Addressing Cold Tumors via Targeted Delivery of Radiopharmaceuticals

Sophie E. Read

Abstract
Over the course of this year, an estimated 2 million people will have been newly diagnosed with cancer. In the last two decades significant progress has been made in treating cancer however, so called “cold tumors”, remain stubbornly difficult to treat. These tumors are “invisible” to the patient’s immune system, hampering the use of immunotherapeutic strategies that have been broadly applied in the treatment of cancer.

The use of radiation in the treatment of cancer is not new. Oncologists have used radiotherapy for over 100 years. However, arming pharmaceuticals with radioactive payloads offers a new era in the precise delivery of radiation for the treatment of tumors at an individual cell level. As the mechanism of tumor cell death to radiation is independent of the immune system, radiopharmaceuticals are a promising future strategy for the treatment of “cold tumors”. This article will review the state-of-the-art of radiopharmaceuticals, their application to treatment of cold-tumors and opportunities for the future.

The unmet need - What is a cold tumor and what tumors are “cold”?

The past decade of technological advances has resulted in large-scale profiling of many cancers and their tumor microenvironments. Solid tumors comprise cancer cells, as well as a mixture of other cells including; fibroblasts, endothelial cells, and a wide variety of tumor-infiltrating immune cells.

This complex interaction of different cell types regulates tumor growth and progression. Early work by Galon et al.,(2006) in colorectal cancer was the first to describe the relationship between tumor immune cells and patient prognosis. Later work by Galon et al.,(2007) and subsequently other authors proposed the concept of a tumor immune score. Tumors with a low density of tumor-infiltrating T lymphocytes (TILs) were termed cold and subdivided into so-called “immune deserts”, in which T cells are absent from the tumor and “immune-excluded” tumors, in which T cells accumulate near the tumor but are unable to efficiently infiltrate it. In contrast, inflamed, or hot tumors are generally defined by robust T cell infiltration and high levels of proinflammatory cytokines.

As an example of the scale of unmet need in the treatment of “cold-tumors”, prostate cancer is traditionally considered as an immunologically “cold” tumor with limited T-cell infiltration. Prostate cancer is the most commonly diagnosed cancer in men, and the second most diagnosed disease for men in the U.S. Estimated new US cases per annum are approximately 268,000 (Siegel et al., 2022). This makes up nearly 21% of all cancer cases in men and with an estimated 34,500 deaths per year, it is the second most common form of cancer related death in the United States. More broadly, most cancers of the breast, ovary, pancreas, and brain (glioblastoma) are also considered cold tumors. All of these tumors are typically highly aggressive, with short life-expectancy.

Therapeutic Challenges of Cold Tumors

Over the last decade, novel therapeutic strategies that seek to harness and amplify a patient’s immune system in the recognition and ultimately removal of cancer calls have made broad impact (Haslam & Prasad 2019). The pathophysiological differences in tumor immunology described previously generally align with responses to immuno-oncology therapies.
Cold tumors generally have poor responses. Whilst lack of T cell infiltration and activation are one of the main barriers to success, other mechanisms such as lack of tumor antigens and defects in antigen presentation also prevent immune system recognition of cancer cells (Berraondo et al. 2019).

Combinations of drugs have been extensively used throughout the history of therapeutic treatment of cancer. One approach to overcome poorly immunogenic tumors have been explored by targeting additional pathways usually in combination with approved anti-PD-1 / PD-L1 immune checkpoint inhibitors. Whilst a detailed review of the various approaches is beyond the scope of this review, the reader is directed to recent reviews such as Zabransky et al.,(2023). Combinations such as dual T-cell activation; vaccine approaches; oncolytic viruses; chemotherapy have all been tried. To date, only a limited number of combinations, including anti-PD-1/PD-L1 with chemotherapy, angiogenesis inhibitors, or anti-CTLA-4, have received regulatory approval. Limited efficacy together with further challenges such as increase in immune related side effects due to the combination of two immune enhancing drugs and /or significant health care costs in using combinations of expensive drugs mean that a new approach is needed. Radiopharmaceuticals may offer such an opportunity.

Radiopharmaceuticals – A new era

A radiopharmaceutical combines a radionuclide that emits either imageable radiation, therapeutic radiation, or both with a carrier molecule that delivers the radionuclide to the target. Many radiopharmaceuticals carry as the radioactive “payload” metallic radionuclides and thus need a third component—a chelator that stably binds the radiometal to the radiopharmaceutical during its transit throughout the body (Figure 1).

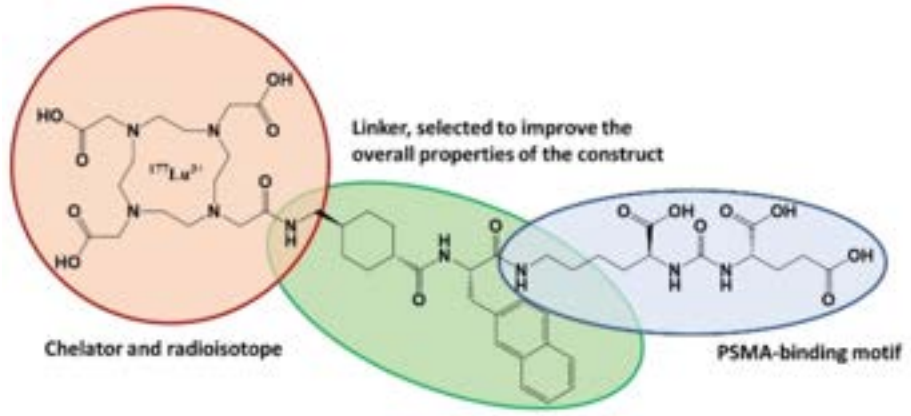

Figure 1 – Structure of lutetium Lu-177 vipivotide tetraxetan (Pluvicto®) indicating target binding region (blue) which binds to prostate-specific membrane antigen on the surface of prostate cancer cells. Also indicated is the radioactive payload ^{177}Lu carried by the chemical “basket” or chelator (orange). Pluvicto also has a short chemical linker (green) between the PSMA binding region of the molecule and the chelator / payload. Generally, these sequences are added to ensure that the payload doesn’t interfere with target binding and/or improves the circulatory properties and penetration of the molecule to the tumor site.

Early examples of radiopharmaceuticals were radio-antibodies, directed towards CD20. Y-90 ibritumomab tiuxetan (Zevalin) and I-131 tositutumomab (Bexxar) were approved in the USA in the early 2000s for use against follicular low-grade non-Hodgkin's lymphoma. Whilst the safety and efficacy of both Bexxar and Zevalin was excellent, they were commercial “flops”. Numerous issues prevented the broad and successful use of these drugs. Not least, hospitals were not ready to deploy radioactive pharmaceutical medicines and complicated supply chains for delivering the drugs to the hospital on time often failed.

Building on the early learnings of how to deploy these therapies in the hospital, new radiopharmaceutical launches have occurred. In 2018, Lutetium Lu 177 dotatate (Lutathera®) was approved in the US for the treatment of neuroendocrine tumors that effect the gastrointestinal system and pancreas. Most recently, in March 2022, the FDA approved lutetium Lu 177 vipivotide tetraxetan (Pluvicto®) for the treatment of metastatic prostate cancer (FDA Website). These drugs have fulfilled a significant need in classically "cold" tumors.

Discovery and development of radiopharmaceuticals

An attractive feature of radiopharmaceuticals is that the drug can be "armed" with a payload for imaging and then the same molecule "armed" with a therapeutic payload. This enables the identification and triage of patients where there is tumor uptake (using the imaging version of the molecule) and then if positive, the treatment of the patient with the therapeutic version. This strategy is termed "theranostic" and is the focus for future radiopharmaceutical personalized treatment of patients.

Whilst early radiopharmaceuticals were based on antibodies, both Lutathera® and Pluvicto® are small molecules. The basic features of small molecules are ideal for radiopharmaceuticals. Radiopharmaceuticals should accumulate rapidly in tumor tissues and be retained in the tumor for an extended period of time. They should avoid healthy tissues and be eliminated as quickly as possible so as not to cause injury to non-cancerous cells. For this to occur, radiopharmaceuticals typically are engineered to bind selectively to a target protein / receptor that is uniquely expressed on tumor cells and not on healthy tissues. Any part of the dose not bound to tumor cells is then eliminated via the kidneys. As such small molecule ligands are preferred over antibodies which have much longer circulation times and are excreted via the liver. The opportunity to cause radiation injury to healthy tissues is therefore higher with an antibody than small molecule targeting agent.

Once the molecule has been engineered it can be used to carry either a radionuclide for imaging or a radionuclide for therapy. For imaging, the radionuclide should emit either positrons for positron emission tomography (PET) imaging or photons for single photon emission computed tomography (SPECT). Examples of these radionuclides include ^{18}F, ^{11}C, ^{64}Cu, ^{68}Ga, ^{86}Y, ^{89}Zr for PET and ^{111}In and ^{99m}Tc for SPECT.

On the other hand, for radiopharmaceutical therapy, radionuclides that emit β particles (electrons) have proven effective in clinical practice (Strosberg et al., 2017, Sartor et al., 2021), Hofman 2021). In addition, isotopes that produce α particles, capable of depositing extremely high amounts of energy across their short pathlengths, have also been used clinically (Miederer 2022, Poty et al., 2018a, Poty et al., 2018b). Examples of these radionuclides include β-emitters such as ^{177}Lu (used in Pluvicto – see figure 1) and α-emitters such as 225Ac.

Radiopharmaceuticals & cold tumors – The Pluvicto Experience

Clinical use of modern radiopharmaceutical and potential impact in the treatment of cold tumors is well demonstrated by the development and commercialization of lutetium Lu-177 vipivotide tetraxetan (Pluvicto®) for the treatment of metastatic prostate cancer.

The ligand portion of Pluvicto is PSMA-617 it selectively targets prostate-specific membrane antigen (PSMA) that is overexpressed in the prostate tumor tissue. As PSMA is barely expressed in healthy tissue, it has a very low background accumulation, avoiding severe side effects. The drug is intended for

patients who have received previous chemotherapy and who no longer respond to hormone deprivation. In the final phase III trial VISION, lutetium Lu-177 vipivotide tetraxetan (Pluvicto®) in combination with the standard therapy reduced the overall mortality by 38% (reference).

PSMA-617 can be labeled either with Ga-68 or Lu-177, with the different payloads providing the ability to image the binding of the molecule to the tumor (Ga-68) and to treat the tumor using lutetium (Lu-177) version of the molecule. As such the imaging agent can also be used to not only select patients but also to track therapeutic response. Figure 2 is a series of scans of the same patient with metastatic prostate cancer followed over time following treatment with Pluvicto®. The numerous metastases are clearly visible in early scans (A & B) and can be contrasted with scan C at completion of therapy (Kratochwil et al., 2016).

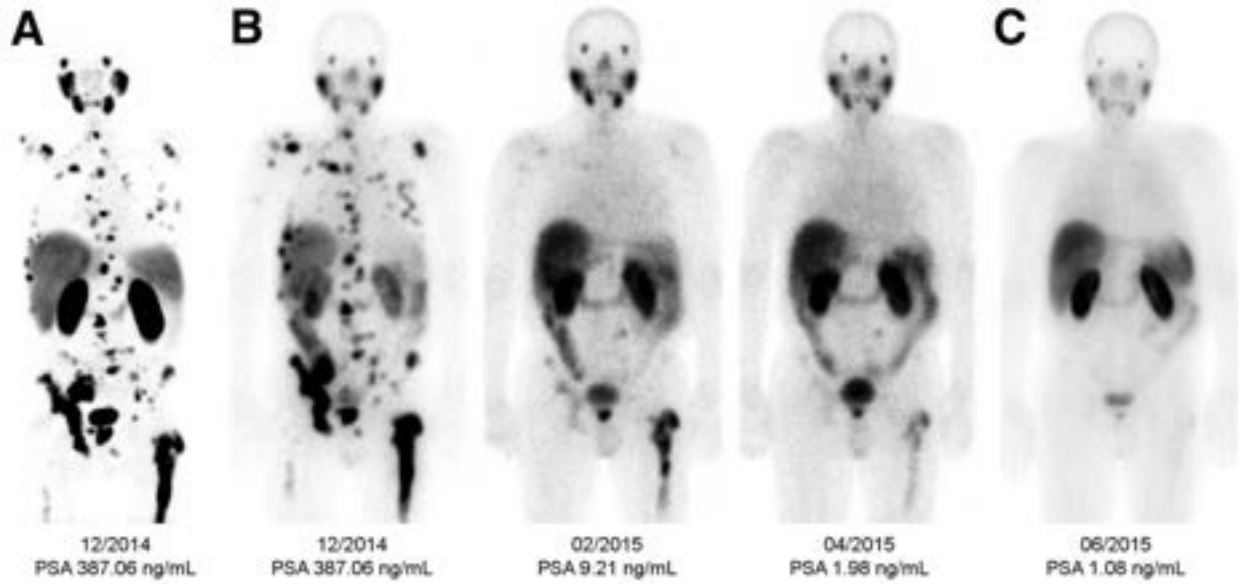

Figure 2 – PSMA imaging before, during and after treatment of a patient with metastatic prostate cancer using lutetium Lu-177 vipivotide tetraxetan (Pluvicto®) (Kratochwil et al., 2016).

Future Outlook - What are the barriers to more widespread use?

The recent launch and successful deployment of Pluvicto in the treatment of metastatic prostate cancer has provided proof that the issues of Bexxar and Zevalin, the prototype radiopharmaceuticals, have now been successfully overcome. As outlined previously the medical need for the treatment of tumors which have a poor standard of care and in which the current wave of immune based therapies have been inadequate underline the opportunity for radiopharmaceuticals.

So, what are the barriers to more widespread use? First, hospitals that are capable of administering radiopharmaceuticals are typically the major, city-based hospitals. Extensive and specialized facilities are needed, not least a radiopharmacy to prepare the dose, infusion clinics to administer the dose together with several medical specialities including medical oncology, nuclear medicine, radio-safety professionals and specialized medical waste handling. Much of these facilities are not available in smaller, provincial hospitals and therefore the broader use of these medicines may rely on simplifying how they are given.

Second, radiopharmaceuticals only have a short shelf life of 5-7 days from manufacture to when they need to be used. This means that drug needs to be potentially delivered and used anywhere in the world within this timeframe or it is useless. Shipping, handling and logistics are extremely important, and many developing or remote countries are simply not able to support these requirements.

Finally, due to radiopharmaceuticals complexity and requirements to be manufactured and shipped "just-in-time", the treatment is expensive. As an example, Pluvicto costs approximately $240,000 per course of treatment. Despite the significant medical need, many countries are not able / or will not pay these costs. For example, the UK has just declined to make Pluvicto available on the National Health Service.

Conclusion

In summary, radiopharmaceuticals are an emerging, novel class of drug able to finally address the significant unmet need of cold tumors. Whilst many of the historical challenges of early radiopharmaceutical drugs like Bexxar and Zevalin have been overcome, making these drugs more cost effective, more broadly available and simpler to deploy will remain key to their widespread use. Nevertheless, Pluvicto and Lutathera have shown what is possible and offers hope for a bright future for patients.

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