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O'Sullivan, J. M. (2019). Where Do We See Alpha Emitters in Clinical Practice? A Radiation Oncology Perspective. *Journal of Medical Imaging and Radiation Sciences*, 50(4, Supplement 1), S31-S33.
<https://doi.org/10.1016/j.jmir.2019.06.044>

Published in:
Journal of Medical Imaging and Radiation Sciences

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
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Where do we see alpha emitters in clinical practice- A radiation oncology perspective.

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This is a summary of a lecture delivered at the Targeted Alpha Therapy Meeting in Ottawa on April 4th 2019

Introduction

Radiation therapy has always required a certain amount of faith. When Willhelm Rontgen first described his laboratory finding of X-Rays to colleagues at the University of Wursburg in 1895, it must have been a pretty hard sell (1). Somehow an invisible energy was being generated which could pass through solid material and still expose a photographic plate. At the time of the discovery, little was known about atomic physics or the behaviour of ionising radiation however, the potential for the technology in medical diagnosis and indeed therapy was soon realised. It wasn't necessary to fully understand the phenomenon of X-Rays in order to gain benefit.

Today, ionising radiation is an essential tool in the healthcare environment in particular for medical imaging including CT and PET. In the therapy arena, the majority of ionising radiations are delivered by linear accelerators. Radiotherapy is now a key component of the management of approximately 50% of solid tumours. My own field of prostate cancer is particularly suited to the use of ionising radiation and recent developments including Image Guided Radiation Therapy (IGRT) and Intensity Modulated Radiation Therapy (IMRT) have led to radiation becoming the most common curative modality used in localised prostate cancer (2). Thanks to the development of radium-223 dichloride ($^{223}\text{RaCl}_2$) for use in metastatic prostate cancer in bone, Alpha particle therapy is now well established as a mainstream therapy. The widespread adoption of $^{223}\text{RaCl}_2$ as a prostate cancer therapy will help this modality become incorporated into the clinic for many other indications. These days faith alone is no longer sufficient to believe in a particular therapy and we require proof of benefit in the form of randomised controlled trials

Prostate Cancer responds well to ionising radiation

In the past 15 years, there has been a 40% reduction in mortality from prostate cancer in the UK (3). The age standardised mortality rate for prostate cancer peaked in the mid 1990's at 74/100,000. Since then there has been a steady improvement in age-standardised mortality rates despite an enormous surge in incidence (largely driven by screening with PSA). Clearly a major improvement in therapy has taken place in those years. I strongly argue that the improvement is largely due to developments in radiation and hormone therapy. The age profile at prostate diagnosis (median 68y) and death (median 84y) and the relatively low rates of surgery in men over 65 years, demonstrate that surgery is not the reason for improved outcomes. The surgical procedure of prostatectomy while more likely these days to be nerve sparing and robot-assisted, is essentially the same operation for the past 30 years. During the same time frame, multiple large randomised trials demonstrated the life-saving advantage of adding hormone therapy to radiation therapy or radiation therapy to hormone therapy (4-6).

Recent data from the largest ever prostate cancer randomised trial, STAMPEDE, have shown that there is a role for localised radiation to the prostate even in the setting of metastatic disease (7). The study which randomised approximately 2000 men with de novo metastatic prostate cancer to receive local prostate radiotherapy or standard care alone. Those patients with low volume metastases who received local radiotherapy, had improved survival.

Alpha Therapy in Prostate Cancer

When metastatic prostate cancer is no longer responding to androgen deprivation therapy (ADT) it is known as Castration Resistant Prostate Cancer (CRPC). CRPC is the lethal variant of prostate cancer and for the vast majority (more than 90%) of patients this involves metastases to the bone. The phenotype of prostate cancer bone metastases is more weighted towards bone formation than bone resorption resulting in the typical radionuclide bone scan appearance of hot spots. These spots are in fact areas of new bone formation caused by the presence of the metastases in the bone marrow which take up the radioactive tracer linked to a bisphosphonate molecule. Bone scans using Technetium-99 remain the gold standard test for the detection of bone metastases.

The bone-forming phenotype can also be used for therapy of bone metastases. By either being an analogue of Calcium (e.g. $^{89}\text{SrCl}_2$ or $^{223}\text{RaCl}_2$) or attached to a phosphate molecule (^{153}Sm), radiation can be delivered close to the site of metastases. This type of radiation therapy is known as molecular radiotherapy.

In prostate cancer, the first wave of radionuclide therapies were beta-emitters in particular Strontium-89 and Samarium-153. These agents were mostly tested in relatively small randomised trials in the late 1990's with pain and quality of life end points rather than survival. The dose-limiting toxicity of these agents was haematological in particular thrombocytopenia (8).

The alpha-emitting radionuclide, $^{223}\text{RaCl}_2$, was first tested in humans in the early 2000's. The hypothesis was that this molecule would behave like calcium, become incorporated in the bone matrix and deliver alpha-particle irradiation to metastases while at the same time offering protection to the bone marrow due to the short range of the particles. Initial animal testing was successful and led to early clinical trials testing single administrations, multiple administrations, and various doses. A suggestion of prolonged survival identified in a phase 2 randomised trial (9), led to a large registration trial, known as ALSYMPCA (10).

The ALSYMPCA trial randomised almost 1000 men with CRPC metastatic to bone to receive best standard of care plus either 6 cycles of $^{223}\text{RaCl}_2$ (given at 55kBq/kg IV every 4 weeks for 6 cycles) or 6 cycles of placebo. The trial demonstrated a significant improvement in overall survival (median 3.6 months) and delay to clinically significant progression (median 6 months). The toxicity levels were as low as predicted with a 6% grade 3 or above rate of thrombocytopenia seen in the treatment arm compared to 2% in the placebo. There were no unexpected toxicities. The success of the ALSYMPCA Trial led to the registration and approval of $^{223}\text{RaCl}_2$ as a therapy in CRPC metastatic to bone. Since the initial licence of the drug in 2014, more than 50,000 men have been treated around the world.

With the success of $^{223}\text{RaCl}_2$ as a single agent, a number of studies have examined the potential for this drug as a combination therapy. Notably, the ERA-223 trial tested the addition of $^{223}\text{RaCl}_2$ to the

novel anti-hormonal, Abiraterone (usually combined with prednisolone) in men with metastatic CRPC in the first line (11). The trial was unblinded early on the recommendation of the independent data monitoring committee due to a higher rate of bone fracture being observed in the radium arm (. In total, 26% of $^{223}\text{RaCl}_2$ plus abiraterone/prednisolone treated patients experienced fractures compared to 8% in the abiraterone/prednisolone. Patients who happened to receive a bone health agent e.g. Zoledronic Acid or Denosumab, (at their clinicians' discretion) experienced a much lower rate of bone fracture. The ERA-223 study results led to new restriction on the licence of $^{223}\text{RaCl}_2$ by The European Medicines Agency.

Mechanism of Action or region

The results of the ERA-223 trial have brought into focus the relative lack of understanding of the mechanism of action of $^{223}\text{RaCl}_2$. In vivo experiments have supported the concept of a due mode of action for drug by attacking prostate cancer cells as well as the cells in the bone micro-environment including osteoblasts and osteoclasts (12). The negative findings from the ERA-223 trial may be as a result of abiraterone and or prednisolone generating a change in the bone micro-environment which would in normal circumstances be repaired. However in the presence of the alpha-particle, the 'healing' cohort of cells may be wiped out.

Future role of $^{223}\text{RaCl}_2$ in prostate cancer

The next exciting area of research with $^{223}\text{RaCl}_2$ is in the ever expanding area of metastatic castration sensitive prostate cancer. The STAMPEDE trial has demonstrated huge improvements in overall survival by using effective agents earlier in the treatment paradigm e.g. Abiraterone and Docetaxel. A study conducted in Belfast called ADRRAD, has demonstrated the safety and tolerability of adding 6 cycles of $^{223}\text{RaCl}_2$ to local radiotherapy and up front Docetaxel in men with de novo metastatic prostate cancer in bones. This study design will now likely become part of the larger STAMPEDE trial in 2020.

Summary

Ionising radiation has a hugely important role in the modern management of prostate cancer. From the treatment of early localised disease to widespread metastatic prostate cancer, radiation therapy is saving and improving lives. It is no surprise that the first widespread use of a targeted alpha therapy in the clinic, $^{223}\text{RaCl}_2$, is in prostate cancer. The ERA-223 trial demonstrates the absolute necessity to test new therapies in properly powered clinical trials where the uncovering of potential toxicity is just as important as demonstrating improved disease outcomes. Prostate cancer is well positioned to fully explore the potential benefits of new targeted alpha therapy opportunities with PSMA directed therapy in particular.

1. Mould RF. Rontgen and his discovery of 'X-rays'. The British journal of radiology; 1995 Nov ; 68(815) 1145-76.

2. National Prostate Cancer Audit. <https://www.npca.org.uk/>.

3. Cancer Research UK. <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/mortality#heading-One>.
4. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial. *Lancet*. 2002;360(9327):103-106.
5. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: A randomised, phase 3 trial. *Lancet*. 2011;378(9809):2104-2111.
6. Pilepich MV, Caplan R, Byhardt RW, et al. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: Report of radiation therapy oncology group protocol 85-31. *J Clin Oncol*. 1997;15(3):1013-1021.
7. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): A randomised controlled phase 3 trial. *Lancet*. 2018;392(10162):2353-2366.
8. Turner PG, O'Sullivan JM. Ra-223 and other bone-targeting radiopharmaceuticals-the translation of radiation biology into clinical practice. *Br J Radiol*. 2015;88(1050):20140752.
9. Nilsson S, Franzen L, Parker C, et al. Two-year survival follow-up of the randomized, double-blind, placebo-controlled phase II study of radium-223 chloride in patients with castration-resistant prostate cancer and bone metastases. *Clin Genitourin Cancer*. 2013;11(1):20-26.
10. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
11. Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(3):408-419.
12. Suominen MI, Fagerlund KM, Rissanen JP, et al. Radium-223 inhibits osseous prostate cancer growth by dual targeting of cancer cells and bone microenvironment in mouse models. *Clin Cancer Res*. 2017;23(15):4335-4346.