

PROSTATE

Is this the natural target for phenoxodiol? Possibly, maybe even probably.

The biological actions of **phenoxodiol** we discussed back in Chapter 13 that are pertinent to the prostate gland suggest so. On the surface, **phenoxodiol** doesn't appear to be any more cytostatic or cytotoxic towards prostate cancer cells than to any other cancer type, but it is some of its other biological actions that suggest a strong predilection for prostate cancer. Actions such as the ability to block the stimulatory effect of testosterone on prostate smooth muscle cells, which then go on to undergo apoptosis. And then there is its ability to block the formation of the most potent form of testosterone, dihydrotestosterone. We also know that **phenoxodiol** concentrates in human prostate cancer tissue xenografted in athymic mice. That, taken together with the fact that prostate cancer tissue expresses the necessary deconjugating enzymes to liberate the active drug from its conjugated form, makes us confident that we can deliver **phenoxodiol** to the cancer tissue in clinically effective amounts.

On the back of this promising pre-clinical data, a small sighting (Phase 2a) study was conducted in Australia in 2002 to see whether it could be translated into a meaningful clinical effect in humans. That study looked at the effect of **phenoxodiol** as a monotherapy in 26 patients with late-stage, androgen-independent prostate cancer. It wasn't a stringently controlled study, in the sense that the inclusion criteria were somewhat wider than might otherwise be employed in a Phase 2 study. PSA levels at the time of enrolment were widely variable, not all patients had clinically apparent metastatic disease, and the range of previous chemotherapies was considerable. Nevertheless, this relatively disparate group of patients represented a good cross-section of patients with end-stage prostate cancer in the wider community, and as such perfectly served the purpose of detecting an anti-cancer effect.

The study also was the first serious test of the new oral dosage formulation. So to that extent it was serving primarily as a safety study. The opening dose of 20 mg 8-hourly was set by the hospital's ethics committee, and allowed to increase progressively to 80, 200 and 400 mg after confirmation at each step of lack of toxicity. Each patient remained on the same dose throughout. Treatment continued until there was disease progression as determined by a

rising PSA level, or the development of new bone metastases, or a deterioration of clinical status. The main outcomes from an anti-cancer point of view were the PSA doubling time and time to disease progression. The PSA doubling time (or PSA velocity) is an indicator of the rate of tumour growth.

Despite the limited number of patients and their somewhat disparate clinical status, an anti-cancer effect was observed. The study showed that **phenoxodiol** delivered a dose-response effect on the progression of the disease, with the 2 higher dosages (200 and 400 mg) giving a statistically significantly ($p < 0.05$) better outcome than the 2 lower (20 and 80 mg) dosages. The interim results of that trial were reported in 2004 as per the following table.

Phenoxodiol (mg per dose)	n	PSA doubling time (mean, weeks)	Time to disease progression (mean, weeks)
20	6	14	13
80	6	22	17
200	5	66 ⁺	55 ⁺
400	9	39 ⁺⁺	42 ⁺⁺

+ One patient remained on **phenoxodiol** therapy with stable PSA levels at week 88.

++ Three patients remained on phenoxodiol therapy with stable PSA levels at 40, 72 and 80 weeks.

Being primarily a safety study, the key objective of the study was met when patients finished therapy or when they had completed 6 months' of therapy. The PSA outcome was a secondary observation and probably accounts for why no final report on the anti-cancer effect has been published.

We regarded the 20 mg dose as an ineffective dose, included purely because of the need to meet the ethics committee's concern over a safe starting dose. So for all intents and purposes it represents a control group. The 80 mg dose group was also there as an incremental dosing step, but again, we regarded that as unlikely to deliver any meaningful clinical effect. All 12 patients in these two groups displayed rapid rises in PSA levels and all 12 patients were deemed to have had disease progression within the nominal 6 month trial duration.

The two higher doses (200 and 400 mg) produced a measurable slowing in the rate of disease progression. The PSA doubling time was decreased substantially and patients remained on therapy without confirmed disease progression well beyond 6 months. Four of the 14 patients remained well and on therapy for 3-4 years because of a substantial slowing in their rate of disease progression. All patients eventually progressed to the point of having to have **phenoxodiol** discontinued, and all patients died. But all concerned were satisfied that we had observed a significant anti-cancer effect in progress.

That outcome led to much deliberation in-house and consultation with leading urologists as to where to go from there. There wasn't too much doubt that we had a highly promising drug for

prostate cancer, and arguably the best-looking prospect among a number of emerging technologies encompassing cytotoxic drugs and vaccines and genomics. The main debate was over the vexed questions of how best to demonstrate an anti-cancer effect and how best to achieve marketing approval.

The *'how best to demonstrate an anti-cancer effect'* debate was tempered by the emerging data at the time on the role of **phenoxodiol** as a chemo-sensitiser. That was having a profound influence on how we regarded the drug, introducing the option of combination therapy compared to the previous notion of monotherapy only. We now had the opportunity to consider whether mixing **phenoxodiol** with another cytotoxic agent would enhance an anti-cancer benefit in patients with late-stage disease.

The *'how best to achieve marketing approval'* consideration was set against a backdrop of much discussion at the time between the FDA and the medical and pharmaceutical communities over the need to relax some of the drug testing requirements when it came to prostate cancer. The generally slow-growing nature of prostate cancer made it challenging for drug developers to run drug trials where it was a strict policy requirement of regulators to demonstrate a survival benefit for any new drug. The FDA was showing willingness in about 2006-2007 to adopt secondary outcomes such as time to disease progression or rate of disease progression across a number of cancer types, including prostate cancer. In the case of prostate cancer specifically, PSA response (a 50% fall in PSA levels) and PSA velocity (the rate of increase in PSA levels) were being proposed as reliable and meaningful indicators of an anti-cancer benefit that would translate into a survival benefit.

The decision finally came down to two options considered to be the most realistic on the basis of the pre-clinical and clinical evidence to date. The first option was to use the drug as a monotherapy in patients with androgen-dependent disease which had failed localised therapy. The second option was to use the drug, also as a monotherapy, but in patients with advanced disease that was androgen-independent. This decision led to the current Phase 2 study in New-Haven and Boston. We will look at the interim data from this study in a minute, but I want to discuss it in the context of two other options that are also worthy of consideration. And before we look at all 4 options, we need to consider the disease of prostate cancer and the various forms that it can take.

The first point to make about the disease is that it varies enormously in its level of aggression. In very broad terms, about 60% of cases are slow-growing, 30% are moderately aggressive, and 10% are highly aggressive. This difference is expressed as the Gleason score, which is a pathologist's score after examining the cancer cells in a biopsy of the prostate gland. The pathologist looks at cancer cells within two separate fields of the biopsy where the cancer is most formed and ranks (1-5) the cells according to how aggressive they look. The two values are added together to give a score out of 10. A Gleason score of between 2 and 6 is a low grade prostate cancer. It is likely to grow very slowly. A Gleason score of 7 is an intermediate grade that will grow at a moderate rate. A Gleason score of 8 to 10 is a high grade cancer that is likely to grow more quickly.

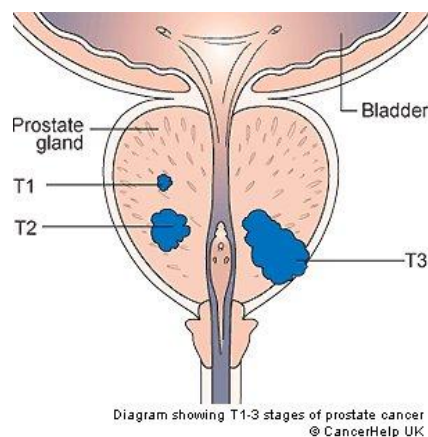
Much of the current debate over the value of PSA screening and interventional treatment such as surgery centres on the relative risks of these three different levels of aggression. Slow-growing prostate cancer presents little risk to the patient providing it is kept under surveillance. These are the so-called 'watchful-waiting' cases where regular PSA measurements and rectal examination (sometimes including prostate gland biopsy), obviate

the need for aggressive therapy, with many of these cancers growing over several decades without causing symptoms. For these men, a doubling in the PSA level within a 3-year period, or an increase in PSA velocity greater than 0.75 ng/mL per year or a worsening biopsy result, is a cause for interventional therapy.

Prostate cancers with a Gleason score in excess of 6, on the other hand, don't have this luxury of time and they need to be treated aggressively from the outset in order to avoid metastasis. Where the cancer is considered to be confined to the prostate gland, a radical (complete) prostatectomy is the preferred treatment. Where the cancer has spread beyond the prostate gland, surgery offers little benefit. Prostate cancer spreads mainly directly from the gland, penetrating the gland's capsule and attaching itself to pelvic structures such as the bladder and rectum. However it also can spread via the blood, lymph vessels and the prostatic nerves. Its preferred site for metastasis is bone, with the cancer in end-stage disease affecting the skeleton broadly.

Another way of ranking the severity of prostate cancer is to look at the extent of its growth. These are referred to as stages as follows.

- **Stage 1 (T1)** - the cancer is very small and completely inside the prostate gland which feels normal during a rectal examination
- **Stage 2 (T2)** - the cancer is still inside the prostate gland, but is larger and a lump or hard area can be felt during a rectal examination
- **Stage 3 (T3)** - the cancer has broken through the covering of the prostate and may have grown into the tubes which carry semen
- **Stage 4 (T4)** - the cancer has grown into the bladder or rectum, or has spread to the lymph nodes or another part of the body, such as the bones, liver or lungs



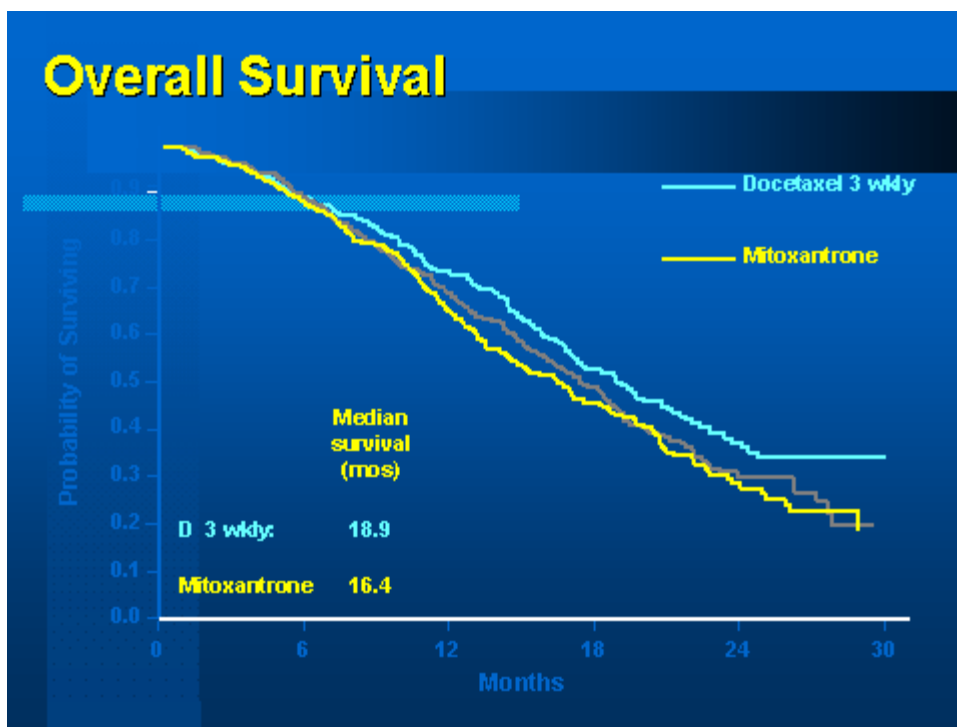
Where the cancer has escaped from the gland (T3 or T4), localised treatment with radiotherapy is the usual treatment. This takes the form of brachytherapy and/or external beam radiotherapy. Brachytherapy is where the radiation source is placed within the prostate gland. In low-dose brachytherapy, small radioactive seeds are implanted in the gland and allowed to decay over time. In high-dose brachytherapy, metal rods are inserted into and around the gland and attached to a radioactive source. Both low-dose and high-dose brachytherapy usually is supplemented with external beam radiotherapy.

Localised therapy (either prostatectomy or high-dose brachytherapy) typically causes the PSA level to fall to very low or undetectable levels. Where it subsequently rises by 2 ng/mL

or more, the patient is deemed to have *'biochemical failure'*, meaning that the cancer has resumed its growth.

At this point, most cases are androgen-dependent, meaning that the cancer is growing in response to the stimulatory effects of the male sex hormone (or *androgens*). Denying the cancer access to androgens either by surgical castration or chemical castration therapy (known as *androgen-ablation therapy*) will put 80-90% of men into remission for between 1-3 years. After remission, the cancer is now androgen-independent and the patient typically has a survival time of between about 18-24 months.

Chemotherapy has minimal effect in androgen-independent disease. The most recently approved drug for this indication is **docetaxel**, which provided a very modest increase in median survival from 16.4 months to 18.9 months.



With that background in the disease process, we can now look at the 4 options for using **phenoxodiol** based on what we know about the drug.

Option 1. In conjunction with localised treatment.

Phenoxodiol is a radio-sensitizer. This is not a function widely spoken about by Novogen, but it is one of the more exciting actions of this drug. It is a function that was confirmed by the National Cancer Institute.

In some ways it is an unsurprising discovery. First, because the plant isoflavone, **genistein**, is a moderately active radio-sensitizer, meaning that it enhances the killing effect of ionising

radiation on cells. The isoflavonoid heritage of **phenoxodiol** would suggest that it would be highly likely to inherit that function, which it clearly has. Second, because **phenoxodiol** is a chemical sensitizer and the cellular mechanisms underlying that function are not that dissimilar to those involved in radio-sensitization. What we weren't expecting however, was just how much more potent a radio-sensitizer **phenoxodiol** is compared to **genistein**. Interestingly, **triphendiol** is an even stronger radio-sensitizer than **phenoxodiol**, but when looked at in the context of the wider range of biological functions relevant to prostate cancer, **phenoxodiol** remains a strong candidate as a radio-sensitizer in the treatment of prostate cancer.

The concept here would be to use **phenoxodiol** in conjunction with brachytherapy and/or external beam radiotherapy as a way of enhancing the lethality of the radiation. **Phenoxodiol** did not show any enhanced killing of normal cells in the test-tube, which is in line with its known high degree of selectivity, although a lack of any safety issues still would have to be confirmed in a clinical study. Soft tissue damage to the bladder and large bowel are a common side-effect of radiotherapy of the prostate and can be debilitating for up to 12 months. Such damage is a strong barrier to the use of radio-sensitizers, but there is every reason to believe that **phenoxodiol** would be without this problem.

Radiotherapy is the best shot that a clinician has to cure prostate cancer when it gets to the T3 or T4 stage. The chances of cure are small, with remission for a year or two being the more usual outcome. But anything that tips the scales in favour of a cure has to become seriously considered.

Option 2. Following failure of local treatment.

One of the two treatment arms being tested in the current Yale/Harvard study of **phenoxodiol** in prostate cancer is testing this scenario.

Prostatectomy or radiotherapy has been successful in putting the patient into remission, but a rising PSA level is pointing now towards regrowth of the tumour. Further localised treatment is not an option, and androgen ablation therapy is the only effective way of controlling tumour growth at this point, although for a proportion of men where the cancer is already androgen-independent, even this will not be an option.

An interim report was presented on this study to a cancer conference earlier in 2009. Only 9 patients (of an ultimate target of 25) had been enrolled in this treatment arm at that time. The patients had a mean PSA level at the time of enrolment of 7.6 ng/mL, indicating significant biochemical progression of the disease. Five of the 9 patients were reported as having stabilised disease (no PSA rise) for a median time of 3 months. We cannot and should not read too much into this data given the small number of patients and the superficiality of the data. However, it is hard not to be encouraged by the response. Androgen ablation therapy is an unwelcome therapy for many men with loss of libido, mood swings, tiredness, loss of muscle mass etc. Anything that delayed the need for androgen ablation therapy would be a welcome addition to a clinician's medical chest.

Option 3. Following failure of hormone therapy.

In this scenario, the growth of the cancer has become independent of androgens. The cancer is heading inexorably towards metastatic growth throughout the body. Chemotherapy with drugs such **docetaxel** or **cisplatin** are the last line of defence, but with little prospect of any meaningful benefit.

This is the second treatment arm being evaluated in the Yale/Harvard study. It involves patients very similar to those used in the earlier Australian prostate cancer study.

At the time of the release of the interim data earlier in 2009, 16 patients had been enrolled. Their median starting PSA level was 38.5 ng/mL. The data refers only to 6 patients, with 4 showing disease progression, 1 showing a response (>50% decline in PSA levels), and 1 showing no disease progression for more than 6 months. Again, we can't make anything from such small data other than to be encouraged that some anti-cancer effect appears to be there, as we saw in the earlier Australian study.

But unless this treatment arm shows a significant response, I am much more attracted to Option 4.

Option 4. Chemo-sensitization.

In this scenario, patients with androgen-independent cancers would be treated with **phenoxodiol** and a second cytotoxic drug such as docetaxel or cisplatin.

As a chemo-sensitiser, **phenoxodiol** shows a particular predilection for prostate cancer. It is highly effective at synergising the anti-cancer effect of agents such as **platinums** and **taxanes** on prostate cancer cells, including in cells with acquired chemo-resistance. And earlier this year an Australian research group showed that **phenoxodiol** enhances the uptake of **cisplatin** by prostate cancer cells, leading to a 3-fold increase in the number of DNA lesions in the cancer cells.

My preference would be to use a **phenoxodiol-cisplatin** combination for no other reason that we have more work to do on the temporal aspects of a **phenoxodiol-docetaxel** combination.