It is well recognized that the vast majority of prostate cancers rely on activation of the androgen receptor (AR) by circulating androgens for growth and survival. Three proven hormonal strategies to impair AR signaling are decreasing gonadal hormone production, inhibiting androgen–AR interaction, and impairing extragonadal androgen synthesis. In this review, we discuss the current strategies to slow initial and castration-resistant tumor growth through the use of hormonal agents such as the gonadotropin-releasing hormone analogues, antiandrogens, and adrenolytic agents, focusing on defining the optimal timing, combinations, and use of these agents, as well as on novel drug development.

Introduction

Androgens, particularly testosterone, play a critical role in promoting the growth of adenocarcinoma of the prostate. Huggins and Hodges [1,2] received the 1967 Nobel prize for their discovery in the 1940s that surgical or medical castration could produce a striking regression of metastatic prostate cancer and improve bone pain, lower urinary tract symptoms, and quality of life. Subsequent work better defined the mechanism underlying this observation, showing that androgens exert their effect on the prostate cancer cell through interaction with the cytoplasmic androgen receptor (AR), which results in cell growth and division and inhibition of apoptosis.

Downregulating AR signaling though disruption of this pathway is the key to slowing the growth of prostate cancer at all disease stages and is most commonly done with the use of treatments collectively referred to as hormonal therapy. Currently, there are three general classes of hormonal agents: the gonadotropin-releasing hormone (GnRH) agonists, which inhibit gonadal secretion of testosterone; the adrenolytic agents and 5α-reductase antagonists, both of which lower extragonadal sources of androgens; and the antiandrogens, which directly bind to and antagonize the AR. Although these treatments are useful in slowing the growth of prostate cancer, their effectiveness is limited by the eventual emergence of a resistant tumor phenotype; thus significant debate remains about the best use of these agents. This review discusses the current research in hormonal approaches to treating prostate cancer, focusing on identifying the optimal timing and use of these agents as well as on novel hormonal drug development.

Inhibiting Gonadal Androgen Production: GnRH Agonists

Early-stage disease: the role of androgen deprivation

Androgen deprivation therapy (ADT) with GnRH agonists such as leuprolide, goserelin, histrelin, and triptorelin decreases circulating testosterone to castrate levels (< 50 ng/mL), thus slowing tumor cell growth. Although in newly diagnosed patients with early-stage (organ-confined) disease there are few data supporting the use of ADT monotherapy over definitive surgery or radiotherapy [3], there is strong evidence of a benefit from combining ADT with primary radiotherapy for intermediate- and high-risk localized disease. The recently reported long-term follow-up of Radiation Therapy Oncology Group 8610, a randomized phase 3 trial of men with locally advanced (T2–4) prostate cancer, showed that the addition of ADT and an antiandrogen to external beam radiation therapy (EBRT) significantly improved 10-year disease-free survival (11% vs 3%; \( P < 0.0001 \)), with a trend toward better 10-year overall survival (OS; 43% vs 34%) when compared with EBRT alone [4•]. These results correlate well with two prior randomized studies showing disease-specific survival and OS benefits of neoadjuvant ADT combined with primary radiotherapy [5,6]. Studies have demonstrated that ADT administered for as little as 4 months is associated with improvements in progression-free survival (PFS) [7], whereas treatment for 6 months can improve OS for those with intermediate risk [8•].
Although the optimal duration of neoadjuvant/adjuvant ADT in combination with radiotherapy (4–6 months vs 2 years) has not been clearly established, it is clear that adding ADT to primary radiotherapy is beneficial in preventing disease relapse.

Although there is strong evidence of a neoadjuvant benefit of ADT in conjunction with primary radiotherapy, the overall benefit of neoadjuvant ADT before prostatectomy is less clear. Although studies have suggested that neoadjuvant ADT reduces the rates of positive margins by up to 50% [9–11], they have not demonstrated significant differences in operative time, operative blood loss, length of hospital stay, or complication rates [12]. More importantly, long-term follow-up of three randomized controlled clinical trials published since the early 1990s has shown little evidence that ADT prevents or delays prostate-specific antigen (PSA) progression after radical prostatectomy [11,13,14]. Thus the present data do not support the routine use of neoadjuvant ADT for patients undergoing a prostatectomy with curative intent.

**Advanced disease: early versus deferred ADT**

For men with locally advanced or metastatic disease, or those with a rising PSA after definitive surgery or radiotherapy, ADT slows time to progression, improves symptomatic bony metastases, and increases OS [15]. Although effective in slowing tumor growth, ADT with a GnRH agonist is not curative and causes significant side effects, including fatigue, sexual dysfunction, vasomotor instability, osteoporosis, changes in body metabolism, and increased risks of diabetes and coronary artery disease. Thus the question of when to initiate ADT in this population, as well as the relative advantages of continuous versus intermittent therapy, is still undecided.

The decision of when to initiate ADT has been addressed in several clinical trials. A Medical Research Council trial found that men with locally advanced or metastatic disease treated with early ADT had fewer episodes of pathologic fracture, ureteral obstruction, spinal cord compression, andextraskeletal metastases than men treated with ADT at the time of objective disease progression [16]. Despite these apparent benefits, the long-term analysis showed no difference in OS in men who received early versus deferred ADT. Similarly, a 2008 update of European Organisation for Research and Treatment of Cancer (EORTC) 30846 did not find any difference in survival between early and deferred treatment for men with untreated N1–3 primary tumors [17].

In contrast, a trial performed by the Eastern Cooperative Oncology Group found that early ADT conferred a significant disease-free survival benefit (77% vs 18%) and an OS benefit (35% vs 15%) at a median follow-up of 12 years for men with node-positive disease at the time of surgery. This trial was criticized, however, for its underpowered, small sample size, as well as the fact that higher Gleason scores did not correlate with worse outcome [15]. A separate trial, EORTC 30891, suggested a modest benefit from early ADT for advanced disease, with trends toward worse OS for patients receiving deferred therapy (hazard ratio [HR], 1.25) [18]. Meta-analysis incorporating these and older trials have found that early therapy provides significantly higher PFS at 5 years (odds ratio [OR], 3.15) and OS at 10 years (OR, 1.5) [19], although these data should be regarded with some caution as most trials were performed before the routine use of PSA testing and thus could not take PSA velocity or doubling time into account before “deferred” therapy was begun.

In summary, although it appears from clinical trials that early ADT reduces symptomatic progression and may offer a survival advantage, these conclusions should be regarded caustiously as most studies began before the routine use of PSA monitoring and therefore may not apply to current clinical practice. The benefits of early therapy must be counterbalanced with significant impairments in quality of life and increased risks of cardiovascular and osteoporotic disease. For men with high-grade metastatic disease or for those with large-volume localized tumors, the risk–benefit ratio appears to favor early ADT; conversely, for men with PSA-only low-grade disease or for those with a small volume of localized disease and a slowly rising PSA (PSA doubling time > 6 months), deferred therapy may be more appropriate.

**Advanced disease: intermittent versus continuous therapy**

Given the known toxicity of ADT with GnRH agonists, significant interest has been generated in using cyclic, or intermittent, androgen deprivation (IAD). IAD involves treating patients for a prespecified period (usually up to 1 year), followed by discontinuation of therapy in patients achieving a significant PSA response, and then active surveillance until the PSA reaches a threshold level at which ADT is reinitiated. There is a twofold rationale for this therapy: 1) intermittent therapy prevents some of the long-term toxic effects of continuous ADT, and 2) preclinical models suggest that it prolongs the time to development of castration-resistant disease by impairing the treatment-mediated selection for castration-resistant cells that naturally occurs after prolonged exposure to ADT [20].

Early results from several trials of IAD versus continuous androgen blockade suggest improved quality of life in the IAD arms, with similar cancer-specific outcomes. In a German study of 335 men with node-positive or metastatic disease, IAD has been associated with a trend toward longer PFS (16.5 vs 11.5 months) and similar OS [21]. Three ongoing multicenter phase 3 trials (EC507, Southwest Oncology Group [SWOG]-JPR7, and SWOG 9436), projected to accrease close to 3000 patients in total, are currently underway in the United States, Europe, and other sites worldwide and should address this question.