Maximal androgen withdrawal for prostate cancer therapy: current status and future potential

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Introduction

Prostate cancer is the most frequent visceral malignancy and the second leading cause of death in American men. It has been estimated that approximately 184,500 new cases will be diagnosed and over 39,200 men will die from prostate cancer in the United States in 1998 (Landis et al. 1998). Despite public awareness of prostate cancer, many apparently localized diseases will be upstaged after pathological evaluations. Subsequently, a substantial proportion of these patients will develop metastatic diseases. In addition, approximately 16% of newly diagnosed patients will present with metastatic disease.

Since the studies of Huggins and Hodges in 1941, androgen withdrawal therapy has been a standard treatment of metastatic prostate cancer. Up to 80% of the patients with metastatic disease will respond to some form of androgen withdrawal. However, the majority of patients with advanced prostate cancer exposed to androgen withdrawal will die of their cancer progression within three years. Currently, not only metastatic diseases but also localized and locally advanced diseases are treated by hormonal therapy. Thus, hormone management continues to occupy a significant portion of the clinical practice of urologists and of clinical trials. For the past 50 years, hormonal strategies have been developed. Maximal androgen withdrawal therapy (combined androgen withdrawal or combined androgen blockade) is one of the strategies that appears to provide optimal treatment. This review will discuss the results of androgen withdrawal monotherapy and the rationale, development, current results, and future trend of maximal androgen withdrawal therapy.

Results of androgen withdrawal monotherapy

Androgen withdrawal therapy can be accomplished using a variety of methods. The common methods used for primary androgen withdrawal are bilateral orchiectomy, estrogen therapy, luteinizing hormone-releasing hormone (LHRH) analog, and antiandrogens.

Bilateral orchiectomy can reduce the circulating testosterone to castration levels approximately 8.6 h after surgery (Lin et al. 1994). Up to 80% of patients have subjective or objective remissions (Byar & Corle 1988). Median survival time of patients with metastatic disease treated with bilateral orchiectomy therapy ranges from 18 to 27 months (Beland et al. 1991, Denis et al. 1993, Janknegt et al. 1993). Rarely, bilateral orchiectomy is useful for immediate androgen suppression in patients with extensive metastatic diseases complicated by such life threatening conditions as spinal cord compression or bilateral ureteral obstruction (Garnick 1997). To allay some of the psychological effects of an empty scrotum, subcapsular orchiectomy is as effective as a simple orchiectomy (Zhang et al. 1996). Bilateral orchiectomy remains the gold standard for withdrawal of testicular androgen and is still recommended in some patients.

Estrogen therapy inhibits the release of LHRH from the hypothalamus, thereby suppressing the release of luteinizing hormone (LH) from the anterior pituitary gland (Bruchovsky 1993) and consequently decreasing testosterone secretion from the testis. In addition, estrogen has a direct action on Leydig cells and cytotoxic effects on prostate cancer cells (Schulz et al. 1990, 1998, Cox & Crawford 1995, Robertson et al. 1996). Estrogens have been used as a medical castration since the 1940s (Herbst 1941). Several estrogen compounds such as chlorotrianisene (TACE) and ethinyl estradiol (Morales & Pujari 1975), polyestradiol phosphate (Bishop et al. 1989), and estramustine phosphate (Bishop et al. 1985) have been used in the treatment of metastatic prostate cancer, but diethylstilbestrol (DES) is the most effective and the one most commonly used. The Veterans' Administrative Cooperative Urological Research Group (VACURG) reported that 5 mg DES/day is as effective as bilateral orchiectomy, but carries a significant risk of cardiovascular complications (VACURG 1967, Byar & Corle...
are cyproterone acetate (CP A), megestrol acetate, and pounds that are utilized in the treatment of prostate cancer have progestational effects. They suppress LHRH and LH androgen action at the androgenic receptor level, but also compounds.

Antiandrogens are classified into two categories: steroidal functions resulting in cell growth (Labrie et al. 1993a). In addition, experimental data suggested that LHRH analogs have a direct inhibitory effect in a prostate cancer cell line (Crawford et al. 1998). In the 1980s, LHRH analogs became widely available as a medical castration tool to treat metastatic cancer (Leuprolide Study Group 1984). LHRH analogs are as effective as estrogen therapy and bilateral orchiectomy in terms of response rates and survival times (Leuprolide Study Group 1984, Koutsilieris et al. 1986, Klioze et al. 1988, Peeling 1989, Crawford et al. 1997b).

A new form of LHRH-related androgen withdrawal is the LHRH antagonist. Experimental data were conducted using LHRH antagonists which directly block the LHRH receptor and result in immediate suppression of androgen production (Pinski et al. 1992). Unfortunately, early results were associated with histamine releasing anaphylactoid reaction, relative water insolubility, and the necessity of using acidic formulation for delivery (Garnick 1997). Some newer compounds have averted some of these local injection problems.

Antiandrogens were introduced into clinical practice in the 1970s. Testosterone is transformed into dihydrotestosterone (DHT) by the 5α-reductase enzyme in prostatic tissue. DHT, a strong more potent androgen, interacts with an androgen receptor to stimulate the expression of genes mediating androgen-specific functions resulting in cell growth (Labrie et al. 1993a). Antiandrogens are purposed to inhibit the interaction between an androgen and the receptor. Currently, antiandrogens are classified into two categories: steroidal antiandrogen compounds and nonsteroidal antiandrogen compounds.

Steroidal antiandrogen compounds not only inhibit androgen action at the androgenic receptor level, but also have progestational effects. They suppress LHRH and LH and consequently decrease testosterone secretion from the testis (Schroder 1993). Steroidal antiandrogen compounds that are utilized in the treatment of prostate cancer are cyproterone acetate (CPA), megestrol acetate, and medroxy-progesterone acetate (MPA) (Pavone-Macaluso et al. 1986, Vener et al. 1988, Patel et al. 1990). CPA, an important steroidal antiandrogen compound, has been widely used in European countries for the treatment of metastatic prostate cancer since 1966 (Scott & Schirmer 1966). The study EORCT 30761 (Pavone-Macaluso et al. 1986) and Jacobti et al. (1980) showed that CPA achieves a survival similar to that of bilateral orchiectomy and estrogen therapy. However, other studies reported a shorter median time to progression when treated with CPA compared with LHRH analogs (Thorpe et al. 1996).

Nonsteroidal antiandrogen compounds are pure antiandrogens because of their inhibition at the androgenic receptor level only. This blockade results in increased LH and testosterone levels in serum and consequently the preservation of libido and potency in approximately 80% of patients (Sogani et al. 1984, Lund & Rasmussen 1988, Migliari et al. 1992).

Flutamide, the first nonsteroidal antiandrogen, was described in 1972 (Neri et al. 1972). Many studies reported subjective and objective response rates of around 50-90% using flutamide as a monotherapy (Sogani & Whitmore 1979, Sogani et al. 1984, Prout et al. 1989, Delaere & Van Thillo 1991). Several investigators have shown that flutamide is as effective as bilateral orchiectomy and 3 mg DES/day (Lund & Rasmussen 1988, Boccon-Gibod 1993). In contrast, Chang et al. (1996) indicated that there was a 17 month difference in survival comparing 750 mg flutamide/day with 3 mg DES/day.

Nilutamide differs from flutamide in its lateral chain. This results in an extension of its half life to 40 h. Thus, it was recommended at a once daily dosage of 300 mg (Mcleod 1993). The data for nilutamide monotherapy are limited (Decensi et al. 1991). In one study mean progression-free survival and overall survival were 9 and 23 months respectively.

Bicalutamide is the newest of the pure antiandrogens with a long half life (Kolvenbag et al. 1998). The objective and subjective responses to bicalutamide monotherapy were approximately 50-55% in metastatic disease (Decensi et al. 1991, Tyrrell 1992, Iversen 1994). Many studies reported that 50 mg bicalutamide were inferior to either surgical or medical castration in terms of time to treatment failure, and time to progression including overall survival (Iversen 1994, Chodak et al. 1995, Bales
Rationale of combined androgen withdrawal therapy

Although both surgical and medical primary androgen withdrawal monotherapies are effective in suppression of testicular androgen in many patients, their diseases continue to progress. It is possible that adrenal androgen remains in circulation and stimulates tumor cell growth. Theoretically, prostate cancer is composed of different clones of cells with varying degrees of androgen sensitivity or androgen resistance. Conventional surgical or medical castration alters the clones that require large amounts of dihydrotestosterone (DHT), but fails significantly to alter the other clones that require a low concentration of DHT (Crawford 1990). Despite serum testosterone at castration levels, intracellular DHT persisted in high concentrations in patients who received androgen withdrawal monotherapy (Farnsworth & Brown 1976, Geller et al. 1978, 1984). Harper et al. (1974) demonstrated that there was radiolabeled DHT in the specimens of the patients who underwent prostatectomy for benign prostatic hyperplasia (BPH) after those isotopes were labeled with androstenedione or dehydroepiandrosterone (DHEA) for half an hour before surgery. Furthermore, other studies showed a significant reduction of prostatic DHT when utilizing ketoconazole for blocking adrenal androgen with conventional monotherapy castration (Geller & Albert 1987). Therefore, it is purposed that the persistence of DHT in prostatic tissue results from conversion of inactive adrenal androgen precursors, DHEA, its sulfate (DHEAS), and androstenedione into testosterone and thus to DHT (Labrie 1991, 1996). However, other randomized studies that compared 50 mg bicalutamide with castration have shown no difference in time to progression (Kaisary 1994).

At present, bilateral orchiectomy, estrogen therapy, and LHRH analogs appear to have a similar efficacy and to be a standard androgen withdrawal monotherapy. Antiandrogen monotherapy appears not to be more effective than the standard surgical or medical castration. However, the treatment options should be considered not only on the efficacy of the treatment but also on the side effects and the cost of each therapy. The advantages and disadvantages of each monotherapy are shown in Table 1. The lethal cardiovascular complications of estrogen therapy are myocardial infarction, congestive heart failure, and pulmonary embolism (Peeling 1989, Lukkarinen & Kontturi 1994). It is purposed that a low dose of aspirin daily may minimize these complications. Unfortunately, there is no study to support this concept (Smith 1995, Garnick 1997). Nevertheless, parenteral estrogen may not have the risk of cardiovascular death that is described with oral estrogen (Cox & Crawford 1995). The initial administration of LHRH analogs cause stimulation of LH and FSH release and subsequent increase in testosterone levels before these hormones are shut down. Flare phenomenon increases pain and causes serious effects such as paralysis from pathological fracture or bilateral ureteral obstruction (Schroeder et al. 1987). The initial administration of CPA (Isurugi et al. 1980), flutamide (Labrie et al. 1987), or nilutamide (Kuhn et al. 1989) is effective in preventing the flare effects.
Since 1945, Huggins and Scott (1945) performed bilateral adrenalectomy as a secondary hormonal therapy in patients whose diseases progressed following bilateral orchiectomy. Unfortunately, because of a high mortality, that procedure was abandoned. In 1983, combined androgen withdrawal (CAW) or maximal androgen withdrawal - the elimination of testicular androgen by surgical or medical castration plus the elimination of adrenal androgen by antiandrogens - was advocated by Labrie et al. (1983). They reported a 97% objective response rate compared with 60-70% in previous castration or estrogen therapy patients. Research or clinical trials of this strategy involve not only metastatic diseases, but also a wide spectrum of the diseases such as neoadjuvant in localized diseases and neoadjuvant or adjuvant in locally advanced diseases.

CAW for metastatic diseases

The definition of metastatic disease has been changed considerably (Table 2) (Crawford & Blumenstein 1997).

According to this concept, hormonal therapy has been an important method in the treatment of metastasis. To improve the response rates, time to progression, and survival time, CAW has been widely investigated and compared with conventional castration monotherapy. Table 3 summarizes the results of randomized studies that support the survival advantage of CAW. The large confirmatory trial conducted by the South West Oncology Group (SWOG-INT 0036) (Crawford et al. 1989) compared leuprolide plus 750 mg flutamide/day with leuprolide plus placebo in metastatic disease. An 18.7% increase in median time to progression and a 25.8% increase in median time of overall survival were demonstrated in the CAW arm which reached statistical significance. The EORTC 30853 study compared goserelin acetate plus 750 mg flutamide/day with bilateral orchiectomy (Denis et al. 1993). A 25-week increase in time to progression and a 7-month increase in overall survival were noted in the CAW arm which reached statistical significance. The Anandron Study Group compared bilateral orchiectomy plus 300 mg nilutamide/day with bilateral orchiectomy alone (Janknegt et al. 1993, Dijkman et al. 1997). Significant benefits of a 7-month prolongation in both time to progression and survival were achieved in the CAW arm. Minimal metastatic disease was defined as an absence of metastasis in skull, rib, long bone, or soft tissue other than lymph node (Eisenberger et al. 1994). The survival benefits of CAW are more apparent in the patients with minimal metastatic disease and good performance in the INT 0036 and EORTC 30853 trials. Although several large well-designed studies indicated the superiority of CAW, the validity of this strategy is still a matter of controversy. Table 4 summarizes randomized studies that do not support the survival advantage of CAW. These randomized studies failed to demonstrate the superiority of CAW compared with the conventional

Table 2 Classifying advanced prostate cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>Pelvic lymph nodes</td>
</tr>
<tr>
<td>D1.5</td>
<td>Rising PSA after failed local therapy</td>
</tr>
<tr>
<td>D2</td>
<td>Metastatic disease in bone and/or other organs</td>
</tr>
<tr>
<td>D2.5</td>
<td>Rising PSA after nadir level</td>
</tr>
<tr>
<td>D3</td>
<td>Hormone refractory prostate cancer</td>
</tr>
<tr>
<td>D3S</td>
<td>Hormonally sensitive</td>
</tr>
<tr>
<td>D3I</td>
<td>Hormonally insensitive</td>
</tr>
</tbody>
</table>


Table 3 Trials that support the survival benefit of CAW

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Response rate</th>
<th>Time to progression</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crawford et al. (1989)</td>
<td>300</td>
<td>Leupro</td>
<td>48 months (max)</td>
<td>36.1%</td>
<td>13.9 months</td>
<td>28.3 months</td>
</tr>
<tr>
<td>(NCI INT 0036)</td>
<td>303</td>
<td>Leupro+flut</td>
<td></td>
<td>42.8%</td>
<td>16.5 months</td>
<td>35.6 months</td>
</tr>
<tr>
<td>Deniz et al. (1993)</td>
<td>155</td>
<td>Orch</td>
<td>5 years (median)</td>
<td>59%</td>
<td>46 weeks</td>
<td>27.1 months</td>
</tr>
<tr>
<td>(EORTC-30853)</td>
<td>155</td>
<td>Goserelin+flut</td>
<td>(obj)</td>
<td>58%</td>
<td>71 weeks</td>
<td>34.4 months</td>
</tr>
<tr>
<td>Janknegt et al. (1993)</td>
<td>232</td>
<td>Orch</td>
<td>8.5 years (max)</td>
<td>24%</td>
<td>14.7 months</td>
<td>29.8 months</td>
</tr>
<tr>
<td>(Anandron Group)</td>
<td>225</td>
<td>Orch+nilut</td>
<td>(obj)</td>
<td>41%</td>
<td>21.2 months</td>
<td>37 months</td>
</tr>
</tbody>
</table>

NCI, National Cancer Institute; INT, Intergroup; EORTC, European Organization for the Research and Treatment of Cancer; orch, orchiectomy; leupro, leuprolide acetate; flut, flutamide; nilut, nilutamide; obj, objective; max, maximum.
androgen withdrawal therapy in terms of a survival in metastatic disease (Beland et al. 1991, Boccardo et al. 1993, Ferrari et al. 1993, Iversen et al. 1993, Klijn et al. 1993, Robinson 1993, Tyrrell et al. 1993, Bertagna et al. 1994, Crawford et al. 1997b). There are some conflicting opinions that state that an insufficient statistical power may be due to insufficient number of patients or that it is too early to consider the significant difference. Good examples for these opinions are the EORTC 30853 and the Anandron Study Group studies. Primary analysis showed no significance of a survival benefit, but after a longer follow-up they showed a statistical significance (Denis et al. 1990, 1993, Janknegt et al. 1993, Dijkman et al. 1997). However, the recent result of a large randomized study (NCI-INT 0105) comparing bilateral orchiectomy alone and bilateral orchiectomy plus 750 mg flutamide/day ($n=1271$) failed to achieve any advantage due to the addition of flutamide to bilateral orchiectomy in terms of both time to progression and survival in the metastatic disease, including patients with a minimal good risk disease (Crawford et al. 1997b).

A large meta-analysis of CAW was reported by the Prostate Cancer Trialists’ Collaborative Group (1995). This study reviewed 22 randomized trials and a total of 5710 patients with advanced prostate cancer. These randomized studies compared conventional castration (surgical or LHRH analogs) versus CAW (conventional castration plus antiandrogens such as flutamide, nilut-

### Table 4 Trials that do not support the survival benefit of CAW

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Response rate</th>
<th>Time to progression</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iversen et al. (1993)</td>
<td>133</td>
<td>Orch</td>
<td>57 months</td>
<td></td>
<td>16.8 months</td>
<td>27.6 months</td>
</tr>
<tr>
<td>(Danish Prostate Cancer Gr)</td>
<td>129</td>
<td>Goserepin+flut</td>
<td>(median)</td>
<td></td>
<td>16.5 months NS</td>
<td>22.7 months NS</td>
</tr>
<tr>
<td>Beland et al. (1991)</td>
<td>103</td>
<td>Orch</td>
<td>48 months</td>
<td>61%</td>
<td>11.7 months NS</td>
<td>18.9 months NS</td>
</tr>
<tr>
<td></td>
<td>105</td>
<td>Orch+nilut</td>
<td>(max)</td>
<td>78%</td>
<td>12.4 months NS</td>
<td>24.3 months NS</td>
</tr>
<tr>
<td>Boccardo et al. (1993)</td>
<td>373</td>
<td>Goserepin</td>
<td>24 months</td>
<td>NS (D only)</td>
<td>12 months</td>
<td>32 months</td>
</tr>
<tr>
<td>(PONCAP) (both C &amp; D)</td>
<td>all</td>
<td>Goserepin+flut</td>
<td>(median)</td>
<td>NS (C &amp; D)</td>
<td>12 months</td>
<td>34 months</td>
</tr>
<tr>
<td>Ferrari et al. (1993)</td>
<td>46</td>
<td>Buserelin</td>
<td>88 weeks</td>
<td>NS</td>
<td>22 weeks</td>
<td>32 weeks</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>Buserelin+flut</td>
<td>(median)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyrrell et al. (1993)</td>
<td>151</td>
<td>Goserepin</td>
<td>56.2 months</td>
<td>NS</td>
<td>189 weeks</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>Goserepin+flut</td>
<td>(median)</td>
<td></td>
<td>189 weeks (C &amp; D)</td>
<td>47%</td>
</tr>
<tr>
<td>Klijn et al. (1993)</td>
<td>48</td>
<td>Orch</td>
<td>189 weeks</td>
<td>54%</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>(EORTC-30843)</td>
<td>36</td>
<td>Buserelin+CPA</td>
<td>(median)</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>Buserelin+(2 weeks of CPA)</td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Robinson (1993)</td>
<td>110</td>
<td>Orch</td>
<td>48 months</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>117</td>
<td>Orch+CPA</td>
<td>(median)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>DES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bertagna et al. (1994)</td>
<td>506</td>
<td>Orch</td>
<td>33%</td>
<td>Odds↓</td>
<td>Odds↓ in CAW</td>
<td></td>
</tr>
<tr>
<td></td>
<td>550</td>
<td>Orch+nilut</td>
<td>P&lt;0.001 P=0.05</td>
<td>in CAW</td>
<td>in CAW</td>
<td></td>
</tr>
<tr>
<td>Crawford et al. (1997b)</td>
<td>681</td>
<td>Orch</td>
<td>61%</td>
<td>18 months</td>
<td>30 months</td>
<td></td>
</tr>
<tr>
<td>(NCI INT 0105)</td>
<td>690</td>
<td>Orch+flut</td>
<td>(max)</td>
<td>81%</td>
<td>21 months</td>
<td>31 months</td>
</tr>
</tbody>
</table>

NCI, National Cancer Institute; INT, Intergroup; EORTC, European Organization for the Research and Treatment of Cancer; PONCAP, Italian Prostatic Cancer Project; orch, orchiectomy; flut, flutamide; nilut, nilutamide; NS, not significant; max, maximum; Odds, Odds Ratio.
amide, and cyproterone acetate). With a median follow-up of 40 months, 57% of patients died. The overall mortality among patients with castration alone was 58.4% compared with 56.3% among those with CAW. Five year survivals were 22.8 and 26.2% respectively. No significant benefit of time to death with the addition of CAW was shown. This study concluded that CAW does not result in longer survival times than conventional castration in the metastatic diseases. Nevertheless, this study partially supported the benefit of CAW in minimal metastatic diseases. However, there are several arguments against this conclusion. The three antiandrogens used have different endocrinological effects and may not represent comparable treatment. It is probably too early to show any statistically significant effect on cancer mortality because of the short median time of follow-up (Waxman et al. 1995). Also, 5 year survival points may not be appropriate in a disease where the median survival is only 3 years. Parameters other than time to progression and survival have been observed. Although many studies do not support the survival benefit, some of those studies confirmed the benefits in terms of subjective and objective responses such as bone pain and levels of tumor marker confirmed the benefits in terms of subjective and objective response rates such as bone pain and levels of tumor marker. 1991, Bertagna et al. 1994, Crawford et al. 1997b).

At present, the controversy over any advantage of CAW as a first line therapy for newly diagnosed metastatic disease remains unresolved. Even though some studies fail to demonstrate statistical significance in terms of survival, most show a benefit of CAW in terms of subjective or objective response rates. Furthermore, a survival benefit was definitely demonstrated in several studies, particularly those involving minimal diseases.

**Antiandrogen withdrawal syndrome**

Since the CAW concept has been widely considered, there is an increasing use of antiandrogen drugs. In 1993, several investigators reported the paradoxical response on withdrawal of flutamide approximately 40% of the patients with progression on LHRH analogue plus flutamide treatment (Dupont et al. 1993, Kelly & Scher 1993). Decreases in prostate specific antigen (PSA), symptoms, and objective signs have been reported. Currently, the paradoxical responses of steroidal antiandrogen (Scher et al. 1996), bicalutamide (Small & Carroll 1994), megestrol acetate (Dawson & McLeod 1995), and DES (Bissada & Kaczmarek 1995) withdrawals have also been demonstrated. Many investigators hypothesized that the androgen receptor probably mutates and recognizes the antiandrogen as a stimulator. This hypothesis was demonstrated with a prostate cancer cell line (Veldscholte et al. 1992). The current recommendation for management in patients who progress after CAW therapy is withdrawal of antiandrogens. An ongoing phase II prospective study (SWOG 9426) was designed to characterize the biological significance of this phenomenon (Crawford et al. 1997a).

**Optimal timing of androgen withdrawal in metastatic disease**

Hormonal therapy is the standard treatment in metastatic disease. Its results are temporary longer survival. The optimal timing, immediate versus deferred, for hormonal therapy is an issue which is widely debated. It is agreed that, for symptomatic metastatic disease, the condition should be treated promptly by hormonal therapy. However, the controversy of immediate versus deferred treatment remains for asymptomatic patients. In 1973, Byar suggested deferring androgen withdrawal until symptoms occur because survival is not prolonged by early androgen withdrawal. Subsequently, and in contrast, Byar & Corle (1988) demonstrated delayed progression and increased survival time following early androgen withdrawal. Crawford and colleagues also showed a benefit in men with good performance and minimal metastatic disease treated with CAW therapy at the time of diagnosis (Crawford et al. 1989, Daneshgari & Crawford 1993). These results suggested that the best outcome is seen in those patients treated early in the course of their diseases. Many studies have shown that progression is prolonged by early hormonal treatment in surgically proven stage N+M0 (D1) patients (Kramolowski 1988, Denis & Murphy 1993, van den Ouden et al. 1993, Zagars et al. 1994). Unfortunately, these studies were not a randomized study for the purpose of resolving the controversy of immediate versus deferred treatment. In 1997, a large randomized study by the Medical Research Council Prostate Cancer Working Party Investigators Group was reported. This study of 938 patients with locally advanced or asymptomatic metastatic disease randomized immediate androgen withdrawal treatment (orchiectomy or LHRH analogs) versus treat-ment deferred until the symptoms occurred. Their results indicated significant advantages in prolongation of progression and development of pain in the immediate androgen withdrawal group. Furthermore, complications from advanced metastatic disease in the deferred group were approximately twice as common as those in the immediate androgen withdrawal group. Importantly, significantly longer overall survival times were seen in the immediate group particularly in patients with stage M0.

Currently, most studies suggest that an immediate androgen withdrawal therapy could delay the progression of metastatic patients, particularly in minimal diseases. Furthermore, it improves the quality of life and prevents complications from advanced metastasis such as bladder
outlet obstruction, uremia, and paralysis from spinal cord compression. Finally, prolongation of survival is addressed in one randomized study (Medical Research Council 1997). However, the strategies of androgen withdrawal consist of monotherapy in most studies. Thus, a definitive benefit between immediate versus deferred treatment with CAW remains unknown and needs a further randomized trial.

Intermittent androgen withdrawal therapy
The rationale of intermittent androgen withdrawal therapy is based on the hypothesis that progression is associated with adaptation of cancer cells to an independent stage by initiation of androgen withdrawal (Bruchovsky et al. 1990). Thus, replacing androgen before the initiation of progression will cause the surviving stem cells to give rise to androgen-dependent cells for retreatment by androgen withdrawal. This concept may improve quality of life, reduce side effects and cost of treatment, and delay time to development of hormone resistance and tumor progression. It was first described by Klotz et al. (1986). Androgen withdrawal continues until the PSA level reaches its nadir and is then continued for a set period of time. Treatment is then stopped until the PSA starts to increase again to a certain level. Laboratory data have shown that the time to hormone-independent cancer may be extended by using this new approach (Akakura et al. 1993). Goldenberg et al. (1995) studied 47 patients treated with two cycles of intermittent CAW therapy. They showed that serum testosterone levels returned to the normal range within 8 weeks of stopping treatment. However, the mean and median time to progression were similar to the results expected of continuous androgen withdrawal. During the non-treatment period, libido and potency returned in those patients who reported normal sexual function before therapy. However, it remains unclear whether intermittent hormonal therapy alters survival.

CAW for neoadjuvant and adjuvant therapy
Currently, besides metastatic disease, androgen withdrawal is more widely used as a neoadjuvant or adjuvant therapy for localized disease and locally advanced disease.

Neoadjuvant androgen withdrawal therapy for localized disease
Despite the development of strategies to improve the diagnosis and staging of prostate cancer, only 40-60% of patients with clinical localized prostate cancer have a pathological organ-confined specimen after radical prostatectomy (Catalona & Bigg 1990, Catalona & Smith 1994, Murphy et al. 1994, Walsh et al. 1994, Zinke et al. 1994). Therefore, the challenge is to improve the proportion of pathological organ-confined cancers and to prolong survival. The concept is that addition of neoadjuvant androgen withdrawal therapy may be able to shrink the volume of the tumor and probably downstage it prior to the definitive treatment. It is observed that some metastatic lesions with androgen-dependent clones of cells may disappear after androgen withdrawal and early small tumors may be entirely composed of androgen-dependent clones of cells (Fair et al. 1997). This observation has been supported by the absence of tumor cells in some radical prostatectomy specimens after neoadjuvant hormonal therapies (Tetu et al. 1991).

CAW was mostly used as a neoadjuvant androgen withdrawal strategy in the published studies. The first randomized study of 3 months of LHRH analog plus flutamide treatment prior to radical prostatectomy was reported by Labrie et al. (1993b, 1997). They found a decrease in positive surgical margin rate from 33.8% in the control group to 7.8% in the neoadjuvant group and an increase in organ-confined disease from 49.3% in the control group to 77.8% in the neoadjuvant group. Furthermore, no cancer was found in 6.7% of specimens in the neoadjuvant group. Soloway et al. (1995) conducted a randomized study of leuprolide acetate plus flutamide treatment given for 3 months before radical prostatectomy in 303 patients. They showed significant lower rates of capsular penetration (47% versus 78%) and positive margin (18% versus 48%) after radical prostatectomy in patients in the neoadjuvant group. Van Poppel et al. (1995) showed a benefit of 6 weeks treatment with estramustine phosphate before radical prostatectomy in terms of positive surgical margin rate in clinical T2 disease. Fair et al. (1997) studied a nonrandomized phase II study of 12 weeks of goserelin plus flutamide treatment before radical prostatectomy in 69 patients compared with 72 patients in the control group. They showed a significant advantage of neoadjuvant therapy in terms of organ-confined rates (74% versus 48%) and positive surgical margin rates (10% versus 33%). Furthermore, they conducted a randomized phase III study with the same drugs and combined phase II and interim phase III results with PSA follow-up. With a mean follow-up of 28.6 months (range 6.2-49.5 months), they found no significant difference between the groups in terms of biochemical failure in pathological organ-confined disease (16% versus 11% respectively). Another randomized study of 3 months of goserelin plus flutamide treatment prior to radical prostatectomy in stage T2 was reported by Witjes et al. (1997). They confirmed the significant pathological downstaging in the neoadjuvant arm, but not in the mean time of PSA progression-free survival (26 to 35 months in the neoadjuvant arm versus 28 to 37 months in the control arm).
Most studies used neoadjuvant hormonal therapy for 3 months. There is an alternative strategy regarding optimal timing before surgery. Gleave et al. (1996a,b) demonstrated that 8 months of neoadjuvant therapy were required before PSA levels reached their nadir in 84% of patients, and the positive margin rate was lower. Furthermore, the longer neoadjuvant therapy did not appear to result in progression of an androgen-independent clone.

In summary, several studies have shown that neoadjuvant androgen withdrawal therapy decreases prostatic volume, organ-confined rate, positive margin rate, and final pathological stage. However, none of these studies have sufficient power to assess a survival end point. An ongoing large phase III randomized study of 1740 patients (SWOG 9615) was recently activated to determine whether neoadjuvant androgen withdrawal therapy had an impact on long term end points in stages T1 and T2 (Crawford et al. 1997a).

Another controversial issue of neoadjuvant androgen withdrawal therapy prior to radical prostatectomy concerns the effects of surgical procedure. Some studies suggested that neoadjuvant androgen withdrawal therapy reduced blood loss and operation time (Tetu et al. 1991), while other results did not show these differences (Soloway et al. 1995, Fair et al. 1997).

Neoadjuvant and adjuvant androgen withdrawal therapy for locally advanced disease

The rationale of neoadjuvant androgen withdrawal therapy in locally advanced disease is to downstage the cancer before radical prostatectomy. In 1969, Scott and Boyd reported the response of 2-42 months of orchiectomy with or without DES prior to radical prostatectomy. They showed fifteen years survival in 29% of patients. In 1993, Oesterling et al. retrospectively analyzed 21 locally advanced disease patients who were receiving neoadjuvant therapy (LHRH analog plus flutamide in 19 of 21 patients). They suggested that neoadjuvant therapy had little or no benefit despite a more than 98% decrease in PSA levels. The Memorial Sloan-Kettering Cancer Center (MSKCC) studied the effect of 3 mg DES/day for 8-12 weeks prior to radical prostatectomy in 55 patients (Fair et al. 1997). They found that 98% of patients had a reduction in PSA below the normal level, but only 33% of these patients had pathological organ-confined disease. Andros et al. (1993) studied 4 months of combined LHRH analog plus flutamide treatment before radical prostatectomy in stage T3 disease. Even with the dramatic decrease both in mean PSA levels (from 39 ng/ml to 0.43 ng/ml) and in prostatic volume (52%), only 19% of patients had pathological organ-confined disease. Soloway et al. (1994) also reported that 41% of 15 and 22 patients in stage T2b and small T3 respectively had positive surgical margin rates in radical prostatectomy specimens after 3-16 months of LHRH analog treatment or bilateral orchiectomy. Cher et al. (1995) conducted a phase II study of LHRH analog plus antiandrogen treatment. They also confirmed a dramatic 96% reduction in mean PSA levels and a 36% shrinking of prostatic volume. However, only 4 patients had a downstage in pathological stage. In addition, Van Poppel et al. (1995) failed to show a benefit of 6 weeks of estramustine phosphate treatment before radical prostatectomy in terms of positive surgical margin rate in clinical stage T3 despite this benefit being present in clinical stage T2. Recently, a randomized study of 3 months of goserelin plus flutamide treatment prior to radical prostatectomy in 155 patients in clinical stage T3 was reported by Witjes et al. (1997). Although they found a significant downstaging to clinical stage T2, they could not demonstrate a different rate of appearance of positive surgical margin rates between the groups in clinical stage T3. In summary, it has been suggested that neoadjuvant androgen withdrawal therapy (mono-therapy or CAW) could reduce prostatic volume by 35-50% and PSA levels by more than 90%. However, there is not sufficient evidence for effective downstaging of clinical locally advanced prostate cancer. Furthermore, the benefit in terms of survival remains unknown.

The rationale of adjuvant androgen withdrawal therapy after radical prostatectomy in locally advanced disease is to prolong time to progression and, probably, survival. Cheng et al. (1993) reported a retrospective analysis of adjuvant therapy on 1035 patients with pathological stage C prostate cancer after radical retropubic prostatectomy. Of these patients, 131, 103, and 661 received, respectively, adjuvant radiotherapy only, adjuvant bilateral orchiectomy only, and no immediate adjuvant therapy. Both adjuvant therapies significantly decreased local, systemic, and overall progression. Adjuvant bilateral orchiectomy and radiation therapies had a similar efficacy in controlling local recurrences. Five year local recurrence-free survival was 95% for both adjuvant therapies compared with 84% for those without immediate adjuvant therapies. However, cause-specific and overall survival did not improve. In 1995, Andriole et al. reported a randomized study of the efficacy of treatment with finasteride compared with placebo in patients who had previously been treated by radical prostatectomy and who had a rising PSA and no evidence of bone metastasis. They suggested that finasteride could delay, but not prevent, a rise in PSA in patients with detectable PSA after radical prostatectomy.

The adjuvant androgen withdrawal therapy in locally advanced disease has the benefit of delaying progression but has no effect on subsequent metastatic rate or overall survival.
survival. The androgen withdrawal strategy used is monotherapy; thus the role of CAW is unknown. Because of different side effects and cost of treatment, adjuvant radiation therapy is an alternative treatment for locally advanced disease after radical prostatectomy.

Androgen withdrawal combined with radiation therapy

The rationale for the addition of radiation therapy to androgen withdrawal therapy in prostate cancer patients is to improve local control and probably survival. This is an alternative treatment for avoiding a higher radiation dose by reducing the tumor prior to definitive radiation therapy and also to treat any disease outside the radiated field (Zietman et al. 1997). In 1984, Green et al. studied the combination of DES with radiation therapy in locally advanced disease. However, they could not prove any benefit. Important data from the Radiation Therapy Oncology Group (RTOG) protocol 8610 was reported by Pilepich et al. (1995). This randomized study compared the effects of 8 weeks of combined treatment with goserelin acetate and flutamide prior to radiation plus 8 weeks of the same drugs during radiation in 226 patients with treatment with radiation alone in 230 patients. With a median follow-up of 4.5 years, they showed a significant benefit of combined androgen withdrawal with radiation therapy in terms of cumulative incidence of local progression at 5 years (46% versus 71% in the control group) and PSA-free survival (36% versus 15% in the control group). However, the 5-year incidence of distant metastases in the combined treatment group was higher than in the control group, but this did not reach statistical significance (34% versus 41% respectively). Also, overall survival did not show a significant difference at the time of reporting. Recently, Bolla et al. (1997) studied a randomized trial of radiation plus 3 years of goserelin acetate treatment compared with radiation alone in 401 patients. With a median follow-up of 45 months, the benefit of combined therapy was significant in terms of overall survival at 5 years (79% versus 48% in the control group). This is the first demonstration that radiation with the addition of androgen withdrawal monotherapy could prolong survival in locally advanced disease.

Future potential of androgen withdrawal therapy

Hormonal therapy for prostate cancer is changing dramatically. Even with improved subjective and objective responses, delay in time to progression and increased survival of CAW in metastatic prostate cancer, progression to an androgen-independent stage occurs in most patients. The hypothesis for this event is adaptation and clonal selection (Isaacs & Kyriianou 1987). It was suggested that the androgen-independent state of cells surviving on androgen withdrawal therapy may result from the ability of a small number of initially androgen-dependent stem cells to adapt to an altered hormone environment (Bruchovsky et al. 1990). These changes appear to occur at a molecular level and seem to occur despite a clinically evident response. Many experimental data suggest that, during the active cell death process as a result of androgen withdrawal, a number of novel RNAs and proteins are induced (Bruchovsky et al. 1990, Furuaya et al. 1990, Rennie et al. 1990). A variety of genes has been implicated in prevention of apoptosis. The p53 gene is induced following androgen withdrawal and inhibits the apoptotic pathway (Colombel et al. 1992, Debba & White 1993). The BCL2 gene also interferes with apoptosis and is correlated with the progression of prostate cancer from androgen dependence to androgen independence (McDonnell et al. 1992). Currently, it has been found that androgen receptor (AR) gene mutations could result in diminished ligand specificity of androgen receptors and are the molecular cause of androgen insensitivity syndrome (Trapman & Brinkmann 1996). Amplification of the AR gene is another novel molecular mechanism that may explain why cancer cells become resistant to androgen withdrawal therapy. It increases the expression of the AR gene, which enables the cancer cells more effectively to utilize the residual low levels of androgens for sustaining cell growth (Koitisto et al. 1996). From the experimental data, it was proposed that the discovery of a new molecular mechanism of androgen withdrawal therapy resistance should result in the development of more effective hormonal therapy regimens, as well as other innovative strategies for inducing active cell death and eradication of stem cells. In addition, immunomodulatory drugs, monoclonal antibody techniques, or genetically engineered programmed cancer cell death (apoptosis) should be available to eradicate tumors in the future.

Quality of life

Besides the clinical results of different androgen withdrawal options, quality of life and patients’ acceptance of the treatment must also be considered. The MSKCC study by Herr et al. (1993) compared patients who underwent immediate androgen withdrawal therapy (DES or LHRH plus flutamide) with patients who did not receive any therapy. Quality of life was assessed before therapy and six months later. The no-therapy group had better physical and sexual functioning. Singer et al. (1991) also determined that 68% of patients may be willing to preserve their sexual function in return for a 10% reduction in 5-year survival. Cassileth et al. (1989)
reported a multicenter study of patients’ choices for treatment involving 147 patients. They found that 78% and 22% of patients selected an LHRH analog treatment and orchitectomy respectively. The primary reasons for men selecting the LHRH analog included the avoidance of surgery (36%), success of treatment (18%), and convenience of the drug (10%). The primary reasons for those who selected surgery were convenience (32%) and success of treatment (29%). Three months later, 93% of the patients and 91% of patients’ wives reported that they would prefer the same treatment again. However, there are several ways to interpret quality of life. Thus, physicians and patients need to take an active role in the decision making, and weigh the risk of side effects versus benefits of the alternative treatment options.

Cost

It has been estimated that, in the USA, annual health care costs for the treatment of prostate cancer are $4.5 billion (Brown et al. 1993). This cost is largely related to the treatments of advanced prostate cancer. The Health Care Financing Administration spent $328 million for LHRH therapies alone in 1993 (Gee et al.). Financing administration spent $328 million for LHRH treatments of advanced prostate cancer. The Health Care Financing Administration spent $328 million for LHRH treatments of advanced prostate cancer (source: University of Colorado Health Sciences Center Pharmacy).

<table>
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<tr>
<th>Option</th>
<th>Dosage</th>
<th>Cost (US $ month/year)</th>
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<tr>
<td>DES</td>
<td>3 mg/day</td>
<td>8.2/98.4</td>
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<tr>
<td>Flutamide</td>
<td>750 mg/day</td>
<td>285.6/3427.2</td>
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<tr>
<td>Bicalutamide</td>
<td>50 mg/day</td>
<td>319.7/3836.4</td>
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<tr>
<td>Leuprolide acetate</td>
<td>7.5 mg/day</td>
<td>506/6072</td>
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<tr>
<td>Goserelin acetate</td>
<td>3.6 mg/every 28 days</td>
<td>410.5/4926</td>
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<td>Orchitectomy</td>
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Data from University of Colorado Health Sciences Center Pharmacy.

Conclusions

CAW is involved not only in metastatic prostate cancer, but also in localized and locally advanced disease. Despite the higher response of CAW compared with the conventional castration in metastatic disease, the controversy of survival benefit remains unresolved. CAW for neoadjuvant therapy seems to be beneficial as regards higher rates of organ-confined specimens and lower rates of positive surgical margin rate in localized disease. However, it is too early to determine its survival benefit. It fails to demonstrate effective downstaging of locally advanced disease. Nevertheless, the combination of radiation therapy with CAW seems to be effective in locally advanced disease. The choices of optimal therapies for prostate cancer depend not only on the survival time, but also on the quality of life and cost effectiveness. Thus, the critical factors for approaching prostate cancer are appropriate patient selection and stratification. Implicit with this approach should be to maximize the benefit from maximal androgen withdrawal therapy for those patients who are likely to profit from it.

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