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UROLOGIC ONCOLOGY

News and topics

Role of collaboration between urologists and medical oncologists in the advanced prostate cancer space

Historical treatment paradigm in advanced prostate cancer

As near as 2009, the transfer in responsibility of care along the prostate cancer spectrum was more easily divisible (Fig.). Urologists were responsible for most of the care beginning with an abnormal screening prostate-specific antigen up to the time of development of castration-resistant metastatic disease, when chemotherapy was the sole remaining approved therapeutic option. Although medical oncologists might have seen patients before the development of castration-resistant status to discuss possible clinical trials or at times administer androgen deprivation therapy (ADT) for biochemical recurrence, this was not the standard. At the time of development of castration-resistant prostate cancer (CRPC) and in particular metastatic CRPC , care would transition to a medical oncologist with limited further interaction with the initial treating urologist. Median overall survival in this era at the point of developing castration-resistant disease was approximately 18 months, with variation based on risk factors [1]. The treatment options, estimated survival, and patient profiles were most suited for the Medical Oncology practice familiar with such scenarios.

Though historically most followed the above model, with referral to Medical Oncology at the CRPC stage, this was subject to some geographic variation. An analysis of data from 2009 to 2010 Adelphi Real World Prostate Cancer Disease Specific Programme, associated physician interviews, and physician-completed patient record forms revealed some significant variations in those who were managing patients with prostate cancer between European nations [2]. Although in general, urologists were more likely to manage patients with early stage disease and medical oncologists manage those with late stage disease; in Germany, urologists' involvement in management of CRPC was greater than other countries. In the United Kingdom, medical oncologists were involved even in the earliest stages of disease, with involvement remaining steady across the disease spectrum. A more recent survey of urologists in Spain conducted in 2012 found that after progression on ADT, urologists were responsible for 96% of secondary hormonal manipulation with limited involvement by medical or radiation oncologists [3]. After secondary hormonal therapy, only 50.5% of patients with CRPC were referred to medical oncology, and even if they were, the vast majority (83.6%) returned to the urologists' care after completion of chemotherapy. This pattern displays a high degree of urologic-patient ownership, and may reflect a desire to maintain continuity of care. In a similar vein, a study conducted in United States in the era predating the introduction of the novel therapies found 48% of urologists were interested in learning more about chemotherapeutic regimens and the logistics of delivering them [4].

The urologic perspective

Beyond early advanced prostate cancer (i.e., biochemical recurrence necessitating ADT), there are multiple stipulated benefits to the continued and even primary involvement of urologists in CRPC care that some of the data on practice patterns suggest. Both providers and patients value the trust that a longitudinal relationship builds. Provision of care by a single physician can minimize treatment delays, the hassles inherent to the referral system, and multiple visits burden. In addition, urologists are also best trained to handle many of the urologic complications of advanced prostate cancer, such as urinary tract bleeding or obstruction and erectile dysfunction [5].

The primary barrier in the past for urologists to continue to treat their patients with CRPC, then, was a lack of expertise in the administration of cytotoxic chemotherapy. Despite nearly 50% of urologists expressing an interest in delivering chemotherapy to their patients, only 4% identified having done so. Those not interested identified lack of knowledge/trained personnel (45%), logistical issues (31%), patient safety concerns (20%), and costs (14%) as the top 3 prohibitive factors [4]. Logistical issues can include limited time during busy clinic schedules, challenges with reimbursement, and development of an infrastructure to deliver chemotherapy. Thus, though interest and potential benefits could be seen to urologists continuing to manage prostate cancer in the

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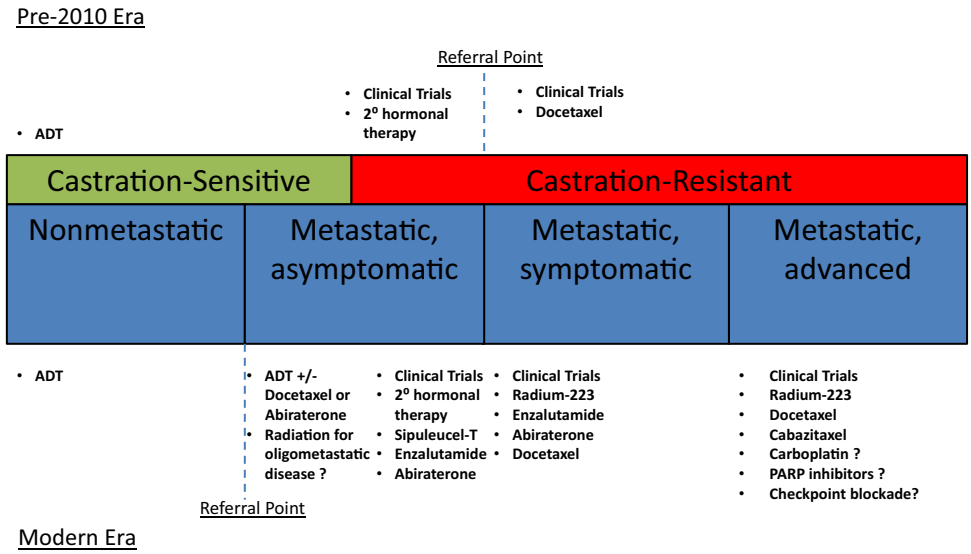

Fig. Therapy options for advanced prostate cancer by era. PARP = poly-ADP ribose polymerase. (Color version of figure is available online.)

castration-resistant stage of disease, cytotoxic chemotherapy was clearly under the purview of medical oncologists.

Changing treatment landscape

In 2010, Provenge (sipeulecel-T) and cabazitaxel were approved for treatment of CRPC after demonstrating a survival benefit compared with placebo [6,7]. This was followed by the approval of Zytiga (abiraterone acetate), the androgen synthesis inhibitor, in combination with prednisone for the treatment of CRPC after progression on docetaxel chemotherapy [8]. A similar approval for the nonsteroidal antiandrogen Xtandi (enzalutamide) followed in 2012 [9]. Ultimately, after demonstrating benefit in the castration-resistant setting even before docetaxel therapy, both were approved in 2014 for use before chemotherapy [10,11]. A final addition to the treatment landscape, Xofigo (Radium-223), was approved in 2014 after demonstrating an overall survival benefit in CRPC with bone-predominant metastatic disease [12]. (Fig) In this new era, estimates of median overall survival for men with metastatic CRPC have more than doubled the prior era, reaching 40 months in some cohorts [13].

The approval of new therapies before chemotherapy in the treatment course has changed the immediacy of involvement of medical oncologists in CRPC care. The challenges posed by cytotoxic chemotherapy administration are no longer paramount. The new agents are not associated with the typical logistical issues and toxicities associated with chemotherapy, with 2 of them (abiraterone acetate and enzalutamide) being oral medications. Sipeulecel-T and Radium-223 are treatments removed from both the usual Medical Oncology and Urology practices, with unique delivery models not predicated on a chemotherapy infusion room infrastructure. Both are time-limited, albeit infusion-based, interventions that require support from the American Red Cross or Nuclear Medicine, respectively. Pharmaceutical companies promoting these medications market their use by urologists as well as medical oncologists, providing avenues for both types of providers to prescribe them.

In addition to the introduction of new agents to the treatment landscape, we have learned from several practice-changing studies that in many patients with hormone-naive disease there is a benefit to earlier systemic treatment beyond ADT alone. In 2015, The CHAARTED and STAMPEDE studies demonstrated a clear role for chemotherapy in a large population of patients even at the time of first diagnosis of metastatic disease [14,15]. Until June of 2017, almost incontrovertibly, one could argue that all eligible patients with high-volume hormone-naïve metastatic burden should receive docetaxel chemotherapy concomitantly with ADT rather than waiting for castration resistance. In the high-volume subgroup in the CHAARTED trial, docetaxel therapy was associated with a dramatic overall survival benefit of 17 months [14,16]. The data were less clear on patients with low-volume metastatic disease, but notably docetaxel treatment effects for failure-free survival and prostate cancer-specific survival from STAMPEDE were similar between those with and without metastatic disease [15]. Paradoxically, in the era of novel therapies that seemed to afford greater independence from chemotherapy, these data suggested chemotherapy must actually be considered even earlier in the prostate cancer disease continuum than previously thought.

Only 2 years later, 2 large trials reported the benefit of abiraterone in addition to ADT at the time of initial diagnosis of metastatic castration-sensitive prostate cancer (mCSPC). LATITUDE, a phase III randomized, placebo-controlled study in high-risk, metastatic, hormone-naïve prostate cancer patients of abiraterone/prednisolone plus ADT vs. ADT alone, was stopped at the first interim analysis owing to a clear benefit to earlier initiation of