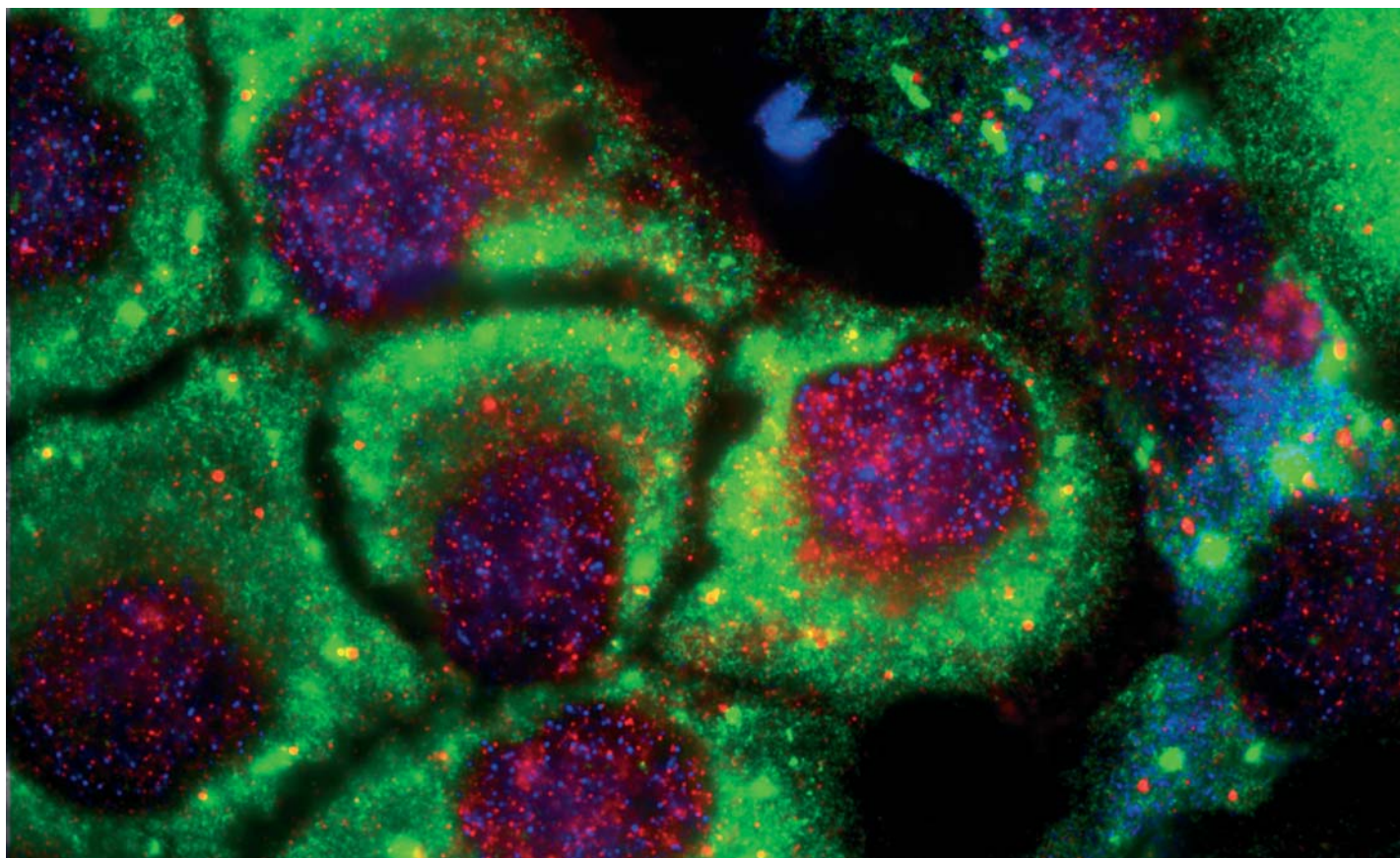


Novel therapies: prostate cancer

In the ninth article in our series looking at developments in drug technologies, **Jenny Bryan** describes new drugs on the horizon for patients with advanced prostate cancer



Nancy Kedersha/SPL

Prostate cancer is one of the most common male cancers, usually affecting the elderly

In a therapeutic area where watchful waiting has traditionally been a valid treatment option, research into novel therapies for advanced prostate cancer is gaining a promising new momentum. First to discover whether the effort has been worthwhile is likely to be Abbott Laboratories with its endothelin-A (ET_A) receptor antagonist atrasentan (Xinlay). Currently on the desks of Food and Drug Administration (FDA) officials in the US, atrasentan's licence application was submitted at the end of 2004 for the treatment of metastatic hormone-refractory prostate cancer.

Given the recent setbacks for AstraZeneca's lung cancer treatment gefitinib (fast-tracked for US approval in 2003, only to disappoint in key survival studies last year), Abbott may be considered bold in moving to license atrasentan on the basis of current data. Results of a pivotal phase III study of atrasentan in 809 men with asymptomatic metastatic hormone refractory prostate cancer showed only a trend towards delayed time to progression in the intention-to-treat population, although this did become significant in an

analysis of the 671 patients who completed treatment according to the trial protocol ($P=0.007$).¹

A subsequent meta analysis of 1,097 patients who took part in comparable phase II and III studies in the atrasentan development programme revealed a significant delay in disease progression in the intention-to-treat population in favour of atrasentan ($P=0.013$),² but whether or not this will be enough for the FDA remains to be seen. Abbott has not yet filed for a licence outside the US.

Endothelin receptors

The endothelin receptor has become a favoured target for pharmaceutical companies involved in cancer research. The efficacy and safety of AstraZeneca's ET_A receptor antagonist ZD4054 is currently being tested in a two year study of prostate cancer patients with bone metastases and rising serum prostate specific antigen (PSA) levels.

Don Newling, medical director, urology, at AstraZeneca, explains that endothelin-1 (ET-1) is not only the most powerful vasoconstrictor in the body but it has direct effects on tumour cells. Both ET_A and ET_B receptors are found on healthy prostate tissues. But, although ET-1 binding to the ET_B receptor is

part of the normal apoptotic mechanism for cell death, ET-1 binding at the ET_A has anti-apoptotic and mitogenic effects, leading to cell proliferation.

ET-1 is also a powerful stimulator of osteoblasts, via ET_A receptors, and part of the role of ET-1 in prostate cancer progression is thought to be in the development of bone metastases. High levels of ET_A expression have been recorded in prostate cancers, especially in patients with bone metastases. Indeed, in clinical trials, men with prostate cancer and bone metastases benefited most from treatment with atrasentan.

Other targets

Endothelin antagonists are just one family of compounds currently in prostate cancer trials. Angiogenesis is a major target for novel agents against many forms of cancer because of its essential role in blood vessel development for metastases. Vascular endothelial growth factor (VEGF), matrix metalloproteins and integrins all regulate this process.

Genentech's anti-VEGF antibody bevacizumab (Avastin) has already demonstrated survival advantages for patients with metastatic colorectal cancer, when combined with fluorouracil-based chemotherapy, and recent

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reports have demonstrated promising activity in prostate cancer, with partial radiographic responses and reductions in PSA in patients with advanced disease.³

Thalidomide is another agent with anti-angiogenic activity that is being tested in prostate cancer as well as a number of other cancers. Thought to be active against platelet-derived growth factor (PDGF), rather than VEGF,² thalidomide demonstrated a trend towards increased progression-free and overall survival when used in combination with docetaxel in a phase II study of hormone resistant prostate cancer.⁴

Also in early trials is cilengitide — a selective integrin antagonist, under development by the US-based EMD Pharmaceuticals — which appears to block endothelial cell proliferation and migration.

Tackling a different mechanism is the anti-sense treatment oblimersen (Genasense). This oligonucleotide therapy is designed to reduce expression of Bcl-2 — a protein that is over expressed in many cancers, including prostate cancer. In prostate cancer models, Bcl-2 has been shown to mediate the transition from androgen-dependent to androgen-independent growth, and is thought to be involved in the development of resistance to cytotoxic agents.³ It is hoped that reducing Bcl-2 levels before chemotherapy will boost clinical response.

Phase I studies combining oblimersen with docetaxel demonstrated a PSA response

and Bcl-2 inhibition in hormone resistant prostate cancer cells.³ A multicentre European Organisation for Research and Treatment of Cancer (EORTC) study is now comparing the oblimersen and docetaxel combination with docetaxel alone.

Optimism

Although it will be several years before these and other novel therapies for advanced and metastatic prostate cancer make their way into routine practice, there is no doubting the new optimism among many prostate cancer specialists.

Heather Payne, consultant in clinical oncology at Middlesex Hospital, London, explains that growing evidence supports the earlier use of adjuvant hormone therapy in combination with radiotherapy or surgery for men with high grade and locally advanced prostate tumours.⁵ Significant benefits are being seen in terms of reduced risk of local failure and distant metastases, and there are improvements in overall and disease-free survival: “The results have been so good that adjuvant hormone therapy combined with definitive local radiation is increasingly being used with curative intent in the treatment of men with poor prognosis, non-metastatic prostate cancer in a similar way to tamoxifen after breast cancer treatment,” Dr Payne said. However, Dr Payne points out that the majority of men with metastatic

prostate cancer who have hormone treatment are likely, at some point, to become resistant to therapy, despite initial good responses. “For this group of men, hormone refractory disease is becoming one of the biggest challenges in the management of prostate cancer,” she said.

And, for these men, a new generation of treatments which tackle different mechanisms of cancer cell proliferation that hormones do not reach could be the answer.

References

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