BEST PRACTICE

Prostate cancer management: (2) an update on locally advanced and metastatic disease

S R J Bott, A J Birtle, C J Taylor, R S Kirby

Postgrad Med J 2003;**79**:643–645

Just under half of men with prostate cancer present with locally advanced or metastatic disease. A multidisciplinary approach is required to improve survival, minimise complications, and provide adequate palliation. Radiotherapy remains the mainstay of treatment for pelvic disease control and encouraging results have been reported with androgen ablation as adjuvant therapy. In metastatic disease androgen ablation is usually first line, although ultimately most tumours become hormone refractory, requiring second or third line treatments. Localised or systemic radiotherapy may be used for palliation in metastatic disease. With the advent of more potent bisphosphonates the common bony complications associated with metastases may be reduced. This, the second review of prostate cancer, explores the various treatments available to the multidisciplinary team.

The management of locally advanced prostatic cancer, like localised disease, depends on the tumour characteristics—the stage and Gleason grade, the prostate specific antigen (PSA) level, the age and health of the patient, and based on a multidisciplinary team approach.

LOCALLY ADVANCED PROSTATE CANCER

In the UK, locally advanced prostate cancers account for 40% of prostate cancers at presentation.¹ These include carcinomas where one or two acini have penetrated through the prostatic capsule to those invading adjacent structures including the trigone of the bladder, the rectum, the urethra, and the pelvic side wall. Therapeutic options include external beam radiotherapy (EBRT) (with or without neoadjuvant or adjuvant androgen ablation), androgen ablation alone, or active monitoring.

External beam radiotherapy and androgen ablation

For men receiving EBRT for T3–4 disease long term adjuvant androgen ablation after radiation offers a significant improvement in both metastatic and biochemical relapse rates when compared with short course androgen ablation given immediately before and during radiotherapy. This has translated into improvements in disease-free survival and overall survival at three years in one study,² although in other trials this survival advantage was confined to poorly differentiated tumours only.³

Androgen ablation involves chemical or surgical orchidectomy. However, reduced libido and increased fatigue are often associated with both these treatments. Non-steroidal antiandrogen monotherapy with bicalutamide 150 mg for T3–4 disease, compared with luteinising hormone releasing hormone (LHRH) agonists has been evaluated in a number of studies. No significant difference has been seen between the two types of drug in terms of overall survival and time to progression, although significant improvements in sexual interest and physical capacity were reported with bicalutamide.⁴

For asymptomatic patients over 70 years old with low grade disease, active monitoring may be a favoured option. Although a significant survival advantage in favour of immediate hormonal therapy was initially demonstrated in a Medical Research Council study, subsequent follow up has shown much less of a survival difference and thus the potential benefits and side effects of early treatment warrant a full patient discussion.⁵

While androgen ablation in patients does delay disease progression the role of EBRT in this context is not known. EBRT probably provides local symptom control in the medium term, though its effect on the long term local symptom control and on survival is unresolved. These issues are currently being addressed in men with T3 disease in the ongoing PR07 trial. This study will also examine the role of EBRT in clinically localised disease with poor prognosis, including men with T2 tumours with Gleason score >8 and PSA >20 ng/ml, or T2 tumours with PSA >40 ng/ml. The results from this trial are awaited.

For selected patients with locally advanced T3 disease, high dose rate iridium brachytherapy together with a shortened course of EBRT as described for poor risk localised prostate cancer,⁶ may be considered, to allow dose escalation and improvement of local control rates.

Intermittent hormone therapy

This may be used in the treatment of both locally advanced and metastatic disease. It has been known for some time that patients who stop androgen ablative treatments may have a period of time being symptom-free from their prostate cancer and side effect-free off treatment. Furthermore, they usually respond again to first

See end of article for authors' affiliations

Correspondence to:
Mr Simon R J Bott, Prostate
Cancer Research Centre,
Charles Bell House, 67
Riding House Street,
London W1W 7EY, UK;
simonrjbott@hotmail.com

Submitted 15 April 2003
Accepted 24 May 2003

Abbreviations: EBRT, external beam radiotherapy;
LHRH, luteinising hormone releasing hormone; PSA,
prostate specific antigen

line therapy at the time of relapse, deferring the time to the development of hormone independent disease.⁷ In locally advanced but asymptomatic recurrent disease, men have a median survival of 7–8 years, and long term hormonal therapy may negatively impact on their quality of life.⁸ Studies have used an initial eight months of treatment with androgen ablation and then a variable period of time off treatment, recommencing when the PSA is greater than 10 ng/ml or 20 ng/ml.⁹ In an open label, non-randomised study patients who had responded to an LHRH analogue, such that their PSA fell to normal or below normal levels, had their therapy stopped.¹⁰ PSA levels were checked every three months and when the PSA rose to >20 ng/ml on two successive occasions or there was clinical disease progression treatment was restarted. When the PSA was suppressed again treatment was stopped and so on. While the periods off treatment got shorter with successive cycles, Lane *et al* demonstrated an overall survival benefit when compared with the immediate and deferred androgen ablation groups of the Medical Research Council study.⁵ The results of ongoing randomised trials of intermittent therapy versus standard therapy are required before a definitive answer will be known. However, these studies show intermittent therapy may well prolong treatment time as well as reduce the incidence of side effects during the off treatment periods.

METASTATIC PROSTATE CANCER

Androgen ablation

The first line treatment in a man with symptomatic metastatic prostate cancer is androgen ablation by medical or surgical castration. This has an initial PSA response rate of around 85%, maintained for 12–18 months. No difference in efficacy has been seen between orchidectomy and the use of the LHRH agonists.¹¹ Patient choice, age, and comorbidity determine which option is favoured.

Although immediate hormonal therapy has shown only a negligible survival benefit in the asymptomatic patient with metastases, there is certainly evidence of a reduction in important complications—including the incidence of spinal cord compression which was reduced from 5% to 2% and ureteric obstruction fell from 11.8% to 7%.⁵ The initiation of an LHRH agonist results in a tumour flare, this is inhibited by using a peripheral antiandrogen such as flutamide for two weeks before and two weeks after the first injection. Cyproterone acetate may also be used in this context but is not recommended as long term monotherapy because of potential hepatic toxicity.

Hormone refractory prostate cancer

Recurrence after first line hormonal therapy reflects a poor outlook, with a mean survival of nine months.¹² Choices of treatment include maximum androgen blockade or the addition of an oestrogen. Surgical or medical castration is known to reduce circulating testosterone levels by ~90%. In an attempt to reduce the action of adrenal testosterone peripheral antagonists may be added to a LHRH agonist. The outcome of combined androgen blockade (maximum androgen blockade) remains unclear as there is conflicting data, although meta-analyses suggest the benefit to be in the order of 1%–2%, predominately in patients with low metastatic load and good performance status.¹³

Stilboestrol 1 mg is widely used in the UK and has shown effective clinical response rates of around 66% in patients with one previous hormonal manipulation and 13% in those with two or more.¹⁴ However, an increase in thromboembolic and cardiovascular side effects are seen and concurrent low dose anticoagulation with warfarin is in common use.¹⁵ The cardiovascular side effects associated with oestrogen therapy are due to clotting factors generated by the metabolism of

oestrogens during their first passage through the liver. An interesting newer method of administering oestrogens is the use of intramuscular polyoestradiol phosphate¹⁶ or hormone replacement therapy patches. The first pass effect is avoided, reducing the risk of cardiovascular events. Long term and large scale trials are awaited, though oestrogens may play a greater part in the future management of men with advanced stage prostate cancer. Prophylactic nipple radiation reduces the incidence of gynaecomastia seen in patients on oestrogens.

Prednisolone started after failure of first line hormonal therapy has elicited subjective symptomatic response rates of 56% compared with a 46% response rate to flutamide.¹⁷ There was also a biochemical response rate of 21% and 23% respectively, but no difference in overall survival between the two groups.

Chemotherapy for metastatic disease

The use of chemotherapy in hormone refractory prostate cancer is the subject of many ongoing studies. Single agent and combination regimens thus far have shown disappointing response rates of <20%. Symptomatic improvements of 29% versus 12% were seen with single agent mitoxantrone added to prednisolone when compared with prednisolone alone but no difference in overall survival was seen.¹⁸ Interest is being shown in tyrosine kinase receptor antagonists and other molecular targets. The outcome of ongoing phase II and III are awaited.

Radiotherapy in metastatic prostate cancer

Local radiotherapy may be useful for perineal pain, bleeding, or bony pain. Any bony metastases in a weightbearing bone requires plain radiography review to assess the cortical integrity, and orthopaedic assessment if >50% of the cortex is affected, to determine whether prophylactic stabilisation is required. Local radiation may be offered in addition post-operatively, or as an alternative if the patient is unfit for surgical intervention. A single fraction of local radiotherapy is effective for pain relief in symptomatic bony metastases in up to 76% of patients.¹⁹ It may, however, take several weeks before its effect is manifest. Hemibody irradiation is utilised where a large treatment field is required, usually encompassing pelvis and the upper femurs, however this frequently results in diarrhoea and nausea.

Strontium-89 as an intravenous injection may be used for pain control in widespread bony metastases. It may be associated with an initial pain flare but approximately 10% of treated patients do experience a complete resolution of pain. However, the presence of any critical metastases potentially able to cause spinal cord compression must be excluded, as strontium may cause oedema at these sites. In addition, the treatment commonly produces prolonged myelosuppression, particularly thrombocytopenia, and in patients with already depleted marrow reserves, either due to disease or treatment, this can be problematic.²⁰ It may also limit future treatment options such as chemotherapy because of its side effects.

Bisphosphonates

Bone complications in prostate cancer occur as a result of skeletal metastases, long term treatment with androgen withdrawal and following radiotherapy. Bisphosphonates, now widely used in breast cancer, have been shown to reduce bony pain in prostatic cancer for 2–3 weeks after a single intravenous infusion, in up to 30% of patients.²¹ More promising results were recently demonstrated with zoledronic acid, the most potent bisphosphonate.²² The authors reported fewer skeletal events compared with placebo (44.2% v 33.2%, 95% confidence interval –20.3% to –1.8%, $p = 0.02$) after a 15 minute infusion of zoledronic acid every three weeks. The median time to first skeletal event was 321 days

with placebo compared with 363 days for patients receiving 4 mg zoledronic acid. Bisphosphonates act by decreasing the rate of bone turnover, reducing the number of osteoclasts, their recruitment, lifespan and activity.

The patient with metastatic disease reflects the need for an integrated multidisciplinary approach to allow symptomatic control. Early involvement of hospital and community based palliative care teams is essential and easy access to both oncology and urology services remains vital.

CONCLUSIONS

Men with more advanced disease can be treated successfully by androgen ablation, though this is usually a holding procedure before eventual disease relapse. Disease relapse may be deferred by intermittent hormonal therapy; results of trials are awaited before this becomes routine. In the meantime bisphosphonates maybe used to prevent or delay bony complications. The role of chemotherapy has yet to be established though radiotherapy is used to control primary local disease, skeletal metastases, and prevent breast side effects. Further developments in our understanding of the genetics of this disease will allow the identification of new molecular markers and novel therapeutic targets.

Authors' affiliations

S R J Bott, A J Birtle, C J Taylor, Institute of Urology, London
R S Kirby, St George's Hospital, London

REFERENCES

- 1 **British Association of Urological Surgeons.** *Analysis of minimum data set for urological cancers.* (Chart 61, 47.) London: British Association of Urological Surgeons, 2002.
- 2 **Bolla M, Gonzalez D, Warde P, et al.** Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;**337**:295–300.
- 3 **Lawton CA, Winter K, Murray K, et al.** Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 85-31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavorable prognosis carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001;**49**:937–46.
- 4 **Iversen P, Tyrrell CJ, Kaisary AV, et al.** Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of follow up. *J Urol* 2000;**164**:1579–82.
- 5 **Medical Research Council Prostate Cancer Working Party Investigators Group.** Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. *Br J Urol* 1997;**79**:235–46.
- 6 **Bott SRJ, Birtle AJ, Taylor CJ, et al.** Prostate cancer management: (1) an update on localised disease. *Postgrad Med J* 2003;**79**:575–80.
- 7 **Horwich A, Huddart RA, Gadd J, et al.** A pilot study of intermittent androgen deprivation in advanced prostate cancer. *Br J Urol* 1998;**81**:96–9.
- 8 **Schellhammer PF, Kuban DA, el Mahdi AM.** Treatment of clinical local failure after radiation therapy for prostate carcinoma. *J Urol* 1993;**150**:1851–5.
- 9 **Crook JM, Szumacher E, Malone S, et al.** Intermittent androgen suppression in the management of prostate cancer. *Urology* 1999;**53**:530–4.
- 10 **Lane T, Ansell W, Williams G, et al.** Long-term outcomes in patients managed with intermittent androgen suppression. *BJU Int* 2002;**suppl 1**:abstract A82.
- 11 **Kaisary AV, Tyrrell CJ, Peeling WB, et al.** Comparison of LHRH analogue (Zoladex) with orchiectomy in patients with metastatic prostatic carcinoma. *Br J Urol* 1991;**67**:502–8.
- 12 **Small EJ, Vogelzang NJ.** Second-line hormonal therapy for advanced prostate cancer: a shifting paradigm. *J Clin Oncol* 1997;**15**:382–8.
- 13 **Prostate Cancer Trialists' Collaborative Group.** Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomised trials with 3283 deaths in 5710 patients. *Lancet* 1995;**346**:265–9.
- 14 **Robinson MR, Smith PH, Richards B, et al.** The final analysis of the EORTC Genito-Urinary Tract Cancer Co-Operative Group phase III clinical trial (protocol 30805) comparing orchiectomy, orchiectomy plus cyproterone acetate and low dose stilboestrol in the management of metastatic carcinoma of the prostate. *Eur Urol* 1995;**28**:273–83.
- 15 **Thodiyil PA, Walsh DC, Kakkar AK.** Thromboprophylaxis in the cancer patient. *Acta Haematol* 2001;**106**(1–2):73–80.
- 16 **Hedlund PO, Henriksson P.** Parenteral estrogen versus total androgen ablation in the treatment of advanced prostate carcinoma: effects on overall survival and cardiovascular mortality. The Scandinavian Prostatic Cancer Group (SPCG)-5 Trial Study. *Urology* 2000;**55**:328–33.
- 17 **Fossa SD, Slee PH, Brausi M, et al.** Flutamide versus prednisone in patients with prostate cancer symptomatically progressing after androgen-ablative therapy: a phase III study of the European organization for research and treatment of cancer genitourinary group. *J Clin Oncol* 2001;**19**:62–71.
- 18 **Tannock IF, Osoba D, Stockler MR, et al.** Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996;**14**:1756–64.
- 19 **Price P, Hoskin PJ, Easton D, et al.** Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986;**6**:247–55.
- 20 **Deamaley DP, Bayly RJ, A'Hern RP, et al.** Palliation of bone metastases in prostate cancer. Hemibody irradiation or strontium-89? *Clin Oncol (R Coll Radiol)* 1992;**4**:101–7.
- 21 **Lipton A, Glover D, Harvey H, et al.** Pamidronate in the treatment of bone metastases: results of 2 dose-ranging trials in patients with breast or prostate cancer. *Ann Oncol* 1994;**5**(suppl 7):S31–5.
- 22 **Saad F, Gleason DM, Murray R, et al.** A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma.