Prostate Cancer UK: the Blue Skies Forum

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The second meeting of the Blue Skies Forum took place in Downing College, Cambridge, in April 2013, with the objective of focusing attention on new initiatives in the diagnosis and treatment of prostate cancer, in particular on areas of research that aim to identify aggressive disease. The meeting was hosted by Prostate Cancer UK and supported by The Howard Foundation.

Prostate-specific antigen has been used as a biomarker in prostate cancer since its identification in 1974, but is not sensitive enough to identify those patients at risk of developing high-risk disease. Genetic variants have now been identified that can recognise men with nearly a five-fold relative risk of developing prostate cancer compared with the risk to the average man in the population.

A case-control study has been set up involving 61 research groups worldwide, called the PRACTICAL consortium, and the genotyping of 25074 prostate cancer cases and 24272 controls from 39 of these groups has been published.1 A total of 23 new prostate cancer loci were identified, 16 of which are associated with aggressive disease (Figure 1). These and other discovered loci now explain 30 per cent of the familial risk for the disease.

On the basis of combined risks conferred by the new and previously known risk loci, the top 1 per cent of the risk distribution had a 4.7-fold risk relative to the population average and the top 10 per cent of men had a 2.7-fold relative risk. Interestingly, one of the variants on chromosome 17, while increasing the risk of prostate cancer, decreases the risk of diabetes. The increase in risk with each variant is small but the overall effect is multiplicative. The detection of these variants has the potential for identification of targeted drug therapy by discovering the pathways within which the genes act. Certain pathways are over-represented within the genetic variants, such as the pathway for cell adhesion, extracellular matrix modelling and, unsurprisingly, transcriptional regulation by the androgen receptor (AR).

Previously, BRCA2 germline mutations have been shown to confer the highest risk of prostate cancer (8.6-fold in men aged ≤65 years),2 while mutations in BRCA1 confer a 3.7-fold risk.3 Additionally, BRCA2 mutations have been associated with aggressive tumour phenotype and poor prostate cancer outcome.4 Further research on the involvement of these mutations has been published recently.5 Germline

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BRCA1/2 mutations were shown to be more frequently associated with Gleason ≥8 \((p=0.00003)\), T3/T4 stage \((p=0.003)\), nodal involvement \((p=0.00005)\) and metastases at diagnosis \((p=0.005)\) than prostate cancer in non-carriers. Cancer-specific survival (CSS) was significantly longer in non-carriers than in carriers \((15.7 \text{ versus } 8.6 \text{ years})\). In localised prostate cancer, five-year CSS and metastasis-free survival were significantly higher in non-carriers \((96 \text{ versus } 82 \text{ per cent \([p=9 \times 10^{-8}\) and 93 versus 77 per cent \([p=0.0001]\) respectively).}

Another genetic association is mutation in the HOXB13 gene, which is associated with limb structure and androgen signalling, and has been shown to increase the risk of prostate cancer 3.63– to 8.66-fold. It is more common in the Scandinavian population.6–8

Future research includes the recently initiated PROFILE study, which will examine the feasibility of targeted prostate cancer screening of men with familial history of prostate cancer through prostate biopsy and association of the outcome with genetic risk profiling.

Figure 1. Manhattan plot showing 23 genetic loci associated with increased risk of prostate cancer1

Studies have been conducted to examine which genes the AR binds in the nucleus and the functional effects. The method used involves binding of the AR to the genome and then disruption of the DNA and sequencing of specific binding sites. In cell lines, AR binding was shown to coordinate a metabolic response promoting aerobic glycolysis.6 A number of novel genes being regulated by AR were identified, including calcium/calmodulin kinase kinase 2 \((\text{CAMKK2})\), which is implicated in the regulation of energy balance and overexpressed in hormone-naive prostate cancer, but is absent following hormone treatment, reappearing when CRPC develops.6 CAMKK20 is a potential drug target and inhibition by STO-609 results in inhibition of prostate cancer growth.9

Sequencing studies have been conducted in benign prostate tissue samples and prostate cancer tissues from patients who were untreated, were responders to androgen deprivation therapy (ADT) or had CRPC, in order to identify AR binding sites.6 The \(\text{PSA}\) gene was identified as a binding site, as well as \(\text{FKBP5, CAMKK2, TMPRSS2 and PGC}\). The AR appears to be reprogrammed in CRPC. Unique AR binding sites at \(\text{E2F, STAT and MYC/MAX}\) were identified that were not observed in cell lines, resulting in the switching on of the \(\text{JAK/STAT}\) pathway. A series of 16 genes have been identified that are upregulated in CRPC and are actually present at diagnosis prior to ADT.10 These genes will provide potential targets for future therapy.
INNOVATION IN SURGICAL THERAPY FOR PROSTATE CANCER
Mr Hashim U. Ahmed

It has been established that not all prostate cancer has the potential to progress to invasive and metastatic cancer, and novel imaging and precision biopsy might allow identification of those lesions that are likely to progress and require treatment. To this aim, focal therapy of prostate cancer has been proposed as an alternative that will tailor treatment with consequent minimisation of treatment morbidity.

A total of 24 focal therapy studies have been conducted involving cryosurgery (n=6), high-intensity focused ultrasound (n=12), photodynamic therapy (n=3), radiofrequency interstitial tumour ablation (n=1), brachytherapy (n=1) and mixed ablation (n=1). Most studies were poorly reported, retrospective in design and at an early phase. Overall, complications and side-effects were low but studies struggled to define disease control outcomes, although biopsy outcomes appeared variable. An increasing number of prospective studies on focal therapy are now underway, with the UK leading many of these.

Current ablative technologies are not perfect, and ongoing research to improve the care of men with localised prostate cancer is needed. Magnetic nanoparticle thermoablation has been researched as a treatment of localised prostate cancer. Temperatures of up to 45°C can be achieved by applying an alternating current to a magnetic field in rabbit prostates injected with iron oxide nanoparticles. Higher temperatures are achieved if the current is applied for longer periods (Figure 2). In man, the therapy has been used as adjuvant salvage therapy in 10 patients. Patients received six thermal therapies of 60-minute duration at weekly intervals using an alternating magnetic field applicator. Maximum temperatures up to 55°C were achieved in the prostates; median urethral and rectal temperatures were 40.5°C (range: 38.4–43.6°C) and 39.8°C (range: 38.2–43.4°C), respectively. Computed tomography scans revealed that the particles stayed within the prostate. A phase 0 study on magnetic nanoparticle thermoablation is to be conducted at University College London involving 18 men prior to radical prostatectomy. Nanoparticles will be injected into the prostates and placement evaluated to determine whether the necessary particle density needed to reach a therapeutic temperature can be achieved. The target temperature is 70°C with the application of 100s of current. A phase 1 study will also be conducted to examine the ablative properties of the technique.

Other research with nanoparticles has focused on conjugating the particles to antibody fragments to allow tumour targeting and optimisation of cancer-specific magnetic resonance imaging. Research is underway at University College London, funded by Prostate Cancer UK, on the fusion of pre-modelled MRI scans to ultrasound imaging to facilitate transrectal biopsies – this will facilitate accurate targeting of the prostate lesion for focal therapy.

TOWARDS PRECISION AND PERSONALISED RADIOTHERAPY
Professor David Dearnaley

Radical changes in radiotherapy have been made over the past 10 years through improvements in imaging, precision engineering and increased computational speeds. This has allowed the development of two different concepts of radiotherapy, namely intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), which provide very accurate treatment. Still lacking in our current knowledge is individual tumour sensitivities to radiotherapy, primarily due to lack of access to tissue samples. Such knowledge will allow dose optimisation with consequent reduction in morbidity.

It would appear that men dying of prostate cancer after radiotherapy have high-risk disease on presentation and recurrence occurs at the site of the dominant intraprostatic lesion. A six-month period of treatment with ADT improves the outcome of patients with intermediate- and high-risk disease who are treated with radiotherapy, including those treated with high-dose radiotherapy. We have hypothesised that ADT interacts with...
Dysfunction are still an issue. Urogenital complications including erectile dysfunction are observed within five years when short-term ADT is added to radiotherapy, whereas dose escalation has not yet been shown to improve survival after 10 years' follow-up.

High-dose radiotherapy is associated with increased side-effects, but improved delivery involving conformal radiotherapy/IMRT resulting in a reduction in treatment margins can reduce these effects. These benefits are observed with rectal complications, but urogenital complications including erectile dysfunction are still an issue.

Functional MRI and positron emission tomography allow detection of prostate tumours and, combined with IMRT, allow specific targeting of different doses to regions of the gland. Margins are required to allow for patient movement during treatment and improved localisation of the treatment area has been made by inserting gold grains to the gland in IGRT. Other improvements have come through the use of the Cyberknife and Calypso. The Cyberknife is totally robot dependent and involves the placement of fiducial markers into the prostate, which are tracked by the robot when treatment is applied. The downside of the treatment is the time taken to apply treatment. Calypso involves the placement of electromagnetic transponders into the prostate and sending a pulse to these. This allows the tracking of the gland during therapy to ensure treatment accuracy.

Proton therapy is another new development in prostate cancer treatment, which benefits from a sharp radiation dose cut-off in non-prostate tissue. Although the treatment is the time taken to apply treatment. Calypso involves the placement of electromagnetic transponders into the prostate and sending a pulse to these. This allows the tracking of the gland during therapy to ensure treatment accuracy.

Proton therapy is another new development in prostate cancer treatment, which benefits from a sharp radiation dose cut-off in non-prostate tissue. Although reduced doses are reported in surrounding tissue, no therapeutic benefit over IMRT has been observed. Tissue biomarkers are being studied in relation to radiotherapy sensitivity; one of these is osteopontin, a marker for tumour hypoxia and angiogenesis, which has been examined in regard to outcome following radiotherapy. Results suggest that the marker is associated with worse prognosis, which may impact on treatment choices.

Another area of research is focused on treatment of the primary disease in patients with metastatic disease, as research in renal cancer implies that there might be a benefit from this approach. Prostate radiotherapy has been added to the treatment with abiraterone acetate in the ongoing Medical Research Council STAMPEDE study. There are also a number of studies targeted at the treatment of oligometastases with stereotactic body radiotherapy (SBRT), which builds on improvements in delivery achieved by IMRT and IGRT (Figure 3). Results indicate that SBRT offers durable local control and the potential for progression-free survival in non-liver, non-lung oligometastatic disease at a range of sites.

Declarations of interests

The Howard Foundation provided sponsorship for the Blue Skies Forum and for the preparation of this article.

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KEY POINTS

- Twenty-three genetic variants have been associated with the risk of prostate cancer. Mutations in the BRCA1 and BRCA2 genes are associated with more aggressive disease and worse outcome.
- The binding of the androgen receptor to specific sites in the genome is predictive of disease progression to castrate-resistant prostate cancer (CRPC).
- The identification of 16 genes that are upregulated in CRPC will provide potentially new therapeutic targets.
- Focal therapy of prostate cancer might offer targeted therapy with reduced side-effects. One new therapy of this type involves magnetic nanoparticles, which cause tissue thermoablation.
- Over the past decade advances have been made in prostate cancer radiotherapy involving improved imaging techniques and application of treatment. Research has also focused on the interaction of radiotherapy with hormonal therapy and identification of biomarkers that might indicate treatment response.

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