A short report on the NCRI CTRad Radiotherapy DDRi combinations workshop

20th November 2019 Manchester

This whole day meeting brought together just under 80 people: scientists from academia and industry, statisticians, clinicians, patient advocates and funding bodies with all their different experience and perspectives on the issues surrounding combining DDR inhibitors (DDRi) with radiotherapy. The quality of the talks was outstanding and there was genuine interaction with the audience.

Professor Anthony Chalmers set the scene by giving an excellent overview of the various DDR pathways and how inhibitors of individual pathways may result in different levels of radiosensitisation. He highlighted that those DDRi that respond to DNA damage in G1 (DNA-PKi) might be associated with late toxicities in non-replicating normal tissues whereas the others that act principally as S and G2/M are likely to be associated with acute toxicity in rapidly proliferating normal tissues.

The range of speakers and their talks are indicated in the agenda which can be found in the Appendix.

What did we learn?

- The choice of DDRi might be dictated by the site of the tumour and whether the normal tissues likely to be in range are proliferating or not.
- The dose of DDRi, may need to be lowered significantly if being used in a chemoradiotherapy combination, as opposed to a radiotherapy alone setting due to overlapping or synergistic toxic effects for example neutropenia. If such overlapping toxicities exist combination strategies with radiotherapy without chemotherapy may be the optimum area for initial exploration.
- Patients are all different, one size doesn't fit all. Trial design needs to involve patients at the concept stage, enough of the right people need to be involved sufficiently to explain how the proposed trial is supposed to work and to help understand if patients will be interested in taking part in these trials. Early engagement is important and there are plenty of opportunities to gain this support (Catharine Raitt).
- Clustered damage from high LET protons might be a good combination with PARPi (Jason Parsons), that not all PARPi are equally good at radiosensitisation – talazoparib is most potent.
- BCL2 overexpression or ARID1A loss might be new determinants of sensitivity to PARPi (Ross Carruthers) and that sensitisation of a peptide receptor radionuclide by PARP inhibition might be model dependent (Julie Nonnekens).
- There is a rationale for combining ATMi with RT for p53 mutant brain tumours as they may protect normal brain as well as radiosensitise tumour cells, interesting, patient derived pre-clinical xenograft data on efficacy and PD (pRAD50) were presented, with this data supporting the development of a clinical trial (Steve Durant).
- DNA-PKi are the most potent radiosensitisers but also with potential for increased toxicity. So conservative dose adaptation with maximum avoidance of organs at risk is crucial.
- Biochemical and preclinical data on a DNA-PKi in combination with radiotherapy that has entered a clinical trial showed good radiosensitisation that was accompanied by transient normal tissue toxicity (Frank Zenke).
- The potential for immune-oncology drugs with these DDRi-RT combinations looks interesting.
- Pharma have some differing priorities from clinicians/academics (getting a drug registered vs answering a clinical/biological question) and work at a different pace with less/different

hierarchy than clinical/academic groups (Saif Ahmed). However, the overarching goal is the same. Meeting unmet need to improve patient outcomes.

- There can be multiple issues with recruitment to RT-DDRi trials as exemplified by the Patriot (ATRi) trial (Magnus Dillon), including an unexpectedly high rate of refusal from patients.
- Different trial designs e.g. Concorde (multi-interventional arm with a single control arm to benchmark efficacy and toxicity) or statistical modelling approaches, e.g. continuous reassessment based on prior assumptions can be considered (Sarah Brown).
- There are a huge variety of potential biomarkers, solid and liquid (Caroline Dive) that can be used to select or monitor patients but these need to be considered early in the development and require different people from a large team in a collaborative venture.
- Imaging biomarkers should also be considered to measure response, including γH2AX for DNA damage (Ferdia Gallagher).
- MRC DPFS is open to funding this type of research, 3 calls/year with no restriction on duration or cost. Cancer currently achieves 15-20% of the funding, it doesn't have to generate IP; health benefit is equally important and there should be no barriers (e.g. from Pharma collaborations) to achieving this (Adam Babbs).

The Way Forward

Overall, the meeting showed perfectly that a multidisciplinary approach is essential to ensure the best clinical trials are developed with the highest chances of success. It was wonderful to see how people embraced this and were genuinely open. RT-DDRi clinical trials need to be hypothesis-driven, based on sound pre-clinical data with close scientific scrutiny of the underlying mechanisms, the appropriate models and potential biomarkers. Patients and statisticians need to be involved at an early stage to ensure that a trial is acceptable for good recruitment and designed properly to generate robust results. Engagement between Pharma and clinicians/academics requires understanding of their different goals. MRC is an excellent place to look for potential support.

Future meetings should focus around the development of specific trial ideas, working in smaller groups and bringing together the multi-disciplinary expertise required. This would demonstrate translation of what we have learned from the workshop into tangible outputs.

On behalf of NCRI CTRad's WS1 and WS2

Appendix: Agenda of workshop

09:30	*Registration and refreshments*	
10:00	Introduction and aims of the day	Richard Adams, Nicola Curtin
Session chairs: Ross Carruthers, Paul Shaw		
10:15	DNA damage repair in the context of radiotherapy: Overview: Where are we now, gaps in our knowledge, UK opportunities	Anthony Chalmers
10:35	Targeting the DDR in combination with proton beam therapy	Jason Parsons
10:50	MRT in combination with DDR inhibitors	Julie Nonnekens
11:05	Discussion	
11:15	*Refreshment break*	
Session chairs: Ricky Sharma, Nicola Curtin		
11:30	Development of the DNA-PK inhibitor M3814 in combination with radiotherapy	Frank Zenke
11:50	PARPi +RT why, how and where next?	Ross Carruthers
12:05	Running a Phase I study of RT+ DDRi: Problem solving	Magnus Dillon
12:20	Barriers to drug-radiotherapy combinations entering the clinic, and how to break them	Saif Ahmad
12:35	Discussion	
12:50	*Networking lunch*	
Session chairs: Sean Buckland, Ananya Choudhury Practicalities, taking DDRi into the clinical RT setting early phase		
13:40	Preclinical, translational and clinical development of the brain penetrant ATM inhibitor AZD1390 for the radio-sensitisation of CNS malignancies	Stephen Durant
14:00	Methodological view	Sarah Brown
14:15	Patient view	Catharine Raitt
14:30	Funders' view: MRC	Adam Babbs
14:45	Discussion	
14:55	*Delegates transfer to breakout rooms*	
15:00	Case based trial design: proposals discussion (with coffee)	
Session chairs: Richard Baird, Tim Ward		
16:00	Optimising translational research to biomarker discovery and validation	Caroline Dive
16:20	Application of imaging biomarkers to the development of novel drug-radiotherapy combinations	Ferdia Gallagher
16:40	Feedback	Nicola Curtin, Richard Adams
17:00	*Meeting close*	