1. INTRODUCTION

Androgen deprivation therapy (ADT) has been the standard of care for patients with advanced prostate cancer for over 50 years. Most patients will respond to this treatment by demonstrating symptomatic improvement, regression of metastases, and almost always by a decline in prostate-specific antigen (PSA) levels. However, the median duration of response to ADT is only 18–24 months for patients with metastatic disease. About 30–40% of patients will respond to further hormonal manipulation, but the majority will become refractory to this treatment within months. Metastatic hormone refractory prostate cancer (HRCaP) is both morbid and rapidly progressive, with a median survival of 18–20 months.

Until recently, no therapy had been shown to prolong life in men with HRCaP. Chemotherapy was historically viewed as ineffective in part because for many years, the development and recognition of effective treatment for prostate cancer was hampered by difficulties in assessing patient response to therapy. Early
clinical trials of chemotherapy in patients with advanced disease enrolled patients with symptomatic disease, high tumor burden, and poor performance status: in these trials, objective response rates were less than 10% (1,2). However, the recognition of both PSA response as an assessment of activity and palliation of symptoms as clinically meaningful led to a reevaluation of the role of chemotherapy in treating HRCaP.

In the 1990s, PSA became widely available and was soon adopted as a marker of response in clinical trials. Evidence showed that post-therapy decline of PSA, and the dynamics of that decline, could be used to predict survival (3–5). In 1999, the Prostate Specific Antigen Working Group established a definition of PSA response as a $\geq 50\%$ decline in PSA, confirmed by a second PSA value at least 4 weeks later, without clinical or radiographic evidence of disease progression (6), a definition now widely accepted by clinical investigators. During these years, investigators also focused on examining whether chemotherapy was of palliative benefit (7). Pain scales and instruments to assess quality of life were developed and used as primary and secondary endpoints in clinical trials. The approval by the US Food and Drug Administration of the first chemotherapeutic agent for use in HRCaP, mitoxantrone, was based largely on its palliative benefit.

In 2004, two important phase III studies were published demonstrating for the first time that chemotherapy provided a survival benefit in patients with HRCaP. Both studies utilized docetaxel-based regimens, and docetaxel plus prednisone has become the standard first-line therapy for HRCaP. As a result, efforts to study this agent both in combination with other established agents and with novel chemotherapeutic and targeted therapies have been initiated. Following the model established in other solid tumors such as colon and breast, docetaxel is also being investigated in patients with early-stage disease at high risk of recurrence after definitive therapy. This chapter will discuss the evolution of chemotherapy’s role in the treatment of HRCaP, the recent trials showing a survival benefit to docetaxel-based regimens in HRCaP, and the promising new regimens for both advanced and early stage disease now in development.

2. CHEMOTHERAPY FOR ANDROGEN-INDEPENDENT PROSTATE CANCER

2.1. Demonstrating Clinical Benefit to Chemotherapy in HRCaP: Mitoxantrone and Prednisone

Clinical trials of chemotherapy conducted in the 1970s and 1980s demonstrated limited benefit in patients with HRCaP. However, with the introduction of PSA response as a measure of drug activity, quality of life measures as clinical outcomes, better supportive therapy, and a more rational approach to the selection of chemotherapeutic agents, there were hints that chemotherapy