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Toward a Common Therapeutic Framework in Castration Resistant Prostate Cancer: A Model for Urologic Oncology and Medical Oncology Interaction

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Abstract

The rapid evolution of palliative therapeutic choices in the last few years for patients with advanced castration resistant prostate cancer (CRPC) has resulted in a dilemma currently troubling a few other epithelial malignancies: which systemic agent to choose and at what time? In addition, which specialty specifically directs the delivery of such care – Urology or Medical Oncology – has not been clearly established. Recognizing the lack of consensus, we propose a framework for Urology and Medical Oncology interactions that is founded on models that have succeeded in the past. This approach aims to focus the care on the CRPC patient rather than on his physicians and promises to improve patient outcomes in this disease state.

BACKGROUND

The therapeutic landscape in castration resistant prostate cancer (CRPC) has rapidly evolved in just the past six years. Five new systemic agents, each with a different mechanism of action, have demonstrated improved survival when compared to a reasonable control arm in various CRPC patient contexts. These agents include enzalutamide (an androgen receptor antagonist)[1], abiraterone (CYP17 inhibitor)[2], sipuleucel-T (immunotherapy)[3], cabazitaxel (cytotoxic chemotherapy)[4], and radium 223 (radioisotope)[5]. Each of these agents has already been approved by the US Food and Drug Administration and has since become commercially available.

This plethora of new agents in CRPC is somewhat comparable to recent developments in the treatment of advanced renal cell cancer (RCC) and colorectal cancer (CRC). In these malignant solid tumors, an “embarrassment of riches” relating to the sudden availability of newer effective agents has led to clinical conundrums that revolve around the optimal sequence of therapies, cost-effectiveness, and appropriate patient selection, among others.[67]

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To this day, these issues remain highly controversial even within the RCC and CRC communities, with no clear consensus reached. It is quickly becoming apparent that CRPC has now joined this club.

It also must be noted that each of the new CRPC agents was evaluated in an era where docetaxel was the predominant standard-of-care, resulting in a clinical classification system based on whether a CRPC patient had previously received docetaxel. These “pre-docetaxel” and “post-docetaxel” designations were of regulatory and administrative value but had no clear biologic or molecular basis. Undoubtedly, this classification system thrust the medical oncologist, the principal prescriber of cytotoxics, as a gatekeeper in the CRPC decision-making algorithm as it pertains to docetaxel use. On the other hand, the urologist has free rein in the pre-docetaxel setting, having typically managed the advanced prostate cancer patient through his evolution to castration resistance. In the pre-docetaxel space, the urologist suddenly has new systemic agents in the therapeutic armamentarium, two of which are orally bioavailable (enzalutamide and abiraterone) and therefore relatively easy to prescribe.

CLINICAL DILEMMAS

This state of affairs has created new clinical dilemmas and questions. Notably, should all patients be treated similarly? Is this the optimal sequence: LHRH agonist or antagonist followed by additional hormonal therapy (such as abiraterone) and after failure on hormonal agents, referral for docetaxel-based chemotherapy? In practice, sipuleucel-T or Radium 223 gets inserted along this continuum according to the individual physician’s and patient’s preference. However, clinical situations exist that already suggest different clinical scenarios based on response to initial LHRH therapy that may direct a different sequencing approach to subsequent therapies. Certainly, we are freed from the old turf wars concerning who should be primarily responsible for treating CRPC patients in the pre-docetaxel context. However, should a urologic oncologist exhaust all available non-chemotherapy options prior to a referral to medical oncology? We contend that this issue should no longer be relevant in the modern era. The guidelines for who gets which therapy when should be determined by the clinical scenario, not by the specialist the patient is seeing at the time. We believe that to establish the best care models, consensus must first be reached. The process needs to be flexible and not over burdensome. Many agents have only recently received FDA approval, other companies are about to apply for such. Therefore, the recommendation on the best sequencing of therapies can be expected over time to change.

These dilemmas have certainly not been lost on the pharmaceutical industry, which stands to benefit from more widespread use of their marketed agents. As a result, high-profile industry presence has become the norm in annual meetings organized by the American Urological Association and the American Society of Clinical Oncology (ASCO). Additionally, many pharmaceutical companies have organized a two-pronged marketing approach that targets urologists and medical oncologists as separate markets. Some have even resorted to a “direct to consumer” strategy, advertising in mass media to influence the CRPC patient (the ultimate consumer) who may in turn influence the upstream prescriber, whether a urologist or medical oncologist. On the other hand, academics and the pharmaceutical industry have

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also quickly recognized that resistance (whether *de novo* or acquired) occurs for all available therapies, thus there is pressure to maximize or optimize each patient's response to *all* the available therapies.

INTEGRATING CARE

The CRPC patient should never be lost in this nebulous clinical scenario. It is in the CRPC patient's best interest for all his caregivers to buy into an integrated and comprehensive approach, one that dissolves artificial boundaries and establishes seamless transitions of care. This requires joint management of the CRPC patient by both specialties from the initial manifestations of castration resistance to the end-of-life. In the academic setting at the professional society level, partnerships between these specialties have already been modeled by inter-society collaborations grounded in medical education or by multi-disciplinary clinical research. For example, the Society of Urologic Oncologists (SUO) has successfully worked with ASCO in planning the annual Genitourinary Cancer Symposium, resulting in an integrated and interactive educational forum. In cooperative groups such as SWOG, phase III trials have been successfully co-developed and conducted by urologic oncologists and medical oncologists. These established mechanisms can be used as a model to establish a framework of clinical cooperation and partnership between specialists who care for the CRPC patient.

However, in the doctor-to-doctor everyday setting, this level of interaction is uncommon, and this needs to change. A necessary product of the urology-medical oncology partnership is the establishment of common management guidelines beyond those promulgated by existing organizations such as the NCCN. These urology-medical oncology CRPC consensus guidelines should not only identify the available therapeutic options (and the sequence of such therapies) but – just as importantly – also clearly define treatment goals and responsibilities of each provider throughout the trajectory of CRPC care, patient selection, evaluation and follow-up. Thus the patient receives state-of-the-art care regardless of which specialist he sees. One strategy to help immediately implement this plan would be to organize a meeting the day before the annual Genitourinary Cancer Symposium since all interested parties are presumably present. This would allow for the established guidelines to be easily reviewed on a yearly basis. In large practice groups, both private and academic, all treating physicians could review and hopefully accept a common course of therapy for patients within their group, regardless of the specialty of the treating physician.

In the community setting, different approaches can be taken. One we have found to be very successful is to have community physicians join the UC Davis Comprehensive Cancer Center GU tumor board via high definition videoconferencing (i.e., tele-medicine). Since nearly all hospitals have a tumor board attended by different specialists, this could initially serve as a platform for guideline discussions. For smaller practices without a multidisciplinary component, the guidelines would help to establish best practices.

Finally, this partnership should be further exploited to develop and pursue clinical studies that will test various models of integrated patient management, similar to how solid organ transplant patients are managed by both surgical and medical specialties. A side benefit from

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these clinical studies would be the incorporation of clinical trials that test novel therapeutic approaches or to optimize the sequencing of available therapies. Presumably when joint CRPC clinical teams exist, they will also have ready access to patient tumor specimens; one can envision that these studies will incorporate translational components for molecular phenotyping to determine *a priori* which patient subset benefits from (or is resistant to) chemotherapy, hormonal therapy, and immunotherapy, among others. Finally, the pursuit of multidisciplinary care has already been piloted in early stage prostate cancer and has been shown to be feasible and adaptable.[89] A recent review noted that multidisciplinary models of care "may be associated with high patient satisfaction rates and may alter practice patterns that minimize physician bias."[10]

It must be acknowledged that there are potential barriers to the successful implementation of this plan. For example, there are financial incentives for physicians to hold on to patients as long as possible. While true, it is also true that when best practice guidelines are provided in an unbiased fashion, the vast majority of physicians follow them. There are also logistical and regulatory barriers for multidisciplinary coordination outside of highly organized health delivery units. However, as stated earlier, "best practice" models can help begin the culture change of collaboration in less organized practice settings. We also suggest wide public dissemination of consensus guidelines to all patient advocacy groups since it is our belief that the well-informed patient can help drive best practice.

SUMMARY

In summary, the CRPC patient deserves no better than an integrated care team that includes both urologic and medical oncology specialties, rather than being managed by a temporal sequence of specialists separated in time and space. In this model, urologists and medical oncologists ought to care for the prostate cancer patient even before the development of castration resistance. There is a critical need to develop these partnerships based on existing models of successful collaboration between specialties. When joint clinics are not possible, joint tumor boards can greatly help. Such boards can be real or virtual, but even where work circumstances preclude the formation of such tumor boards or clinical teams, the treatment of the patient in terms of which therapy he receives and when should be unaltered regardless of the specialty or the doctor treating him. This "call to action" comes at a time when there are suddenly several new systemic therapies available for the CRPC patient. It is anticipated that such a framework will enhance not only patient care, but also yield advancements in clinical research.

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