Prostate cancer is one of the most common forms of cancer in men and, after lung cancer, is the most common cause of male cancer death (Figure 1). The incidence of prostate cancer varies around the world and is highest in Western countries such as the USA and Scandinavia (Parker et al, 1997). In the USA, the incidence and prevalence of prostate cancer is increasing, with an estimate (based on deaths from 1979 to 1993) of 334 000 new cases and 41 800 deaths for 1997 (Parker et al, 1997; Wingo et al, 1997). The incidence of prostate cancer in Japan, although low at one-tenth of North America, is also rising rapidly, perhaps because of adoption of a more Westernized lifestyle (Dearnaley, 1994).

Prostate cancer is rarely diagnosed before the age of 50 and the incidence increases markedly between the ages of 60 and 80 years, with a median age at diagnosis of 72 years (Brawley and Kramer, 1994). As the male population over 75 years increases, so too do the number of men at risk from prostate cancer. Prostate cancer growth is stimulated by androgens, principally testosterone, therefore androgen deprivation is an essential component in the treatment of this disease. Advanced prostate cancer is usually defined as a disease which has become metastatic or locally advanced, and is, therefore, incurable. Traditional treatment for advanced prostate cancer is castration (surgical or medical) which reduces serum testosterone levels by about 90% (Labrie et al, 1985; Lunglmayr et al, 1988). However, castration does not affect androgen biosynthesis in the adrenal glands and addition of an anti-androgen may be used to block the effect of remaining testosterone on prostate cells. The addition of anti-androgen to castration is termed combined androgen blockade (CAB). CAB has now been compared with castration alone (medical and surgical) in numerous clinical trials. Some trials show advantage of CAB over castration, whereas others report no significant difference. The author favours the view that CAB has an advantage over castration. No study has reported that CAB is less effective than castration. Of the anti-androgens which are available for use in CAB, bicalutamide may be associated with a lower incidence of side-effects compared with the other non-steroidal anti-androgens and, in common with nilutamide, has the advantage of once-daily dosing. Only one study has compared anti-androgens within CAB: bicalutamide plus LH-RH analogue and flutamide plus LH-RH analogue. At 160-week follow-up, the groups were equivalent in terms of survival and time to progression. However, bicalutamide caused significantly less diarrhoea than flutamide. Withdrawal and intermittent therapy with anti-androgens extend the range of treatment options.

**Keywords:** hormonal therapy; advanced prostate cancer; combined androgen blockade; luteinizing hormone-releasing hormone analogues; surgical castration; anti-androgens

**MAIN HORMONAL TREATMENTS AVAILABLE**

First-line hormonal treatment of advanced prostate cancer is either castration alone or in combination with an anti-androgen. This section reviews surgical castration, medical castration and anti-androgens, followed by their use in combination therapy (CAB).

**Surgical castration (orchidectomy)**

Bilateral orchidectomy, either total or subcapsular, has been the mainstay of treatment for advanced prostate cancer and is the comparator against which other treatments are assessed. Orchidectomy produces symptom relief in 70–80% of patients (Kaisary et al, 1991), and provides pain relief from symptoms of bone metastases in 80–90% of patients. The size of the prostate tumour shrinks within 4–6 weeks of orchidectomy (Paulson, 1981). Because testosterone levels are reduced so quickly, orchidectomy is often the best treatment for men with metastases in the spine who are at severe risk of paralysis (Korman, 1989). If a surgical option...
is not possible, then ketoconazole can be used to lower testosterone levels very rapidly (Lowe and Bamberger, 1990).

Surgical castration is a relatively simple, safe and inexpensive operation which can be performed under local or light general anaesthesia (Geller et al, 1988; Griffiths et al, 1993). Although the convenience of a ‘one-off’ procedure, as opposed to medical therapy, means patient compliance is not a problem, surgical castration is not acceptable to all patients (Catalona, 1994), mainly because of psychological trauma (Cassileth et al, 1992; Denis, 1993; Fossa et al, 1994). The trauma of castration can be avoided to some extent by use of the subcapsular technique which removes only the functional part of the testicle.

Disadvantages of orchidectomy include loss of libido, impotence and hot flushes (Varenhorst, 1993), which occur in around 60% of men. A further disadvantage is that the operation is irreversible. Patients with non-hormone responsive prostate cancer may, therefore, have undergone unnecessary surgery. If intermittent androgen blockade proves beneficial (see later), then orchidectomy may not be the best treatment option because of its irreversibility.

Orchidectomy reduces circulating testosterone by around 90% (Labrie et al, 1985). However, the intraprostatic concentration of the active androgen, dihydrotestosterone (DHT), after castration is less affected and may amount to 30–40% of normal levels (Labrie et al, 1987; Geller et al, 1988). This residue must be derived from adrenal androgens which make a sizeable contribution to androgen metabolism within the prostate gland.

**Medical castration**

_Luteinizing hormone-releasing hormone (LH-RH) analogues_

LH-RH analogues provide one method of medical castration and are a widely used alternative to surgical castration. LH-RH, produced by the hypothalamus, stimulates production of

| Treatment | Advantages | Disadvantages |
|-----------|------------|---------------|
| Orchidectomy | Symptom relief, Rapid reduction in circulating testosterone, No compliance problems | Does not eliminate adrenal androgens, Psychological trauma, Irreversible, Loss of libido, Impotence |
| Medical castration | As effective as orchidectomy without surgery, Reversible, Low risk of cardiovascular side-effects, Longer acting formulations, e.g. goserelin acetate 12-week depot | Does not eliminate adrenal androgens, Risk of tumour flare, Loss of libido, Impotence |
| Luteinizing hormone-releasing hormone (LH-RH) analogues (e.g. leuprolide, goserelin acetate, buserelin) | As effective as orchidectomy, without surgery | Risk of cardiovascular complications, Loss of libido, Gynaecomastia, Nausea |
| Diethylstilboestrol (DES) | | |
| Anti-androgens | Avoids surgery, As effective as oestrogens | Loss of libido, Impotence, Disturbances in liver function, Thromboembolism, Steroidal effects, e.g. fluid retention, Diarrhoea (incidence with flutamide twice that with bicalutamide), Liver toxicity (flutamide), Visual problems (nilutamide only), Alcohol intolerance (nilutamide only) |
| Steroidal (e.g. cyproterone acetate) | | Gynaecomastia, Hot flushes |
| Non-steroidal (e.g. flutamide, bicalutamide, nilutamide) | Blocks action of dihydrotestosterone and testosterone, Reduces risk of testosterone flare, Avoids surgery, Most commonly used in combination with surgical or medical castration (CAB), Less cardiovascular toxicity than DES, Preservation of potency in 75% of men | |
luteinizing hormone (LH) from the pituitary gland. Testosterone is produced by the testes in response to LH. Negative feedback occurs via the rise in testosterone levels, which brings about a decrease in hypothalamic release of LH-RH. The continuous infusion of LH-RH analogues renders the pituitary refractory to hypothalamic regulation, thus suppressing the release of androgen from the testes. Goserelin acetate, buserelin, leuproide and triptorelin have all been administered as LH-RH analogues (e.g. Labrie et al, 1985; Crawford et al, 1989). All have similar modes of action and efficacy and plasma testosterone levels are reduced to castrate levels within 2–4 weeks of starting the treatment. Both leuproide and goserelin acetate have been shown to be as effective as diethylstilboestrol (DES), with objective responses of 50–85% for DES and 70–86% for the LH-RH analogues (Leuprolide Study Group, 1984; Emtage et al, 1988). However, goserelin acetate has superior tolerability to DES (Emtage et al, 1988). Only goserelin acetate has been shown, in major comparative studies, to be equivalent to surgical castration on the basis of the degree of serum testosterone suppression, objective response rates (71% vs 72%), duration of response (53.7 vs 50.1 weeks) and survival (27.5 vs 24.8 months; Debruyne et al, 1988; Kaisary et al, 1991). In a comparison of the effects of surgical castration and goserelin acetate treatment on patients’ quality of life (QOL), a significant improvement in two scores of QOL were observed in patients treated with goserelin acetate, but not in those who had surgical castration (Cassileth et al, 1992).

A variety of routes of administration are available for LH-RH analogues and ease of administration may be the deciding factor in the choice of agent. Buserelin is given initially by subcutaneous injection three times daily, then intranasally six times daily, with obvious problems of compliance. The inconvenience of daily injections and the uncertainty of intranasal administration has been overcome by the introduction of biodegradable depot formulations which provide controlled release of LH-RH analogue over a prolonged period. Goserelin acetate, leuproide and triptorelin are all available as monthly intramuscular or subcutaneous injections. Goserelin acetate is now also available in a 12-weekly depot preparation for subcutaneous injection (Dijkman et al, 1995; Debruyne et al, 1996c), and leuproide is also available as a 3-month depot in some countries (Fernandez Del Moral et al, 1996). These controlled-release preparations have obvious advantages in terms of patient compliance and acceptability.

As expected of an LH-RH agonist, the initial administration may cause a temporary rise in testosterone, which may account for the worsening of symptoms, particularly bone pain, seen in up to 5% of patients (Brewster and Gillatt, 1993; Bruchovsky et al, 1993; Dijkman et al, 1995). This flare phenomenon can have potentially serious effects in patients with spinal secondaries, precipitating spinal cord compression and resulting in paraplegia. Treatment with an anti-androgen 7–10 days before, or concomitantly with, the first injection of LH-RH analogue can prevent the surge of serum testosterone and control the exacerbation of symptoms (Boccon-Gibod et al, 1986; Kuhn et al, 1989; Tyrell et al, 1991). With continued LH-RH analogue treatment, serum testosterone falls to castrate levels and no rise is seen with subsequent injections (Bruchovsky et al, 1993; Brogden and Faulds, 1995).

LH-RH analogues are generally well tolerated: the main side-effects are similar to surgical castration, i.e. loss of libido, impotence and hot flushes (Varenhorst, 1993). Libido and impotence occur in most men treated with LH-RH analogues or surgical castration, whereas hot flushes occur in about 60% of patients (Kaisary et al, 1991; Denis et al, 1993).

**Oestrogens**

For many years, DES was the only hormonal alternative to orchidectomy. Oestrogens produce their effect partly by suppressing the secretion of LH-RH from the hypothalamus, thereby inhibiting the release of LH from the pituitary, resulting in castrate levels of testosterone, and partly by directly opposing the action of androgens on prostate cells. However, the use of high-dose oestrogens was associated with significant mortality and morbidity because of cardiovascular complications (in up to 25% of patients), including increased incidence of thromboembolism and fluid retention (Veterans Administration Co-operative Urological Research Group, 1967; Allvizatos and Oosterhof, 1993). This led to their use in the treatment of prostate cancer being greatly reduced in the 1970s.

In Scandinavia, oestrogens are still an acceptable therapy for prostate cancer; the drugs commonly used are estramustine phosphate or ethinyl oestradiol in combination with polyestradiol phosphate (Henriksen and Edhag, 1986; Lundgren et al, 1986, 1995). As a primary treatment, estramustine phosphate is reported to be as effective as conventional antineoplastic agents in the treatment of advanced prostate cancer (Perry and McTavish, 1995). As a second-line treatment, estramustine phosphate is no more effective after bilateral orchidectomy than placebo (Iversen et al, 1997a; Janknegt et al, 1997).

Recent investigations using high-dose intramuscular-depot oestrogen (estradiurin) indicate that cardiovascular side-effects may be lower with this method of administration than with oral administration (Stege et al, 1995). In addition, parenteral administration of polysteradiol phosphate may have bone preserving capacity in patients with prostate cancer (Carlstrom et al, 1997). Further studies by the Scandinavian Prostatic Cancer Group are ongoing and results from a study (SPCG 5) involving over 900 patients on the efficacy and tolerability of parenterally administered polysteradiol phosphate compared with decapetyl plus flutamide are due to be analysed in 1998.

Recently, there has been increased interest in the use of low-dose oestrogens. Low-dose DES (1 mg day⁻¹) was found to be as effective as orchidectomy and associated with fewer malignant disease-related deaths than the more conventional higher dose (3 mg or more). However, it was associated with slightly more deaths (16 out of 108 patients) due to cardiovascular causes than orchidectomy (9 out of 108 patients) (Robinson, 1993). If the risk of cardiovascular toxicity could be controlled, then oestrogens may become a more acceptable option in the management of prostate cancer.

**Other**

Used in high doses, ketoconazole causes castrate levels of testosterone within 24–48 h and, therefore, has been assessed to determine its role in the treatment of advanced prostate cancer (Lowe and Bamberger, 1990). One clear indication for its use is for treatment of men with metastases of the spine who require a prompt therapeutic response (Bamberger and Lowe, 1988). Other indications include: when orchidectomy is contraindicated, when oestrogens are contraindicated, initial empirical therapy, and hormonally refractory disease. It can also be used in conjunction with LH-RH analogues. However, ketoconazole can cause liver toxicity and
adrenal suppression, although hydrocortisone may be used to minimize toxicity (Small et al, 1997a, 1997b). Ketoconazole is useful for short-term treatment, but is not particularly useful for long-term therapy (Lowe and Bamberger, 1990).

Anti-androgens

Anti-androgens act by competitively blocking the binding of testosterone, and its metabolite DHT, to nuclear receptors in prostate cancer cells (Neumann and Jacobi, 1982) and may be steroidal or non-steroidal.

The main steroidal anti-androgen cyproterone acetate (CPA) has been used as oral monotherapy in advanced prostate cancer. This drug reduces testosterone to near castrate levels by its progestogenic effect, suppressing LH-RH and LH. CPA is typically given in a dosage of 200–300 mg day \(^{-1}\) in two or three divided doses, and has been shown to be as effective as oestrogen in terms of objective response (40% vs 55%), rate of progression (52% vs 47%) and overall survival (Pavone-Macaluso et al, 1986). Equivalence with surgical castration or LH-RH analogues has not been demonstrated. CPA reduces libido and potency in around 86% of men, a similar incidence to that of surgical and medical castration (Barradell and Faulds, 1994). Other side-effects of CPA include changes in body weight, fatigue, disturbances in liver function (Ohri et al, 1991; Drakos et al, 1992; Watanabe et al, 1994) and thromboembolism (Barradell and Faulds, 1994). CPA has also been evaluated in combined therapy (refer to CAB section).

Non-steroidal anti-androgens, such as nilutamide, flutamide and bicalutamide, have been evaluated for both monotherapy (discussed here) and for combined therapy (discussed in the CAB section) in patients with advanced prostate cancer. The efficacy of nilutamide and flutamide as monotherapy has only been investigated in small non-comparative studies. Only one study showed equal mean time to progression between monotherapy and orchidectomy; in a comparison of flutamide (250 mg three times daily) and orchidectomy involving 104 patients, at the 24-month follow-up, mean time to progression was similar in each group (320 vs 352 days, \(P = 0.49\); Boccon-Gibod et al, 1994).

Bicalutamide monotherapy has been evaluated in much larger trials than those carried out for other anti-androgens. Such studies, therefore, are more likely to show up small differences between treatments. A combined analysis of more than 1000 patients showed that bicalutamide monotherapy (50 mg once daily) had a higher treatment failure rate (53% vs 41%), higher objective progression (46% vs 35%) and lower survival (25 vs 28 months, \(P = 0.0001\)) compared with castration (Bales and Chodak, 1996) demonstrating that although bicalutamide is an effective anti-androgen, it is not equivalent to castration at a dose of 50 mg. Although statistically significant, the clinical significance is open to interpretation. In addition, in two of these trials the survival difference was not significant.

A combined analysis of two multicentre randomized trials comparing bicalutamide 150 mg once daily with castration (goserelin acetate or orchidectomy) showed a survival benefit for castration in metastatic patients, but the survival difference was only 6 weeks (Tyrrell et al, 1996). In addition, the dose of 150 mg had an identical tolerability to the 50-mg dose. In patients with non-metastatic disease (M0), preliminary results suggest that bicalutamide 150 mg may prove equivalent to castration in terms of survival (Tyrrell et al, 1996; Iversen et al, 1997b).

When the patient’s QOL, tolerability of treatment and sexual function are considered, bicalutamide, either 50 mg or 150 mg, provides significantly better symptom relief, a better QOL and greater preservation of sexual interest compared with castration (Bales and Chodak, 1996; Tyrrell et al, 1996). Higher doses of bicalutamide for use as monotherapy are currently being investigated (Kaisary, 1997).

The non-steroidal anti-androgens obviously do not have the steroidal events associated with CPA. For non-steroidal anti-androgens used as monotherapy, loss of libido and potency is reported in only 20–30% of men (Decensi et al, 1991; Kaisary, 1994), compared with 86% for CPA. As a class, non-steroidal anti-androgens are associated with side-effects such as gynaecomastia (around 40–62% of patients affected), hot flushes (23–50%) and breast pain (26–63%), however there are differences in the side-effect profiles of flutamide, nilutamide and bicalutamide which are unrelated to their anti-androgenic properties.

Nilutamide is associated with a high incidence (20%) of reversible visual abnormalities (Boccardo et al, 1991; Decensi et al, 1991). Approximately one-fifth of patients treated with nilutamide experience alcohol intolerance (Decensi et al, 1991), a problem not reported with any other anti-androgens. Reversible pulmonary interstitial lung disease has been reported with an incidence of approximately 1% in patients treated with nilutamide (Pitztenmeyer et al, 1992). Nilutamide is not currently available in the UK.

Flutamide monotherapy is associated with a much higher incidence of diarrhoea (29%, Narayan et al, 1996; 20%, Delare and Van Thillo, 1991; 9%, Chang et al, 1996) than bicalutamide monotherapy (2.5%, Kaisary, 1994; 1.9%, Langlmaier and the International Casodex Study Group, 1995). Raised liver enzymes have been noted in up to 32% of patients after flutamide treatment (Lundgren, 1987). Serious hepatotoxicity has been reported at an annual rate of 3 per 10 000 flutamide users (Wysowski et al, 1993, Wysowski and Foureroy, 1996). Of 19 cases of serious hepatotoxicity reported to the US Food and Drug Administration (FDA) over a 3-year period, five died of progressive liver disease (Wysowski et al, 1993).

Bicalutamide is associated with a lower incidence of side-effects than other anti-androgens. In clinical studies, the incidence of adverse hepatic events, such as raised liver enzymes, during bicalutamide therapy is low (Tyrrell, 1992; Kaisary et al, 1996), and to date there have been no reports of fatal hepatic adverse effects of bicalutamide (Kolvenbag and Blackledge, 1996). Used in combination therapy, bicalutamide was associated with significantly less diarrhoea than flutamide (10% vs 24%; see CAB section; Schellhammer et al, 1996a).

Combined androgen blockade (CAB)

Although LH-RH analogues offer a more acceptable method of castration than surgery, they offer no advantage over orchidectomy in terms of prognosis. This is because the effect of both LH-RH analogues and orchidectomy is limited to blocking production of testicular androgens. Addition of anti-androgens, which block the action of androgens of testicular and adrenal origin, to medical or surgical castration was developed to provide additional androgen blockade (CAB) and so prolong survival of patients with advanced prostate cancer. Bracci and colleagues were the first to utilize CAB, combining CPA treatment with bilateral orchidectomy (Bracci and...
De Silverio, 1977; Bracci, 1979). Clinical trials suggesting the efficacy of CAB using flutamide and leuprolide were first reported by Labrie and co-workers (Labrie et al 1982, 1987).

CAB has now been compared with castration alone (medical and surgical) in numerous clinical trials. Some trials show advantage of CAB over castration whereas others report no significant difference (Table 2). No study has reported that CAB is less effective than castration. There is, therefore, considerable debate about the benefits of CAB over castration alone.

Three large, randomized, double-blind, controlled trials comparing CAB with castration have demonstrated a statistically significant improvement for CAB in time to progression and length of survival (Crawford et al, 1989; Denis et al, 1993; Janknegt et al, 1993, 1996). The largest of these trials (603 patients) compared CAB using daily leuprolide and flutamide with leuprolide treatment alone (Crawford et al, 1989). Patients treated with CAB had a longer progression-free survival (16.5 vs 13.9 months, \( P = 0.039 \)) than patients treated with the LH-RH analogue alone. Their median length of survival was also significantly longer (35.6 vs 28.3 months, \( P = 0.035 \)). A subsequent European Organization for Research and Treatment of Cancer (EORTC) trial including 527 patients compared CAB using goserelin acetate plus flutamide with surgical castration (Denis et al, 1993). This trial also demonstrated a statistically significant advantage in favour of CAB for time to progression (33.3 vs 21.3 months, \( P = 0.008 \)) and survival (34.4 vs 27.1 months, \( P = 0.02 \)). In a comparison of orchidectomy plus nilutamide with orchidectomy alone involving 457 patients (Janknegt et al, 1993), a significant (\( P < 0.05 \)) 7-month increase in median survival, before death from cancer, and a progression-free survival advantage of 5.9 months were observed. Long-term follow-up (up to 8 years) also indicated significant benefits in survival and progression-free survival (Janknegt et al, 1996). Additional studies are in progress.

A number of studies have reported equivalence for CAB and castration. Six studies of flutamide in combination with LH-RH analogue compared with LH-RH analogue or orchidectomy alone, with patient numbers of 50–571, showed median times to progression of 16–32 months and median survival of 23–36 months with no statistically significant differences between the treatment arms (Jurincic et al, 1991; Tyrrell et al, 1991; Boccardo et al, 1993; Ferrari et al, 1993; Fourcade et al, 1993; Iversen et al, 1993). Crawford et al (1997) have recently reported results from a prospective, randomized trial comparing flutamide plus orchidectomy with placebo plus orchidectomy in 1387 patients with stage D2 prostate cancer. No statistically significant differences between the groups were found with respect to either time to progression (mean 21 and 18 months respectively) or survival (mean 31 and 30 months). Similarly, studies with nilutamide in combination with either orchidectomy or LH-RH analogue showed no statistically significant difference in time to progression and median survival from the castration alone treatment (medical or surgical; Brisset et al, 1987; Knöngel et al, 1989; Béland et al, 1990; Crawford et al, 1990; Le Duc et al, 1990; Namer et al, 1990). CPA has also been evaluated in combination therapy and there was no significant difference in survival between CPA plus goserelin acetate and the LH-RH analogue alone (Di Silverio et al, 1990; Brewster et al, 1992). With the exception of the recently reported large study by Crawford et al (1997), the individual trials reported above generally have small numbers of patients and, therefore, do not provide sufficient statistical power to demonstrate effect or to statistically refute the results of the three large positive trials (Trachtenberg, 1997). To determine a significant survival benefit in favour of CAB and to ensure treatment groups are balanced, it has been estimated...
that it is necessary to include at least 300 patients per treatment arm (Van Tinteren and Dalesio, 1993). The lack of a sufficiently long follow-up period or even a lack of a clear end point, such as survival, were also important factors (Denis, 1995; Trachtenberg, 1997). Interim analyses based on too short a follow-up period can result in too few patients being followed to disease progression to make definite conclusions. Meta-analyses, pooling the results of all studies, is one method to overcome some of these problems.

Meta-analyses, however, also differ on whether CAB shows benefit over castration. A meta-analysis of the individual data from 22 randomized, controlled trials involving 5710 patients treated with either castration (medical or surgical) or various forms of CAB showed a non-significant difference in survival (Prostate Cancer Trialist’s Collaborative Group, 1995). Five-year survival rates were 26.2% in the CAB group and 22.8% in the conventional therapy group (these rates are currently being re-evaluated). The Ontario Cancer Treatment Practice Guidelines Initiative suggested that there were a number of methodological weaknesses in the above meta-analysis. These included: the absence of an initial protocol document; no detailed description of search strategy and inclusion/exclusion criteria; no assessment of the quality of the trials, particularly unpublished studies; and the inclusion of data on patients with non-metastatic disease. The authors also noted that a statistically significant difference favouring CAB would have been produced if a one-sided t-test (testing the hypothesis that CAB is of benefit or neutral), rather than a two-sided test had been used. Consequently, they conducted a sensitivity analysis of the randomized trials (Klotz and Newman, 1996). An analysis based only on published data (20 studies) demonstrated that therapy with CAB was associated with a clear benefit of 2 years additional survival over castration alone. In addition, the meta-analysis of the Prostate Cancer Trialist’s Collaborative Group (1995) was criticized for grouping results of trials that used both steroidal and non-steroidal anti-androgens and the use of immature data (Labrie and Crawford, 1995; Quartey, 1995; Waxman and Pandha, 1995).

An earlier meta-analysis of seven randomized, double-blind trials (1191 patients), which compared CAB (orchidectomy plus nilutamide) with orchidectomy plus placebo in patients who had received no previous hormonal treatment, showed significant delay to disease progression in the nilutamide group compared with the placebo group (Bertagna et al, 1994). Nilutamide used in combination therapy resulted in a statistically significant reduction in risk of progression (16%, $P = 0.05$) and a non-significant 10% reduction in the risk of death. In an update of this analysis, after a further 2-year follow-up, the reduction in risk of progression was maintained (17%, $P = 0.031$, Debruyne et al, 1996b). The risk of death from cancer was reduced by 16% ($P = 0.053$). A smaller, meta-analysis of selected trials showed a statistically significant benefit for CAB (Cauba et al, 1996).

Some studies reported a high incidence of withdrawal because of the side-effects of flutamide (Boccardo et al, 1990; Tyrrell et al, 1991; Boccon-Gibod et al, 1992). This may have skewed the results in favour of castration alone, particularly in those trials which did not employ a placebo. It is clear, however, that the tolerability and comparative efficacy of the various anti-androgens should be considered when choosing which anti-androgen to use in CAB treatment.

Only one study has compared anti-androgens in the context of CAB. The study compared treatment with bicalutamide plus LH-RH analogue with flutamide plus LH-RH analogue in 813 patients with untreated metastatic (stage D2) prostate cancer (Schellhammer et al, 1996a–1996c; 1997; Soloway et al, 1996). At the latest follow-up (median duration 160 weeks), there was an improvement in time to treatment failure with bicalutamide plus LH-RH analogue, although this was non-significant. In terms of survival at 160 weeks, 53% of patients in the bicalutamide group died compared with 57% in the flutamide group. The median survival time was 180 weeks for the bicalutamide group compared with 148 weeks for the flutamide group. The incidence of treatment-related diarrhoea was significantly higher in the flutamide group (26% vs 12%, $P < 0.001$) and caused more treatment withdrawals (25) than in the bicalutamide group (two) (Schellhammer et al, 1997). Diarrhoea has been reported with similar incidence in other flutamide CAB studies (Crawford et al, 1989; Tyrrell et al, 1991). The incidence of diarrhoea in the Crawford study, irrespective of relation to therapy, was reported to the FDA Advisory Committee meeting as 23.8% for the flutamide group and 11.2% for placebo (Schellhammer et al, 1996d). Episodes of diarrhoea in flutamide-treated patients have been of sufficient intensity to require withdrawal from therapy in 2–10% of patients (Boccardo et al, 1990; Iversen et al, 1990; Tyrrell et al, 1991).

Other factors, such as the stage and extent of disease, can also influence the outcome of CAB treatment. The study by Crawford et al (1989) shows that patients with minimal metastatic disease (defined as five or fewer hotspots on bone scan) and good performance status, who received combined therapy of leuprolide and flutamide, had improved median time to progression compared with patients who received LH-RH analogue alone (48 months vs 19.1 months). Their overall survival was lengthened by 20 months (Crawford et al, 1995). The EORTC meta-analysis, although it had small subgroups, indicated that patients with fewer than five bone metastases and good performance status tended to benefit most from CAB (Denis et al, 1993).

In summary, the overall results of a large number of studies suggest that CAB is at least equivalent to conventional therapy in terms of time to progression and survival. However, opinion is divided on whether CAB has an additional beneficial effect over conventional therapy. CAB’s demonstrated equivalence and strong therapeutic rationale suggest that it could be a primary treatment option in advanced prostate cancer. In the absence of a statistically significant difference in the effectiveness of available anti-androgens in CAB, selection may be based on factors such as tolerability. In this respect, bicalutamide may have benefits over flutamide.

**RELATED TREATMENT OPTIONS**

**Intermittent therapy**

The proposal that prostate cancer cells adapt to androgen deprivation and grow more rapidly in the presence of androgen blockade has resulted in the development of intermittent therapy. The idea is that the patient is treated with androgen blockade until prostate-specific antigen (PSA) is in the normal range, then treatment is stopped until there is evidence of further tumour development (a rise in PSA) when treatment can be started again. It is hypothesized that after the period of androgen exposure (no anti-androgen therapy) the cells will remain sensitive to androgen deprivation and react a second time to anti-androgens rather than progressing to become hormone insensitive. It may not be necessary, therefore, for all patients with limited disease to stay on therapy indefinitely, as
some patients could have intermittent androgen blockade. Preliminary clinical data indicate that this approach is feasible and may offer benefits in terms of QOL and preservation of sexual function (Goldenberg et al., 1995). A randomized prospective study (by the Southwest Oncology Group, SWOG) and an open, non-randomized study (by the European Organization for Research and Treatment of Cancer, EORTC) are currently under way to assess further the value and feasibility of intermittent therapy.

**Withdrawal**

There have been several recent reports of favourable clinical and PSA responses to the withdrawal of non-steroidal anti-androgens in patients with progression of disease after lengthy remission while taking CAB (Dupont et al., 1993; Kelly and Scher, 1993; Scher and Kelly, 1993; Nieh, 1995). Scher and Kelly (1993) found that in patients who relapsed while receiving combination therapy of LH-RH analogue and flutamide, if the anti-androgen alone was stopped, the patients went back into remission, some for as long as 2 years. This was not only subjective remission with a falling PSA, but, in those patients with measurable lesions, there was also evidence of objective remission. This withdrawal response is seen in up to 30% of patients, almost exactly the same proportion of patients who respond to single-agent chemotherapy after relapse on hormone therapy. The mechanism for this withdrawal effect is unknown, but it may be related to the development of cancer cell clones that have mutated to be dependent on the anti-androgen as a substrate.

**ADDITIONAL FACTORS IN SELECTION OF TREATMENT OPTIONS**

Patients are increasingly involved in decisions about treatment and physicians need to consider the requirements and preferences of individual patients when evaluating treatment options. Physicians both under- and overestimate their patients’ subjective morbidity and impact of symptoms on QOL (Osoha, 1994; Calais da Silva et al., 1996). Improvement of QOL and symptom control has become a major end point in clinical trials of prostate cancer (Fossa, 1996). The following issues are relevant to improved QOL of patients with advanced prostate cancer: bone pain, micturition, sexuality, vitality, hot flushes and gynaecomastia. As these factors may be of equal importance to the patient as length of survival, QOL results will need to be incorporated into the overall evaluation of treatment together with survival and health economic considerations.

In studies of patient choice, 78–86% of patients preferred medical castration with the LH-RH analogue goserelin acetate to orchidectomy (Lunglmayr and Girsh, 1987; Cassileth et al., 1989; Fossa et al., 1994). The main motives for choosing LH-RH analogues were avoidance of surgery (36%), success of treatment (18%) and convenience of drug treatment (10%). The reversibility of treatment with goserelin acetate if ineffective was the primary or secondary reason for choosing the drug for 50% of urologists. The primary reasons for patients choosing surgical castration were the convenience of surgical procedure (32%) and success of treatment (29%).

The stage and grade of the disease and the timing of treatment may also give an indication of the success of a particular treatment option. CAB may be more beneficial in minimal disease patients (Crawford et al., 1989; Denis et al., 1993). Disease progression occurs more rapidly and the chance of developing serious complications is increased in patients who receive delayed hormonal treatment compared with those who receive immediate treatment (Kirk, 1996).

Patient compliance is another factor to be considered in selection of treatment for prostate cancer. Compliance is influenced by factors such as efficacy, tolerability and complexity and convenience of the dosing regimen. Differences between the anti-androgens in respect of dosing regimen and tolerability may result in different rates of compliance (Kaisary, 1996). For example, once-daily dosing regimens are associated with significantly better compliance than regimens involving three or four daily doses (Greenberg, 1984). The long elimination half-life of bicalutamide (approximately 7 days; Cockshott et al., 1990) enables once-daily dosing and offers an advantage over anti-androgens with shorter elimination half-lives and more frequent dosing regimens. The active metabolite of flutamide, hydroxyflutamide, has a half-life of 4.3–6.6 h (Brogden and Clissold, 1989) and the drug requires three times daily dosing. Nilutamide, with a half-life of 23–87 h permits once-daily dosing (Harris et al., 1993).

**CONCLUSIONS**

Surgical castration is the main hormone treatment for advanced prostate cancer against which other treatments are assessed, although medical castration is an acceptable alternative. CAB combines the benefits of medical or surgical castration with effective blockade of adrenal androgens. The results of clinical trials so far show that CAB is at least equivalent to conventional therapy in terms of survival and progression-free survival. However, opinion is divided on whether CAB has an additional beneficial effect over conventional therapy in advanced prostate cancer. The choice of components for CAB is dependent on the efficacy and tolerability of the various treatments and patient preference. In terms of choice of anti-androgen, bicalutamide may be associated with a lower incidence of side-effects compared with the other non-steroidal anti-androgens and may offer CAB with a lower risk of discontinuation because of intolerance.

Hormonal agents for treating advanced prostate cancer represent a wide range of treatment options. Physicians and patients need to determine the most appropriate option for a given patient based on factors such as the staging extent of the disease, the patient’s performance status and the patient’s requirements in terms of QOL and survival.

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