Advances in the Treatment of Castration-resistant Prostate Cancer

a report by
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Prostate cancer is now the most common cancer in Australia – even if women are included in the denominator – and represents 14.5% of all cancers.[1] In comparison, colorectal cancer accounts for 13.5% of cancers in Australia and breast cancer for 12.8%. Prostate cancer is an Australian National Health Priority Area. Its incidence is increasing, probably due to improved diagnosis of early-stage disease, but to date no convincing reduction in mortality has accompanied the pattern of early diagnosis. When prostate cancer is confined to the prostate it is potentially curable; therefore, considerable activity is currently being devoted to improving primary therapies for localised prostate cancer, including newer surgical techniques or the application of new radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) or image-gated radiotherapy (IGRT). However, once prostate cancer has spread to other tissues, it is generally incurable and treatment is usually palliative in intent. Most clinical research in the latter setting has involved the use of cytotoxic chemotherapy; however, recent insights into the biology of prostate cancer have provided clues to new therapeutic possibilities.

Hormonal Therapy

Androgen ablation has long been the mainstay of treatment of advanced prostate cancer; however, development of resistance to this treatment modality is a frequent occurrence. This clinical condition is known variously as castration-resistant prostate cancer (CRPC), androgen-independent prostate cancer (AIPC) or hormone-refractory prostate cancer (HRPC). CRPC is probably the most accurate term: prostate cancer that progresses after androgen ablation may still respond to other hormones, so it is not 'hormone-refractory', and an 'androgen-independent' cancer simply may not have been treated with adequate systemic or tissue androgen ablation and may also respond to non-androgen hormone manipulation. Abiraterone has recently been featured in the media and there is substantial interest from both patients and clinicians. This drug is a CYP17 inhibitor, blocking 17α-hydroxylase and C17,20 lyase. This leads to reduction of androgen synthesis with corresponding upregulation of adrenocorticotropic hormone (ACTH), deoxycorticosterone and corticosterone. This in turn leads to problems with mineralocorticoid excess (hypertension, hypokalaemia, fluid overload); however, this can essentially be abrogated by concurrent treatment with relatively low doses of prednisone or prednisolone. This combination is then very well tolerated. Abiraterone is currently being developed as an agent for the treatment of CRPC. Several abiraterone studies were presented at the American Society for Clinical Oncology meeting in Chicago in 2008. In the COU-AA-004 phase II study, men with CRPC after docetaxel therapy were treated with abiraterone acetate 100 mg/d plus prednisone 5mg twice daily (bid).[2] The primary end-point was prostate-specific antigen (PSA) decline. Visceral disease was present in 26% of these men. PSA declines of >50% according to PSA Working Group Criteria version 1 were seen in 17 of 38 men, regardless of whether they had received prior ketoconazole. In separate studies, abiraterone was shown to induce PSA responses of more than 50% decline in 70% of docetaxel-naïve patients and in 47% of docetaxel-treated patients,[3,4] and PSA response rates of more than 50% were observed in men previously treated with ketoconazole.[5] Visceral and bone responses were also shown to occur. These results suggest that abiraterone will have useful activity at several points in the course of CRPC, and possibly before castration resistance occurs.

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Chemotherapy

The most significant recent advance in systemic chemotherapy for prostate cancer has been the use of docetaxel. Two studies published in 2004 demonstrated benefits of docetaxel as a single agent in combination with either prednisone[6] or with estramustine.[7] The first study (TAX327)[6] involved 1,006 men with metastatic CRPC with clinical or radiological evidence of progressive metastatic disease. Patients were randomised to one of three arms: mitoxantrone 12mg/m^2 every three weeks, docetaxel 75mg/m^2 every three weeks or docetaxel 30mg/m^2 weekly for five of every six weeks. All patients also received prednisone 5mg twice daily. The study showed a benefit for the primary end-point of overall survival in the three-weekly regimen of docetaxel, with a hazard ratio (HR) for death of 0.76 (p=0.009) and a median survival of 18.9 months for docetaxel versus 16.5 months for mitoxantrone. A statistically significant survival benefit was not observed for the weekly docetaxel regimen; however, the weekly regimen was comparable to the three-weekly regimen for all other clinically relevant end-points (pain response, PSA response rate, quality of life). Most adverse events were more common in the docetaxel arm, with a trend towards a lower frequency in the weekly docetaxel group; adverse events did not affect the observed improvement in quality of life. Objective response rates were not significantly different between the three arms. The TAX327 data have recently been updated, and the response and survival data are comparable.[8–10] The median survival for docetaxel every three weeks was 19.2 months compared with 17.8 months in the weekly docetaxel arm and 16.3 months in the mitoxantrone arm. Survival for more than three years was superior in patients receiving docetaxel. Patients crossing over to receive docetaxel after mitoxantone had a higher response rate than patients crossing in the other direction, although median survival was similar (10 months).[9] In the second study,[7] 770 men with progressive CRPC were randomised to receive either estramustine 280mg three times daily on

days one to five with docetaxel 60mg/m^2 on day two, with dexamethasone as a pre-medication, or mitoxantrone 12mg/m^2 on day one with prednisone 5mg twice daily; 674 patients were eligible. This study showed that the combination of docetaxel and estramustine provided a survival benefit (median 17.5 months compared with 15.6 months; p=0.02) with an HR of 0.8. Improvements were also seen in time to progression and PSA response rate, although objective tumour response rates were not significantly different and pain relief was similar between the two groups. These two studies have established docetaxel as the most active cytotoxic agent currently available for use in advanced prostate cancer, and it is now standard practice to use this agent in many countries, contingent on funding or reimbursement issues. In Australia, docetaxel has been reimbursed for this indication since 1 November 2007, although only the three-weekly regimen is approved. It is not surprising that regulatory authorities have concentrated on the small but real improvement in survival conferred by the three-weekly regimen; however, some oncologists are more convinced by the palliative benefits and might be more inclined to use the weekly regimen if it were available.

Other cytotoxic drugs are also under investigation and are showing promise. One interesting agent in development is satraplatin (*bis*-(acetato)-ammine dichloro-(cyclohexylamine) platinum IV [JM-216], Pharmion), a platinum analogue with good oral bioavailability.[11] Satraplatin has activity against multiple cancer types, including prostate cancer. Its toxicity is comparable to that of carboplatin: its main effect is bone marrow suppression and it lacks the neurotoxicity and nephrotoxicity seen with cisplatin. Phase II trials suggested useful activity against CRPC, and the European Organisation for the Research and Treatment of Cancer (EORTC) Satraplatin and Prednisone Against Refractory Cancer (SPARC) phase III trial has recently been reported.[12] This study included 950 men with CRPC who had failed prior cytotoxic chemotherapy. Patients were randomised to receive either satraplatin 80mg/m^2/day on days one to five every five weeks plus prednisone, or placebo plus prednisone. The primary end-point was progression-free survival (PFS). The study showed an improvement in the HR for PFS (0.69, 95% confidence interval [CI] 0.60–0.80; p<0.00001) and pain progression (HR 0.67, 95% CI 0.54–0.83; p=0.00028), with benefits also seen in terms of PSA responses (25 versus 12%; p=0.00007), objective tumour responses (7 versus 1%; p<0.002), pain response (24 versus 14%; p<0.005) and duration of pain response (HR 0.59, 95% CI 0.35–1.00; p=0.049). Treatment was well tolerated overall, with 4% grade 4 neutropenia, one patient with grade 4 thrombocytopenia and other grade 3 or 4 events <5% (4% infection, 2% vomiting, 2% diarrhoea). Satraplatin will now need to be compared against docetaxel.

Another class of cytotoxic agent currently under investigation is the epothilones. These drugs are non-taxane tubulin-polymerising agents and often have *in vitro* activity against taxane-resistant cell lines.[13] Ixabepilone (BMS-247550) is an epothilone B analogue and has been tested in phase II trials. The Southwest Oncology Group (SWOG) S0111 study included 42 eligible chemo-naïve patients. Ixabepilone was administered at a dose of 40mg/m^2 over three hours every three weeks. Fourteen PSA responses (33%) were observed and two patients achieved undetectable serum PSA levels. In the Eastern Cooperative Oncology Group (ECOG) E3803 study, 59 patients were entered and preliminary data have been reported on 56, of whom 24 were chemo-naïve and 32 had received prior taxane chemotherapy. A weekly regimen was used in this study of 20mg/m^2 for three doses every four weeks. PSA and objective responses were observed, but further data are not yet available. In both the SWOG and the ECOG studies the main toxicities were neuropathy and marrow suppression. In a randomised phase II trial of second-line treatment, 82 patients who had progressed within 60 days of taxane-based chemotherapy were randomised to receive ixabepilone or mitoxantrone, with cross-over allowed between treatment groups if patients progressed. PSA responses were observed in 17% of ixabepilone patients and 20% of mitoxantrone patients; responses were also observed if patients crossed to the other treatment group on progression, suggesting a lack of cross-resistance. One partial response was observed with ixabepilone and two with mitoxantrone.[14–16]

Other drugs and combinations are also under investigation. These include: vinorelbine (PSA response rate approximately 30% as a single agent[17] and close to 40% in combination with docetaxel);[18,19] capecitabine alone (PSA responses in only 12%)[20] or with docetaxel (41% PSA response rate, including 6% complete responses);[21] and paclitaxel (PSA responses in 36% and objective partial responses in 31% using a weekly regimen).[22] Even cyclophosphamide, an old drug in prostate cancer, can lead to PSA responses in 34% of patients when given in a metronomic (continuous low-dose) regimen.[23] It is clear that substantial opportunities still exist to optimise the efficacy and safety of cytotoxic chemotherapy combinations using both old and new drugs.

'Targeted' or 'Biological' Therapies

These terms are really misnomers, since very few of the treatments characterised as such are truly cancer-specific or restricted to a single biological target. In some cases, off-target effects where the drug may have low affinity may still lead to biologically important effects when the agent is administered at pharmacological doses. Nevertheless, it is gratifying to see that new treatments are being developed on the basis of an understanding of the biology of the cancer, rather than on empiricism. Some agents currently under investigation are listed below.

Vitamin D/Calcitriol and Other Micronutrients

Vitamin D receptors are present in most prostate cancer cell lines. Culture in the presence of vitamin D leads to induction of differentiation, decreased proliferation, decreased invasiveness and increased apoptosis. The ASCENT trial involved 250 men with CRPC treated with docetaxel with or without calcitriol.[24] The primary end-point was PSA response. A trend towards increased PSA response rate was observed in the combination arm (63 versus 52%; p=0.07), but the HR for death achieved statistical significance (0.67; p=0.04), suggesting that PSA responses may not correlate with ultimate clinical outcome in the setting of this combination. The ASCENT 2 trial was planned to involve 900 patients with the primary end-point of overall survival; however, this trial has recently been terminated early due to an imbalance of deaths between the treatment arms. Several large clinical trials are assessing the role of other nutrients, such as the SELECT trial, which is testing vitamin E and/or selenium, in which over 32,000 men were expected to participate (clinicaltrials.gov identifier: NCT00006392).

Endothelin Antagonists

The endothelin pathway involves three ligands (ET-1, ET-2 and ET-3) and two receptors (ET_A and ET_B). Signalling via this pathway promotes mitogenesis and bone matrix formation. ET_A is expressed in more than 70% of prostate cancers, and pathway activation is also enhanced by the activation of mechanisms that reduce clearance of the ligands. Atrasentan (ABT-627) is an orally bioavailable ET-1 inhibitor. In a phase III study, 808 patients received atrasentan or placebo.[25] The primary end-point was time to disease progression. No difference was observed

in this end-point (HR 0.89, 95% CI 0.76–1.04; p=0.136), predominantly because changes suggesting progressive disease were seen on the first bone scan – performed at 12 weeks – without necessarily evidence of clinical progression. Exploratory analysis showed an apparently longer time to alkaline phosphatase increase in the atrasentan group, an observation that requires confirmation and further study. Atrasentan was overall well tolerated. The SWOG 0421 study will test the combination of atrasentan with docetaxel.

Other Anti-angiogenic Approaches

Vascular endothelial growth factor (VEGF) is highly expressed in most prostate cancers, and VEGF levels in serum correlate with disease burden: higher levels predict earlier risk of PSA relapse and increased risk of death. Strategies aimed at targeting angiogenesis have already entered the clinic. Bevacizumab is a monoclonal antibody specific for VEGF-A. It has little activity as a single agent in prostate cancer; however, in combination with docetaxel and estramustine PSA response rates of 65% and objective response rates of 53% have been observed, suggesting a possible synergistic relationship.[26,27] The combination of bevacizumab plus docetaxel and prednisone is being tested in the Cancer and Leukemia Group B (CALGB) 90401 study, which will involve 1,020 men. The small-molecule multitargeted kinase inhibitor sunitinib causes more than 50% reduction in PSA in only about 10% of patients, although interestingly about 50% of patients show an initial increase followed by a reduction, suggesting that the response involves a more complex biological process than simple reduction in tumour volume.[28] Another multiple kinase inhibitor, sorafenib, causes PSA responses only infrequently, but leads to stable disease in 35% of patients with progressive HPRC.[29] In one study there was a clear disconnect between PSA progression and response to bony metastases.[30] This will be a fruitful area of future research and will probably lead to re-assessment of methods of evaluation of disease status in these patients.

Other Potential Growth Factor Targets

Several other growth factors are known to be of biological significance in prostate cancer and may become relevant as new agents that modulate their effects become available. Candidates include insulin-like growth factor-1 (IGF-1), which is produced by stromal cells under the influence of androgen. IGF-1 is known to promote the survival of prostate cancer cells. Members of the fibroblast growth factor (FGF) family are mitogenic for stromal cells and hence may indirectly support the growth of prostate cancer cells. Transforming growth factor-beta (TGF-β), secreted by stromal cells, has inhibitory effects on proliferation and promotes apoptosis.[31] Loss of TGF-β receptor subtypes, particularly TGF-βRII, leads to progression of prostate cancer.[31] Even oestrogen receptors, long overlooked in a disease dominated by androgens, seem to play an important role: oestrogen is produced locally within the tumour through the effects of aromatase, and oestrogen receptor-alpha (ERα) is involved with abnormal proliferation, inflammatory responses and prostate carcinogenesis; whereas ERβ tends to inhibit proliferation, promote differentiation and induce apoptosis.[32] In animal models, both androgen and oestrogen are required for prostate carcinogenesis; androgens alone are insufficient if oestrogen levels are low.[33]

Bcl-2

Bcl-2 (B-cell CLL/lymphoma 2) and related molecules are involved in the regulation of apoptosis; Bcl-2 itself and some other family members inhibit apoptosis. Overexpression of Bcl-2 is an important mechanism for progression to a castration-resistant state or to chemo- or radio-resistance. Abnormal Bcl-2 expression is associated with higher tumour stage, Gleason score and PSA and earlier time to progression, and is an important predictor of treatment outcome.[34–36] Interestingly, the action of docetaxel inhibits depolymerisation of cellular microtubules, which in turn causes phosphorylation of Bcl-2 and inhibition of its function.[37] This raises the possibility of synergy between docetaxel and agents that inhibit Bcl-2 function. Oblimersen is a synthetically modified DNA antisense oligonucleotide that inhibits messenger RNA (mRNA) translation into Bcl-2 protein. In a phase II trial, 52% of patients treated with oblimersen plus docetaxel had a PSA response and 33% of those with measurable disease had a partial response by Response Evaluation Criteria in Solid Tumors (RECIST).[38] The randomised EORTC 30021 trial involved 115 patients treated with docetaxel with or without oblimersen, and data from this trial have recently been updated for 111 patients.[39] Although no improvement in outcome was seen with the combination, this may have been influenced by the study design and the study population. Further studies of Bcl-2 inhibition are warranted.

Immunotherapy

Prostate cancer is known to be immunogenic[40–42] and to express various cancer antigens, including cancer-testis antigens, PSA, prostatic acid phosphatase, prostate-specific membrane antigen, p53 and others. Multiple approaches have been used to attempt to induce immune attack against prostate cancers. Two approaches that have undergone the greatest degree of development include APC8015 (sipuleucel-T, Provenge® [Dendreon]) and GVAX. APC8015 is an autologous dendritic cell vaccine pulsed with a prostatic acid phosphatase/granulocyte macrophage colony-stimulating factor (GM-CSF) fusion protein. In a phase III trial, 127 patients with metastatic asymptomatic CRPC were treated with APC8015 or placebo.[43] The primary end-point was time to progression, and all patients were followed for 36 months. At the time of analysis, 115 patients had progressed, with a median time to progression of 11.7 weeks for APC8015 compared with 10.0 weeks for the placebo patients (p=0.052). The median survival was 25.9 months compared with 21.4 months (p=0.01). Treatment was well tolerated overall. APC8015 is awaiting US Food and Drug Administration (FDA) approval, and other studies are being performed, including a combination study with bevacizumab. A phase III placebo-controlled trial of over 500 patients has just completed accrual. The GVAX vaccine consists of two allogeneic cell lines (LNCaP and PC3) transfected with the GM-CSF gene. A phase I/II multicentre study was performed on 55 patients, of whom 34 had metastases and 21 had rising PSA.[44] The end-points of the study were PSA responses, time to progression and survival. GVAX was well tolerated and no autoimmunity was observed. In the metastatic group, median survival was 26.2 months. In the PSA group, the median time to bone scan progression was 5.9 months, with a median survival of 37.5 months. These results were thought to be encouraging, and phase III trials are under way. Unfortunately, the phase III VITAL-2 trial of GVAX plus docetaxel versus docetaxel plus prednisone was halted early after accruing over 400 participants due to an excess of deaths in the GVAX arm (67 compared with 47). Other approaches currently under investigation include the monoclonal antibody ipilimumab, which targets cytolytic T lymphocyte-associated antigen-4 (CTLA-4) on T cells and blocks inhibitory signals mediated by that receptor. In a pilot study of 14 patients, two had PSA responses.[45]

Supportive Care

The propensity of prostate cancer to metastasise to bones has stimulated research interest into agents that reduce skeletal events such as fracture,

pain or need for surgery or radiotherapy. Bisphosphonates have been shown to be beneficial for prophylaxis of skeletal-related events in multiple myeloma and breast cancer, and there are some data to suggest benefit in prostate cancer, especially for zoledronic acid.[46] In particular, bisphosphonates may be useful in the prevention of bone pain.[47] However, there is by no means consensus that bisphosphonates should be used universally in patients with prostate cancer, nor what the optimum clinical scenario for their use or the duration of therapy should be.[48] Osteonecrosis of the jaw is a devastating but uncommon side effect of long-term bisphosphonate use. Receptor activator of NF-κB (RANK) ligand plays an important role in osteoclast biology, and new agents such as denosumab, a monoclonal antibody specific for RANK ligand, are currently being tested in clinical trials.

Conclusions

CRPC is a highly heterogeneous disease and its management is complex. Treatment remains palliative and multiple modalities of treatment are available. Empirical treatment approaches have generally been of little benefit, although active cytotoxic chemotherapy agents are now available. Systematic study and understanding of the basic biology of prostate cancer is providing clues to new treatment possibilities. Many new agents and technologies are entering the clinic and are likely to complement or even supplant older treatments. Unfortunately, there is still plenty of scope for improvement of the management of this disease. ■

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