Institution: King's College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Improved understanding of the risk of cardiovascular disease with hormone therapy for prostate cancer

1. Summary of the impact

Research carried out at King's College London (KCL) has raised awareness of the potential risks associated with certain hormone therapies used to treat prostate cancer. The group found that such hormone therapy can raise the risk of heart attack by 24% and the risk of dying from heart disease by 21%. However, for men receiving anti-androgen hormone therapy, the risk of dying from heart disease was lower compared to other hormone therapies such as gonadotropin-releasing hormone agonists. With anti-androgen hormone therapy there was a chance of heart failure but the risk was 5% compared to 34% for other hormone therapies which reduce testosterone production.

The research has had very considerable impact in terms of reach, as over 600 articles have been published in newspapers and other media which refer to the KCL finding that men with prostate cancer treated with certain hormone therapies have a higher risk of heart disease and strokes.

The findings had a very significant impact on US Food and Drug Administration (FDA) advice to healthcare professionals on the benefits and risks of hormone therapy. The FDA also required manufacturers of certain hormone therapy drugs to add safety information to labels.

2. Underpinning research

Hormone treatment for prostate cancer: Hormone treatment has been the cornerstone of treatment for prostate cancer for decades. It is currently the only effective treatment for advanced prostate cancer, and can keep the disease in check for months or even years. Each year, around 36,000 men in the UK are diagnosed with prostate cancer. In the USA, 600,000 of the 2 million men diagnosed with prostate cancer receive hormone treatment. Some of the hormone treatments interrupt the supply of testosterone – thought to protect the heart – to the prostate. Cardiovascular disease is recognised as a potential adverse side effect of hormone treatment for prostate cancer. The rise of screening for prostate cancer means earlier detection and that more men receive hormone treatment for a longer time. Longer treatments are more likely to result in patients suffering adverse side effects from hormone treatments.

Research on risks of heart disease in hormone treatment for prostate cancer: The research was conducted at KCL by Lars Holmberg (Professor of Cancer Epidemiology, 2007–present), Mieke Van Hemelrijck (Lecturer in Cancer Epidemiology, 2008–present) and Hans Garmo (Senior Statistician 2008–present) of the Cancer Epidemiology Group. At the time of the research, there was no published quantitative data on the risks of cardiovascular disease in men with prostate cancer.

Largest, most comprehensive study of prostate cancer in a population: The study was the largest, most comprehensive study of prostate cancer in a population and is very significant in its focus on different types of cardiovascular disease associated with hormone therapy (1-3).

KCL collaborates with PCBaSe Sweden, which has data on more than 76,600 prostate cancer patients in the Swedish National Prostate Cancer Register (96% of Swedish cases). The KCL group analysed patient information in PCBaSe on age, serum prostate-specific antigen (PSA) level, treatment at the time of diagnosis, the condition and stage of tumours, socioeconomic status, history of cardiovascular disease, and the cause and date of deaths. The condition of tumours was assessed using tumour size, serum PSA and the Gleason score.

The KCL research group identified more than 30,000 men who had been treated with a hormone (endocrine) therapy between 1997 and 2006 (1-3). Hormone treatments included anti-androgens, oestrogens, orchiectomy, gonadotropin-releasing hormone (GnRH) agonists, GnRH agonist combined

with long term anti-androgens, and other treatments.

The group compared the frequency of heart problems in the group of prostate cancer patients to the frequency in the Swedish population (the control group) by calculating standardised incidence ratios and standardised mortality ratios of ischemic heart disease, acute myocardial infarction (heart attack), arrhythmia, heart failure and stroke.

Higher risk of cardiovascular disease with hormone treatment established: The research established that prostate cancer patients have a 21% higher chance of dying from heart disease and are 28% more likely to have a fatal heart attack than men without prostate cancer. Prostate cancer patients receiving hormone treatments run the most pronounced risk. There are about eight extra deaths a year from cardiovascular disease for every 1,000 prostate cancer patients treated with hormone drugs. However, men receiving anti-androgen hormone therapy had a lower risk of heart disease than those receiving other hormone therapies.

Risks do not outweigh the gains but require consideration: The very significant finding of the research was that in absolute terms the risks of cardiovascular disease with hormone treatment for prostate cancer are low. Hormone treatment is currently the only effective treatment for prostate cancer. The investigation indicates that the risk of cardiovascular disease should be taken into account when prescribing hormone treatment, but should not discourage hormone treatment when the balance between benefit and risks is considered to be positive. Anti-androgen therapy may have a lower risk than other types of hormone therapy.

3. References to the research

1. **Van Hemelrijck M**, **Garmo H**, **Holmberg L**, et al. Absolute and relative risk of cardiovascular disease in men with prostate cancer: Results from the population-based PCBaSe Sweden. *J Clin Oncol.* 2010;28:3448-56.

2. **Van Hemelrijck M**, **Garmo H**, **Holmberg L**, et al. Increased morbidity and mortality following endocrine treatment for prostate cancer: An analysis in 30,642 men in PCBaSe Sweden. Abstract presented at the joint 15th Congress of the European CanCer Organisation (ECCO) and 34th Congress of the European Society for Medical Oncology (ESMO). *Eur J Cancer* 2009;7(3): Abstract 1BA.

3. **Van Hemelrijck M, Adolfsson J, Garmo H,** et al. Risk of thromboembolic diseases in men with prostate cancer: Results from the population-based PCBaSe Sweden. *Lancet Oncol.* 2010; 11:450-8.

4. Details of the impact

Outstanding impact on US Food and Drug Administration (FDA) review of prostate cancer drugs: The most notable impact of the research is in a review of the safety of commonly used prostate cancer drugs by the FDA in May 2010 (4). The review was based on the KCL research, as the largest population-based study of its kind, and six other studies. The FDA review concluded that the risk of certain cardiovascular diseases was higher in men treated with one of the main hormone therapies: gonadotropin-releasing hormone agonists.

Substantial impact on requirements for drug safety information: In October 2010, the FDA notified the manufacturers of gonadotropin-releasing hormone agonists that they should add new safety information to the Warnings and Precautions section on drug labels (5). The warning alerts users to the risk of cardiovascular disease associated with certain hormone therapies for the treatment of prostate cancer. The World Health Organization issued similar advice.

Substantial impact on FDA treatment guidelines: The KCL research findings provided evidence underpinning FDA guidelines for healthcare professionals (5) on treatment for patients with prostate

cancer:
1) Healthcare professionals should be aware of the potential risks and carefully weigh up the benefits and risks of gonadotropin-releasing hormone agonists when determining treatment for patients with prostate cancer
2) Patients receiving gonadotropin-releasing hormone agonists should be closely monitored for signs of diabetes and cardiovascular disease
3) Cardiovascular risk factors such as smoking, hypertension, hypercholesterolemia, hyperglycaemia and obesity should be managed according to current clinical practice
4) Patients should not stop treatment with a gonadotropin-releasing hormone agonist unless instructed to do so by a healthcare professional.

Research corroborated by major US bodies: The research finding "Based on the small absolute risk difference, the high absolute risk of dying from prostate cancer when undergoing hormone treatment, and the fact that hormone treatment is currently the only effective treatment for metastatic disease, these findings indicate that cardiovascular disease risk should be considered when prescribing hormone treatment, but should not contraindicate when the expected gain is tangible" was corroborated by the American Heart Association, the American Cancer Society and the American Urological Association (6).

Substantial impact on treatment recommendations: Other organisations making similar recommendations to those of the FDA and based partly on the research include the Prostate Cancer Foundation, American Cancer Society, US Too International, Prostate Cancer International, Prostate Health Education Network, Prostate Cancer Research Institute, Men's Health Network, Prostate Cancer Roundtable, Patient Advocates for Advanced Cancer Treatment, and Zero – The Project to End Prostate Cancer.

Wide implications for management of prostate cancer patients: The research showed that the risk of non-fatal and fatal cardiovascular disease increases in prostate cancer patients receiving hormone treatment. The risk of cardiovascular disease is also greater in patients who are receiving curative treatment or who are under surveillance. This finding supports growing evidence that diseases associated with prostate cancer are a significant risk and has an impact on management of prostate cancer patients beyond the original intent of the research. It also showed that anti-androgen therapy carries lower risk than other forms of hormone therapy, and so may affect choice of therapy.

Very considerable public-facing impact: The research has had very considerable impact in terms of reach. At the joint European CanCer Organisation (ECCO) and European Society for Medical Oncology (ESMO) meeting in September 2009 (7) the researchers were interviewed. Newspapers and other media then published more than 600 articles worldwide (e.g. 8-11). All refer to the research finding that men with prostate cancer treated with certain hormone therapies have a higher risk of heart disease and strokes.

The research findings are actively disseminated in news stories on the KCL website which also provides a link to the initial press conference.

Relevant to treatment of prostate cancer globally: Prostate cancer is the most common male cancer in Europe, accounting for a quarter of all newly diagnosed cases, or about 380,000 men every year. Moreover, prostate cancer is the third most common cause of death from cancer in European men, with 94,000 deaths a year. There are more than 8 million men living with prostate cancer globally, of whom 2 million live in the United States. Wide awareness of this research (such as through the considerable media coverage generated) thus has a very considerable impact on the health of a very large number of prostate cancer patients and their families.

Improvements in the health of prostate cancer patients and fewer deaths: The impact on the ultimate beneficiaries, patients with prostate cancer, is significant. Doctors consider the research findings when prescribing therapies. The overall health of prostate cancer patients has improved and there have been fewer deaths as a result of this and other research.

5. Sources to corroborate the impact

Impact on safe use of hormone therapy for prostate cancer

4. Jefferson E. FDA Conducting Safety Review of Commonly Used Prostate Cancer Drugs. Preliminary review suggests an increase in the risk of diabetes and certain cardiovascular diseases in men treated with GnRH agonists. FDA News Release on 3 May 2010. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm210549.htm

5. FDA Drug Safety Communication: Update to Ongoing Safety Review of GnRH Agonists and Notification to Manufacturers of GnRH Agonists to Add New Safety Information to Labeling Regarding Increased Risk of Diabetes and Certain Cardiovascular Diseases. http://www.fda.gov/Drugs/DrugSafety/ucm229986.htm (Cites ref [1] on this web page)

Impact on advice for treatment of prostate cancer

6. Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL, et al. Androgen-Deprivation Therapy in Prostate Cancer and Cardiovascular Risk: A Science Advisory From the American Heart Association, American Cancer Society, and American Urological Association: Endorsed by the American Society for Radiation Oncology. *Circulation* 2010;121:833–40.

Public-facing communication

7. “Prostate cancer patients on hormone therapy at increased risk for various heart diseases.” Mieke **Van Hemelrijck** of King's College, London, speaking at an official press conference at ECCO 15 ESMO 34, Berlin, 2009. http://www.ecancermedicalscience.com/tv/?play=248&cid=0&scid=0&q (11,490 views as of 16 October 2013)

8. “Hormone therapy for prostate cancer 'increases risk of heart problems'” Hormone therapy used to treat prostate cancer can increase the risk of suffering heart problems by more than a quarter, scientists have found. Telegraph 23 September 2009 (Quotes **Van Hemelrijck**, cancer epidemiologist at KCL) http://www.telegraph.co.uk/health/healthnews/6218754/Hormone-therapy-for-prostate-cancer-increases-risk-of-heart-problems.html

9. “Prostate Cancer May Spark Heart Problems” ThirdAge.com 2 October 2009 (Quotes **Van Hemelrijck**, cancer epidemiologist at KCL) http://www.thirdage.com/prostate-conditions/prostate-cancer-treatment-may-spark-heart-problems

10. “Fragwürdige Antihormontherapie bei Prostatakarzinom - Anti-Androgene erhöhen Risiko für Herzinfarkte und Arrhyhthmien - Engmaschige Kontrollen erforderlich” derStandard 22 September 2009 (Quotes **Van Hemelrijck**) http://derstandard.at/1253596294721/KrebskongressFragwuerdige-Antihormontherapie-bei-Prostatakarzinom

11. “Absolute And Relative Risk Of Cardiovascular Disease In Men With Prostate Cancer: Results From The Population-Based PCBaSe Sweden” MEDINEWS 11 August 2010 http://www.medicalnewstoday.com/articles/197370.php