Department of Health

NCRI National Cancer Research Institute

NCRI Lung CSG Mesothelioma workshop

in association with Department of Health

Workshop Report

The Royal Society of Medicine, London
2nd May 2014

Mesothelioma workshop

Workshop Report

Workshop summary

80 delegates from a variety of specialities attended the one-day workshop, held at the Royal Society of Medicine in London.

Chaired by Dr Marianne Nicolson (Chair of NCRI Lung CSG) and organised by the Mesothelioma Workshop Steering Group: Dr Robert Rintoul (Chair of NCRI Lung Screening/Early Diagnosis Subgroup and steering group), Mr Ian Jarrold (British Lung Foundation), Ms Michelle Cashin-Cox (NCRI Research Project Officer), Professor Dean Fennell (Chair of NCRI Mesothelioma Subgroup) and Dr Eileen Loucaides, Head of NCRI CSGs Secretariat, the workshop aimed to:

1. Encourage research, particularly basic research, in the field of mesothelioma, by raising awareness of available funding and resources

2. Communicate the current status of mesothelioma research

3. Address the important clinical questions and how they may be implemented

4. Generate ideas for proposals on basic and translational research in mesothelioma

The key points of the day are summarised in this report.

Introduction

On 2nd May, 2014, the NCRI Lung Clinical Studies Group (CSG) and Mesothelioma Subgroup, in association with the Department of Health (DH) and British Lung Foundation (BLF), ran a workshop on mesothelioma at the Royal Society of Medicine, London. This workshop aimed to attract delegates who are current researchers in the field of mesothelioma and to also attract fresh research talent, from various applicable disciplines (such as basic scientists, surgeons, clinicians, epidemiologists, geneticists, computational biologists and bioinformaticians), by raising awareness of available funding, resources and promoting collaboration for mesothelioma research. Invitation was extended to funding representatives in Medical Research Council (MRC), Cancer Research UK (CRUK), British Lung Foundation (BLF), Experimental Cancer Medical Centres (ECMC) and those in the pharmaceutical industry who are involved in decision-making processes during drug-development in lung cancer research.

Dr Marianne Nicolson opened the meeting, welcomed delegates and introduced the Lung CSG and their work streams. Dr Nicolson explained the importance of the workshop, highlighted the upward trend of mesothelioma occurrence, current research interest in and gave an overview of open clinical trials in mesothelioma within the UK via the NCRI Lung Clinical Studies Group portfolio maps. Dr Nicolson also spoke briefly on the current state of mesothelioma research, poor prognosis for this condition and the growing need to 'pull together' and to harness research and funding opportunities.

Mr Ian Jarrold (BLF) gave an overview of current funded research in mesothelioma and current funding opportunities, detailing mesothelioma as a research priority for the BLF. £3M has been made available for research into mesothelioma and the BLF was selected to administer this fund. All of this funding has now been allocated and all grants are ongoing and enabling research in areas such as the genetics of mesothelioma and have boosted research in mesothelioma, laying foundations for the next stages of research.

It is predicted that the incidence of mesothelioma and mesothelioma-related deaths will peak in the UK and worldwide, before 2025. Therefore, funding must be sourced for further research into treatment and curative measures. The BLF has secured a further £250,000 from sources in the insurance industry. Mr Jarrold emphasised this meeting was of critical importance to increase leverage for further funding.

Sessions

A brief summary of each session is given below

1. Session One - Harnessing current resources in mesothelioma research

Chair: Dr Peter Szlosarek, Barts Cancer Institute, Queen Mary University

Session one included presentations on the following:

1. Mesothelioma research and funding within the UK
2. The genetic landscape of mesothelioma
3. Key note lecture: Anti-mesothelin immunotoxin therapy for malignant mesothelioma
4. Pre-clinical platforms for identifying new drugs
5. Novel agents in mesothelioma
   This was followed by a panel discussion

1.1 Mesothelioma research and funding within the UK

Professor Anne Willis & Professor Marion MacFarlane, Medical Research Council

Of the £96m fund allocated each year to cancer research, the MRC spends £10m on lung cancer research. Since 2012, there has been significant investment in mesothelioma research and the majority of mesothelioma-relevant research now takes place at the MRC units.

From a research perspective, there is ongoing research in the following topics: cell lines established from freshly resected tumours; genetic profiling, cell lines with a p16 deletion (although the viability of these cell lines is unclear) and the cell-types that contribute to mesothelioma – do these cells modify mesothelioma cells? Professor MacFarlane also presented on pathogenicity of fibres in the pleural cavity and investigations into the molecular changes which occur at the mesothelium, as a consequence of direct exposure to fibres such as long length asbestos and carbon nanotubes (CNT). Long length asbestos fibres and CNTs have been shown to induce pleural lesion development, which may progress into mesothelioma.

1.2 The genetic landscape of mesothelioma

Dr Peter Campbell, Wellcome Trust Sanger Institute

Sequencing technologies are becoming cheaper and more sophisticated. This may present the opportunity for worldwide collaboration to tackle cancer. With sequencing costs becoming cheaper, there is a need to consider whether all patients entering UK clinical trials should have genetic profiling. Protocols are being developed for use in the clinic, such as whole exome sequencing and targeted gene screening, to identify driver

mutations. Mesothelioma exome sequencing has revealed a different genetic profile to other toxicologically induced cancers with mutations. This appears to be age-related. Future work requires further characterisation of clinical indicators of driver mutations and more work on targeted screens.

1.3 Key note lecture: Anti-mesothelin immunotoxin therapy for malignant mesothelioma

Dr Raffit Hassan, National Cancer Institute

Dr Hassan spoke about current research on malignant mesothelioma with a focus on pleural mesothelioma; an aggressive disease with poor prognosis. He noted surgery as part of multi-modality therapy prolongs survival in selected patients and most chemotherapy drugs are ineffective. At present, pemetrexed plus cisplatin is the only FDA approved treatment.

Research collaboration has led to the discovery of mesothelin, a 40kDa protein, highly expressed in many types of tumours. The function of this protein is currently unknown; there are no phenotypes in knockout mice, however, there are indications that mesothelin may play a role in cell adherence. Mesothelin is expressed in 100% of mesothelioma and pancreatic tumours; 67-71% of ovarian cancer and 41-53% lung adenocarcinomas. Heavy expression of mesothelin in these poor prognosis tumours suggests it may be a good target for cancer therapy. In 1999, a monoclonal antibody targeting mesothelin (SSP1) was produced, which specifically localised to the tumour. Subsequently, an anti-mesothelin antibody fused to Pseudomonas exotoxin A was developed, which delivers the toxin to the cancer cell and induces localised cell death.

Preclinical data led to the first clinical trial of patients with ovarian & pancreatic cancer and mesothelioma. Subsequent findings led to further trials, including the 'SS1P plus pemetrexed and cisplatin mesothelioma' study which concluded chemotherapy plus SS1P was well tolerated. At the maximum tolerated dose, of the 13 patients treated, 10 had a partial response (PR) and 1 achieved stable disease (SD). The number of PRs was more than expected from pemetrexed and cisplatin alone, but this needs to be confirmed in a larger trial. It was observed that most patients only received one cycle of SS1P, because antibodies formed and patients probably would have done better with more cycles. Decreases in anti-SS1P antibody formation allow patients to receive more doses of SS1P and there were dramatic tumour responses in patients with extensive treatment refractory mesothelioma. These responses are durable without additional therapy. Dr Hassan also outlined other approaches, in addition to immunotoxins, to exploit mesothelin for cancer immunotherapy.

1.4 Pre-clinical platforms for identifying new drugs

Dr Ultan McDermott, Wellcome Trust Sanger Institute

Dr McDermot presented on solutions to patient drug sensitivity and resistance. He highlighted the challenges that lie in tissue specific reactions to drugs and the growing need to develop more cell lines to improve conditions and provisions for testing. He expanded, for a personalized medicine approach, developing and matching short-term cell lines will show predictive signatures, resistance and outcomes of various drugs, e.g. BRAF inhibitors. Dr McDermot also presented on the genomics of drug sensitivity in cancer and current work in the MANOVA of drug where gene interactions are measured to identify mutations. Drug biomarker discovery and predictive signatures of drug response may be applied specifically to mesothelioma. Organoids as next generation cancer models were also discussed and highlighted as:

- Better representation of genomic landscape
- Matched tumour biopsy, normal organoid and linked clinical data
- More physiologically relevant 3D model
- Tractable experimental system (e.g. CRISPR, over-expression)

1.5 Novel agents in mesothelioma

Professor Dean Fennell, University of Leicester; NCRI Mesothelioma Subgroup Chair

The UK has the highest incidence of mesothelioma and this is increasing. Global incidences of mesothelioma correlate with the highest use of asbestos. Professor Fennell presented on the potential of drawing on what has been observed from past studies and on the future of treatment for mesothelioma as it moves from empirical to rational therapies, such as, synthetic lethal targeting; network targeted therapy; immune targeting and immunomodulation. Further classification of mesothelioma into multiple subgroups is needed; therefore, further characterisations are required to identify specific biomarkers and targets. The question remains whether we should now focus on a stratified therapy paradigm for mesothelioma.

1.6 Panel discussion I

Key points from the panel discussion session are summarised below.

- The mouse model was created by injecting fibres directly into the pleural membranes.
- CNTs are carcinogenic at occupational exposure levels, rather than non-occupational levels (regulated in UK, but not elsewhere)
- Stromal tissue could be useful to examine in mesothelioma, given the limited metastatic nature of mesothelioma and may give an early selective advantage.

- A decision is required from patients prior to donating samples, as whether or not they would like to know about unexpected findings following results of tissue sequencing.
- Patient information currently states that any findings won't be fed back from retrospective sample analysis.

2. Session Two - Priority setting and funding success

Chair: Mr John Edwards, Sheffield Thoracic Institute, University of Sheffield

Session two included presentations on the following:

1. MesobanK
2. European research links with the UK – Mesoscape
3. Update of the James Lind Alliance priorities

This was followed by a panel discussion

2.1 MesobanK

Dr Robert Rintoul, Cambridge Cancer Centre; NCRI Screening and Early Diagnosis (lung) Chair

The aims and objectives of MesobanK are to establish a bioresource of mesothelioma tissue linked to a clinical database for retrospective tissue microarray (TMA) and prospective fresh tissue collection. The initiative aims to develop a web-based IT infrastructure for annotating, searching the bioresource and an annotated cell culture collection service with a robust infrastructure to allow long-term sustainability at a reasonable cost. MesobanK has a remit to advance mesothelioma research by providing access to samples and data and providing support for biomedical research directly concerned with asbestos-related disease diagnosis and treatment in the UK, EEA, USA, Canada, Australia and New Zealand.

Progress for MesobanK has been seen with retrospective Formalin-fixed, paraffin-embedded (FFPE) tissue collection for TMA and strategies, such as a prospective tissue collection strategy. Collaborations are in progress with Marion MacFarlane, Dean Fennell and Stefan Marciniak to develop novel mesothelioma cell lines. Up to 200 more cell lines are required, in addition to standardised SOPs, sequencing and drug screening.

2.2 European research links with the UK - Mesoscape

Professor Paul Baas, Netherlands Cancer Institute

The aims and objectives of Mesoscape include the coverage, collection and review of data generated in the mesothelioma community. Professor Paul Baas presented an overview of studies within Mesoscape such as the MESO 1 study, a pS6 observational

study, conducted as part of the ETOP Mesoscape programme and the expression and clinical significance of pS6, comparing samples with an epidemiology cohort consisting of all patients diagnosed at, or referred to, all participating sites in 2011 and 2012. The MESO 2 study is in preparation. UK and European collaboration is also in progress to combine resources and studies, to boost clinical research in malignant pleural mesothelioma (MPM). Mesoscape is also partaking in a European Organisation for Research and Treatment of Cancer (EORTC) collaboration with E1205, a phase II study of extended pleurectomy/decortications, combined with (neo)-adjuvant chemotherapy in patients with early stage MPM. Other initiatives include the MINE (EEC grant) and Specta-Lung - screening patients with thoracic tumours for efficient clinical trial access.

Finally, Professor Baas expanded on the important clinical questions regarding mesothelioma, including the need to improve MPM treatments. A high number of patients with MPM show a recurrence after first line therapy and there is currently no second line treatment in MPM as well as differential sensitivity for drugs in patients with MPM.

2.3 Update of the James Lind Alliance priorities

Mr Ian Jarrold, British Lung Foundation

On behalf of the James Lind Alliance, Mr Ian Jarrold (BLF) updated delegates on the JLA priorities. The Priority Setting Partnership for mesothelioma was set up in December of 2013, through the James Lind Alliance (JLA) and funded by the National Institute for Health Research (NIHR). The project is supported by a number of charities with mesothelioma as a focus.

To date, a steering group, chaired by Katherine Cowan from JLA, has been setup. It is responsible for facilitating the process, ensuring that it follows the JLA principles of transparency and equal involvement of patients, carers and clinicians.

Present and future work will include further investigation into the uncertainties around the diagnosis, treatment and care of mesothelioma. A survey is underway to collect treatment uncertainties and is due to be completed at the end of April in 2014. Upon identification of these ‘uncertainties’, a workshop will be organised for patients, carers and health professionals to agree on the final ‘top 10’ priority questions for researchers to answer.

2.4 Panel discussion II

Key points from the panel discussion session are summarised below.

- If the current tissue being banked with MesobanK is not sufficient to sustain tissue needs from the research community, there would be a good business case for increased funding for this project.

- The storage capacity at MesobanK at present does not allow for data to be re-captured from MesobanK tissue being used for research. Researchers using the tissue will be encouraged to make their results publicly available.
- A condition of data sharing from the pharmaceutical industry is speculative at this point, and the balance between access to tissues and constraints on its use will be important.
- MesobanK could be linked in with NCIN data on co-morbidity and treatment.
- Specialised MDTs would be key to this process and the opportunity to ensure this happens is present within NHS reforms. There will be a discussion on specialist mesothelioma multi-disciplinary teams (MDTs) at a networks meeting in September.
- Coordination of tissue sharing across EU countries can be a challenge from a regulatory point of view.
- Patient uptake of sample donation has been good for both extra blood and tumour samples.
- It was suggested that funders recommend mesothelioma studies to 'opt out' of collecting tissue to increase donations.
- There is map of early-phase trials available. It would be good to have an overview of what is in progress to avoid potential overlap of work and to show patients where to go for therapy.
- What are the implications of intra-tumour heterogeneity?

3. Session Three - Potential studies, trials & concepts

Chair: Dr Robert Rintoul, Cambridge Cancer Centre

3.1 Breakout Group 1: Tissue collection & logistics

Chair: Dr Robert Rintoul, Cambridge Cancer Centre

The tissue collection & logistics breakout group aimed to gain a consensus on who might use MesobanK, whether they are collecting the correct types of tissue and using the correct procedures for these processes. The group discussed patient consent, ethics and explored whether there is value in a single collection of tissue, comparing various tissues or if there is scope to also partake in virtual collecting, i.e. digital images, data and sequence.

Based on the discussions during this breakout session, the project is moving in the right direction and some procedures in MesobanK need to be fine tuned rather than completely changed.

For more information, please refer to Appendix I

3.2 Breakout Group 2: Basic science & genomics

Chairs: Dr Peter Campbell & Dr Ultan McDermott, Wellcome Trust Sanger Institute.

The basic science and genomic breakout session highlighted problem areas for potential 'bottle-necks' in mesothelioma research, as well as the future of mesothelioma basic science.

There is a need for better science, better research projects and more funding. Although the incidence for mesothelioma is lower than many other cancers, it is rising. Funding in mesothelioma research is generally overlooked. This disease tends to have a long latency period (around 40 years) and remains relatively unknown to the wider public. In this case, the public tend not to donate to this cause and, therefore, not enough money is generated for the research.

The breakout group also discussed topics including concerns of causative agents and increased incidences; early diagnosis, early detection and measuring risk exposure; genetics, inheritance and high risk populations; drug development and identification of biomarkers; clinical trials and career development funding, in order to attract more talented scientists into the field of mesothelioma research.

For more information, please refer to Appendix II

3.3 Breakout Group 3: Translational & clinical questions

Chairs: Professor Dean Fennell, University of Leicester, Mr John Edwards, Sheffield Thoracic Institute, University of Sheffield; Dr Marianne Nicolson Aberdeen, Royal Infirmary & Dr Peter Szlosarek, Bart's Cancer Institute (Two groups, A&B merged)

Professor Fennell introduced the session and explained the purpose of the breakout session as generating ideas and highlighting areas for further work**.** This was examined through considering imaging in mesothelioma; histopathology; tissue; epidemiology; trial maps; trials and design; radiotherapy; palliative and supportive care for mesothelioma; surgery and the potential for new consortium addressing a series of themes in mesothelioma

For more information, please refer to Appendix III

3.4 Summary and outcomes of the day: Closing remarks and next steps

Closing remarks - Dr Robert Rintoul

Dr Rintoul noted, five to six years ago it would have been a challenge to have so many people come together with a focus on mesothelioma research. In this capacity, the workshop has been a great day and a very positive step towards boosting research in mesothelioma. He stressed the importance of pursuing and following through on ideas which have been generated at the workshop. Over the next few years, the mesothelioma research community are in a good position to do this.

The following key points and potential outcomes should be noted

Tissue collection & logistics

- There is a need to collect and examine multiple tissues: abnormal vs. normal
- There is a need to provide more validated and standardized collection procedures – current resources may benefit from a virtual system. Temporal biopsying is very important but difficult to do. It is important to start biopsying from different areas and start sequencing
- It is difficult to determine a 'one size fits all' collection procedure for tissue used in future scientific methods.
- Some fine-tuning is required for MesobanK procedures

Basic science & genomics

- The key to improving survival in mesothelioma is an early marker of disease and it needs to be identified quickly.
- A biomarker is needed to distinguish between plaques vs. mesothelioma.
- An early detection strategy is need: screening is not enough; there is a need to identify drug targets and develop a treatment strategy.
- There is a strong need to increase and improve cell lines. It is important to put money and resources into developing mouse models.
- Insufficient communication of basic science of mesothelioma is perceived to exist within the surgical research community. More communication links are required to develop effective trials.
- Mesothelioma is rare so the public don't donate to the cause. As a result, there is little funding for research

Translational & clinical questions

- More consideration needs to be given to imaging in mesothelioma, to cover all grounds.
- There is a great need for staging of mesothelioma
- There is a potential proposal for national prospective and retrospective P16 testing on tissue samples as an outcome for patient.
- For epidemiology, it would be helpful to develop a national registry service to identify all patients.
- The need for better IT was highlighted to improve patient registration and establish better links with specialist MDTs. This may tie in with NCIN work.
- There is a potential proposal for a questionnaire for all treating physicians in the UK

- More discussions are needed to build on and improve radiotherapy in mesothelioma treatments. A positive step would be to combine resources by forming a short-term Mesothelioma Subgroup/ CTRad working group to tackle radio-oncology in mesothelioma.
- There is a need to address funding issues with tissue collection in hospitals
- There is a potential proposal for a mesothelioma consortium addressing a series of themes and bottle-necks in mesothelioma research

For more information, please refer to overleaf to Appendices

Appendices

Breakout sessions

Appendix I

Tissue collection & logistics

Chair: Dr Robert Rintoul, Cambridge Cancer Centre

- **Usage of collected tissues**

It is essential that collected tissue is used. There are currently 12 samples in the tissue bank and now is a good time to evaluate what we have, who might use it and how it might be used. MesobanK is collecting fresh tissue that will then be frozen such as tumour, serum and plasma samples and pleural fluid. If MesobanK are not collecting the right tissue, what should we be collecting instead? A potential problem is that it is impossible to predict what researchers are going to do or what tests are going to be applied to the samples; hence, there is a need to be quite generic so that samples may be used for various types of research.

- **Standardisation of collection procedures**

There are unresolved issues on standardised tissue collection, due to the unpredictability of future usages. If it is known for which procedures one is collecting for, it is a simple to decide upon suitable collection methods; however, future methods cannot be predicted. There is also a need to ensure clinicians are following the protocol when collecting the samples.

There may be benefits in having a virtual system, as it is easier to standardise collection and storage procedures and implement guidelines across collection sites. MesobanK have put a robust system in place. Where possible, there is a signed agreement that they will follow the SOPs. Furthermore, strict QA & QC procedures for cell lines are covered by the HTA. However, some QA & QC procedures may render some samples unfit for certain assays, e.g. found some tissues had little tumour content and TTCA rejected 90% of the samples sent into them.

- **Logistics**

Standard operating procedures are in place for MesobanK and are regularly revisited and revised. The baseline data for sample logistics is complete and collected directly from patients and their case notes. Further samples and downstream data regarding chemotherapy and radiotherapy, has not yet been collated due to collection starting just recently.

- **Donor consent**

Gaining donor consent for collection appears to be easier when patients have had an informed experience with their cancer. Patient information regarding MesobanK is very clear and the patients, who have been approached, have no objections to the process. Doctors have been instructed to only approach patients that are highly likely to have mesothelioma. When approaching patients who are awaiting diagnosis, physicians must be honest and inform the patient of suspected mesothelioma

- **Ethics**

Family consent has presented as a leading issue in ethics. There have been experiences where patients and family members have been upset when they have discovered their tissue is on medical record and had been given to a biobank. “Anonymised link” is in place where linkage and patient can be worked out if necessary. Outside UK, consent is sought only if the person is known but not needed if not.

MesobanK has specifically stated the tissue will only be given to asbestos related disease/mesothelioma. There are also questions about the robustness of ‘informed consent’: asking patients to donate tissue in stressful hospital environment may not be conducive to full patient understanding – is this really informed consent? MesobanK consent forms explicitly explain everything about tissue donation and allow the patient time to go through the process and think about everything.

- **Mesothelioma a multi-focal disease**

Early changes in disease must be considered, but there is no ongoing investigation into

abnormal vs. normal cells. This should be addressed as the opportunity is present to take samples of various tissues.

It is difficult to insist on mapping, but it would be a definitive move to request from biopsies from different tissues. It is important to start biopsying from different areas and start sequencing. Temporal biopsying is very important but difficult; patients fitted with plural drains while on hospital leave, can drain themselves and, theoretically, we could collect samples from patients every few weeks.

- **Access to samples and the database**

Collaborators with MesobanK will have access to the database and they will be charged. The steering committee will decide if a research project is to receive the samples and this will be dependent on where the database and work will take place. A consensus is still to be reached on this. The core data available with each sample is standard. 5 tumour samples from each patient and multiple serum and plasmas (about 10 of each).

Appendix II

Basic science & genomics

Chairs: Dr Peter Campbell & Dr Ultan McDermott, Wellcome Trust Sanger Institute.

- **Causative agents and increased incidences**

Further concern exists with causative agents and increased incidences. Asbestos still frequently occurs in living environments and there is growing evidence for mesothelioma induced by carbon nanotubes. A gender bias in samples is also emerging with increased incidences reported in females (washing clothes containing fibres). A recent BLF survey, sent to people in the trade industry, revealed poor public knowledge on mesothelioma. Mesothelioma needs increased public awareness, as there is a lack of knowledge as to who is affected. Globally, incidence is on the increase, notably in Australia, India and China.

- **Early diagnosis, early detection and measuring risk exposure**

The breakout group discussed needs for an early marker of disease for mesothelioma. There is no known mechanism of disease in mesothelioma and, therefore, no biomarkers. More funding is needed to investigate mechanism of disease.

We need a non-biased approach to look for biomarkers and need a biomarker to distinguish between plaques vs. mesothelioma. Over 50% of patients have granuloma plaques, which can be used as a measure of exposure. In the US, these are followed annually, however, in the UK they are not, as progression to mesothelioma is low.

An early detection strategy is needed as screening is not enough. Identification of patients and new treatment strategies are needed in parallel. 1% of the male population alive in the 1950s are likely to die of mesothelioma. There are also socio-economic issues to be examined here, in the context of co-morbidities. It would be helpful to look at cases of mesothelioma in isolation.

- **Genetics, inheritance and high risk populations**

The breakout group discussed the role of genetics in mesothelioma susceptibility. Among GP patients; 10-15% never had a known exposure to asbestos. Within Hull, there is increased incidence of mesothelioma; however, there are no specialist centres. The prognosis is bad and patient outcomes are poor. Professor Julian Peto's cohort study of occupational history includes specimen, age and sex, matches controls. Examining fibre count in biopsy specimens may identify a high risk population.

- **Drug development**

The same compounds are always being used; we need a protein to target in order to develop a drug. Phase I trials are perfect for mesothelioma, but a very strong hypothesis is needed to test in phase I. There is a strong need to identify new drug targets. There are many drugs in development to identify mechanisms of disease. However the question remains if these targets exist.

Another area to investigate is 'response to asbestos' in the context of inflammation. There

is a great need to increase and improve cell lines and animal models for early events. At present, cell lines are grossly inadequate to examine inflammation. More funding is required to develop testing models.

- **Clinical trials**

Intra-tumour heterogeneity is a problem, as targeted therapy will not kill all tumour cells. Development of treatments for this is difficult. Educating patients and clinicians is very important. Presently, insufficient communication of basic science of mesothelioma is perceived to exist within the surgical research community. Further communication links are required to develop collaborations and effective trials. A themed call for surgical studies in mesothelioma is needed as a follow on from MARS2. We need better functional imaging to measure the effect of the drug in drug trials.

- **Career development funding**

In primary care, mesothelioma is often misdiagnosed. It remains a challenge to encourage interest in this area. Further career development for scientists is required to generate more research. As funders do not generally ring-fence money into specific areas, an adaptive cross-discipline training or fellowship exchange may work.

Appendix III

Translational & clinical questions

Chairs: Professor Dean Fennell, University of Leicester, Mr John Edwards, Sheffield Thoracic Institute, University of Sheffield; Dr Marianne Nicolson Aberdeen, Royal Infirmary & Dr Peter Szlosarek, Bart's Cancer Institute

- **Imaging in mesothelioma**

A plea was made to improve imaging in mesothelioma. MRI is useful for T-stage, monitoring metastasis and monitoring plural disease; however, there is a great need for exploring further methods of staging.

Validation and standardisation may be an issue as there is no validation in place for imaging as a visual tool for monitoring predictive PFS endpoint. Imaging results, based on modified resistance, can give an indication or additional information on whether drug has worked. Need for standardisation in both frequency and practice.

PET imaging was suggested as a possible means to see if a given drug effects cancer. Pre-clinical data could be used and biomarker behaviours must be better understood. Immunotherapy may only be applicable in CT, however, the staging needs to be radiological. Targeted to mesothelin antibody, radio-labelled I-11 has been used in PET and CT, and modified to show response. CAT is different to quantity, so also investigating the use PET scan to see other ways they can score. This is currently in development. Need more consideration in imaging to cover all grounds.

- **Histopathology**

There is a need for investigations specifically for mesothelioma. There is a potential approach in lymph nodes, but further work is needed on grading of tumours via histology and further collection of data needed. The Royal College of Pathology is currently looking at mesothelioma. At present, there insufficient data to generate guidelines for mesothelioma grading, as there are no specialities or standardisation in mesothelioma, but there is data available and some papers in progress.

P16 may be promising as a biomarker for mesothelioma prognosis. Similar applications have been established with FISH, an approved test for treatment with pemetrexed, cisplatin and carboplatin. Emerging data indicates loss of P16 as a predictive marker for outcomes; P16 loss is reportedly only found in short-term, 'catastrophic' relapse in retrospective tissue samples. There is potential for retrospective P16 testing as an indicator for patient outcome, to try characterising why some people live longer than others. This could help with decision-making in regards to further treatment such as surgery.

It may be possible to look at P16 in tissue samples and it may be possible for every centre in the UK to gather data on this, prospectively and retrospectively. Before this could be initiated, a specialised bank is required. Researchers would need to obtain

blocks via a national initiative and to make this a small, but specialised resource, rather than going through a rigorous process.

- **Epidemiology**

The future of mesothelioma epidemiological studies in the UK lies in targeting the youngest patients to predict future burdens. A national project is underway to identify patients and data, which may shed further light on genetics and chemoresistance in mesothelioma.

It would be helpful to develop a national registry service to identify all patients. Treating physicians may supply this patient information. The need for better IT was highlighted to improve patient registration and establish better links with specialist MDTs. The UK has a large population of patients we could learn from – with ample patients presenting at each MDT.

There is research ongoing in gap analysis: the British Lung Foundation has funded a study with Professor Peto for pnuemothorax fibre burden in patients. The NCIN may have data to generate a project exploring retrospective outcomes. Retrospective work on response, treatment and outcomes is possible. Data is also available on 900+ patients on chemotherapy, in addition to data on drug regimen, number of cycles and treating oncologist. While NCIN do have the potential, it was noted specificity is essential. A questionnaire on chemotherapy treatments, long-term survivors, access to tissue and use of imaging would be helpful for all physicians involved in mesothelioma.

- **Tissue**

With whole exome sequencing possible on tissue samples over ten years old, there is the possibility of testing and sequencing older tissues and matching this with patient outcome.

There are moral and ethical implications in tissue collection. There is the question of whether patients should be asked to donate to MesobanK. Collecting tissue can be an invasive procedure, e.g. IP catheter. Problems may also present regarding the size of sample, as there may not be enough to cover all departments for patient treatment. If the pathologist has insufficient material, they have first preference to available tissue.

Funding tissue collection may be difficult and not every centre will have the resources for tissue collection. Costs are approximately £50 per biopsy. MesobanK may be well placed for ring-fenced funding and a body for standardisation by simplifying tissue collection by production of SOPs. Commercial trials are required to collect tissues, why not academic? Surplus tissue can be used for diagnosis.

- **Trial maps**

It would be very useful to have a patient portal for clinical trials. MesoUK charitable group could possibly provide more information on national trials and treatments. This may also improve communications with MDTs, who could make links on funding and communication of trials

- **Trials and design**

There is a need for more biomarkers for mesothelioma. It would be a positive move to have trials in immunotherapy, but more arms and fewer restrictions required to accommodate more 'fit' patients. Many therapies are now immunotherapy based, which are now 'trumping' chemotherapy and allow more coverage of patients. The PIT and SMART trials in IMRT have been successful due to simple designs.

- **Radiotherapy**

More discussions are required to build on and improve radiotherapy in mesothelioma treatments within palliative care, diagnostics, standardisation and quality assurance. There is a need for access to advanced technologies in radiotherapy. There is also scope to build-on current treatments using adjuvant therapy with other therapies like IMRT/proton therapy to treat the thorax with lungs in place.

NCRI CTRad exists to tackle this issue. Could they facilitate these discussions? It would be a very positive step to combine resources from individual institutions, by forming a short-term Mesothelioma Subgroup/ CTRad Working Group to tackle radio-oncology in mesothelioma.

- **Palliative and supportive care for mesothelioma**

Research, trials and treatment are under-represented in mesothelioma and they need further development. This could be aided by epidemiological studies and a registry of patients. There is also a need for occupational and behavioural data to inform more initiatives and further investigations with PPI to develop specialised palliative and supportive care themes.

- **Surgery**

Trials are progressing such as MesoVats (open to recruitment) and MARS2 (opening soon). MesoVats is seeing better outcomes in patients who have undergone lung expansion. There are decision issues for surgeons in regards to procedures, e.g. trapped lung expansion vs. pleural catheter? It would be helpful to explore these areas in trials. The MARS2 feasibility study also has a quality of life arm. To help decide on treatments and surgery, we need to define how we stage mesothelioma.

- **Potential for Mesothelioma Consortium**

It is proposed that a mesothelioma consortium is set up to address a series of themes such as MesobanK/tissue banking, epidemiology; basic research and novel therapies; staging; ongoing clinical trials and palliative and supportive care. Funding for this may be difficult to obtain, but growing evidence of modern materials as causative agents, such as long fibre carbon nanotubes, may encourage further funding in mesothelioma research