Advances in Prostate Cancer Chemotherapy: A New Era Begins[1]

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ABSTRACT Prostate cancer continues to be the most common lethal malignancy diagnosed in American men and the second leading cause of male cancer mortality. Over 60 years ago, Huggins and Hodges discovered androgen deprivation as a first-line therapy for metastatic prostate cancer, which leads to remissions typically lasting 2 to 3 years, but in most men prostate cancer ultimately progresses to an androgen-independent state resulting in death due to widespread metastases. Multiple mechanisms of androgen independence have now been documented, including amplification of the androgen receptor as well as signal transduction pathways that bypass the androgen receptor completely. In 2004, two landmark studies demonstrated a survival advantage in androgen-independent prostate cancer patients utilizing docetaxel chemotherapy, setting a new standard of care for this disease. In addition, treatments with the bisphosphonate zoledronic acid and systemic radioisotopes have also been shown to have palliative benefits in this population. Building on these advances, several new traditional chemotherapeutic agents as well as new targeted therapies are under development. (*CA Cancer J Clin 2005;55:300–318.*)

INTRODUCTION

Prostate cancer continues to be the most common lethal malignancy diagnosed in American men and the second leading cause of male cancer mortality. The American Cancer Society estimates that during 2005 about 232,090 new cases of prostate cancer will be diagnosed in the United States and 30,350 men will die of metastatic disease.[1] About 1 man in 5 will be diagnosed with prostate cancer during his lifetime, and 1 man in 33 will die of this disease. As the population ages, these numbers are expected to increase. Over 60 years ago, Huggins and Hodges discovered androgen deprivation as a first-line therapy for metastatic prostate cancer.[2,3] Hormonal therapy leads to remissions typically lasting 2 to 3 years, but in most men metastatic prostate cancer ultimately progresses to an androgen-independent state resulting in death due to widespread metastases.[4–8] Bone metastases are accompanied by an osteoblastic reaction in the bone that is unmatched by any other type of cancer (Figure 1). Autopsy studies reveal that metastases to other organs are prevalent with common sites including lymph nodes, lung, adrenal glands, and liver.

MECHANISMS OF ANDROGEN RESISTANCE

During androgen-dependent progression, prostate cancer cells depend primarily on the androgen receptor for growth and survival.[9–11] When testosterone enters the cell, it is converted to its active metabolite dihydrotestosterone (DHT) by the enzyme 5α reductase. DHT then binds androgen receptors in the cytoplasm and translocates into the nucleus, binding to the androgen-response elements within the DNA and thereby activating genes involved in cell growth.[9] During androgen-independent progression, prostate cancer cells develop a variety of cellular pathways to survive and flourish in the androgen depleted environment (Figure 2).[9–14] The first pathway has been referred to as the *hypersensitive pathway*. In this pathway, more androgen receptor (AR) is produced by the cell and may be activated despite reduced levels of

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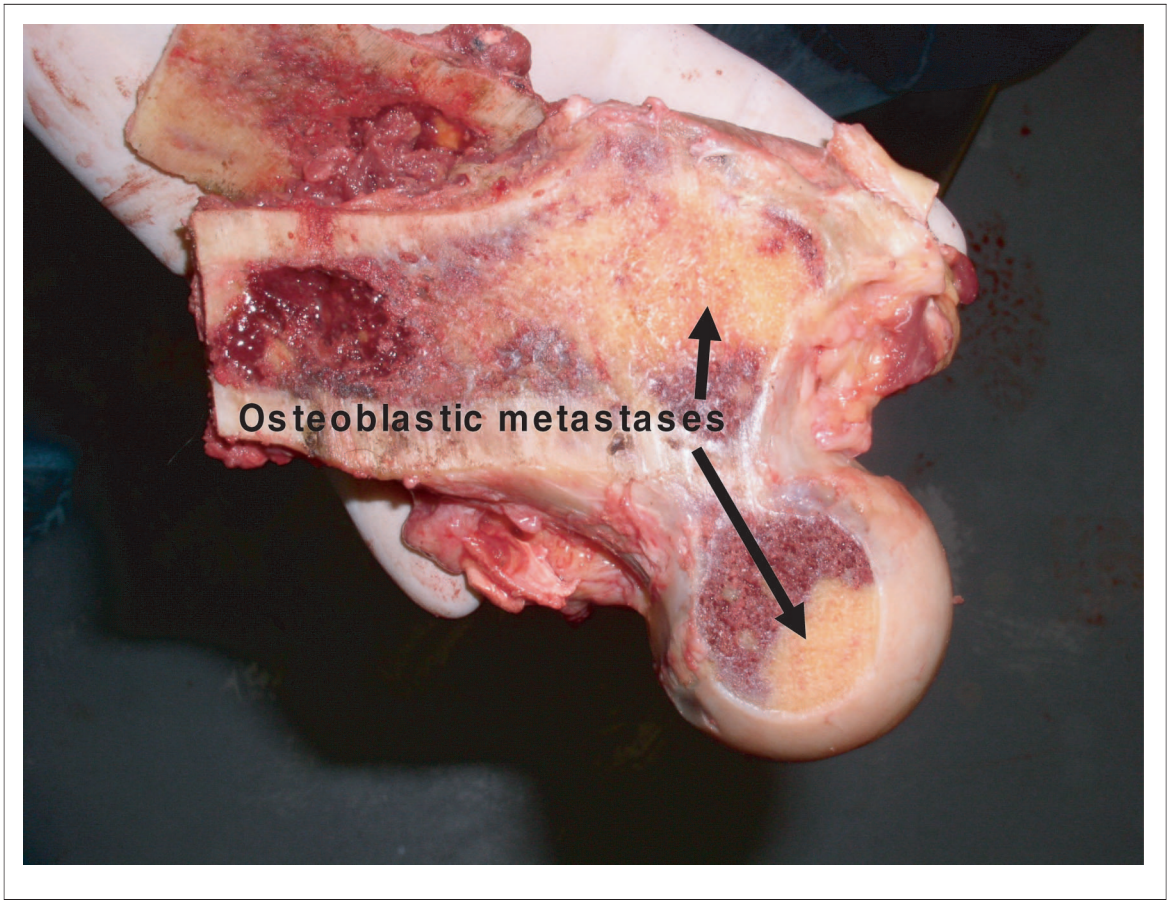

FIGURE 1 Osteoblastic Metastases in Bone. The osteoblastic reaction common to prostate cancer is demonstrated in the hip of a patient with late-stage prostate cancer.

dihydrotestosterone. This increased production of AR is likely the result of the prostate cancer cells developing more copies of the AR gene (gene amplification) as a result of mutation or through selective pressure of the androgen-depleted environment, causing the cells with fewer androgen receptors to die off and the clonal expansion of cells with more AR. It is likely that hormone refractory prostate cancer is not "androgen independent" in the classic sense, but rather "castration independent" and that the cancer is now able to use very low levels of androgen to grow.

The specificity of the AR can also be broadened by mutations, creating a *promiscuous receptor* that can be activated by nonandrogenic steroid molecules normally present in the circulation.[9–11] To be activated, the AR must be phosphorylated and this phosphorylation can be accomplished by other nonsteroid molecules through two separate pathways. In one pathway, termed the *outlaw pathway*, molecules such as deregulated growth factors and cytokines directly phosphorylate and activate the AR. In the second pathway, termed the *bypass pathway*, cell survival occurs independent of AR activation. The best example of this pathway is the upregulation of the molecule BCL-2 by androgen-independent prostate cancer cells which protect them from apoptosis or programmed cell death when they are exposed to lack of testosterone.

Other postulated mechanisms of androgen independence include the involvement of cells that support the growth of the cancer cells. For example, neuroendocrine cells may secrete neuropeptides that induce the growth of androgen-independent cancer cells. Alternatively, prostate cancer stem cells may be present in the prostate tumor, supporting the growth of androgen-independent cells as the androgen dependent cells regress as a result of hormone therapy.

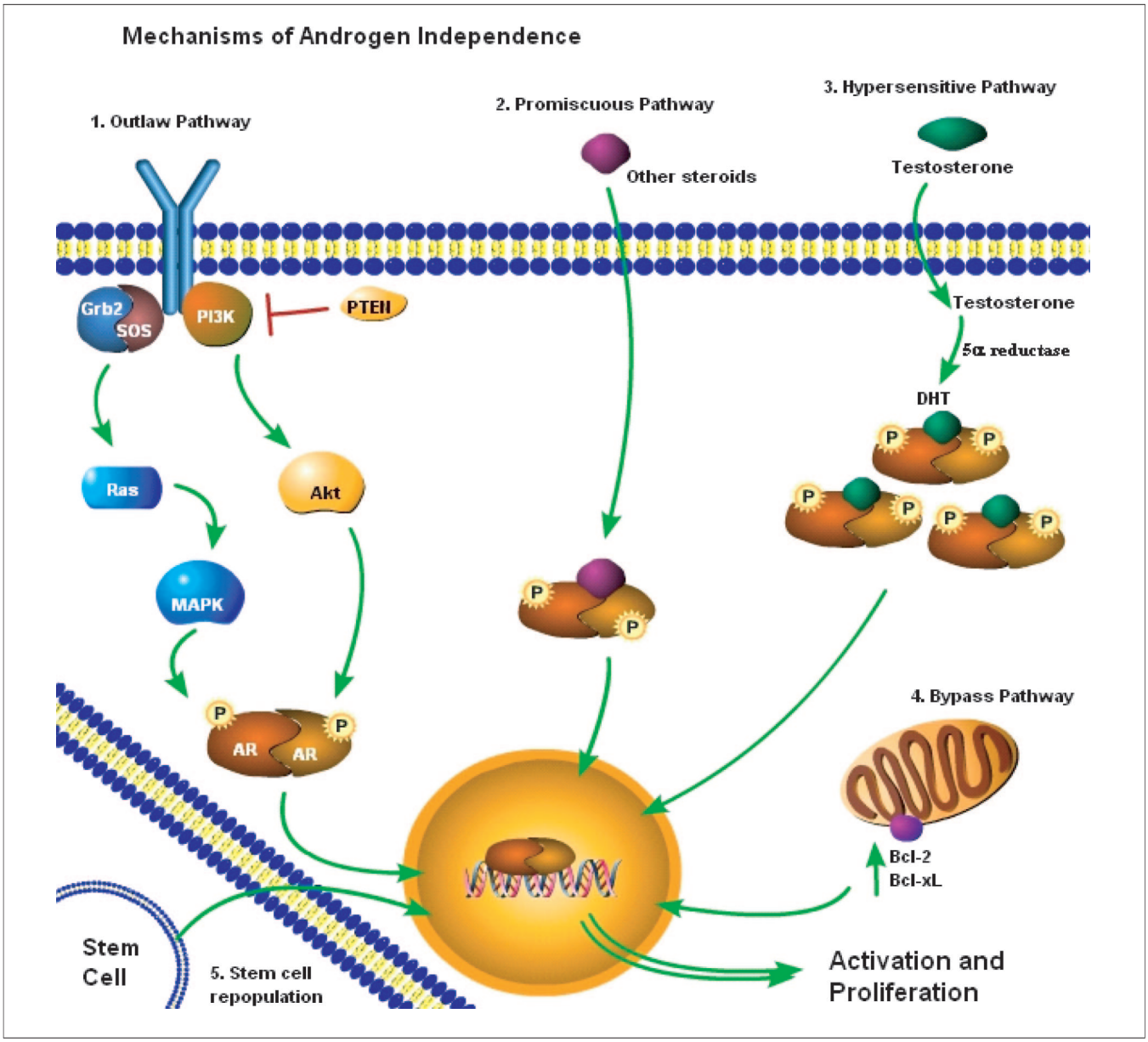

FIGURE **2** Possible Pathways to Androgen Independence. (1) In the *outlaw pathway*, receptor tyrosine kinases (RTKs) are activated, and the androgen receptor (AR) is phosphorylated by either the AKT (protein kinase B) or the mitogen-activated protein kinase (MAPK) pathway, producing a ligand-independent AR. (2) In the *promiscuous pathway*, the specificity of the AR is broadened so that it can be activated by nonandrogenic steroid molecules normally present in the circulation. (3) In the *hypersensitive pathway*, more AR is produced (usually by gene amplification), AR has enhanced sensitivity to compensate for low levels of androgen, or more testosterone is converted to the more potent androgen, dihydrotestosterone (DHT), by 5α reductase. (4) In the *bypass pathway*, parallel survival pathways, such as that involving the antiapoptotic protein BCL-2 (B-cell lymphoma 2), obviate the need for AR or its ligand. (5) In the *stem-cell repopulation pathway*, androgen-independent cancer stem cells are resistant to therapy and eventually grow out and eventually become the primary population within the tumor.

THE EVOLUTION OF CHEMOTHERAPY FOR HORMONE REFRACTORY PROSTATE CANCER: THE PRETEXANE ERA

In 1993, Yagoda and Petrylak wrote a definitive review on the use of chemotherapy in patients with hormone refractory prostate cancer.[15] Earlier reviews had reported objective responses in the form of complete and partial remissions in approximately 6.5% of patients treated with anthracyclines, alkylating agents, antimetabolites, platinums, and topoisomerase inhibitors. In their review of 26 new trials published in the years 1987 to 1991, they found an overall response rate of 8.7% (95% confidence interval, 6.4% to 9.0%)

and concluded that hormone-refractory prostate cancer was unresponsive to cytotoxic agents.[15] They further noted that documentation of response was complicated by a lack of established criteria to judge activity in a disease in which few patients had measurable soft tissue lesions. They noted that: "Chaos will continue to reign when the efficacy of one drug is reported to be 0 to 85%...when investigators continue to include stable disease findings within a so-called objective response category, thereby intimating that significant prostate cancer cell death has occurred."[15] In 1997, Raghavan and colleagues reinforced the concept that the clinical utility of cytotoxic therapy in advanced prostate cancer was undefined and that this was partially attributable to the lack of established criteria for judging response in treatment of a disease that was largely evident by bone scan only.[16]

Before the prostate-specific antigen (PSA) era, classic response rates could only be determined in the minority of patients with measurable disease (approximately 10% to 20%). Controversy existed as to whether these patients with soft tissue disease were representative of advanced prostate cancer patients in general who only had metastases to bone. In the early 1990s, PSA assays became widely available and response to agents in clinical trials began to be measured and reported in terms of PSA response.[17–21] In Phase II trials, a decline in PSA by 50% appeared to correlate with increased survival.[17] In 1999, a consensus conference suggested that a partial response in clinical trials be defined as a minimum a PSA decline of at least 50% confirmed by a second PSA value 4 or more weeks later in the absence of clinical or radiographic evidence of disease progression during this time period.[19] The use of the PSA endpoint, although not validated in a Phase III trial as a surrogate for response or survival, has become the standard method to screen for activity in Phase II trials.

CHEMOTHERAPY FOR HORMONE REFRACTORY PROSTATE CANCER: THE TAXANES

Starting in the 1990s, preclinical studies demonstrated that prostate cancer cells appeared to be especially sensitive to mitotic spindle inhibitors including vinblastine, paclitaxel, and docetaxel.[22–27] Several Phase II studies were initiated based on the preclinical data. The most active agent preclinically and clinically was docetaxel, either alone or in combination with estramustine.[28–30] Docetaxel, a semisynthetic taxane, likely has multiple mechanisms of antineoplastic activity. Microtubule stabilization, the most widely accepted mechanism of action, involves binding of docetaxel to β-tubulin, thus promoting polymerization (Figure 3). In normal cellular division, microtubules act as the cytoskeleton for the mitotic spindle. Under usual conditions, microtubules undergo polymerization in the presence of microtubule-associated proteins. Once bound by taxanes, microtubules cannot be disassembled. This static polymerization disrupts the normal mitotic process, usually arresting cells in the G_2M phase of the cell cycle, ultimately leading to apoptosis. Estramustine is known to bind to microtubule associated proteins and one proposed mechanism for this agent is to act in concert with the taxanes to inhibit microtubule function.

A second proposed mechanism for the cytotoxicity of docetaxel is that it can counter the prosurvival effects of *BCL-2* expression. It has been demonstrated that *BCL-2* overexpression protects prostate cancer cells from apoptosis after androgen withdrawal, and that increased *BCL-2* expression confers both chemo- and androgen-resistance.[31–33] The *BCL-2* gene is part of a class of oncogenes that contributes to neoplastic progression by inhibition of apoptotic cell death. Phosphorylation of BCL-2 protein leads to loss of BCL-2 antiapoptotic function.[34] Docetaxel induced microtubule stabilization arrests cells in the G_2M phase, inducing BCL-2 phosphorylation and forcing the continued activation of the caspase cascade, leading to increased apoptosis. Other studies have reported multiple other proapoptotic effects of docetaxel, including effects on *BCL-xL*, induction of p53, ability to overcome multidrug resistance and antiangiogenic properties.[28]

PHASE I/II CLINICAL STUDIES OF DOCETAXEL

Several Phase II trials evaluated docetaxel as a single agent in patients with hormone refrac-

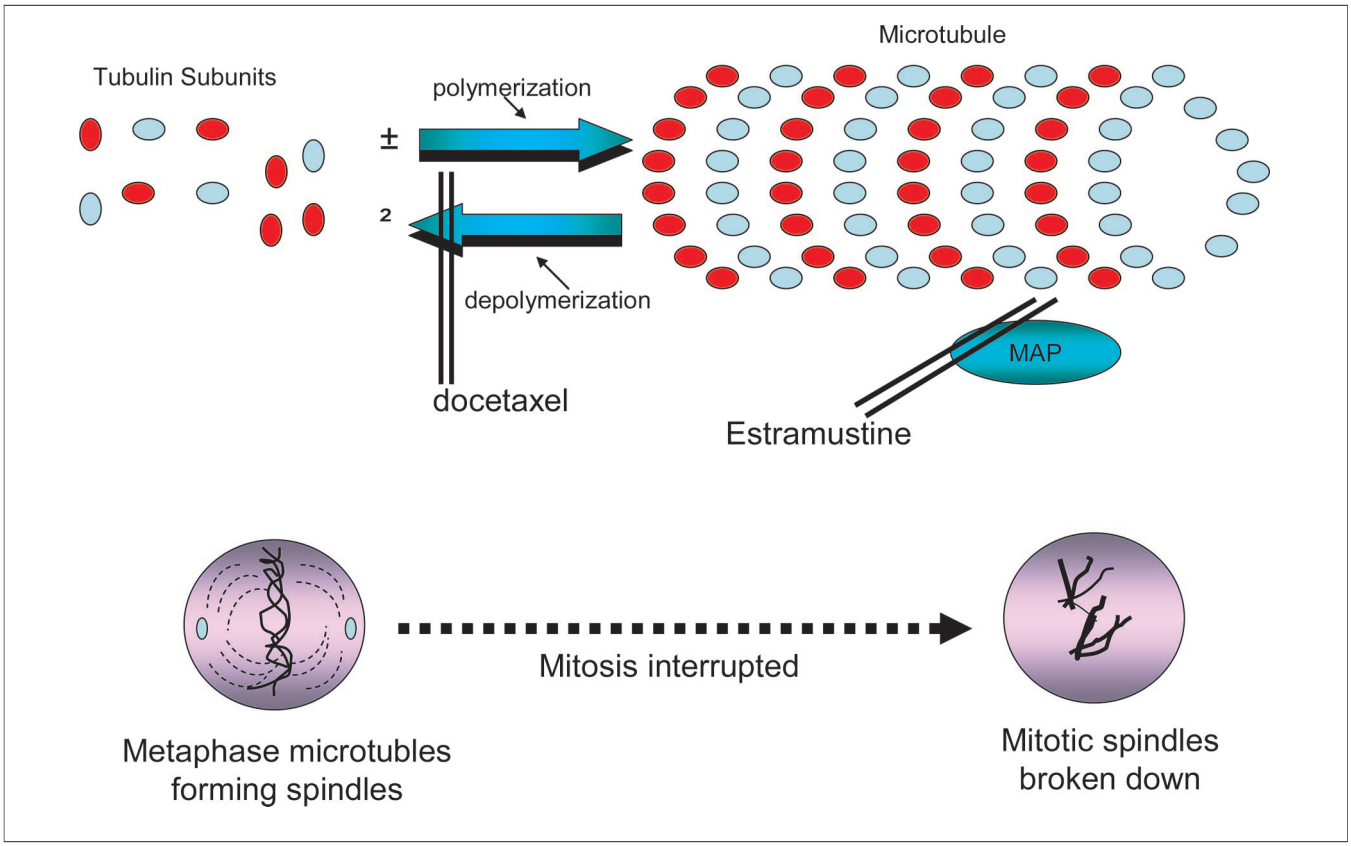

FIGURE 3 Docetaxel Has Multiple Mechanisms of Antineoplastic Activity. Microtubule stabilization involves binding of docetaxel to β-tubulin, thus promoting polymerization. In normal cellular division, microtubules act as the cytoskeleton for the mitotic spindle. Under usual conditions, microtubules undergo polymerization in the presence of microtubule-associated proteins. Once bound by taxanes, microtubules cannot be disassembled, disrupting the cell and leading to programmed cell death (apoptosis).

tory prostate cancer. The pharmacokinetics of docetaxel are linear with dose and remain independent of schedule. A variety of weekly and every 3-week schedules have been evaluated.[35] Results of these studies are summarized in Table 1. Response rates by PSA criteria ranged from 38% to 48%. Neutropenia was the principal toxicity, occurring in up to 70% of patients treated on an every 3-week schedule. Neutropenia was less common on the weekly schedule with similar response rates. Clearance of docetaxel is primarily via hepatic metabolism with increased toxicity associated with decreased hepatic metabolism. Other notable toxicities include fluid retention, rash, and peripheral neuropathy. Premedication with steroids is used to decrease the risk of fluid retention. Response rates as high as 70% were seen in the studies that investigated the combination of estramustine and docetaxel. Side effects were significant, with neutropenia in up to 70% of patients and thrombosis in up to 10%. Fatigue and hyperglycemia were also common. Based on these studies, Phase III trials of docetaxel and the combination of docetaxel and estramustine were designed.

PHASE III STUDIES OF DOCETAXEL IN HORMONE REFRACTORY PROSTATE CANCER

Two Phase III trials of docetaxel in men with hormone refractory disease were reported in 2004. Both demonstrated a survival advantage and docetaxel has become the new standard of care for first-line treatment in this setting. Both trials randomized docetaxel verses mitoxantrone, an agent that has been shown to improve quality of life but failed to demonstrate a survival benefit.[44]

The Southwest Oncology Group (SWOG) 9916 trial, docetaxel and estramustine compared

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