there were not enough hospitals prepared to offer Lutathera. Next, with neuroendocrine tumors being a specialized disease often treated in dedicated centers, sometimes these neuroendocrine tumor centers did not have nuclear medicine departments organized to deliver this new therapy. Additionally, overall, there are low numbers of neuroendocrine tumors, with approximately 12,000 patients diagnosed each year in the United States (*6*). When starting with a relatively low number of patients, and adding not having enough centers to provide Lutathera treatment, economies of scale, or an average cost decrease as output increases, was not allowed to occur. Will the story be different for Pluvicto? One advantage is that prostate cancer is more common, with over 260,000 new cases per year in the United States (*7*). But how can we make sure that all patients can be reached and that the last mile does not prevent sustainable success of radioligand therapy?

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Securing patient access clearly depends on scaling up the delivery of radioligand therapy to many more clinical institutions capable of administering the therapy. Conservative estimates predict that 70–280 theranostic centers will be needed in the United States to treat neuroendocrine and prostate cancer alone, depending on how many treatments are performed per day per site (*8*). In addition, with more studies under way to investigate the utility of radioligand therapy as earlier-line therapy and in other cancers, even more centers may be required. The 5 key pillars of successfully implementing radioligand therapy include drug supply, infrastructure and regulatory requirements (e.g., radioactive material program license), staff (including authorized users), reimbursement, and referred patients. The first pillar, drug supply, is not without challenges. Production can be affected by several issues, including ^{177}Lu shortages due to reactor shutdowns, inability to meet increasing governmental requirements, and site contamination. Although the pharmaceutical companies handle the first pillar, our field, nuclear medicine, has to pay attention to the remaining pillars. To identify eligible patients, experts in radioligand therapy should be present in multidisciplinary tumor boards, form reliable collaborations and patient referral pathways, and ensure that patients then return to the primary leading physician for further follow-up care. To ensure that there is enough staff to care for the patients, specialty training will be required for nurses, technologists, pharmacists, medical doctors, medical physicists, and more professionals. To guarantee high-quality training for all subspecialities involved, curricula need to be established and to some degree standardized. Another important aspect is to overcome financial disincentives for patient-referring collaborators by potentially considering revenue share options.

Infrastructure investment (e.g., infusion chairs, shielding, and waste management systems), as well as reimbursement, require the buy-in of major stakeholders such as payers, hospital administrations, and government organizations (requiring coordinated lobbying on behalf of patient interests). Reimbursement needs to include not only payment for the drug but also payment for all associated procedures such as administration, dosimetry, and imaging required for patient selection. Without a clear pathway to pay off the investment into new infrastructure, the required ramp-up of theranostic centers will not be successful. Advocacy, collaboration, consistency, and hard work are needed to build these 5 strong pillars. Recent joint efforts by the European Association of Nuclear Medicine, Society of Nuclear Medicine and Molecular Imaging, and International Atomic Energy Agency have been

initiated to ignite the establishment of theranostic centers, but this is only the beginning (*9*).

After reviewing the essential pillars for radioligand therapy delivery, what are the concrete necessary action items that need to be completed? Each center needs to create an individual viable business plan including strategies for infrastructure development, staff preparation, and creation of revenue with reimbursements. A regulatory framework must be locally established such as licensing, proper storage, and waste management and disposal. Contracts need to be established, with the availability of vendors on site for assistance. Educational sessions ought to be organized to inform nuclear medicine staff, referring clinicians, and patients about the new therapies. Patient acceptance is also an important part of success, and with education, this should be attainable because of high patient convenience (intravenous therapy) and low side effects.

For those who are not yet convinced of the importance of the last mile, let us turn to the logistics giant Deutsche Post DHL Group for an example. The company encompasses a vast portfolio of logistics services and is thereby suited to analyze the significance of last-mile businesses in terms of barriers to entry and financial attractiveness. Deutsche Post DHL Group's services range from international door-to-door express services to domestic and international parcel networks, forwarding of freight over international air, sea, and ground routes (door-to-port and port-to-door services), warehousing, and customer-dedicated domestic transport. The group's published financial figures (*10*) consistently suggest higher returns for business models including last-mile activities. In 2021, the activities with less of a focus on the last mile generated between a 5.1% and 5.7% earnings-before-interest-and-taxes margin, whereas the divisions including distributed last-mile services generated up to a 17.4% margin in the same year.

Whereas successfully tackling the last mile goes along with a significant economic upside in the logistics industry, it is a prerequisite to turn theranostics into a major oncologic therapy option. However, distributing specific therapies with a limited shelf-life around the globe in a secure and traceable way is considered the most challenging task in this industry, often performed by highly specialized niche players.

The renaissance of theranostics brings along one of the most exciting times in our field. Apart from the clinical effectiveness and the regulatory approval, successfully establishing the winning pillars of radioligand therapy's last mile will determine the sustainable success of theranostics.

DISCLOSURE

Ken Herrmann reports personal fees from Bayer, Sofie Biosciences, SIRTEX, Adacap, Curium, Endocyte, BTG, IPSEN, Siemens Healthineers, GE Healthcare, Amgen, Novartis, ymabs, Aktis Oncology, Theragnostics, Pharma15, Debiopharm, AstraZeneca, and Janssen; other fees from Sofie Biosciences; nonfinancial support from ABX; and grants from BTG outside the submitted work. Kelsey Pomykala reports personal fees from ABX outside the submitted work. Marcus Würker is an employee of Deutsche Post DHL Group not involved in the delivery of radiopharmaceuticals. No other potential conflict of interest relevant to this article was reported.

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