The changing face of hormonal therapy for prostate cancer

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Introduction

With the increasing use of prostate-specific antigen (PSA) screening, the incidence of prostate cancer has increased and most men are diagnosed with localized disease [1]. Men diagnosed with prostate cancer are also younger than in the past, with a median age of 65 at diagnosis, and 25%–30% of patients are younger than 60 [2]. The majority of men with prostate cancer die of causes unrelated to the cancer itself and cardiovascular (CV) disease is the most common cause of non-prostate cancer-related deaths [3]. Younger men with prostate cancer have less competing risks for death and a higher chance of dying of prostate cancer.

Almost all prostate cancers express androgen receptors and initial use of androgen deprivation therapy (ADT), achieved most often by bilateral orchiectomy or by gonadotropin-releasing hormone (GnRH) agonists, is effective in reducing serum levels of PSA and alleviating symptoms in men with metastatic disease. The use of ADT has been increasing steadily in all stages of prostate cancer: as initial therapy for those with indolent local disease or who are unfit for radical local treatment, as an adjunct to radiotherapy or surgery for those with locally aggressive disease, in asymptomatic men with rising PSA after local therapy, and as treatment for men with metastatic disease, with and without symptoms [4]. At the same time, there is increasing evidence, discussed below, that ADT causes toxicity, and increases the incidence and/or severity of CV disease, which is the most common cause of noncancer-related death in men with prostate cancer. Thus, it is important to reassess the benefits and risks of ADT, especially when given to asymptomatic men where death from prostate cancer represents a low and/or distant risk, and to use the least toxic form of ADT when its use is indicated, such as for alleviation of symptoms in men with metastatic prostate cancer.

Toxicity of Hormonal Therapy

There is a reason that professional athletes have taken androgens! It has long been known that testosterone and other androgens improve bone density, muscle mass and hemoglobin levels, and that men with prostate cancer receiving ADT may develop osteopenia or osteoporosis with attendant danger of bone fracture [5], loss of muscle mass and low-grade anemia. ADT also causes sexual dysfunction, hot flushes and gynecomastia, all of which may reduce quality of life, and there is low-level evidence that ADT may hasten cognitive decline [6]. Exercise, if feasible, is probably the best means of preventing loss of muscle and bone, but in men who cannot exercise an annual injection of zoledronate is effective in reversing a decline in bone density [7].

In addition to the above toxicities, recent evidence has disclosed a more sinister effect of ADT to be an independent risk factor for the development of metabolic syndrome (characterized by reduced glucose tolerance, increased body fat content, changed lipid profile and/or increased blood pressure). A low level of testosterone is known to be a risk factor for metabolic syndrome in the aging male population [8] and metabolic syndrome is in turn a risk factor for CV mortality, even in the absence of other known risk factors [9]. In an observational study of a population-based cohort of 73,196 men with loco-regional prostate cancer, those treated with continuous ADT had significantly increased risk for CV morbidity and mortality [10]. In a cross-sectional study >50% of men with prostate cancer receiving ADT for ≥12 months had metabolic syndrome compared with <25% of men who did not receive ADT [11]. Metabolic changes associated with metabolic syndrome and ‘stiffness’ of the arteries were observed after only 3 months of ADT in men with prostate cancer [12, 13] (Table 1).

ADT has the potential to have an impact on noncancer-specific mortality, not only by increased CV mortality but also by causing or enhancing other conditions that can independently increase mortality: diabetes mellitus, fractures [5], anemia and fatigue with psychological distress, which cause general frailty. The side-effects of ADT also have substantial potential to impair quality of life. Decisions to use ADT in any man with prostate cancer should therefore rely on high-level evidence indicating that the benefits of treatment are likely to outweigh the potential harms.

Hormonal Treatment as Primary Management of Localized Prostate Cancer

Options for management of men with localized prostate cancer include radical prostatectomy (RP), radical radiation therapy or ‘conservative therapy’ using watchful waiting or ADT. Although a Scandinavian study has shown a small survival
difference in favor of RP for men with clinically detected cancer after 10 years of follow-up, and only in men aged 65 or less, as compared with watchful waiting [14], many men who decline or are not offered radical treatment receive ADT. This is partly because of recommendations of urologists and other oncologists, and partly because men with a diagnosis of prostate cancer ‘want to do something’. However, recent evidence based on the large US Surveillance, Epidemiology and End Results (SEER) database of men with a median age of 77 years suggests that ADT does not confer a survival advantage for men with localized prostate cancer, except perhaps in patients with poorly differentiated cancer [15].

### Adjuvant Hormonal Treatment with Radiation or Surgery in Locally Advanced Prostate Cancer

Randomized controlled phase III clinical trials (RCTs) have examined the efficacy of immediate ADT as adjunctive therapy to prostatectomy [16–18] and radiation therapy [19–26] (Table 2) in men with unfavorable localized or locally advanced prostate cancer.

Neo-adjuvant hormonal treatment before radical prostatectomy did not lead to improvement in overall survival or in clinical progression [16, 17] and is not considered standard treatment. In a small RCT (N = 98) adjuvant ADT improved overall survival and other prostate cancer-specific end points in men with nodal metastases who underwent prostatectomy and lymphadenectomy, compared with those who received deferred treatment with ADT [18]. As yet, no large RCT has addressed the benefits of adjuvant ADT after radical prostatectomy and use of such treatment is not recommended outside of the context of a clinical trial.

The combination of ADT given before, during and/or after radiation therapy is supported by the results of RCTs and is considered standard of care for men at high risk of recurrence. Some studies report improvement in disease progression but not overall survival from the addition of ADT to radiation therapy [22, 24], or for long-term ADT in comparison to short-term ADT in combination with radiotherapy [26] (Table 2). A recent randomized European Organization for Research and Treatment of Cancer (EORTC) trial suggested that 6 months of ADT was not as effective as 2 years of ADT in improving survival after radiotherapy for locally advanced prostate cancer [21]. Recent updates from the RTOG 86-10 and RTOG 92-02 studies failed to detect a significant increase in CV mortality with ADT added to radiation therapy or for use of long-term as compared to shorter term ADT [22, 27]. In a pooled analysis of 1372 men with localized or locally advanced prostate cancer from three RCTs, however, the use of ADT in combination with radiotherapy was associated with earlier onset of fatal myocardial infarction in men of age ≥65 years who were treated for only 6 months with ADT as compared with men who were not treated [28] (Table 1). This finding is consistent with a recent hypothesis-generating subgroup analysis of an RCT, which compared the combination of 6 months of ADT and radiation therapy with radiation therapy alone in men with unfavorable localized prostate cancer; combination therapy resulted in significantly improved overall survival only in a subgroup with no or minimal co-morbidities and showed a trend to a detrimental effect in a subgroup with moderate or severe co-morbidities [19].

Accumulating data indicating possible detrimental effects of ADT (even with the use of short-term ADT) in men with localized and locally advanced prostate cancer and other risk factors for CV disease are a strong signal that future RCTs evaluating ADT should use stratification by co-morbidities. Before results from such trials are available, ADT should be used critically, especially in the elderly, those with co-morbidities and those with slowly progressive prostate cancer.

### Role of Hormonal Therapy for Biochemical Relapse

Biochemical (PSA-only) relapse is the most common form of advanced prostate cancer today. Every third patient after radical

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**Table 1.** Summary of trials evaluating association between androgen deprivation therapy with metabolic syndrome, cardiovascular morbidity and cardiovascular mortality in men with a prostate cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Type of study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Amico et al. [28] (2007)</td>
<td>1372</td>
<td>Pooled analysis of three randomized trials with RT ± HT</td>
<td>Six months of ADT associated with significantly shorter time to fatal MI in men ≥65 years compared with men not treated with ADT or men &lt;65 years</td>
</tr>
<tr>
<td>Keating et al. [10] (2006)</td>
<td>73,196</td>
<td>Retrospective cohort study</td>
<td>ADT significantly associated with increased risk of Diabetes (HR 1.44) coronary heart disease (HR 1.16) MI (HR 1.11) Sudden cardiac death (HR 1.16)</td>
</tr>
<tr>
<td>Dockery et al. [13] (2003)</td>
<td>31</td>
<td>Prospective cohort study</td>
<td>Three months of ADT associated with significantly increased arterial stiffness, fasting insulin levels, cholesterol and HDL levels</td>
</tr>
<tr>
<td>Smith et al. [12] (2001)</td>
<td>22</td>
<td>Prospective cohort study</td>
<td>Three months of ADT associated with significantly increased arterial stiffness, increased fat, decreased lean body mass and increased insulin levels</td>
</tr>
</tbody>
</table>

RT, radiotherapy; HT, hormonal therapy; ADT, androgen deprivation therapy; MI, myocardial infarction; HDL, high-density lipoprotein.
prostatectomy or radiation therapy experiences biochemical relapse [29, 30], but only a subset of these patients develops overt metastatic disease and an even smaller subset die as a result of prostate cancer [31]. The natural course of biochemical recurrence is generally indolent but may be variable. A median time of 8 years was reported from biochemical recurrence to the development of overt metastases and a median time of 4 years from metastases to death, in an earlier retrospective analysis [32]. In a review of a large series of patients, the median time from biochemical recurrence to prostate cancer death was not reached after 16 years [33].

A subset of patients with biochemical relapse will develop overt metastatic disease and die of prostate cancer. A short PSA doubling time (PSADT), high pathologic Gleason score and short time from primary local treatment to biochemical recurrence have emerged as predictive factors for an aggressive course of the disease and for subsequent death due to prostate cancer [33, 34]. Radiation therapy is the only potential curative therapy for men with biochemical recurrence after radical prostatectomy, but there are no randomized data to support its use. Many patients with biochemical recurrence receive ADT. There are no randomized data to support the use of hormonal therapy in the treatment of biochemical recurrence, which cannot cure these patients, and it is often given because of anxiety of patients and doctors about the rising PSA [35]. In a retrospective study of 1352 men with biochemical recurrence, early hormonal therapy had no apparent overall effect on the time to development of metastases in comparison to delayed hormonal treatment, although a subgroup analysis suggested that ADT might decrease the risk of metastases in men with Gleason score 8 and PSADT <12 months [36]. In another retrospective study of men with biochemical recurrence after radiation therapy, men receiving ADT appeared to have improved overall and cancer-specific survival as compared with radiation therapy, men receiving ADT appeared to have improved overall and cancer-specific survival as compared with ADT alone. In men with no or minimal co-morbidities early hormonal therapy had no apparent overall effect on the time to development of metastases in comparison to delayed hormonal treatment, although a subgroup analysis suggested that ADT might decrease the risk of metastases in men with Gleason score 8 and PSADT <12 months [36]. In another retrospective study of men with biochemical recurrence after radiation therapy, men receiving ADT appeared to have improved overall and cancer-specific survival as compared with men who were given hormonal therapy after development of metastases [37].

### Table 2. Summary of randomized controlled trials evaluating a combination of radiation and hormone therapy for non-metastatic prostate cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Setting</th>
<th>Treatment (months)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Amico et al. [19]</td>
<td>206</td>
<td>T1b-2b N0 (unfavorable)</td>
<td>Goserelin + (leuprolide) flutamide (2) Goserelin + (leuprolide) flutamide (2) Goserelin+ (leuprolide) flutamide (2)</td>
<td>Eight-year OS significantly better for HT + RT versus RT in men with no or minimal co-morbidities</td>
</tr>
<tr>
<td>Roach et al. [22]</td>
<td>456</td>
<td>T2-4, N0-1</td>
<td>Goserelin + flutamide (2) Goserelin + flutamide (2) _</td>
<td>Ten-year OS similar for HT + RT versus RT alone</td>
</tr>
<tr>
<td>Bolla et al. [21]</td>
<td>970</td>
<td>T1c-2b, N1-2 T2c-4, N0-2</td>
<td>_</td>
<td>Survival data indicate non-inferiority of short HT + RT versus long HT + RT cannot be confirmed</td>
</tr>
<tr>
<td>Lawton et al. [23]</td>
<td>1323</td>
<td>T1c-4, N0</td>
<td>Goserelin (leuprolide) + flutamide (2) _ Goserelin (leuprolide) + flutamide (2) Goserelin (leuprolide) + flutamide (4)</td>
<td>No difference in OS or PFS for neo-adjuvant and concurrent HT + RT versus adjuvant HT + RT</td>
</tr>
<tr>
<td>Denham et al. [24]</td>
<td>818</td>
<td>T2-4, N0</td>
<td>Goserelin + flutamide (2) Goserelin + flutamide (1) _</td>
<td>Five-year cancer-specific survival better for 6 months HT + RT versus RT alone; no data for OS; no consistent differences between 5 and 6 months of HT + RT</td>
</tr>
<tr>
<td>Pilepich et al. [25]</td>
<td>977</td>
<td>T3-4 or N1</td>
<td>_</td>
<td>Ten-year OS significantly better for HT + RT versus RT</td>
</tr>
<tr>
<td>Hanks et al. [26]</td>
<td>1554</td>
<td>T2c-4, N0</td>
<td>Goserelin (2) Goserelin (2) Goserelin (24) _</td>
<td>Five-year OS similar for HT (longer) + RT versus HT (shorter) + RT</td>
</tr>
<tr>
<td>Bolla et al. [20]</td>
<td>415</td>
<td>T1-2, N0, G3 T2-4, N0-1</td>
<td>Goserelin + cyproteron (2) _</td>
<td>Five-year OS survival better for HT + RT versus RT alone</td>
</tr>
</tbody>
</table>

OS, overall survival; HT, hormonal therapy; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group; ASCO, American Society of Clinical Oncology; CAB, combined androgen blockade; GnRH, gonadotropin-releasing hormone; PFS, progression-free survival; TTROG, Trans-Tasman Radiation Oncology Group; EORTC, European Organisation of Research and Treatment of Cancer.
Given the very limited evidence of benefit in men with biochemical recurrence and increasing evidence of possible harms, hormonal therapy cannot be considered a standard of care for men with biochemical recurrence. It is reasonable to consider treatment only for a subgroup of men with high-risk for cancer-specific death. Any guidelines for tailored hormonal treatment in the setting of biochemical recurrence will require future RCTs. In the absence of such data, the discovery of PSA has probably been a disservice to these patients. Whereas previously men were blissfully unaware that their disease was still present, and often died without ever having symptoms from metastatic prostate cancer, we have now given them anxiety of knowing that they are not ‘cured’ and in some cases might be shortening their survival by applying potentially harmful treatment.

**timing of hormonal treatment for men with metastatic disease**

There is no doubt that men with symptomatic metastatic prostate cancer benefit from ADT. There are many men with metastases diagnosed by computed tomography or bone scan, however, who remain asymptomatic for considerable periods of time. Given the known toxicities of ADT, it is critical to determine the benefits and risks of starting ADT in men with asymptomatic metastases. In a recent meta-analysis of the literature regarding the timing of ADT in advanced cancer there was a moderate decrease (17%) in relative risk for cancer-specific mortality, a moderate increase (15%) in relative risk for non-prostate cancer-specific mortality and no overall survival advantage for early treatment versus waiting until symptoms develop [38]. It seems reasonable to offer ADT to men with asymptomatic metastatic disease and rapid PSA progression, but not to those with slowly progressive disease.

**methods for androgen deprivation**

Maximal androgen blockade (MAB) with the addition of anti-androgens to GnRH agonists allows inhibition of adrenal androgens as well as testosterone and it was a reasonable hypothesis that MAB might be more effective that a GnRH agonist (or orchiectomy) alone. In a patient-based meta-analysis of 27 trials and >8000 patients, however, MAB did not show significant survival benefit over monotherapy in locally advanced and metastatic prostate cancer (5-year survival 25.4% versus 23.6%, $P = 0.11$). A sensitivity analysis of trials using nonsteroidal anti-androgens indicated that a small survival advantage is likely with nonsteroid MAB (5-year survival 27.6% versus 24.7%, $P = 0.005$, 95% confidence interval 1%–5%) [39]. The trials showing larger differences, however, tended to be older ones where the GnRH was given daily and compliance might have been a problem—a large trial published after the meta-analysis showed no benefit for MAB and poorer quality of life [40, 41]. Based on the meta-analysis, the number needed to treat to prevent one death was 20–100 patients treated for 5 years with MAB. The cost effectiveness of MAB compared with castration was over US$ 1 million per quality-adjusted life year [42]. Because of its at most minimal effects on survival, increased toxicity and cost, continuous MAB should not be used as primary hormonal treatment in prostate cancer.

**intermittent hormonal treatment**

Several years ago, investigators working in Vancouver reported a series of experiments using animal models for prostate cancer, which showed that intermittent ADT prolonged substantially the time to development of androgen-independent disease as compared with use of continuous ADT [43, 44]. These preclinical results provided support for clinical trials of intermittent ADT for men with prostate cancer, with the aim of minimizing side-effects while maximizing clinical benefits and quality of life. The consistent features of intermittent ADT are that the serum PSA is monitored and treatment is stopped when a low PSA level is reached. The PSA level is allowed to rise until it reaches an empirically determined level, when ADT is restarted. Cycles of intermittent ADT are then continued until clinical or PSA progression is evident. The concept assumes recovery of testosterone levels during periods off treatment.

Investigators have now reported results from four RCTs, which compare continuous and intermittent ADT in >1000 men with different settings of prostate cancer (Table 3). Only one of the studies has been published and the three others have been presented at major international meetings with reports available in abstract form. All of these studies support non-inferiority in time to disease progression and survival for intermittent ADT, with at least trends to improved quality of life.

The only published study randomized 68 patients with advanced prostate cancer to receive intermittent or continuous

**Table 3. Randomized controlled trials comparing intermittent and continuous androgen deprivation therapy in prostate cancer**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N Setting</th>
<th>Treatment</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tunn et al. [46] AUA 2007</td>
<td>167 Rising PSA after RP</td>
<td>Leuprolide (flare-up prophylaxis with cyproterone acetate) Gosorelin + bicalutamide</td>
<td>Similar time to androgen-independence progression, improved QoL.</td>
</tr>
<tr>
<td>Miller et al. [47] ASCO 2007</td>
<td>335 N+, M+</td>
<td>Triptorelin + cyproterone acetate Triptorelin + cyproterone acetate</td>
<td>Similar time to disease progression and survival, improved QoL.</td>
</tr>
<tr>
<td>Calais da Silva et al. ASCO 2006 [48]</td>
<td>626 T3-4, N+, M+</td>
<td>Triptorelin + cyproterone acetate</td>
<td>Similar time to disease progression and survival, improved QoL.</td>
</tr>
</tbody>
</table>

AUA, American Urological Association; PSA, prostate-specific antigen; RP, radical prostatectomy; QoL, quality of life; ASCO, American Society of Clinical Oncology; N+, metastases in locoregional lymph nodes; M+, distant metastases.
ADT therapy with goserelin acetate and flutamide [45]. After a median follow-up of 30.8 months there was a substantially lower rate of progression to androgen independence in the intermittent arm. Patients receiving intermittent therapy were off treatment 59% of the time.

The European phase III study EC 507 (RELAPSE) compared intermittent and continuous ADT with leuprolide acetate (and flare prophylaxis with cyproterone acetate) in patients with biochemical relapse after radical prostatectomy [46]. After randomization of 167 patients there was no significant difference in time to androgen-independent progression in the two treatment groups. Intermittent ADT led to improvement in quality of life.

The multicentric phase III German study (AUO AP 17/95) compared intermittent versus continuous ADT with goserelin acetate and bicalutamide in 335 patients with loco-regional or distant metastases [47]. At a median follow-up of 50.5 months, time to progression and survival were comparable in the treatment arms. Most patients receiving intermittent ADT spent ≥50% of time off therapy and had improved general well-being and sexual function.

A phase III study of the South European Urological Group (SEUG) is comparing intermittent and continuous ADT with triptoreline pamoate and cyproterone acetate in locally advanced and advanced prostate cancer [48]. After randomization of 626 patients and median follow-up time of 51 months, progression-free and overall survival were comparable in both arms, with better quality of life, improved sexual activity and decreased hot flushes in the intermittent arm. Patients with an initial good PSA response have spent a median of 82% off therapy in the intermittent arm.

Results are expected soon from two large phase III North American trials: NCIC PR7/ SWOG JPR7 and NCIC PR8/ SWOG 9346, which are comparing intermittent and continuous ADT in patients with biochemical relapse after radiotherapy and with metastatic disease, respectively. The primary end points in both studies are overall survival and quality of life.

Some important questions need to be addressed in future trials of intermittent hormonal therapy. All but one of the RCTs evaluating intermittent ADT is using a combination of a GnRH analogue and an anti-androgen in both arms (i.e. MAB), and the control arm of continuous MAB cannot be considered a standard of care. Future clinical trials comparing continuous intermittent ADT should evaluate monotherapy with GnRH analogues (using an anti-androgen only briefly to prevent tumor flare). Information is also needed about optimal scheduling of intermittent ADT: at present we do not know the optimal duration of initial ADT or the optimal serum PSA levels at which to stop and resume treatment.

The main advantages of intermittent ADT are (i) less time on a potentially toxic therapy and improved quality of life and (ii) marked decrease in the costs of treatment. Even with the caveat that most studies have thus far been reported only in abstract form, their consistent findings of (at least) non-inferiority in time to progression and overall survival, with decreased side-effects and cost, plus supporting preclinical data and increasing awareness of the serious toxicity of continuous ADT, lead us to conclude that intermittent ADT should now replace continuous ADT as the standard of care.

resistance to hormonal therapy: second- and third-line treatment

Multiple small trials indicate that some men with prostate cancer that have disease progression after primary treatment with a GnRH agonist may respond sequentially (albeit with lower probability) to (i) adding an anti-androgen such as bicalutamide, (ii) subsequent withdrawal of the anti-androgen (but only if there was initial response on adding it), (iii) treatment with ketoconazole, an inhibitor of steroid synthesis, given with a glucocorticoid, or use of a glucocorticoid such as dexamethasone alone, (iv) treatment with an estrogen such as diethylstilbestrol, or (v) adding an alternative anti-androgen (e.g. nilutamide). There is also evidence that some men may regain responsiveness to hormonal therapy after receiving chemotherapy [49]. Thus it is very difficult to define a state of absolute resistance to hormonal therapy, especially in men with a history of slowly progressive prostate cancer. There is recent evidence that levels of androgens may be high within prostatic cancers, even when they are suppressed in serum by ADT [50–52]. It seems likely that androgens might be synthesized within some tumors, thus limiting the effectiveness of conventional ADT. There is potential for development of new therapies that target the androgen receptor and its signaling pathways, even in men with castration-resistant disease.

The most promising new agent is abiraterone, a specific and potent inhibitor of androgen synthesis. In small phase II studies this agent has led to a high rate of PSA response (~60%) in small series of men with advanced castration-resistant prostate cancer, either without or with prior chemotherapy with docetaxel [53, 54]. Large phase III trials are being launched to evaluate the therapeutic potential of this agent.

summary

Hormonal therapy, the oldest systemic treatment for men with prostate cancer, is evolving rapidly. There is increasing evidence that continuous long-term ADT causes multiple side-effects, including a potentially lethal increase in CV disease. Thus, risks and benefits of ADT must be weighed in any clinical situation, and ADT should be used rarely as initial therapy for localized prostate cancer or for treatment of asymptomatic men with biochemical relapse after local treatment. There is evidence to support use of ADT as an adjunct to radiotherapy for locally advanced disease, but not as an adjunct to radical prostatectomy. When ADT is appropriate, MAB should not be prescribed and intermittent therapy should now be regarded as the standard of care. The androgen receptor pathway remains an appropriate and promising target for new agents in men with castration-resistant disease.

disclosures

No significant relationships.

references


