Future Prospects for Luteinizing Hormone-Releasing Hormone Analogues in Prostate Cancer Treatment

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Key Words

Prostate cancer · Luteinizing hormone-releasing hormone analogues

Abstract

Luteinizing hormone-releasing hormone (LHRH) analogues play a pivotal role in hormonal therapy regimens for the treatment of prostate cancer. Hormonal therapy has traditionally been used as a palliative treatment for patients with advanced disease, and international treatment guidelines do not recommend its use as a first-line therapy at earlier disease stages. However, there appears to be a gap between international guideline recommendations and actual clinical practice regarding the use of primary androgen deprivation therapy (PADT) for prostate cancer therapy. Despite limited evidence to date for the impact on clinical outcomes, the use of PADT in patients with localized or locally advanced prostate cancer has increased in many countries, most notably Japan. Clinical evidence is now accumulating to confirm the valuable role of PADT, both as monotherapy but particularly when used as part of a maximal androgen blockade regimen, on the long-term control of both localized and locally advanced disease, and importantly on survival outcomes in these patients.

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Introduction

The use of luteinizing hormone-releasing hormone (LHRH) analogues for the management of a range of steroid-dependent malignancies has increased rapidly since the beginning of the 1990s. These agents now play a pivotal role in hormonal therapy regimens for the treatment of prostate cancer, one of the most common causes of cancer death among men in many regions of the world.

The available treatment options for men diagnosed with prostate cancer include radical prostatectomy, external beam radiotherapy, brachytherapy, hormonal therapy and 'active surveillance', but the choice of treatment depends on a variety of factors including patient considerations – age, any comorbidities, and their own preference – disease characteristics such as prostate-specific antigen (PSA) level, Gleason score, and tumor stage, in addition to psychosocial factors such as sexual function.

Hormonal therapy has traditionally been used predominantly as a palliative treatment for patients with advanced disease. Indeed, guidelines published in the USA and Europe recommend that primary androgen deprivation therapy (PADT) with agents such as LHRH analogues, as a first-line treatment, should be restricted to cases of advanced disease and some cases of locally advanced disease, and is not recommended for localized

disease [1, 2], however this concept is now being challenged. Accumulating data regarding the safety and efficacy of hormonal therapy has resulted in increased usage of LHRH analogues throughout the world at earlier stages of the disease, despite relatively limited evidence as yet for its impact on clinical outcomes.

Of particular note is Japan which has the highest consumption of LHRH analogues in the world, most commonly leuporelin, where it is often the treatment of choice for localized or locally advanced prostate cancer in preference to surgery, radiation or conservative management. Over the past few years a similar increase in the use of PADT for localized and locally advanced disease has also been observed in the USA.

This paper will outline the current clinical evidence for the efficacy of LHRH analogues, at the different disease stages and the implications for patient prognosis and future prostate cancer management guidelines globally.

Recent developments in therapy have seen LHRH analogues used as part of maximal androgen blockade (MAB) or combined androgen blockade (CAB) regimens, whereby chemical castration with an LHRH analogue – to suppress testicular testosterone – is combined with antiandrogen therapy – to suppress testosterone produced by the adrenal glands. The role and use of LHRH analogue-containing MAB in prostate cancer therapy will be reviewed.

Published data have reported that cardiovascular (CV) and other related metabolic and hemodynamic adverse events can occur with hormonal therapy for prostate cancer; similarly it may also have implications for a patient's quality of life. While hormonal therapy is undoubtedly an invaluable therapeutic option for men with prostate cancer, its benefits need to be weighed against the potential risks for individual patients. The potential adverse events that may occur with LHRH analogue therapy will be reviewed along with recommendations for strategies to help prevent treatment-related adverse events.

LHRH analogues have a long and well-established history in the treatment of prostate cancer. This article aims to review the clinical evidence for their role in the treatment paradigm for prostate cancer and discuss how this might develop into the future.

Hormonal Therapy for Prostate Cancer

The concept that endocrine therapy can have a therapeutic effect on disorders of the prostate is over a century old. In 1895, White [3] reported the beneficial effects of

orchiectomy in patients with prostatic hypertrophy. Since that time, key milestones in the development of hormonal therapy for prostate cancer have been the isolation of testosterone in 1935 [4] followed in 1941 by Huggins and Hodges' [5, 6] reports of the successful use of androgen deprivation for the treatment of advanced disease, a discovery for which Huggins subsequently received the Nobel Prize. In the intervening decades, the role of the hypothalamo-pituitary-adrenal axis in controlling testosterone production, and the specific function of LHRH, has been elucidated and this has led to the development of different classes of antiandrogenic compounds that act on different steps in the pathway, including LHRH agonists, LHRH antagonists, antiandrogens, and 5 α -reductase inhibitors.

Initially research into endocrine therapy for prostate cancer focused on strategies to reduce testosterone levels either surgically – by orchiectomy – or chemically using treatment with estrogens. Both of these approaches however were found to have disadvantages: orchiectomy is an invasive surgical procedure with associated morbidity and can be both physically and psychologically unacceptable to some patients, while estrogens may be associated with significant CV adverse effects.

The introduction of LHRH agonists in the 1980s completely changed the treatment landscape for prostate cancer patients. These agents were able to reduce testosterone to castrate levels but avoided the need for surgery and were not associated with the adverse effects experienced with estrogen therapy.

The most commonly prescribed LHRH agonists for prostate cancer are leuporelin and goserelin but other compounds in this class are also available in certain countries, namely triptorelin, buserelin and histrelin. Leuporelin was first synthesized for clinical use in 1974 and is characterized by having a longer half-life and being 80 times more potent than naturally occurring LHRH due to its enhanced binding affinity and increased resistance to degradation by peptidases [7, 8]. It was subsequently approved by the US Food and Drug Administration (FDA) in 1985 for the treatment of advanced prostate cancer.

Continuous treatment with LHRH agonists results in downregulation of the receptors in the pituitary and inhibition of LH and FSH release which in turn decreases testosterone production to castrate levels. Initial treatment however causes a surge in LH release and in testosterone production which can result in the so-called 'flare' of disease and a worsening of symptoms temporarily.

The development of LHRH antagonists for the treatment of prostate cancer, such as the compounds abarelix

and degarelix, has had a more difficult course. Since these compounds are direct antagonists, they can avoid the flare phenomenon seen with agonist compounds. However, there have been reports of serious allergic reactions to abarelix which has limited its use for the treatment of prostate cancer and it was withdrawn from the US market in 2005. Degarelix has been launched onto the US and European markets in 2009 for the treatment of advanced prostate cancer [9] but its benefit on long-term clinical outcomes in comparison with established LHRH compounds remains to be determined.

When LHRH agonists were first introduced in the 1980s it was necessary to give daily subcutaneous or intramuscular injections. Since that time, advances in drug delivery technology have resulted in longer-acting, depot formulations which have considerable advantages for patient comfort and convenience, in addition to consume fewer healthcare resources. The first long-acting leuprorelin formulation, a monthly injection, was approved by the FDA in 1989 for the treatment of advanced prostate cancer [10] and there are now 1-, 3-, 4- and 6-monthly depot formulations available (dosages and indications may differ in different countries) [11].

Around 90% of a man's circulating testosterone is produced by the testes with the remainder being produced by the adrenal glands. Thus, despite treatment with LHRH agonists to reduced testicular testosterone production, there can still be low levels of circulating testosterone of adrenal origin that can stimulate prostate cancer growth. Non-steroidal antiandrogens such as bicalutamide, flutamide, and nilutamide interfere with the binding of testosterone and dihydrotestosterone to the androgen receptor and have therefore been used to help eliminate the effects of these additional adrenal androgens, either as monotherapy or in combination with LHRH agonists.

The Place of LHRH Analogues in Hormonal Therapy Regimens

How are LHRH analogues currently used within treatment regimens for prostate cancer? Traditionally, primary hormonal therapy has been reserved for the palliative treatment of prostate cancer patients with advanced disease and has been demonstrated to have survival benefits, particularly when treatment is given immediately, rather than deferred [12].

LHRH analogues have now been available for many years and the accumulating data regarding the safety and

efficacy of hormonal therapy with these agents has resulted in their increased usage at earlier stages of the disease. Reports from the USA and Japan have found that rates of PADT are increasing across risk groups and treatment types [13, 14]; these national trends will be discussed in more detail within a subsequent section of this paper.

A contributing factor to this wider use is the discovery of PSA in 1979 and the advent of PSA screening which has resulted in earlier detection and downward stage migration of newly diagnosed cases of prostate cancer – a greater incidence of cases diagnosed with localized or locally advanced disease are being observed compared to previous years – and, as a result, new treatment options are being investigated.

In addition to its role as a primary therapy, hormonal treatment may also be used in the neoadjuvant or adjuvant setting for localized or locally advanced prostate cancer. Neoadjuvant hormonal therapy (NHT) with at least 3 months of treatment is often used as a method of downstaging tumors and potentially eradicating micrometastatic disease immediately prior to surgery or radiation therapy. The goal of radical prostatectomy (RP) is to remove all cancer cells and the role of NHT given prior to RP is to reduce the likelihood of positive surgical margins with the aim of minimizing disease recurrence rates. Although there is evidence of clinical benefits and improved local control, to date there have been no reports of survival benefits or improvements in surrogate endpoints, such as PSA-defined recurrence with NHT in this setting [15, 16]. In the case of external beam radiotherapy (EBRT), some studies have demonstrated survival benefits with the addition of NHT in patients with locally advanced disease [17, 18].

Adjuvant hormonal therapy (AHT) is often used as a treatment option following surgery or radiation. A recent meta-analysis of randomized clinical trials comparing AHT plus primary therapy (radiotherapy or RP) with primary therapy alone concluded that there are significant clinical and survival benefits associated with the use of AHT for early prostate cancer [19].

Hormonal therapy is also used as part of 'maximal androgen blockade' (MAB) regimens (also known as combined androgen blockade – CAB) whereby a non-steroidal antiandrogen is combined with either an LHRH agonist or surgical castration. The benefits of MAB therapy over LHRH agonist monotherapy have been the subject of considerable debate over the years. Recent clinical studies with MAB regimens will be discussed in more detail within a subsequent section of this paper.

Table 1. Characteristics of patients treated with leuporelin at the time of diagnosis (data from J-CaP)

Age, years (mean 73.4) (n = 15,461)	<70	28.1%
	>70	71.9%
PSA level, ng/ml (n = 15,461)	<4	3.4%
	4–10	24.2%
	10–20	21.8%
	>20	50.2%
T-stage, TNM classification (n = 15,446)	T1	22.8%
	T2	36.2%
	T3	33.0%
	T4	7.6%
Gleason score (n = 15,461)	2–4	7.0%
	5–6	25.8%
	7	25.6%
	8–10	29.0%
Type of therapy (n = 15,461)	Adjuvant	4.0%
	Main	77.1%
	Neoadjuvant	18.9%

Values for PSA level, T-stage and Gleason score may not total 100% as some investigators did not record this value.

Use of LHRH Analogues in Japan

In Japan, in contrast to Europe and the USA and also to international guideline recommendations, PADT has been used for many years in a large number of patients with localized or locally advanced prostate cancer. The reasons why Japanese patients prefer hormonal therapy to surgical or radiation options for localized disease have been postulated to be that medical treatment, such as PADT, is more acceptable for many Japanese patients than more invasive treatments such as surgery. Japanese urologists are happy to prescribe PADT as they have experience of its effectiveness in their daily practice. In addition, it has been proposed that sensitivity to hormonal therapy may be higher in Japanese than in Caucasian patients [20].

In 2000, the Japanese Urological Association (JUA) launched a system for registering patients who were newly diagnosed with prostate cancer at institutions authorized by the JUA. The system aimed to collect background factors about prostate cancer patients and reported its findings in 2005 [21]. A total of 4,529 patients from 173 institutions who were diagnosed with prostate cancer in 2000 were registered. Hormone therapy alone was the initial treatment option in 45% of cases with T1c to T3

Fig. 1. Treatment options given to new prostate cancer patients in Japan registered in the 2000 report from the JUA [reproduced from 21, with permission]. W/W = Watchful waiting; RRP = radical retropubic prostatectomy; Rx = radiotherapy; Hx = hormonal therapy; w/o meta = without metastases.

disease without lymph node or distant metastases (fig. 1).

In 2001 the Japan Study Group of Prostate Cancer (J-CaP Study Group; <http://www.j-cap.net>) supported by the Japan Kidney Foundation and authorized by the JUA commenced a study to gather information about hormone therapy administered to Japanese prostate cancer patients living in Japan and to analyze the outcomes of treatment. The overall aim was to develop evidence-based guidelines for optimal hormone therapy. The J-CaP surveillance study was a nationwide longitudinal, observational study of patients newly starting hormone therapy for prostate cancer from January 2001 to December 2003. Institutions participating in the program registered individual cases, with entry of information pertaining to endocrine therapy via secure server over the internet. After registration, information on the prognosis of individual registered cases and changes in treatment, if any, were entered periodically. The rationale for the study and an interim analysis of the registration status of the patients and their background variables were reported in 2003 [22]. More recently, treatment patterns with PADT have been reported along with an interim analysis of prognosis [23]. Of the 19,409 patients who initially received PADT after diagnosis of prostate cancer, 1,513 (7.8%) were given antiandrogen monotherapy, 955 (4.9%) surgical castration only, 3,015 (15.5%) LHRH monotherapy, 1,658 (8.5%)

Fig. 2. Trends in initial endocrine therapy according to T category, clinical stage and D'Amico's risk classification: data from J-CaP [reproduced from 23, with permission]. AA = Antiandrogen monotherapy; SC = surgical castration only; SC + AA = surgical castration + antiandrogen; LHRH = LHRH agonist monotherapy; LHRH + short AA = LHRH agonist + short-term antiandrogen; LHRH + AA = LHRH agonist + antiandrogen; WW = watchful waiting.

with LHRH + short-term antiandrogen, 1,001 (5.2%) with surgical castration + antiandrogen, 10,434 (53.8%) with LHRH + antiandrogen, 37 (0.2%) with watchful waiting, and 796 patients (4.1%) with other therapy. When the results were analyzed by T-category, disease stage and risk category there was a trend to increasing use of MAB rather than LHRH monotherapy (fig. 2). The results showed that 59.0% of all patients received MAB and these regimens were most often selected for patients who were considered to be at high risk of disease progression.

A preliminary analysis of the influence of these different types of hormonal therapy on disease outcomes was undertaken by this group [23]. The authors concluded that MAB therapy is possibly superior to LHRH monotherapy in terms of progression-free survival (PFS) for stage II and III prostate cancer and overall survival (OS) for stage III and IV prostate cancer, however they acknowledged that the number of events was too small to allow any definite conclusions to be drawn at that stage.

The latest data for 15,461 prostate cancer patients treated with leuporelin-containing regimens are now available and their overall characteristics are summarized in table 1 [unpubl. data]. Comparisons of PFS and OS with MAB and non-MAB therapy at different disease stages are presented in figures 3 and 4 [unpubl. data].

It can be concluded from these data that MAB therapy may be superior to leuporelin monotherapy in terms of PFS for stage II disease. In addition, the progression of prostate cancer appears to be inhibited with the use of a

PADT regimen containing leuporelin and patients with stage II and III disease were found to have a life expectancy similar to that of the normal population.

The J-CaP investigators will continue the analysis and plan to investigate adverse events, quality of life, long-term prognosis and cause of death in prostate cancer patients receiving PADT.

To help improve the selection of patients for PADT, recently a novel risk instrument has been developed and validated for patients undergoing PADT, named 'J-CAPRA' [24]. It is applicable to patients with both localized and advanced disease, and performs well in different populations. To develop this tool, data were analyzed from 13,740 men in the US community-based Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry and 19,265 men in the J-CaP database and risk distribution compared between the two datasets using three well-described multivariable instruments. J-CAPRA was designed and validated to be specifically applicable to PADT patients, and more relevant to high-risk patients than existing instruments. It was found J-CaP patients were more likely than CaPSURE patients to be diagnosed with high-risk features: 43% of J-CaP versus 5% of CaPSURE patients had locally advanced or metastatic disease that could not be stratified with the standard risk assessment tools. J-CAPRA was found to be able to predict PFS among PADT patients in J-CaP and cancer-specific survival among PADT patients in CaPSURE with a high degree of accuracy.

Fig. 3. Progression-free survival at **a** clinical stage II, **b** clinical stage III and **c** clinical stage IV (data from J-CaP).

Fig. 4. Overall survival at **a** clinical stage II, **b** clinical stage III and **c** clinical stage IV (data from J-CaP).

Trends in the Use of Hormonal Therapy for Localized and Locally Advanced Disease

As noted earlier, there appears to be a gap between actual clinical practice and international guidelines in terms of the use of PADT for prostate cancer therapy. Guidelines published by the European Association of Urology (EAU) [1], the American Urological Association (AUA) [2], the National Cancer Institute-Physician Data Query (NCI-PDQ) of the USA [25] do not recommend PADT for the majority of localized or locally advanced cases. However, the American Society for Clinical Oncology (ASCO) mentions within their guidelines that MAB may be used for locally advanced cases [26].

Guidelines published by the JUA recommend that endocrine therapy should be used as a first-line option primarily in advanced disease (T4, N0, M0, N1 or M1) although they recognize that it may be useful in certain cases of earlier stage disease (T1b-c/T2, N0, M0), for example in patients who have a Gleason score ≤ 6 , serum PSA ≤ 20 ng/ml and a life expectancy < 10 years [27].

So, why do guidelines and clinical practice differ? Guidelines are generally developed in the light of definitive clinical evidence and while this is slowly accumulating for PADT in early stage prostate cancer, these data are not yet sufficiently robust to change the recommendations.

Several investigators, both in Japan and the USA, have reported the changing patterns of use of PADT in clinical practice. In the USA, Cooperberg et al. [13] undertook an analysis of the CaPSURE database, which includes data for over 10,000 men with prostate cancer accrued at 31 primarily community-based sites across the USA, and found that rates of PADT use had risen sharply between 1989 and 2001, and that this increase was seen across risk groups and treatment types. They noted that the presentation and management of prostate cancer had changed substantially over the last decade with an increasing number of patients diagnosed with low-risk clinical characteristics. Over this time period, patients have become less likely to pursue watchful waiting and more likely to receive brachytherapy or hormonal therapy [28].

Akaza et al. [29] have analyzed data from both the CaPSURE and J-CaP databases and PADT. They concluded that with the advent of screening and diagnosis of early stage disease coupled with the higher proportion of older patients, local therapies are less attractive. However, patients often wish to have some form of active therapy when they are told they have cancer so active surveillance may be a less popular option. PADT fills this gap.

Several other publications have commented on this trend and noted that the potential benefits of hormone therapy may be underutilized in early stage disease [30, 31].

Clinical data are now emerging from Japan, Europe and the USA that support the use of PADT in early stage prostate cancer. In Japan, Ueno et al. [32] undertook a retrospective review of patients with localized and locally advanced prostate cancer to evaluate the efficacy of primary hormonal therapy and the impact on long-term prognosis in these patients. A total of 628 patients who were diagnosed with stage T1c to T3 prostate cancer were treated with PADT: 399 patients (63.5%) with MAB and 229 (36.5%) with castration monotherapy. The disease-specific survival rate of all 628 patients was 89.1% at 8 years. One third of patients showed a good response to PADT (pretreatment PSA level ≤ 20 ng/ml, Gleason score ≤ 7 , and time to nadir PSA ≤ 6 months). This group of patients achieved disease-specific survival and PFS rates at 8 years of 98.9 and 82.0%, respectively, for those who received castration monotherapy, which increased to 100 and 87.3%, respectively, in patients receiving MAB.

Another study from Japan analyzed the 10-year survival rates of men with localized or locally advanced prostate cancer treated with PADT or prostatectomy [33]. From February 1993 to March 1995, men with T1b, T1c or T2-3 N0M0 prostate cancer were enrolled into two study arms: 176 men who had a prostatectomy were assigned to Study 1 and received adjuvant LHRH agonist; 151 men who did not have a prostatectomy were assigned to Study 2 and received LHRH agonist monotherapy or CAB. In Study 1, the 10-year OS rate was 73% and the 10-year cause-specific survival rate was 86%, compared with 41 and 78%, respectively, in Study 2. The authors concluded that the progression of prostate cancer was inhibited with the use of PADT in men with localized or locally advanced disease. Importantly, these patients had a life expectancy similar to that of the normal population.

Similar positive results have been reported in Canada and in Europe [34–36]. Labrie et al. [34, 35] in Canada have reported the results of a series of studies which have demonstrated a major reduction in deaths from prostate cancer ranging from 31 to 87% at 5 years of follow-up in patients with localized or locally advanced prostate cancer. Notably, they report that CAB can lead to a 90% long-term control or probable cure of prostate cancer in this setting. Wirth et al. [36] in Germany investigated efficacy and tolerability of hormone therapy with the antiandrogen bicalutamide (150 mg daily) given in addition to standard care, in patients with localized or locally advanced

prostate cancer. They found that patients receiving bicalutamide had a significant (28%) improvement in PFS compared with the placebo group but no difference in OS was observed at the 5.4-year timepoint. The authors concluded that bicalutamide is beneficial in patients with locally advanced disease but an advantage in localized disease could not be confirmed.

Maximal Androgen Blockade

MAB describes the concept of eliminating all androgens from the body utilizing a combination of an antiandrogen with an LHRH analogue or surgical castration. As with other forms of hormonal therapy, MAB has traditionally been used for the treatment of advanced, metastatic prostate cancer. Even in this setting there has been considerable debate regarding the relative benefits of MAB compared with LHRH monotherapy [37]. A large number of studies had shown no additional benefit from MAB treatment, therefore a meta-analysis was performed combining the results from all 27 MAB studies available at that time. The analysis revealed a small but statistically significant survival benefit for MAB (3%) in advanced disease, although many experts believed this benefit was overshadowed by the therapy's cost and side effects [38].

More recently the results of a phase III, randomized, controlled trial of MAB in advanced prostate cancer have provided us with additional evidence of the benefits of MAB [39–41]; this is the first controlled study to directly compare these two regimens. Akaza et al. [39] undertook a study to evaluate the efficacy of bicalutamide (80 mg) as a component of MAB in Japanese patients with previously untreated advanced prostate cancer. A total of 205 patients with stage C/D prostate cancer were randomized to receive either a LHRH agonist plus once-daily oral bicalutamide (80 mg) or placebo. A report of the primary efficacy findings showed that bicalutamide in combination with an LHRH agonist was superior to LHRH agonist monotherapy in terms of the antitumor response at 12 weeks, and also time to treatment failure and progression. A later report found that first-line combination therapy with bicalutamide 80 mg in this patient group offered significant benefits ($p < 0.001$) over a LHRH agonist alone in terms of time to treatment failure and time to progression, but the difference in the interim OS was not statistically significant [40]. A recent report analyzed the survival data from a long-term follow-up of these patients [41]. At a median follow-up of 5.2 years, a signifi-

cant OS advantage was observed in favor of MAB over LHRH agonist monotherapy (hazard ratio 0.78; 95% confidence interval 0.60–0.99). Notably the achievement of a PSA nadir concentration ≤ 1 ng/ml was a prognostic factor for improved survival, and more patients achieved this level with CAB compared with patients who received LHRH agonist monotherapy (81.4 vs. 33.7%; $p < 0.001$).

Thus, this study has also demonstrated a survival advantage for MAB compared with LHRH monotherapy in stage C disease, but not in stage D disease, and this was achieved without any reduction in tolerability. One of the main barriers to the use of MAB is the potential for increased adverse events compared with LHRH agonist monotherapy. The role of MAB in earlier disease stages remains to be determined.

Potential Adverse Events with Hormonal Therapy

As we have seen from the data presented in this paper, hormonal therapy is undoubtedly an invaluable therapeutic option for men with prostate cancer, however, as with all medications, the benefits of hormonal therapy need to be weighed against the potential risks for individual patients.

An analysis of the published literature has shown that hormonal therapy has been reported in a range of studies to be associated with an increased risk of diabetes, coronary heart disease (CHD), myocardial infarction (MI), sudden cardiac death (SCD), and metabolic syndrome, and changes in hepatic glucose production, insulin sensitivity, lean body mass/fat body mass, QT interval, arterial stiffness, and a decrease in bone mineral density [42–47]. Many of these parameters were known to increase the risk of developing CV disease. Often, data from these studies are conflicting and some have important limitations and confounding factors which need to be taken into account when interpreting the results.

Keating et al. [42] reported an increased risk of diabetes, CHD, MI and SCD with LHRH analogue therapy versus no treatment. However, this was not a randomized study, therefore patients in the two groups might have had different background characteristics, for example older men who are more likely to receive LHRH therapy are also more likely to have diabetes or CHD. D'Amico et al. [43] described how a subset of patients aged ≥ 65 receiving 6 months of androgen deprivation therapy had an earlier onset of fatal MI. This paper was recently criticized as there was no difference between groups in the total number of MIs. The study was of short duration and

information on patients CV risk factors was limited, plus it was not designed to evaluate CV disease. In addition there was no ‘active surveillance’ group for comparison.

Efstathiou et al. [44] assessed the relationship between LHRH agonists and CV mortality in a large, randomized, phase III trial of men treated with or without adjuvant LHRH agonist therapy after radiation for locally advanced prostate cancer. After a median follow-up of 8.1 years, there was no treatment-related increase in CV mortality and the authors concluded that LHRH agonists do not seem to increase CV mortality in men with locally advanced prostate cancer.

Importantly, results from other recent randomized, controlled trials of different hormonal modalities (RTOG 8610, EORTC 30891, RTOG 92-02), which are able to control for confounders, have also shown no significant increase in CV mortality with hormonal therapy in men with prostate cancer [48–50].

Data regarding CV events with hormone therapy have also been reported from large databases, such as J-CaP, SEER and CaPSURE [33, 51, 52], and again the data are conflicting. Akaza et al. [33] demonstrated no difference in OS for patients with localized prostate cancer treated with PADT and men of the same age in the general population, suggesting that there is no significant increase in mortality in men treated with PADT. These findings are supported by recent analyses showing that the incidence of CV events in patients registered in J-CaP database from 2001 to 2003 and treated with leuporelin was no greater than that expected in the general Japanese population [unpubl. data] (table 2).

In contrast, an analysis of 22,816 subjects in the SEER database found that newly diagnosed prostate cancer patients who received PADT for at least 1 year were found to have a 20% higher risk of serious CV morbidity compared with similar men who did not receive PADT [51].

An analysis of the CaPSURE database of 3,262 patients treated with RP and 1,630 patients treated with EBRT, brachytherapy, or cryotherapy for localized prostate cancer found that among patients 65 years or older treated with RP, the 5-year cumulative incidence of CV death was 5.5% in those who received androgen deprivation therapy and 2.0% in those who did not [52].

Based on this current evidence it can be proposed that hormonal therapy should not be withheld from prostate cancer patients who are likely to benefit in the hope of preventing a less likely CV event. In the future it will be important to direct our research efforts into identifying patients who are at high risk of experiencing adverse events with this form of therapy. In our clinical practice

Table 2. CV deaths among leuporelin-treated patients compared to a similar-sized general Japanese population cohort in the years 2001–2006 (data from J-CaP)

Year	Observed number of leuporelin-treated patients	CV deaths in leuporelin-treated patients	Estimated CV mortality rate/Japanese general population cohort
2001	800	2	4.0/800
2002	1,666	5	9.1/1,666
2003	2,515	16	15.1/2,515
2004	2,243	9	14.5/2,243
2005	1,835	10	12.7/1,835
2006	1,470	7	11.0/1,470

we need to develop strategies to aid the early recognition and management of treatment-related adverse events such as diabetes, CV disease and other unwanted side effects that may occur with hormonal therapy [53].

Conclusions

LHRH analogues continue to play a pivotal role in the treatment of prostate cancer. The trend now appears to be a move away from their traditional use as palliative therapy for advanced disease and recognition of their benefits, both as monotherapy but particularly when used as part of a MAB regimen, in both localized and locally advanced disease. This is reflected in the earlier use of PADT in the treatment paradigm in prostate cancer patients in many countries, however there is a notable gap between clinical practice and treatment guidelines. Although the concept of use of LHRH analogues in earlier disease stages is not currently recommended in international treatment guidelines, accumulating clinical evidence confirms the valuable role of primary hormonal therapy for the long-term control of both localized and locally advanced prostate cancer, and importantly on survival outcomes in these patients. The emerging data on long-term outcomes with PADT can be used to help inform future treatment guidelines internationally.

It is clear therefore that LHRH analogues, alone or in combination with other agents, will to continue to form a critical part of treatment algorithm for prostate cancer patients, and possibly have an expanded role, in the future.

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