REVIEW PAPER

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Evidence-based recommendations on androgen deprivation therapy for localized and advanced prostate cancer

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Introduction The management of prostate cancer (PC) is still evolving. Although, androgen deprivation therapy (ADT) is an established treatment option, particularly in patients with disseminated disease, important data regarding hormonal manipulation have recently emerged. The aim of this paper is to review the evidence on ADT, make recommendations and address areas of controversy associated with its use in men with PC.

Material and methods An expert panel was convened. Areas related to the hormonal management of patients with PC requiring evidence review were identified and questions to be addressed by the panel were determined. Appropriate literature review was performed and included a search of online databases, bibliographic reviews and consultation with experts.

Results The panel was able to provide recommendations on: 1) which patients with localised PC should receive androgen deprivation in conjunction with radiotherapy (RT); 2) what standard initial treatment should be used in metastatic hormone-naïve PC (MHNPC); 3) efficacy of androgen deprivation agents; 4) whether ADT should be continued in patients with castration resistant PC (CRPC). However, no recommendations could be made for combined ADT and very high-dose RT in patients with an intermediate-risk disease.

Conclusions ADT remains the cornerstone of treatment for both metastatic hormone-naïve and castration-resistant PC. According to the expert panel's opinion, based on the ERG report, luteinizing hormone-releasing hormone agonists might not be equivalent but this needs to be confirmed in long-term data. The combined use of ADT and RT improves outcome and survival in men with high-risk localised disease. The benefits in patients with intermediate-risk disease, particularly those subject to escalated dose RT are controversial.

Key Words: prostate cancer ‹› androgen deprivation therapy ‹› recommendations

INTRODUCTION

Prostate cancer is the most prevalent male urogenital malignancy in developed countries [1]. In Poland, PC is the second most commonly diagnosed cancer in men and accounts for more than 13% of all male malignancies. In 2013, a total of 12,162 new PC cases were diagnosed. The PC incidence rate has risen

continuously over the last 30 years, however, there has been a clear improvement in survival. The Polish National Cancer Register statistics reveal that the 5-year relative survival rate increased from 64.2% in 2000–2002 to 76.4% in 2003–2005 [2].

Early stages of the disease can be managed with active surveillance, radical prostatectomy or radiation therapy, however, no curative treatment exists for advanced disease (i.e. metastatic PC), which eventually develops in approximately 30% of patients with PC [3]. Androgen deprivation therapy is predominantly used for treatment of disseminated disease. However, its role in patients with localised cancer is less clear. An Expert Panel Meeting was organised to discuss recent important data regarding ADT in the management of patients with PC. The objective of the panel discussion was to provide recommendations in areas associated with ADT in men with PC.

METHODS

Expert opinion was explored at the Expert Panel Meeting assembled in Warsaw, Poland on 22 January 2016. The meeting was supported by Ipsen Poland. Ipsen or any other pharmaceutical company had no influence over topics or speakers. The panel included eight PC experts from Poland and one public health and health economics expert from the United Kingdom (see panel members listed in the Appendix). The panel members agreed upon the four therapeutic areas for discussion:

1. Androgen deprivation in conjunction with radiotherapy in patients with localised PC;
2. Initial management of patients with metastatic hormone-naïve PC;
3. Value of testicular androgen deprivation in patients with castration resistant PC;
4. Efficacy of testicular androgen deprivation agents in management of patients with metastatic PC.

Four clinically relevant questions suitable for consensus discussion were formulated based on the areas of controversy listed above. Participants reviewed related literature on the subject areas before the meeting. At the meeting, the experts discussed and reached consensus on recommendations relating to each question. Decisions were based primarily on studies published in peer-reviewed journals unless no other relevant data were identified; in such cases expert opinion was considered. A systematic review was not carried out; however, all pertinent publications as identified by the expert panel were examined. Following the meeting, the draft recommendations were circulated to the panel for their final review and approval. The recommendations presented herein have been approved by all the participants.

Table 1. *Level of evidence*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one type well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Table 2. *Grade of recommendation*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

The modified Oxford Centre for Evidence-based Medicine Levels of Evidence grading system was used for level of evidence and strength of recommendation for each question raised (Table 1, Table 2) [4].

Which patients with localised PC should receive androgen deprivation in conjunction with RT?

Radiation is used as a definitive treatment for men with PC in approximately 25% of cases [5]. Following the discovery that PC cells are androgen-dependent [6], ADT is also used in patients with metastatic PC. Following results from animal experiments which showed that ADT prior to RT resulted in better tumor eradication than RT alone [7], several trials of combined treatment in men with localised PC have been carried out. A robust evidence base supports the use of combined treatment in patients with intermediate- or high-risk PC but not in men with a low-risk disease [8–13]. However, there is some controversy regarding the optimal RT management of patients with intermediate-risk PC in terms of duration of ADT and associated toxicities. Currently, short-term androgen deprivation combined with RT in this group of patients is considered the best approach [4, 14]. Supporting evidence comes from the DFCI 95096 trial, a study by Laverdière et al., together with the Trans-Tasman Radiation Oncology Group (TROG) 9601 and TROG 9408 trials [9–13]. In DFCI 95096 combined treatment with RT and

short-term ADT *versus* RT alone resulted in 5-year overall survival (OS) benefit of 88% *versus* 78% (p = 0.04), and 8-year OS of 74% *versus* 61%, p = 0.01 [10]. In the study by Laverdière et al., the 7-year biochemical disease-free survival (BDFS) was better in the group receiving 3 months of neo-adjuvant ADT than in the group receiving RT alone (42% *versus* 66%, p = 0.009) [11]. Moreover, the authors also compared neo-adjuvant, concurrent and adjuvant ADT for a total of 10 months *versus* no hormonal treatment and found that combination therapy was associated with a better 7-year BDFS (42% and 69%, respectively, p = 0.003). Similar outcomes were achieved in the TROG 9601 and TROG 9408 trials [12, 13]. In TROG 9601, RT alone was compared to RT combined with 3 months ADT (initiated 2 months before RT) and to RT combined with 6 months ADT (initiated 5 months before RT) in PC patients with stage T2b-T4 N0M0 disease [12]. After a 10-year follow up period, a significant reduction in the risk of biochemical and local progression were observed in men treated with combination therapy, and results improved with longer duration of ADT [13]. TROG 9408 evaluated combination therapy with RT and ADT (as 2 months neo-adjuvant and 2 months concurrent regime) *versus* RT alone in PC patients with predominantly intermediate-risk of progression [9]. In this subgroup of patients 8-year OS was 72% *versus* 66%, respectively, p = 0.03. Although clear benefit was associated with treatment of intermediate-risk PC patients with RT plus ADT in these studies, it should be noted that the total radiation dose of 66–70Gy used was lower than that typically used in current practice. Given that contemporarily used higher doses of RT in the intermittent-risk PC patients may achieve similar benefits to those reported by trials with lower doses of RT combined with AD, the role of short-term hormonal treatment in this group of patients receiving doses of RT greater than 70Gy remains unanswered [15, 16, 17]. Six ongoing trials (RTOG 0815, NCT 00936390; EORTC 22991, NCT 00021450; GETUG 14, NCT 00104741) are expected to provide a definitive answer to whether intermediate-risk PC patients need androgen deprivation at all when treated with dose-escalation RT.

For high-risk PC, several clinical trials have unquestionably confirmed the efficacy of combination treatment in form of a long-term ADT and RT. The Radiation Therapy Oncology Group (RTOG) 92-02 study reported a significant benefit in distant metastasis, local progression, biochemical failure and disease-free survival, but not in OS [18]. However, a subgroup analysis found improved OS in men with a Gleason score of 8–10. Strong evidence supporting the use of long-term ADT in conjunction with RT in high-risk PC patients comes from the European Organisation for Research and Treatment of Cancer (EORTC) studies, particularly EORTC 22863 and EORTC 22961 [19, 20]. In EORTC 22863, 415 men with predominately high-risk PC (91%) received external beam radiotherapy (EBRT) with or without 3 years of ADT commencing on the first day of treatment. OS benefit at 5 and 10 years was observed in the combined treatment group *versus* the EBRT-alone group (5-year OS: 72% *versus* 62%, p = 0.001 and 10-year OS: 58% *versus* 40%, p = 0.001) [20]. In EORTC 22961, a 36-month ADT regimen was compared with a 6-month ADT regimen [19]. Hormone therapy used for 36 months achieved better 5-year OS rates than a 6-month ADT (85% *versus* 81%, respectively). Other studies have confirmed the role of long-term ADT combined with RT in the treatment of high-risk PC patients [21, 22, 23].

In summary, based on prospective randomised clinical trials, the benefit of treatment of high-risk PC patients with combination of ADT and RT has been established, since such treatment improves local control and OS. The benefit in intermediate-risk patients has also been demonstrated for doses of radiation between 66 and 70Gy. However, new technological advances allowing for dose escalation are currently being evaluated, since doses of radiation <76Gy are considered unacceptably low in current practice [4]. No benefit has been observed with combined treatment in patients with low-risk disease.

Recommendation: For high-risk PC patients, long-term ADT (28–36 months) before and during RT is recommended.
Level of evidence: 1b
Strength of recommendation: A

Recommendation: For intermediate-risk PC patients, no recommendation can be given pending the results of clinical trials investigating the use of ADT with RT with dose escalation.
Level of evidence: Not applicable
Strength of recommendation: Not applicable

Recommendation: For low-risk PC patients, RT (intensity modulated RT with dose escalation or brachytherapy) without ADT is recommended.
Level of evidence: 2a
Strength of recommendation: B

What standard initial treatment should be used in metastatic hormone-naïve prostate cancer?

MHNPC is defined as disease with dissemination to the bones, visceral sites or lymph nodes outside the pelvis, detected by imaging in a patient with

no prior hormonal therapy. Androgen suppression is an effective standard treatment in delaying tumor progression in men with metastatic PC, as it adequately achieves castrate levels of testosterone and leads to tumor cell apoptosis. The majority of patients with MHNPC initially respond to ADT with both tumor and biochemical responses, but most of them will eventually develop progressive disease over time, referred to as CRPC [24, 25].

There are two standard ways to achieve immediate ADT: surgical or pharmacological, both of which are equally effective [4]. Surgical castration is executed by bilateral orchidectomy, whereas pharmacological castration is accomplished by the use of luteinising hormone releasing hormone (LHRH) agonists or antagonist, with or without an anti-androgen [26, 27, 28]. Bilateral orchidectomy is considered the reference for ADT as it lowers serum testosterone level well below 50 ng/dl in <12 hours [4]. Although it is a simple and cost-effective procedure, it is non-reversible and carries significant psychological burden in some patients. Treatment with LHRH agonists results in a 1 or 2-week rise in luteinising hormone (LH) with subsequent temporary rise in testosterone, the so called biochemical flare-up phenomenon, which may lead to temporal clinical flare with worsening of signs and symptoms of the disease. Thus, LHRH agonists (triptorelin, leuprorelin, goserelin) are not recommended as monotherapy in men with impending spinal cord compression, urinary obstruction or pain due to the potential for exacerbation of symptoms. Other options including combination of anti-androgen for 1 month, definitive surgical castration, or a LHRH antagonist (degarelix) (as no flare-up), could be considered. Maximal androgen blockade (MAB) over castration alone has not demonstrated clinically relevant survival advantage [29, 30, 31]. Studies which suggest superior efficacy with MAB over ADT monotherapy have a range of uncertainty greater than the size of the benefit or greater toxicity, increased adverse events and resulting decline in quality of life associated with MAB which outweigh the small survival benefit, whether or not all androgen receptor inhibitors were included in the analyses [30, 31].

In summary, the use of the LHRH antagonist, degarelix, for ADT has good efficacy for symptomatic patients with locally advanced and metastatic disease, particularly those at high risk of the detrimental effects of testosterone flare-up, but shows no superiority to LHRH agonists. In addition, in patients with MHNPC treatment with degarelix cannot be considered cost-effective, contrary to the use of LHRH agonists particularly triptorelin [32].

Recently, a number of studies have examined early docetaxel therapy in hormone-naïve PC. The results of GETUG-AFU 15, CHAARTED and STAMPEDE randomised controlled trials have raised the question of whether docetaxel should become a standard concurrent therapy with ADT in MHNPC [33, 34, 35]. Although the primary results of GETUG-AFU 15 demonstrated no survival benefit in the combined treatment group *versus* the ADT-alone group (median OS: 58.9 months *versus* 54.2 months, HR = 1.01, 95% CI = 0.75–1.36), both the CHAARTED and STAMPEDE trials showed improved survival with chemohormonal therapy. The median OS in the CHAARTED trial was 57.6 months for ADT plus docetaxel *versus* 44.0 months for ADT alone, whereas in STAMPEDE it was 81 months and 71 months, respectively. It should be noted that the effect of docetaxel on survival was positive, but clinically significant toxicity occurred more commonly. The survival benefit from the addition of docetaxel to ADT in men with metastatic PC has also been confirmed by recently published meta-analysis [36]. The study provided high-grade evidence that chemohormonal therapy (docetaxel plus ADT) results in an absolute improvement of survival of around 9% at 4 years.

Recommendation: Continuous pharmacological or immediate surgical castration is the preferred treatment option for MHNPC. A combination treatment in form of docetaxel chemotherapy and a long-term ADT or castration should be offered to men who are fit to receive chemotherapy.
Level of evidence: 1a
Strength of recommendation: A

Recommendation: 3–4 weeks of concomitant anti-androgens should be given when starting ADT to reduce the risk of testosterone flare-up phenomenon in patients with MHNPC.
Level of evidence: 2a
Strength of recommendation: A

Are all androgen deprivation agents equal in efficacy for management of patients with metastatic prostate cancer?

LHRH agonists are currently the preferred first-line treatment for patients with metastatic PC, with LHRH antagonist therapy (degarelix) as an alternative treatment [37–40]. Although ADT is not a curative option in this group of patients, it results in tumor regression, extended OS and cancer-specific survival (CSS), as well as relief of urinary symptoms and bone pain [40, 41, 42].

Published meta-analyses showed similar efficacy between the LHRH agonists in suppressing testoster-

one to below castrate levels and phase III comparative, randomised trials confirmed non-inferiority of degarelix at maintaining castrate testosterone levels over a 1-year treatment period compared with leuprolide or goserelin with or without anti-androgen [40, 43, 44, 45]. Unfortunately, there are no head-to-head trials which compare all the LHRH agonists and degarelix. However, one mixed treatment comparison, which is a statistical method of indirect combined analysis of all relevant data, has explored clinical efficacy among all the LHRH agonists (triptorelin, goserelin and leuprorelin) and degarelix. It was carried out upon request of the National Institute for Health and Care Excellence (NICE) by the University of Shefflied as Evidence Review Group (ERG), and demonstrated a difference in mortality risk with triptorelin when compared with leuprorelin [32]. Triptorelin was associated with lower mortality risk, which was statistically significantly lower *versus* leuprorelin (hazard ratio (HR) = 0.28, 95% confidence interval (CI) = 0.07–0.95). No other significant differences in mortality were found if this tool was used.

The report from the Evidence Review Group suggests that LHRH agonists are not equal in their efficacy in patients with metastatic PC. The ERG analysis demonstrated that triptorelin was associated with significantly lower mortality risk than leuprorelin. Although the estimate of the HR was 0.28, the confidence intervals were wide (0.07–0.95) so it is difficult to estimate with precision the true magnitude of the effect on mortality. It should be noted that all the studies included in the mixed treatment comparison were of short duration and not designed to detect differences in survival, including the one that showed a potential difference in OS associated with triptorelin when compared with leuprorelin. Therefore, the results for OS should be interpreted with caution, as long-term data from adequately designed trails are required to determine the clinical significance of this observation.

The recent European Association of Urology guidelines on PC assume that although there is no formal direct comparison between the various LHRH, they are considered to be equally effective and comparable to orchiectomy. In addition, the guidelines also indicate that different products have practical differences that need to be considered in everyday practice, including storage temperature, whether a drug is ready for immediate use or requires reconstitution, and mode of administration (intramuscular or subcutaneous injection) [4].

Recommendation: LHRH agonists should be used in men with metastatic PC. Mortality risk might be additionally reduced with triptorelin when compared with leuprorelin but this observation needs to be confirmed in long-term data from trials specifically designed to detect differences in survival.
Level of evidence: 1b
Strength of recommendation: A

Should androgen deprivation be continued in patients with CRPC?

Although the majority of men (>90%) with advanced PC achieve disease control with ADT, most patients will eventually develop CRPC after a median of 18–24 months [3]. However, the role of continued ADT in men with CRPC has been less well examined. The only supporting evidence comes from one retrospective study: a multivariate analysis of survival data from 341 patients treated in four clinical trials of secondary therapy for CRPC [46]. In this analysis, continued androgen suppression was associated with a modest advantage in survival duration of 2 to 6 months. However, contrary results have been achieved by a retrospective analysis of five consecutive Southwest Oncology Group (SWOG) phase II chemotherapy trials [47], which failed to show an obvious survival advantage with continued gonadal suppression. Nevertheless, several urological and oncological associations, including the EAU, the American Urological Association, the European Society for Medical Oncology, the International Society of Geriatric Oncology, the National Comprehensive Cancer Network and the American Society of Clinical Oncology recommend use of continuous ADT in men with CRPC [4, 48–52].

It seems prudent to maintain ADT in patients with CRPC indefinitely, given the absence of prospective trials demonstrating a lack of deleterious effect of discontinuation, some evidence for a possible modest survival benefit in continuing castration and taking into consideration that all subsequent prospective chemotherapy trials have been studied in men with ongoing ADT. Therefore, ADT is the recommended treatment in men with CRPC based upon the lack of any data to refute this recommendation.

Recommendation: ADT should be continued in patients with CRPC indefinitely regardless of additional therapies.
Level of evidence: 4
Strength of recommendation: C

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DISCLOSURE

Jonathan Belsey (consultancy payments from Ipsen Pharma (France) for analytical services and from Ipsen Poland for presentation of data to an advisory board)
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Tomasz Drewa (advisory board role for - Astellas, Medtronic, lectures fee from Astellas, Ipsen, Janssen)
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Anna Kołodziej (lecture fees from Astellas, Janssen,Ipsen, Medac)
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Appendix

Members of the panel
Prof. Tomasz Drewa (Chair of Urology, Ludwik Rydygier Medical College in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland and Department of Urology Nicolaus Copernicus Hospital in Toruń, Poland) was unable to attend the meeting, but had a major contribution in the preparatory work for the conference and final manuscript.
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