Debating controversies in the management of advanced prostate cancer

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In the previous issue of this journal, Heather Payne and colleagues discussed a debate on the management of locally advanced prostate cancer, which took place at the 7th Annual Meeting of the British Uro-oncology Group. Here, they continue with a summary of discussions about the challenges of managing advanced prostate cancer.

The first-line and mainstay of medical treatment for advanced prostate cancer is with androgen deprivation therapy in the form of medical castration. These treatments have been shown to reduce the painful symptoms of the disease and also to slow overall cancer progression. However, it is recognised that after a period of time, most prostate cancers will ultimately progress in spite of castrate levels of testosterone (i.e. serum testosterone <50ng/dl or <1.7nmol/l) and these tumours are considered to be castration resistant.

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However, castration-resistant prostate cancers (CRPC) can remain sensitive to further hormonal manipulation in combination with continued luteinising hormone-releasing hormone (LHRH) agonist therapy. The addition of antiandrogens (combined androgen blockade), or further hormonal manipulation with antiandrogen withdrawal, oestrogens or corticosteroids, may all be effective treatment strategies. The term CRPC is different to that previously used to describe hormone-refractory prostate cancers, which are resistant to all further hormonal measures.

THE CASE
Professor David Dearnaley presented the case of a 58-year-old man with CRPC who had been previously treated with LHRH agonist therapy and antiandrogens, followed by antiandrogen withdrawal. He had maintained a good symptomatic and biochemical response to therapy for two years but now presented with an increasing prostate-specific antigen (PSA) level and progression of bone metastases. He had no significant comorbid conditions and a performance status of 1.

THE DEBATE
The group was asked to estimate this man’s life expectancy using keypad voting (Figure 1). Three-quarters of the oncologists at this meeting would expect the patient to live for a further 19 months and 25 per cent thought that he could survive for up to 10 further years. The group then voted on their preferred next hormonal treatment option for this man with CRPC after antiandrogen withdrawal (Figure 2). The favoured options were those of the addition of stilboestrol (54 per cent) or low-dose dexamethasone (33 per cent).
THE EVIDENCE
Oestrogen therapy with diethylstilboestrol (DES) demonstrated comparable efficacy to castration in early studies of hormone therapy for prostate cancer. However, the final results revealed that early treatment of advanced prostate cancer with 5mg DES did not increase overall survival when compared to placebo, as the drug was associated with an increased incidence of cardiovascular deaths.

A second study compared the 5mg dose to 1mg of DES, and the results showed that this lower dose was equally effective but also had the advantage of a much lower incidence of cardiovascular deaths. DES continues to be used as third-line hormone therapy in the UK and would have been the treatment of choice for more than half of the oncologists attending this session. It is usually prescribed in combination with aspirin or low-dose warfarin to reduce the risks of thrombotic complications.

Corticosteroids (prednisolone and hydrocortisone) have traditionally been used as third- or fourth-line therapy for prostate cancer for many years. A recent study evaluated the efficacy of low-dose oral dexamethasone (0.5mg) as treatment for progressive CRPC. In total, 50 out of the 102 patients entered in the study demonstrated a PSA response to low-dose dexamethasone. The median time to PSA progression for the entire cohort was 7.4 (1–28) months. In responders, the median duration of the PSA response was 11.6 (1–24) months. The authors concluded that dexamethasone could become the corticosteroid of choice in the management of CRPC, and its potential for use in combination with other novel agents should be explored.

Low-dose dexamethasone and DES would both appear to have efficacy in CRPC and there has been little guidance as to the order in which these therapies should be prescribed. A phase 3 trial of 270 men with CRPC published earlier this year investigated the sequencing of these therapies. Men were randomised to receive dexamethasone and aspirin with either the immediate or deferred (at progression) addition of DES. The results of the study showed that there were no significant advantages in using both drugs in combination as initial therapy in terms of PSA response rate, progression-free survival (8.1 months in both arms), overall survival or quality of life. In view of the fact that the potential toxicity of DES is higher than that of dexamethasone, the authors have concluded that a preferred strategy could be to defer DES until failure of dexamethasone when using these agents in CRPC.

THE FUTURE
The optimism shown for the outcome of this man with metastatic CRPC (see Figure 1) stems from the fact that there are now further options available after sequential hormone therapies. In 2004, the chemotherapy agent, docetaxel, was shown significantly to increase overall survival in addition to improving pain control and quality of life for men with advanced prostate cancer. This heralded a new era for the management of men with CRPC.
Results from recent clinical trials have shown further survival advantages with second-line chemotherapy regimens such as cabazitaxel, immunotherapy treatment with sipuleucel-T and novel hormone agents such as abiraterone acetate.

There are many other promising agents currently being evaluated in late-phase clinical studies that are likely to be involved in sequential therapy algorithms. We hope and anticipate that these treatments will continue to reduce the risk of death and improve disease-related symptoms for our patients in the future.

Declaration of interests
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REFERENCES