GENITOURINARY CANCER

Castration-Resistant Prostate Cancer: Hormonal and Nonhormonal Agents

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Nonhormone Therapy for Metastatic Castration-Resistant Prostate Cancer: Chemotherapy, Bone-Targeted Treatments, and Others

Karim Fizazi, MD, PhD

OVERVIEW

There is no doubt that more therapeutic progress has been achieved during the last 3 years for patients with metastatic castration-resistant prostate cancer (mCRPC) than during the previous 30 years. During this limited time frame, not only have six compounds (sipuleucel-T, cabazitaxel, denosumab, abiraterone, radium-223, and enzalutamide, listed in chronologic order) yielded positive results in phase III trials, we have also learned that their mechanisms of action are different, making it quite likely that part of their anticancer activity may be incremental. Most of these agents have already been approved. Further progress may well soon complete this recently enlarged armamentarium, with important trials testing new agents derived from existing families of compounds (new endocrine therapies, new immunotherapies, etc.) and exploring the activity of new families of agents (tyrosine kinase inhibitors such as cabozantinib, inhibitors of chaperone proteins like OGX-011 and OGX-427). The availability of these agents creates a new major challenge for those who conduct clinical research in mCRPC. Will we be able to personalize therapy based on the biology of the individual’s tumor, as we are already doing in other neoplasms?

Endocrine therapy remains the most commonly used treatment for patients with metastatic prostate cancer; however, abiraterone acetate and enzalutamide now demonstrate improved survival in patients in whom androgen deprivation therapy has failed, and agents with other mechanisms of action also demonstrate clinical activity in randomized trials, including chemotherapeutic agents (cabazitaxel), bone-targeted agents (denosumab), radiotherapeutics (radium-223), and immunotherapy (sipuleucel-T). An algorithm summarizing the incorporation of novel agents for the management of advanced prostate cancer (defined as either with metastases or castrate-resistant disease, or both) is proposed in Table 1. This report will focus on nonhormone, nonimmunotherapy agents.

TAXANES: STILL A MAJOR ROLE IN mCRPC

Since 2004, docetaxel has been the standard first-line chemotherapy for patients with mCRPC. The most successful phase III trials recently conducted in mCRPC focused on patients experiencing cancer progression after first-line docetaxel chemotherapy. Indeed, improving their outcome was the most critical unmet need, and this stage also provided an opportunity to demonstrate an overall survival improvement more rapidly with an active drug over a shorter time frame. To date, four drugs have afforded an overall survival benefit on top of other clinical improvements for patients whose disease progressed after docetaxel: cabazitaxel, abiraterone, radium-223, and enzalutamide. When available, their use should now be preferred over a rechallenge with docetaxel, which was regarded before 2010 as a reasonable option, without any proof of a gain in survival for patients who were experiencing progression several months after discontinuation of first-line docetaxel.

Cabazitaxel, a “second-generation” taxane with broader preclinical activity than docetaxel, was shown to improve overall survival when added to prednisone compared with mitoxantrone plus prednisone in the TROPIC trial (hazard ratio [HR] 0.72, 95% CI 0.61 to 0.84; median overall survival, 15.1 vs. 12.7 months; p < 0.0001) in 745 patients with mCRPC progressing after treatment with docetaxel. Progression-free survival (PFS) was also improved with cabazitaxel/prednisone (HR 0.75, 95% CI 0.65 to 0.87). The main side effects included hematologic toxicity and diarrhea; consequently, the use of prophylactic granulocyte colony-stimulating factor with the currently recommended dose of 25 mg/m² will be discussed on an individual basis in routine practice. Preliminary data suggested maintained antitumor activity of cabazitaxel in patients in whom both docetaxel and abiraterone failed, with a prostate-specific antigen (PSA)
response rate of approximately 50%. Two ongoing phase III trials aim to optimize the use of cabazitaxel in patients with mCRPC: a front-to-front comparison trial compared with docetaxel in the first-line chemotherapy setting (FIRSTANA, NCT01308567), and a trial aimed at defining the optimal dose (20 or 25 mg/m²) in the second-line setting (PROSELICA, NCT01308580). Another large phase III trial (PEACE 2) testing cabazitaxel in patients with localized prostate cancer and very high-risk features of relapse is also scheduled to begin its accrual in 2013.

So far, the development of nontaxane chemotherapy has ended with failures, with the development of epothilones almost at a standstill and only modestly improved progression-free survival being reported for satraplatin in the post-docetaxel setting in a phase III trial, although platin-based combinations retain activity at this stage of the disease, regardless of whether a neuroendocrine phenotype is present. More efforts should be made to identify patients with mCRPC who could benefit from these approaches, and programs searching for those with a BRCA-ness phenotype are ongoing.

**TABLE 1. A Proposed Evidence-Based Treatment Algorithm for Patients with Advanced Prostate Cancer.**

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Standard Treatment</th>
<th>Alternative Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-metastatic CRPC</td>
<td>None (continuing ADT)</td>
<td>Endocrine manipulations denosumab*</td>
</tr>
<tr>
<td>Metastases, hormone-naive</td>
<td>ADT</td>
<td>CAB: ADT + AR inhibitor</td>
</tr>
<tr>
<td>Metastatic CRPC</td>
<td>Bone metastases from CRPC</td>
<td>Denosumab*</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic CRPC</td>
<td>Zoledronic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Symptomatic CRPC</td>
<td>Docetaxel</td>
<td>Docetaxel + estramustine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alpharadin (patients with bone metastases, unfit for docetaxel)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abiraterone*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enzalutamide*</td>
</tr>
<tr>
<td>CRPC progressing after docetaxel</td>
<td>Cabazitaxel*</td>
<td>Docetaxel rechallenge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abiraterone*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alpharadin*</td>
</tr>
<tr>
<td>CRPC progressing after docetaxel and novel drugs with an overall survival benefit</td>
<td>None (ADT)</td>
<td>Clinical trial</td>
</tr>
</tbody>
</table>

* Agents recently incorporated in the CRPC armamentarium based on positive phase III data

**KEY POINTS**

- Besides endocrine therapy, taxanes, immunotherapy (sipuleucel-T), and bone-targeted agents (zoledronic acid, denosumab, and radium-223) have reported positive phase III trials in metastatic castration-resistant prostate cancer.
- New promising drugs are currently being developed, including tyrosine kinase inhibitors (cabozantinib), immunotherapies (ipilimumab, rilimogene galvacirepvec), and oligonucleotide antisense (OGX-011 and OGX-427).
- Personalizing treatment based on the individual cancer biology is becoming a priority.

**TARGETING THE BONE MICROENVIRONMENT WITH OSTEOCLAST INHIBITORS IN mCRPC: NOW AN ESTABLISHED STANDARD**

In the 2000s, zoledronic acid was the only drug capable of demonstrating an improvement in time to skeletal-related events (SRE) over a placebo in patients with bone metastases from mCRPC, without any demonstrated improvement in overall survival. RANKL is a key protein secreted by osteoblasts that promotes osteoclast differentiation and bone resorption. Evidence of increased RANKL expression and decreased osteoprotegerin (a RANKL natural inhibitor) was provided in preclinical models of bone metastases from mCRPC. Denosumab is a RANKL inhibitor that was originally developed in a proof-of-concept randomized phase II trial in patients with uncontrolled osteolysis (assessed on uNTx, a urine marker of ongoing bone resorption) while on intravenous (IV) bisphosphonate: significantly more patients (p < 0.001) achieved normalized urinary NTx levels, and further development was undertaken. The “103” phase III trial compared denosumab (120 mg for 4 weeks injected subcutaneously [SC]) with IV zoledronic acid in 1,901 patients with mCRPC. Denosumab was superior to zoledronic acid in delaying/preventing SREs, as shown by the time to the first SRE (fracture, radiation or bone surgery, or spinal cord compression) of 20.7 versus 17.1 months, respectively (HR 0.82; p = 0.008). Denosumab also extended the time to the first and subsequent on-study SRE (rate ratio 0.82; p = 0.008). Both uNTx and serum bone alkaline phosphatase were significantly suppressed in the denosumab arm compared with the zoledronic acid arm (p < 0.0001 for both). A similar tolerance pattern was observed, with both drugs associated with hypocalcemia and a rare (< 2%) risk of osteonecrosis of the jaw, two events requiring prevention and monitoring. Based on these data,
denosumab is now approved for use in mCRPC in Europe and the United States.

A second large study, the “147” phase III trial, enrolled 1,432 men with nonmetastatic CRPC and at least one of the following factors associated with a high risk for bone metastases: PSA of 8.0 ng/L or higher, or PSA doubling time of 10.0 months or shorter. Patients were randomly assigned to denosumab (120 mg SC) or a placebo every 4 weeks. The trial was considered statistically positive because denosumab increased the primary endpoint of bone-metastasis–free survival by 15% (29.5 vs. 25.2 months; HR 0.85, 95% CI 0.73 to 0.98; p = 0.028), although the risk/benefit ratio of denosumab in this setting is being challenged because this difference may be regarded as modest. There was no overall survival difference, and long-term exposure to denosumab is associated with an increased risk of osteonecrosis of the jaw.

**RADIOPHARMACEUTICALS: THEY FINALLY MADE IT!**

Bone-targeting radiopharmaceuticals have a high affinity to bone enabling the delivery of radiation preferentially to areas of high bone turnover after IV injection. Whether they also improve overall survival is unclear, and even higher efficacy was reported in patients with chemosensitive mCRPC.

Radium-223 (also called alpharadin) is a calcium-mimetic radiopharmaceutical with high bone affinity. As an alpha emitter, it has two theoretical advantages over beta-emitters: (1) only a few “hits” are required to induce double-strand breaks in cancer cells, and (2) the first cell layer can stop its penetration in the bone marrow, thus preventing hematologic toxicity. Radium-223 was first studied in a proof-of-concept randomized phase II trial, with favorable results compared with a placebo in patients with bone metastases from mCRPC. The ALSYMPCA phase III trial was then conducted in 922 patients (approximately 60% of whom had been pretreated with docetaxel, and 40% had been considered unfit for docetaxel) who were randomly assigned in a 2:1 fashion between radium-223 (50 kBq/Kg for 4 weeks for 6 cycles) and a placebo. The updated analysis showed improved overall survival (HR 0.695, 95% CI 0.581 to 0.832; p = 0.00007) with a median duration of 14.9 and 11.3 months, respectively. A similar trend toward better overall survival in favor of the radium-223 arm was found in various subgroups (according to the use of bisphosphonates, prior docetaxel, and the performance status). Patients with baseline elevated serum alkaline phosphatase tend to reap an even stronger overall survival benefit. Time to the first SRE was also improved (HR 0.658, 95% CI 0.522 to 0.830; p = 0.00037) with a median duration of 15.6 compared with 9.8 months. Overall, tolerance was good, with 25% experiencing diarrhea compared with 15% in the radium-223 arm (the drug is excreted by the small bowel), but there were no excess grade 3 to 4 events.

An expanded access program for radium-223 is ongoing.

**MORE TO COME?**

**More to Come with Bone Targeting?**

c-Met is a tyrosine kinase expressed by osteoblasts and osteoclasts, and overexpressed by prostate cancer cells. Cabozantinib (XL-184), a c-Met and vascular endothelial growth factor receptor-2 inhibitor, was tested in patients with mCRPC. Impressive results from a phase II study that enrolled 171 patients were recently reported, notably including a partial or complete improvement in the bone scan in 68% and pain improvement in 67% of the patients. Median PFS was 23.9 weeks (95% CI 10.7 to 62.4 weeks) with cabozantinib and 5.9 weeks (95% CI 5.4 to 6.6 weeks) with a placebo (HR 0.12; p < 0.001). Toxicity is as expected for a tyrosine kinase inhibitor, including fatigue, hypertension, and palmar-plantar syndrome, and constitutes a challenge for the original 100 mg/day dose for further development. Two phase III trials were recently initiated: one with pain as the primary endpoint (COMET-2, NCT01522443) and a global phase III trial with overall survival as the primary endpoint in patients with mCRPC in whom docetaxel and abiraterone failed (COMET-1, NCT01605227). The exact mechanism of action of cabozantinib in patients with mCRPC remains to be elucidated, since another c-Met inhibitor, rilotumumab, failed to demonstrate efficacy in a randomized phase II trial.

Another potential target for therapy in mCRPC is Src, which is expressed by osteoclasts and by some prostate cancer cells. Dasatinib, a Src inhibitor, was tested in patients with mCRPC as a single agent and combined with chemotherapy. The results of a large phase III trial testing docetaxel with and without dasatinib (NCT00744497) was very recently reported to be negative.

**More to Come: Novel Drugs with Original Targets?**

Many potential targets for mCRPC have been identified in the recent past, and numerous trials testing inhibitors are ongoing (which cannot all be presented in detail in this article). Among them, original technologies include antisense oligonucleotides like OGX-011 (which targets clusterin, a chaperone protein) and OGX-427 (which targets heat-shock protein 27). OGX-011 was tested in a randomized phase II trial in combination with docetaxel. A better overall survival duration was reported in the combination arm (median, 23.8 and 16.9 months, respectively). Two phase III trials are ongoing to confirm these results in combination with chemotherapy: one in the first-line setting (SYNERGY, testing docetaxel with or without cabirixinsen, NCT01188187), the other in the second-line setting (AFFINITY, testing cabazitaxel with and without cabirixinsen, NCT01578655). OGX-427 was tested in a randomized phase II trial compared with prednisone with, respectively, 71% and 40% of patients alive and free of progression at 12 weeks, and activity also reported in terms of PSA response, RECIST criteria, and circulating tumor cell conversion.

Tasquinimod targets S100A9; its antiangiogenic and immune-modulation properties are still incompletely understood. This oral compound was tested in a randomized...
phase II trial in 201 asymptomatic patients with mCRPC: the primary endpoint, PFS, was significantly improved (7.6 vs. 3.3 months; \( p = 0.0042 \)). A confirmatory phase III trial is ongoing in the same setting. A proof-of-concept “switch maintenance” randomized study is also ongoing with tasquinimod in patients with disease response or stabilization on first-line docetaxel chemotherapy (NCT01732549).

**Disclosures of Potential Conflicts of Interest**

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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Therapeutic Vaccines and Immunotherapy in Castration-Resistant Prostate Cancer: Current Progress and Clinical Applications

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OVERVIEW

Results of recent clinical trials have intensified interest in immunotherapy for cancer. Among the most promising candidates for immunotherapy are patients with prostate cancer. Results of therapeutic vaccine clinical trials in this population have suggested statistically significant and clinically meaningful improvements in overall survival, with substantially fewer side effects than with chemotherapy. Of particular interest are sipuleucel-T, the first U.S. Food and Drug Administration-approved therapeutic cancer vaccine, and PSA-TRICOM (PROSTVAC), a therapeutic cancer vaccine in phase III testing. The immune checkpoint inhibitor ipilimumab is also stirring considerable interest, with two phase III trials ongoing in prostate cancer. This article highlights data emerging from these trials and addresses remaining questions and practical clinical implications of this therapeutic strategy.

The goal of immunotherapy for cancer is to induce the immune system to attack tumor tissue. Strategies for generating a therapeutic immune response include the use of therapeutic vaccines designed to target specific tumor epitopes, and immune checkpoint inhibitors that allow for the expansion of an underlying immune response and that may also target regulatory T cells at the site of the tumor. Prostate cancer is particularly amenable to immunotherapy for a variety of reasons. First, because the prostate is a non-essential organ, eradication of residual normal prostate tissue by an immune response results in no clinical sequelae to patients. More importantly, many well-defined prostate-associated antigens are known to be immunogenic. One of these, prostate-specific antigen (PSA), can also serve as an excellent marker of disease progression. Finally, because prostate cancer is relatively indolent, potentially immune suppressive chemotherapy is generally not used until later in the disease course.

SIPULEUCEL-T

Sipuleucel-T (Provenge, Dendreon Corporation) was recently approved by the U.S. Food and Drug Administration for use in patients with mCRPC. Sipuleucel-T is a unique vaccine platform that requires leukapheresis of patient blood samples. At a central processing laboratory, antigen-presenting cells obtained from patient samples are enriched and incubated with a fusion protein consisting of prostatic acid phosphatase linked to the immunomodulatory cytokine granulocyte-macrophage colony-stimulating factor. The vaccine is then returned to the patient’s health care provider for infusion. This procedure is performed three times over approximately 1 month. Results from a randomized phase III trial of sipuleucel-T demonstrated a median overall survival of 25.8 months compared with 21.7 months for the placebo (H9004 4.1 month; Fig. 1A). Interestingly, although the primary end point of survival was clearly attained (p = 0.032), there was no statistical difference in time to progression (TTP) compared with the results from the placebo. These results were almost identical with a previous phase III trial with sipuleucel-T, in which the primary end point was TTP. Both studies showed no improvement in TTP, but demonstrated a clear statistical improvement in median overall survival compared with the placebo. Data from the later phase III study also suggest that patients with more potent immune responses following vaccine have improved overall survival.

PSA-TRICOM

PSA-TRICOM (PROSTVAC) is another cancer vaccine that has been evaluated in metastatic castration-resistant prostate cancer (mCRPC). This off-the-shelf, vector-based vaccine consists of a prime-boost regimen (recombinant vaccinia priming and five to six recombinant fowlpox boosts). Each of the recombinant poxviruses contains transgenes for PSA and three co-stimulatory molecules (TRICOM) designed to

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boost the immune system. A multicenter randomized phase II trial in mCRPC demonstrated that patients who received PROSTVAC had improved overall survival. At three years poststudy, 30% of vaccinated patients were alive compared with 17% of the controls. The median overall survival was 8.5 months. The survival rate was longer for vaccinated patients than for the controls (25.1 vs. 16.6 months, p = 0.0061, hazard ratio: 0.56; Fig. 1B). Notably, as in the two sipuleucel-T trials, there was no difference between the two arms in terms of TTP, and toxicity was minimal. Another study suggested that patients who mount the most vigorous immune response to vaccine may have improved survival. A subsequent analysis of samples from these two studies suggested that a pre-existing antibody to a glycoprotein antigen in the vector was also associated with improved outcome in patients treated with vaccine, but not the wild-type vector.

**IPILIMUMAB**

Ipilimumab (Yervoy, Bristol-Myers Squibb) is a human immunoglobulin G-1 kappa monoclonal antibody that targets cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). Ipilimumab was the first in a class of therapies targeting T-cell activation and regulation to be licensed in the broad category of agents known as immune checkpoint inhibitors, based on improved overall survival in patients with metastatic melanoma. Interestingly, the melanoma study demonstrated a lack of improvement in median TTP similar to that seen in prostate studies, suggesting that this kinetic profile may be characteristic of immunotherapies as a class. A unique set of toxicities referred to as immune-related adverse events has been seen with the use of anti–CTLA-4 antibodies, including infiltration of inflammatory cells into nonsterile epithelial surfaces (i.e., colon and skin, which likely have ongoing immune activity) and endocrine organs (i.e., thyroid, adrenals, and pituitary, which have been associated with autoimmune disease). In most instances, these immune-related adverse events can be readily managed medically.

Early studies of ipilimumab in prostate cancer have led to two phase III clinical trials, one in chemotherapy-naïve patients with mCRPC and a second in combination with radiation in patients with mCRPC previously treated with chemotherapy. Results from the latter trial are expected in spring 2013. In addition, two phase I dose-escalation trials of ipilimumab in combination with therapeutic vaccines in patients with mCRPC have demonstrated encouraging activity. Finally, other immune checkpoint inhibitors such as

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**KEY POINTS**

- Therapeutic vaccines can improve overall survival in patients with metastatic castration-resistant prostate cancer (mCRPC) without significant treatment-related side effects.
- The kinetics of a clinical response to a therapeutic vaccine may be completely different from the kinetics of a clinical response to conventional cytotoxic therapy as shown by randomized multicenter trials that demonstrated increased overall survival in the absence of increased median progression-free survival with two therapeutic vaccines (in prostate cancer) and ipilimumab (in melanoma).
- Therapeutic vaccines may induce a broader, and potentially more clinically relevant, immune response than the one initially targeted by the vaccine, a phenomenon known as antigen spreading or antigen cascade.
- PROSTVAC, an “off-the-shelf” experimental therapy with promising initial results, is currently in phase III clinical testing.
- Immune checkpoint-blockade strategies using ipilimumab are in phase III clinical trials in patients with mCRPC.
anti-PD1 or anti-PDL1 may find utility in prostate cancer either as single agents or in combination with therapeutic vaccines or other strategies.

PARADOX
The clinical trials of sipuleucel-T and PROSTVAC demonstrated a significant and clinically meaningful improvement in overall survival in patients with mCRPC, with no associated improvement in TTP, which may be a class effect of immunotherapies. In the context of traditional cytotoxic therapies, this may seem counterintuitive. However, it must be understood that therapeutic cancer vaccines differ from conventional therapies in several distinct ways (Table 1). First, their primary target is not the tumor itself, but the immune system, which subsequently targets the tumor. It may take weeks to months to mount a clinically significant immune response following vaccination. However, vaccines may induce the development of long-lived memory cells with the potential to provide continuous immunologic pressure that results in a slowing of the tumor’s net growth rate. Within a tumor, new cells are constantly being produced while other cells are dying. The rate of tumor growth is thus influenced by tumor biology (the intrinsic rate at which new daughter cells are formed) offset by host biology (the rate of tumor-cell loss resulting from antitumor immune response), combined with factors introduced into the tumor environment (e.g., killing of tumor cells by conventional therapies).

An effective anticancer immune response may reset the tumor-growth equilibrium so that more tumor cells are killed by the immune system. This effect may not translate into objective responses or short-term improvements (within 3 to 4 months) in TTP, but because this effect may be both long-lasting and augmented by subsequent therapies, the end result may be eventual slowing of the tumor growth rate, leading to improved overall survival (Fig. 2). Indeed, recently published data from prostate cancer vaccine trials at the National Cancer Institute support the concept of eventual decreased tumor growth rate following treatment with a therapeutic vaccine. Furthermore, unlike traditional therapies, an ongoing, dynamic immune response can adapt to subsequent mutations within the tumor, continuing or expanding a therapeutic response.

This new understanding of the kinetics of clinical response following treatment with a therapeutic vaccine, coupled with clinical experience showing that an end point of overall survival may be the only valid discriminator of activity in single-agent vaccine studies, poses a dilemma for accelerating proof-of-concept studies. Because trials with a survival end point typically take years to accrue and mature, identifying and validating intermediate end points is crucial to

**TABLE 1. Comparisons between Conventional Therapies and Therapeutic Vaccines**

<table>
<thead>
<tr>
<th></th>
<th>Conventional Therapies</th>
<th>Therapeutic Vaccines</th>
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<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Tumor/tumor microenvironment</td>
<td>Immune system</td>
</tr>
<tr>
<td><strong>Pharmacodynamics</strong></td>
<td>Action often immediate</td>
<td>Delayed action</td>
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<tr>
<td><strong>Memory Response</strong></td>
<td>No</td>
<td>Yes</td>
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<tr>
<td><strong>Tumor Evolution/New Mutations</strong></td>
<td>Create resistance to therapy</td>
<td>Create new immunogenic targets</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>Toxicity</td>
<td>Require adequate immune function systemically and at tumor site</td>
</tr>
</tbody>
</table>

FIG 2. Tumor growth is a dynamic biologic process that is the combined result of cells dividing and other cells dying. Intrinsic tumor biology, as well as extrinsic factors such as therapies, affect the tumor’s growth rate. However, chemotherapy (red line) only affects the tumor growth rate while it is being administered, which may result in a dramatic but transient response. Following discontinuation of chemotherapy, the growth rate returns to its pretreatment slope, driven by the underlying biology of the tumor. Immunotherapy (blue line), on the other hand, can alter the biology of the host by inducing an active antitumor immune response including a memory response. This may not cause an immediate or dramatic change in tumor burden, but continued cumulative slowing pressure on tumor growth rate, especially if started early in the disease course, may lead to substantially longer overall survival. The arrow indicates the initiation of treatment; cross indicates time of death as a result of cancer. Adapted from Madan, The Oncologist, © 2010 AlphaMed Press.
facilitating efficient life cycles for phase II studies in immunotherapy for prostate cancer.

**IMMUNE END POINTS AND ANTIGEN CASCADE**

It has been suggested that a broader immune response caused by expansion of a T-cell response to epitopes not found in the vaccine may lead to a more clinically relevant antitumor immune response. This concept, known as epitope spreading, antigen spreading, or antigen cascade, has been associated with both major histocompatibility complex class I- and II-restricted responses and reflects cross-presentation of tumor antigens. Thus, when tumor-specific T cells lyse tumor cells, the dead or dying tumor cells may be taken up by antigen-presenting cells, with the result that multiple, perhaps even more immunogenic, tumor antigens can be presented to immune cells, initiating a broader immune response.

As a consequence of antigen cascade, it is possible that the same vaccine may induce completely different immune responses in different patients with the same type of cancer. Furthermore, the immune response to antigens not present in the vaccine may continue over time, eventually broadening into an immune response that could be even more clinically relevant than the initial response to the epitope in the vaccine. Many examples of T-cell antigen cascade have been reported in clinical trials of therapeutic vaccines in patients with cancer, and several of these trials have suggested improved clinical outcomes for patients who demonstrated a broadened immune response.

Clearly, additional markers of efficacy would speed proof-of-concept studies; significant efforts are underway to meet this need. Emerging data suggest that TTP may be a meaningful discriminator of efficacy when immunotherapy is combined with standard-of-care therapies, compared with those therapies alone.

**CLINICAL APPLICATION**

The available data suggest that in patients with rapidly progressive or significantly symptomatic disease, vaccines will likely not be very effective and should not be used as a monotherapy. Indeed, the greatest clinical benefit is seen in patients with earlier-stage or less aggressive disease. After initiating a therapeutic vaccine, most patients will not experience a rapid, sustained decrease in PSA. Although this has been observed, it is typically seen in less than 5% of patients. Thus, effective treatment with immunotherapy, when given alone, requires careful selection of patients who are not likely to progress clinically within 3 to 6 months. In 20% to 30% of patients, treatment with ipilimumab may result in PSA decreases of at least 50%. Data from phase III clinical studies should soon confirm whether ipilimumab can improve overall survival in mCRPC.

The widespread use of glucocorticoids in therapeutic regimens for prostate cancer raises questions about the influence of these compounds on the immune response. It is quite possible that the ability to maintain, or even mount, an immune response in the face of daily glucocorticoids is not as problematic as one would expect, given that memory cells are relatively resistant to steroid-induced killing compared with naive cells.

A clinical trial of sipuleucel-T with abiraterone and prednisone demonstrated that sipuleucel-T can be manufactured during treatment with abiraterone and prednisone with product potency and prime boost similar to that of sipuleucel-T alone.

Immune-oncology combinations have already demonstrated the potential for synergistic responses. Eventually, combining immunotherapies with other effective therapeutic strategies in prostate cancer may lead to improved disease control, delayed symptoms, and greatly improved survival. However, the path to this eagerly anticipated outcome must be paved with carefully designed, controlled clinical trials.

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**Disclosures of Potential Conflicts of Interest**

The author(s) indicated no potential conflicts of interest.

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GENITOURINARY CANCER

Clinical Management, Molecular Alterations, and Future Perspectives in Urothelial Cancer

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Andrea B. Apolo, MD, and David J. Kwiatkowski, MD, PhD

OVERVIEW

Advances in tumor biology and cancer genetics have led to the development of effective targeted therapies in oncology over the past decade. However, targeted drug development for urothelial carcinoma has been slower than for some other malignancies. The path forward in drug development is through a better understanding of the aberrant pathways driving urothelial tumor development. Steady progress has been made in the characterization of genomic alterations in urothelial carcinoma. The Cancer Genome Atlas (TCGA) project is well underway in the analysis of a large set of urothelial cancer specimens using multiple approaches and technologies. In addition, there are already many well-established mutations and genetic alterations in urothelial carcinoma that likely contribute in an important way to tumor development. In addition, urothelial cancer genome-wide association studies have identified common variants associated with urothelial cancer risk and protein expression that can potentially be therapeutically targeted. Furthermore, the MET pathway has emerged as an exciting target in multiple tumors, including urothelial carcinoma. Our knowledge of how to clinically target many emerging molecular aberrations in urothelial cancer is still in the early stages of development. However, there is much promise in the ongoing research being conducted in urothelial cancer molecular pathogenesis.

Urothelial carcinoma of the bladder is a common malignancy, causing approximately 15,000 deaths per year in the United States and 150,000 deaths per year worldwide. However, targeted drug development for urothelial carcinoma has been slower than that seen in some other malignancies such as melanoma, chronic myeloid leukemia (CML), gastrointestinal stromal tumors (GIST), and lung adenocarcinoma. The discovery of vemurafenib for melanoma tumors that harbor the B-Raf V600E mutations and the inhibition of ABL and c-Kit by imatinib for CML and GIST, respectively, have significantly changed clinical practice.

Unfortunately, no drug has been approved by the United States Food and Drug Administration (FDA) for urothelial cancer in more than two decades. Other genitourinary malignancies such as renal cell carcinoma and prostate cancer have had more than a dozen new agents approved by the FDA in the past 7 years (Table 1). It is through our better understanding of the aberrant pathways driving tumor progression in renal cell carcinoma through the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways and in prostate cancer through the androgen receptor that we have made these therapeutic advances.

Urothelial cancer is a heterogeneous disease driven by a diverse array of molecular alterations; however, we still have not discovered a drug or combinations of drugs that interfere with the critical driver events involved in the development of urothelial cancers. Clinical trials using targeted agents known to be effective in other tumors have been disappointing to date in urothelial carcinoma with uniform low response rates (Table 2). Efforts are ongoing to identify important molecular targets and test novel therapeutics in clinical trials.

The National Cancer Institute (NCI) and the National Human Genome Research Institute have developed the TCGA project in 2006 with the goal of creating a genomic atlas of human cancer. The goal of the TCGA effort is to define the genetic and molecular characteristics of all common, and a number of less common, cancers. Arguably, the most important secondary goal of the TCGA project is to identify novel driver mutations of cancer development that can be targeted therapeutically. The TCGA project on urothelial carcinoma is well underway in the analysis of a large (> 100) set of specimens using multiple approaches and technologies with many new findings. There is an expected major publication on the TCGA findings in urothelial carcinoma later in 2013, and there is no doubt that many new potential targets for directed therapy will be unveiled at that time.

Apart from TCGA effort, there has been steady progress in the characterization of genomic alterations in urothelial
carcinoma, dating back to the discovery of the first oncogene, HRAS, in a urothelial cancer cell line more than 3 decades ago. Several recent discoveries are notable. Gui et al described whole-exome sequencing of nine urothelial carcinoma specimens, with confirmatory studies of novel genes with mutations in a larger set of 88 urothelial carcinoma samples. Mutations were frequently (13% to 21%) identified in multiple genes involved in chromatin remodeling, including loss of function that was important in urothelial carcinoma development. Chromatin remodeling genes play critical roles in the regulation of the epigenetic structure of chromatin. They have various activities including “writing” of covalent histone modifications (acetylation, methylation), “erasing” of such modifications (deacetylases, demethylases), insulating chromatin regions from modification or expression, and remodeling the three dimensional structure of chromatin to either enhance or repress transcription. The report by Gui et al and the TCGA findings indicate that mutations in chromatin regulator genes are very common, perhaps nearly universal in urothelial carcinoma, and seen at a higher rate than perhaps any other common adult malignancy. Hence, these alterations are very likely to contribute in an important way to urothelial carcinoma development by altering gene expression in a global manner. Unfortunately, our knowledge of how to clinically target mutations in these chromatin regulator genes is at a very early stage, and it is likely that each specific alteration will require a different approach.

**PIK3CA, TSC1, and most recently TSC2 (the latter two genes are the cause of the human tumor suppressor gene syndrome tuberous sclerosis complex [TSC]) are recognized to be mutated in a collective 20% to 30% of urothelial carcinoma (COSMIC [www.sanger.ac.uk/genetics/CGP/cosmic/ and TCGA data]).** These mutations have common effects in activating mTOR, a master kinase that regulates cell growth through enhancement of protein synthesis and other effects. Hence, patients with urothelial carcinoma with mutations in these genes are potential candidates for therapy targeting mTOR (for TSC1, TSC2 mutations) or more directly PIK3CA for mutations in that gene. Multiple drugs that target PI3K are in current clinical development for diverse cancers (e.g., ZSTK474, GDC-0941), and it is hoped that these drugs will show effectiveness for PIK3CA-mutant urothelial carcinoma. Notably, PIK3CA mutations in urothelial carcinoma are primarily in the central PIK domain, not H1047R, and effectiveness of these agents for that category of mutation will require further evaluation. Recently Iyer et al reported that a single patient on a clinical trial of everolimus (mTOR inhibitor) for urothelial carcinoma had a sustained complete response lasting more than 2 years. This patient’s cancer was found to have mutations in both TSC1 and NF2, as well as other genes. At least four other patients on this clinical trial also had TSC1 mutations and transient minor responses to everolimus. It is unknown what caused the dramatic response of the single complete responder. Everolimus has been shown to be effective for the treatment of several tumors that develop in TSC and for PEComas—a type of sarcoma in which TSC1/TSC2 gene mutations are common. Complete loss of either TSC1 or TSC2 is known to occur in TSC tumors. Hence, collectively these observations suggest that the TSC1 mutation was an important factor in the complete response to everolimus by the patient with urothelial carcinoma.

Urothelial carcinoma has been known for many years to have a wide variety of genomic copy number changes, including loss of chromosome 9p containing the CDKN2A gene and amplification of multiple genomic regions. We have recently used multiplex inversion probe analysis to perform a genome-wide screen for copy number alterations in urothelial cancer. We then selected nine genomic regions of amplification and developed a multiplex ligation-dependent probe analysis (MLPA) assay, which was then used on a
TABLE 2. Selected Clinical Trials of Single-Agent Targeted Therapy with Metastatic Urothelial Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Line</th>
<th>Agent</th>
<th>Target</th>
<th>No.</th>
<th>RR %</th>
<th>OS Months</th>
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<tbody>
<tr>
<td>Bellmunt</td>
<td>First</td>
<td>Sunitinib</td>
<td>EGFR, VEGFR-1/2, c-KIT, PDGFR a/b, FLT3, and RET</td>
<td>38</td>
<td>8</td>
<td>8.1</td>
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<tr>
<td>Quinn</td>
<td>First</td>
<td>Eribulin</td>
<td>tubulin</td>
<td>37</td>
<td>38</td>
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<tr>
<td>Sridhar</td>
<td>First</td>
<td>Sorafenib</td>
<td>B-Raf, c-Raf, VEGFR-2/3, PDGFR-b</td>
<td>17</td>
<td>0</td>
<td>5.9</td>
</tr>
<tr>
<td>Gomez-Abuin</td>
<td>Second</td>
<td>Bortezomib</td>
<td>Proteasome inhibitor</td>
<td>20</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Wulffing</td>
<td>Second</td>
<td>Lapatinib</td>
<td>HER1 and HER2</td>
<td>59</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
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<td>Second</td>
<td>Gefitinib</td>
<td>EGFR</td>
<td>31</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dreicer</td>
<td>Second</td>
<td>Sorafenib</td>
<td>B-Raf, c-Raf, VEGFR-2/3, PDGFR-b</td>
<td>27</td>
<td>0</td>
<td>6.8</td>
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<tr>
<td>Gallagher</td>
<td>Second</td>
<td>Sunitinib</td>
<td>EGFR, VEGFR-1/2, c-KIT, PDGFR a/b, FLT3 and RET</td>
<td>45</td>
<td>7</td>
<td>6.9</td>
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<tr>
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<td>Second</td>
<td>Afibercept</td>
<td>VEGF, PDGF</td>
<td>22</td>
<td>4.5</td>
<td>NR</td>
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<tr>
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<td>Second</td>
<td>Everolimus</td>
<td>PI3K/AKT/mTOR</td>
<td>45</td>
<td>5</td>
<td>10.5</td>
</tr>
<tr>
<td>Necchi</td>
<td>Second</td>
<td>Pazopanib</td>
<td>VEGFR-1/2/3, PDGFR a/b, and c-KIT</td>
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<td>17.1</td>
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<tr>
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<td>Second</td>
<td>Dovitinib</td>
<td>FGFR3</td>
<td>44</td>
<td>3</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: EGFR, epidermal growth factor receptor; FGFR3, fibroblast growth factor receptor 3; FLT3, Fms-like tyrosine kinase 3; mTOR, mammalian target of rapamycin; NR, not reported; OS, overall survival; PDGFR, platelet-derived growth factor receptor; RR, response rate; VEGFR, vascular endothelial growth factor receptor.

set of both early-stage and more advanced-stage urothelial carcinomas. One or more amplification events for one of the nine genomic regions were seen in only two of 23 (9%) Ta grade 1 or grade 1 to 2 cancers. In contrast, one or more amplifications were seen in 11 of 20 (55%) Ta grade 3 cancers and in 20 of 41 (49%) T2 grade 2 cancers (p = 0.0020 and 0.0011, respectively). Furthermore, amplification of the E2F3/SOX4 region alone was also seen more commonly in the Ta grade 3 and T2 grade 2 cancers (11 of 61) than in Ta grade 1 or 1 to 2 cancers (0 of 23, p = 0.03). Several of the genomic regions analyzed for amplification by MLPA included genes that are potential therapeutic targets: CCND1 (CDK4 inhibitors), ERBB2 (lapatinib, trastuzumab), and MDM2. These preliminary results suggest that analysis of these nine genomic regions might have use as a prognostic and therapeutic marker in urothelial carcinoma, although further study and validation is required.

Urothelial cancer genome-wide association studies have identified common variants associated with urothelial cancer risk. A missense variant rs2294008 in the prostate stem cell antigen (PSCA) gene showed consistent association with urothelial urothelial carcinoma. Resequencing of the PSCA genomic region showed that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as a new urothelial cancer susceptibility locus. We have found nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymorphism in PSCA, identifying rs2294008 as showing that rs2294008 is the only common missense single nucleotide polymer...
increased intratumoral hypoxia and apoptosis, and reduced tumor invasiveness and metastasis in vivo.\textsuperscript{18,19} Thus, simultaneous inhibition of both MET and VEGFR2 should result in near-complete inhibition of major survival pathways induced by hypoxia. Cabozantinib (XL184) is an oral agent that inhibits multiple receptor tyrosine kinases, primarily targeting MET and VEGFR2. Cabozantinib has shown activity in multiple solid tumors in phase I, II, and III clinical trials. Preclinical data supports the use of cabozantinib in urothelial cancer.\textsuperscript{20} Currently, there is an ongoing phase II trial of cabozantinib for patients with advanced urothelial cancer.

There are currently over 100 oncology therapeutic clinical trials using MET inhibitors. The Center for Cancer Research (CCR) at the NCI maintains a webpage of these trials: https://ccrod.cancer.gov/confluence/display/CCRHGF/Home. Targeting the HGF/MET signaling pathway is an exciting approach to inhibiting tumor growth and metastases.

**CONCLUSION**

The current emphasis in oncology drug development is on targeted therapies that exploit the vast amount of knowledge we are acquiring from tumor pathogenesis. Current available therapies targeting molecular aberrations in other tumors have not demonstrated significant efficacy as single agents in urothelial cancers. The development of effective therapies for this devastating disease remains dependent on the progress we make in scientific discovery. Furthermore, it appears clear from the existing genomic datasets that the diversity of mutations seen in urothelial carcinoma will require personalized targeted therapy—similar to lung adenocarcinoma, in which multiple different agents are used for different mutation subsets. Hence, going forward, we can anticipate that targeted clinical trials for urothelial carcinoma will be designed in a mutation-specific manner.

So are we almost there? No, but we are well on our way.


A Multidisciplinary Approach in Muscle-Invasive Disease: Novel Chemotherapy Combinations and Targets in Chemoradiation

Nicholas D. James, PhD, and Syed A. Hussain, MD

OVERVIEW

The basic management of bladder cancer has changed depressingly little in the last 20 years, with a largely unquestioning acceptance of the role of surgery as the standard of care despite a rising mean age at diagnosis, now well into the mid-70s, meaning many patients will be high risk for a major surgical procedure. Overall survival rates for those diagnosed with bladder cancer have not improved for many years. There is a growing body of studies demonstrating the safety and efficacy of bladder preservation with combined chemoradiation with good long-term function after such treatment. Two recent studies from the United Kingdom compared radiation alone with sensitized radiotherapy using distinct strategies, one (BCON) focusing on trying to improve tumor oxygenation, one (BC2001) using the combination of 5FU and mitomycin C. Importantly, both studies collected data on late toxicity and showed both good function and low rates of serious side effects with no increase with radio-sensitization. Furthermore, there is good evidence that survival after salvage cystectomy is similar to that seen after primary surgery, suggesting a strategy of primary chemoradiation with salvage surgery (as used, for example, in anal cancer) may be both rational and safe. This article reviews the evidence on outcomes with chemoradiation and calls for a rethink in our approaches to this major cancer killer.

The basic management of bladder tumors has remained largely unchanged for over 50 years and despite its importance in terms of incidence,1 prognosis, and cost, bladder cancer research remains underfunded.2 Over 385,000 new cases were diagnosed in 2008, approximately 20% of which were invasive and median age at diagnosis was above age 70. Because the tumor is smoking related, many patients are elderly with significant comorbidity, posing a considerable risk for radical surgical approaches. Survival rates are poor with around 45% for patients with muscle-invasive cancer surviving five years irrespective of treatment modality.3-6 Given the very high costs to health care systems from long-term surveillance and treatment of the disease,7 it is surprising that there has not been more emphasis on the disease from health policy makers and pharmaceutical companies.

SURGERY COMPARED WITH BLADDER PRESERVATION

In addition, a rethink of the view that cystectomy is the gold standard for invasive bladder cancer is long overdue. Comparisons of large surgical4 and radiotherapy5 series suggest very similar long-term survival rates, and population-based studies do not appear to show any survival differences linked to mode of treatment.5 Furthermore, most large surgical series have a median age of mid-60s,3-4 well below the (rising) disease-population median, suggesting the results may well not be applicable to many or even most patients with invasive bladder cancer. Use of bladder preservation varies worldwide from around 10% in the United States8 to 25% in Scandinavia9 to around 50% in the United Kingdom.10 Moreover, there is good evidence that older or less-fit patients in low-volume centers are less likely to be referred for radical therapy, despite the likelihood of them being fit for radiotherapy even if surgically unfit.8,9,11 A recent study by our group showed that only 3% of newly diagnosed patients over age 80 underwent cystectomy in our region, compared with 55% who received radiotherapy.12 Salvage cystectomy remains an option for local radiotherapy failure. Particularly intriguing in this regard is a comparison of survival rate following primary surgery with the survival rate following salvage surgery after failed radiotherapy from the Christie Hospital in Manchester, United Kingdom. The group examined the outcomes in 552 patients who underwent radical cystectomy between 1970 and 2005. Of these, 313 patients underwent primary surgery and 239 underwent salvage radical cystectomy. The median age was 62.5 for the primary group compared with age 65.5 for the salvage group. Overall 5-year survivals reported were 45.5% for the primary group compared with age 65.5 for the salvage group. Overall 5-year survivals reported were 45.5% and 42% for the primary and salvage group with cause-specific survivals of 51% and 50%, respectively. These differences persisted after stratification for stage, and the authors concluded that a policy of primary surgery...
radiotherapy with surgical salvage did not compromise the long-term survival chances of patients.13

Another way to compare outcomes between surgery and radiotherapy is to look at large population-based series. A recent paper from Munro and et al.14 examined outcomes in 458 patients with invasive bladder cancer treated in Yorkshire between 1993 and 1996. The ratio of cystectomy to radiotherapy was 1:3, reflecting United Kingdom practice at the time. Overall 10-year survival was similar between those who underwent radiotherapy (22%) and radical cystectomy (24%). Prognostic factors for inferior outcome at 10 years were: female compared with male, poor-performance status, hydronephrosis and increasing T stage. Treatment modality was not a prognostic factor.

ORGAN PRESERVATION THERAPY

Whatever the merits or otherwise of radiotherapy, its use in the United States has declined markedly since the 1980s and the treatment is now used mainly in certain centers such as Boston in carefully selected patients rather than as a mainstream alternative to surgery—usually termed “selective bladder preservation.” In North America, radiotherapy is administered as part of a complex package of care comprising of maximal trans-urethral resection of a bladder tumor (TURBT), chemotherapy, and radiotherapy—so-called “trimodality therapy” (Fig. 1).

Split schedules often used are 39 to 40 Gy in 1.8 to 2 Gy fractions with an interval cystoscopy; patients with responding disease proceed to a total dose of 64 to 66 Gy. Generally, these schedules achieve long-term survival comparable with surgical series.15 A risk of cystectomy remains however with 22% undergoing immediate cystectomy, 13% delayed cystectomy for local recurrence, and 65% retaining a functioning bladder. In some countries, particularly the United Kingdom and Australia, an alternative schema is used. As in the trimodality approach, patients will undergo maximal TURBT followed by primary radiotherapy with or without neoadjuvant chemotherapy. In the United Kingdom, the radiotherapy itself is given as a single radical course, usually to the whole bladder only with no attempt to treat the nodes. Typical dose schedules would be 64 Gy in 32 fractions or hypofractionated schedules such as 55 Gy in 20 fractions. Following radiotherapy patients undergo cystoscopic surveillance with salvage cystectomy for isolated local failure.

U.S.-style trimodality therapy is unusual in having a break in radiotherapy to check response. To understand how this approach has arisen, it has to be understood that trimodality therapy is offered as an alternative to cystectomy in countries where the prevailing opinion is that surgery is the treatment

KEY POINTS

- Survival with muscle-invasive bladder cancer remains poor with little improvement in the last 20 years.
- Age at diagnosis is rising in the developed world and is now well above 70 years with many patients over 80, calling into question whether surgery should be regarded as the standard of care.
- Primary radiotherapy with salvage surgery appears to carry similar long-term survival to primary surgery, reflecting the fact that the prognosis driver is metastatic spread.
- Radio-sensitization with either chemotherapy or modifiers of tumor oxygenation improves loco-regional control with evidence of good long-term bladder function.
- Further trials are needed to build on the relatively small number of trials carried out in this important cause of mortality and morbidity worldwide.
of choice. Patients undergoing this treatment are offered what is termed “selective bladder preservation” with the multiple checkpoints allowing early exit to surgery, aimed at providing reassurance to surgeons in particular that the opportunity for cure is not being lost. The median ages (mid-60s) reported in papers using this approach reflect this patient selection16–19 and are similar to large surgical series.4,20,21 The United Kingdom approach is completely different in this respect as there is a long tradition of using radical radiotherapy after TURBT in the much older patient groups. Trials such as BCON22 and BC2001,23 compared with surgical series, reflect a different decision-making process in which younger fitter patients are more likely to get surgery and older or less fit patients are more likely to receive radiotherapy. Interestingly, the long-term bladder preservation rates in the older series seem similar to the U.S. trimodality approach with salvage cystectomy postradiotherapy occurring in around a quarter of patients managed with radiotherapy alone at 10-years median follow-up,24 with around two-thirds of surviving patients retaining their bladders. Our own more recent chemoradiotherapy series suggests a lower rate of salvage surgery of around 10% with the use of synchronous chemoradiotherapy combined with full-dose radical radiotherapy.23

SYNCHRONOUS CHEMORADIATION

There are a large number of phase I or phase II trials looking at various chemotherapy agents including cisplatinum, taxanes, 5-fluorouracil (5FU), and gemcitabine in combination with radiotherapy from North America,16,25–42 Mainland Europe,5,43–45 and the United Kingdom.46,47 In general they all report good tolerability and feasibility but little in the way of comparative data. There are, however, very few trials in the literature in which radiotherapy alone is compared with synchronous chemoradiotherapy. The only randomized study using the trimodality therapy approach was carried out by the Canadian Cancer Society Research Institute (formerly the National Cancer Institute of Canada) and reported in 1996. This study compared radiotherapy to 40 Gy in 20 fractions with the same schedule combined with cisplatinum 100 mg/m² twice weekly for three weeks. Patients then underwent interim cystoscopy and either consolidation radiotherapy to 20 Gy in 10 fractions or cystectomy, depending on response and fitness for surgery. Synchronous cisplatinum had no effect on the rate of distant metastasis, consistent with a lack of effect of similar schedules in neoadjuvant trials.24,48 The study was however relatively small and, therefore, could only have detected very large effects. Concurrent cisplatinum had a highly significant effect on pelvic recurrence with 25 of the 48 control patients having a pelvic recurrence, compared with 15 of the 51 cisplatinum-treated patients (p = 0.036) giving a hazard ratio of 0.50; 90% confidence interval [CI], 0.29 to 0.86; p = 0.036.19

There are two randomized trials of radio-sensitization using United Kingdom schedules—the BC2001 and BCON studies already discussed. These two large phase-III randomized control trials reported results in 2009/2010. These trials used radio-sensitisation with either concurrent chemotherapy (BC2001) or carbogen and nicotinamide (BCON). BC2001 has shown a significant improvement in locoregional disease-free survival with concurrent 5FU and mitomycin C (MMC) of 34% (HR 0.66 [95% CI: 0.46 – 0.95]) driven by a reduction of 47% in invasive locoregional recurrences (HR 0.53, p = 0.007) (Fig. 2), which is very similar to that observed in the Canadian Cancer Society Research Institute trial with cisplatinum using the trimodality approach.19 Survival data show a trend toward an improvement in overall survival (HR = 0.81, p = 0.16) although the data are immature. The BCON trial with synchronous carbogen and nicotinamide,22 narrowly failed to meet its primary end point of an improvement in local relapse-free survival (HR 0.87, 63% vs. 74%, p = 0.1) but did report an improvement in

FIG 2. Locoregional disease-free survival (LRDFS) in the BC2001 trial. Left panel: primary trial analysis with overall LRDFS incorporating noninvasive and invasive bladder recurrence, pelvic nodal recurrence. Right panel: invasive bladder recurrence LRDFS.
overall survival at 3 years (46% vs. 59%, HR 0.86 [95% CI: 0.745–0.996], p = 0.04).

Taken together the trial data with chemoradiotherapy suggests good tolerability even in relatively elderly patients with excellent late-toxicity profiles in the majority of patients whether treated with the North American trimodality approach or the United Kingdom single treatment block. The similar hazard ratios observed with cisplatinum and 5FU/MMC suggests that a range of chemotherapy approaches can probably be used with the selection on the basis of toxicity. It is noteworthy that comparisons of platinum and 5FU-based chemoradiotherapy combinations have been carried out in anal cancer with the two approaches, and a recent study suggested that 5FU/MMC was superior. Primary chemoradiation with salvage surgery is well established as the standard of care for anal cancer. The high rates of locoregional control seen make primary radical chemoradiotherapy a viable treatment option for patients presenting with muscle-invasive bladder cancer.

TOXICITY OF SYNCHRONOUS CHEMORADIATION

The toxicity of radical radiotherapy varies with the dose and schedule used. Within BC2001 and BCON there were two schedules: 55 Gy in 20 fractions and 64 Gy in 32 fractions. The majority of patients experienced only grade 1 to 2 toxicity with very low rates of grade 4 events. Synchronous chemotherapy increased toxicity in BC2001 but was predominantly grade 1 to 2 with a nonstatistically significant effect on grade 3/4 events (27.5% vs. 36%, p = 0.07; boundary for significance set at 0.01 to reflect multiplicity of testing). The reduced volume randomization failed to demonstrate a reduction in overall toxicity. However, volume of bowel irradiated did correlate with risk of grade 3/4 toxicity. There was no increase in acute toxicity observed in BC2001 if patients had received prior neoadjuvant chemotherapy. Radiotherapy treatment completion rates in both trials were very high with in excess of 95% of patients receiving the prescribed dose. The majority of patients who did not complete treatment did so for tumor-related reasons rather than toxicity.

Late toxicity was of great interest in both trials and was analyzed somewhat differently. In BCON, the cumulative rates of grade 3/4 events were reported, giving the “worst case” scenario but did not reflect the overall toxicity at any given time point post-treatment. BC2001 reports the toxicity rates at prespecified time points. There are several points of note here. First, late toxicity was the same with both randomizations in BC2001, i.e., reduced volume radiotherapy did not influence late toxicity. More significantly, the addition of synchronous chemotherapy also had no effect on reported late side effects. In addition, at any given point, 75% to 80% of patients reported no late toxicity at all. This is supported by bladder-capacity measurements in BC2001, which showed a mean change in bladder volume at 1 and 2 years of less than 50 mls. Of those reporting side effects, fewer than 5% report grade 4 and fewer than 10% overall grade 3.

The good toxicity and functional results associated with radiotherapy are borne out by surveys of patient quality of life and symptoms in patients with cystectomy and radiotherapy carried out by Henningsohn et al. Radiotherapy and cystectomy patients report different patterns of symptoms with sexual dysfunction being more prominent in surgical patients and bowel symptoms more prominent in radiotherapy patients. The preservation of sexual function by radiotherapy is particularly striking given that the patients were an average of around 10-years older.
PATeRNS OF TREATMENT FAILURE
A proportion of patients experience local failure and undergo salvage surgery. The BC2001 trial gives a good indication of patterns of failure using the single-block approach to radical radiotherapy. Figure 3 illustrates the failure patterns in the chemoradiation patients.

There are several features of note here. First, the majority of locoregional failures are in the bladder, and there are more noninvasive than invasive recurrences. This underlines the need for regular surveillance postradiotherapy and the requirement for good integration of radiotherapy and surgical services if patients are to be managed by bladder conservation. In our experience, the majority of noninvasive recurrences can be successfully managed conservatively without the need for cystectomy. For those with invasive recurrence, cystectomy remains an option if they are sufficiently fit. The low rate of nodal relapse is also of interest as no attempt was made to irradiate pelvic nodes, although lower pelvic nodes will have been in the treated volume. For improvement in the metastatic relapse rate we must look to better systemic therapies. Improved uptake of neoadjuvant chemotherapy may effect further improving systemic disease control. The high rate of second cancers is also noteworthy and reflects the patient age and smoking history.

CHAnge in Paradigm leAnDing to Acceptance of ORGAn-PREServation TherApY
The European Association of Urology accepts the role of organ-preservation treatment for select patients with muscle-invasive bladder cancer. The U.S. National Comprehensive Cancer Network has updated the 2012 guidelines reflecting the mounting evidence supporting the use of organ-preservation treatment in select patients. Taken together, the randomized trial data with chemoradiotherapy suggests good tolerability even in relatively elderly patients with excellent late-toxicity profiles in the majority of patients whether treated with the North American trimodality approach or the United Kingdom single treatment block. Concurrent chemoradiotherapy should be considered as the standard of care for patients opting for bladder preservation treatment.

Conclusion
Surgery or bladder preservation treatments are not competing but complementary treatments that an improved understanding on the basis of tumor characteristics, staging information, and in not-so-distant future tumor biology will help to select patients for these treatment modalities. Chemoradiotherapy is the standard of care for patients opting for bladder preservation. Once a patient embarks on the journey of bladder preservation it is important that the patient understands the risk of local relapse requiring salvage cystectomy and need for regular bladder surveillance. Bladder cancer provides an excellent model of multidisciplinary team working, in which urologist, medical oncologist, and radiation oncologist must work closely to get the best results for patients.

Disclosures of Potential Conflicts of Interest
Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.


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GENITOURINARY CANCER

Renal Cell Carcinoma: New Insights for the Future

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Sequencing Systemic Therapies in Advanced RCC: Is There a Best Strategy?

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OVERVIEW

There is a strong rationale for sequencing targeted therapy in metastatic clear cell renal cancer. However, the timing of the switch and the best agent to switch to remains unclear. Randomized data currently are supportive of the sequence of axitinib, followed by everolimus in those patients in which first-line vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) therapy fails. Everolimus is also justified in the second-line setting, and the overall survival data for sorafenib in VEGF TKI-resistant disease is impressive. A degree of cross-resistance appears to exist between all these current agents and has resulted in a drive toward the development of new therapies with novel modes of action.

There are seven approved targeted agents for the treatment of metastatic clear cell renal cancer (RCC). These agents focus on two targets, which include the mammalian target of rapamycin (mTOR) and VEGF. Although there appears to be some cross-resistance between these two classes of agents, the reasons for this are unclear.

Randomized data (RECORD – 1) showed mTOR inhibition notably delayed progression-free survival (PFS) compared with placebo after failure of VEGF-targeted therapy. This has driven the widespread use of sequential therapy in RCC. Before this study, sequencing of sorafenib and sunitinib was routinely used, driven by retrospective data and clinical experience. This led to a culture of switching therapy at progression of disease. Indeed, oncologists have developed a low threshold to change therapy, and patients are often exposed to multiple lines of therapy, including a rechallenge with the same agent.

Two years ago, a randomized phase III trial further supported the rational for switching one VEGF-targeted therapy to another. The AXIS study compared axitinib and sorafenib in patients in whom either sunitinib or immune therapy failed. Axitinib significantly delayed PFS in the patients in whom sunitinib failed (4.8 vs 3.4 months, p = 0.01). It is speculated that this is because axitinib is more potent at targeting VEGF receptors. However, the results with axitinib were more impressive in those patients who had not previously received VEGF tyrosine kinase inhibitor (TKI) therapy. There was no survival benefit with axitinib, despite the lack of crossover in the trial. Despite these issues, the AXIS data supports the use of axitinib after VEGF TKI therapy. The study also shows that subsequent therapies become increasingly less effective in RCC, following a “law of diminishing returns.” Today, randomized data support the use of both VEGF-targeted therapy and mTOR inhibitors in VEGF TKI-resistant disease. The lack of biomarkers to direct personalized therapy means there is no clear preferred choice between these two agents in this setting. The inherent differences between the trials and the differing mechanisms of action of the agents prohibit any meaningful comparison in efficacy and toxicity between axitinib and everolimus.

A more recent randomized phase III study (INTORSECT) has made the landscape more complex. This study compared temsirolimus (mTOR inhibitor) and sorafenib (VEGF TKI) in sunitinib-refractory metastatic RCC. Results showed there was no significant difference in PFS between these two agents; however, the sorafenib arm had significantly longer overall survival (4.3 months increase [12.3 months for temsirolimus vs. 16.6 months for sorafenib: p < 0.001]). Again, there was no crossover in this study. One could speculate that had this survival advantage been associated with a new trial drug in RCC, and not sorafenib, it would be seen as a major breakthrough. These data raise two major issues which need to be addressed in detail: first, is PFS a good surrogate marker for outcome in VEGF TKI-refractory RCC and second, is continued VEGF-targeted therapy required to maximize outcome?

PFS AS ENDPOINT IN VEGF-REFRACTORY DISEASE

The breakdown in the relationship between PFS and overall survival in the INTORSECT study requires particular attention. The reason for the breakdown is unclear, but factors such as immunologic effects of agents or subsequent
treatments may play a role. PFS has been used for the registration approval of all agents in the VEGF TKI-refractory setting in RCC.3,6,8 PFS, determined by RECIST criteria, is radiologically precise but may be less robust in determining treatment failure, potentially making it clinically less relevant.7 A combination of clinical factors and radiologic factors are used in other tumors such as prostate cancer, which may be useful in RCC in the future. An issue is whether PFS should be used as the primary endpoint of future trials. Importantly, the most recent randomized phase III study in this setting (comparing PD-1 inhibitors and mTOR-targeted therapy) is using overall survival as the primary endpoint.

WHEN TO SWITCH THERAPY IN CLINICAL PRACTICE
Clinical trial data support the use of active therapy at disease progression and switching from one VEGF-targeted therapy to another is well established.3,6,8 The timing of the switch, however, has never been tested. Radiologic assessment by RECIST dictates that the development of as little as one new disease-related lesion defines disease progression. This often occurs in the face of what is felt to be ongoing clinical benefit.11 In routine clinical practice, using a more complete clinical assessment may be considered, and an immediate switch at RECIST progression may not be required. Other factors such as the burden of disease, the sites of tumor growth, and changing prognostic factors could be assessed. It is conceivable that switching from more potent VEGF targeted therapies (such as tivozanib) to less potent agents (such as sorafenib) may even be counterproductive. Therefore, careful consideration should be used before a switch occurs.

BIOMARKERS TO DETERMINE SUBSEQUENT THERAPIES
Forest plot analysis was unable to identify specific factors associated with clinical benefit in AXIS or the INTORSECT study.6,8 Specifically, those patients who did not respond well to first-line VEGF-targeted therapy did not appear to benefit from switching the mode of action to mTOR. These results are particularly disappointing as we are no further forward in selecting between VEGF-targeted therapy and mTOR inhibitors for individual patients.

Prospective data shows single nucleotide polymorphisms (SNPs) to VEGF receptors may be able to differentiate patients who benefit from axitinib rather than sorafenib.6 Further data in this area is required. This type of analysis using blood or germ-line material is perhaps the most promising area for a breakthrough as it is easily collected and reproducible.

ARE TARGETED THERAPIES FROM THE SAME CLASS OF DRUG THE SAME?
There is a plethora of data showing pharmacokinetic and pharmacodynamic differences between VEGF TKI therapy, which is largely because of distinct “off-target” effects and different potency of VEGF targeting. This translates into differences in efficacy and toxicity profiles.11 Indeed, randomized data (the EFFECT study) with sunitinib shows that even the dosing of the same agent can potentially influence both toxicity and activity.12

The differences between temsirolimus and everolimus are more subtle. The drugs have identical metabolites, although this process of metabolism is different. The mode and frequency of administration are also different. Therefore the assumption that clinical trial results with different mTOR inhibitors are interchangeable is flawed.

THE EFFECT OF NEW AGENTS ON SEQUENCING
In the near future, a pivotal third-line study comparing dovitinib (a VEGF- and FGF-2-targeted therapy) and sorafenib in patients whose disease progressed through first-line VEGF-targeted therapy and second-line mTOR inhibition will report results (the GOLD study). PFS is the primary endpoint of this study. In view of the issues with AXIS and INTORSECT, many clinicians may wish to see an overall survival signal as well as a PFS signal before adopting this approach as standard of care. A positive study may redress the balance, which currently is tipping toward continued VEGF TKI therapy in the second-line setting.

Recent phase I results with a PD-1 inhibitor were assessed and the drug was moved straight into a phase III setting in VEGF-refractory metastatic RCC.13 Overall survival is the primary endpoint of this study. However, it is speculated that immune therapy is more effective earlier in the disease process. Also, VEGF targeting has an immunological component in its own right, which may have an effect on biomarker expression and response.9 Nevertheless, results of this study are eagerly awaited.

TOXICITY IN DETERMINING SEQUENCE OF TARGETED THERAPY IN RCC
mTOR inhibitors and VEGF-targeted therapies have very distinct toxicity profiles.3,6 Therefore, switching the mode of action in patients who have encountered particular problems with previous VEGF therapies in the first-line setting would appear logical. This may be one of the most compelling reasons for choosing subsequent therapies in subgroups of patients.

KEY POINTS
- Randomized data support sequencing of target therapy.
- A switch to mTOR inhibitors (everolimus) or VEGF-targeted therapies (axitinib/sorafenib) is justified in VEGF refractory disease.
- Cross-resistance between these agents results in shorter clinical benefits associated with subsequent therapies.
- There are currently no clinical features or biomarkers to predict which therapy will work best in VEGF refractory disease.
- Randomized data support the use of everolimus in the third-line setting, suggesting a sequence of axitinib followed by everolimus in VEGF refractory disease to be attractive.
TREATMENT FOR PATIENTS WHO DO NOT RECEIVE FIRST-LINE VEGF-TARGETED THERAPY

There is a lack of data on the subsequent treatment of poor-risk patients in whom first-line temsirolimus fails. These patients have a short median survival, however, VEGF-targeted therapy in the second-line setting appears clinically justified despite the lack of data. Even today, a small proportion of patients are given first-line immune therapy (interferon or IL-2). Data with axitinib in these patients (from the AXIS study) appears particularly impressive.6

SUMMARY

Overall, there is strong rationale for sequencing of VEGF-targeted therapy, although the exact timing of the switch and the best agent to switch to remains unclear. There are genuine questions regarding the survival advantage associated with switching therapy, compared with continuing with existing therapy regardless of progression. Randomized data currently support the sequence of axitinib, followed by everolimus in patients in whom first-line VEGF TKI therapy failed. Everolimus is also justified in the second-line setting, but if given as a second-line therapy, subsequent third-line treatment then becomes challenging based on current evidence. The GOLD study may address this. Finally, the overall survival data for sorafenib in VEGF TKI-resistant disease is impressive in all the randomized studies. A degree of cross-resistance appears to exist between all these current agents and is resulting in a drive toward the development of new therapies with novel modes of action (PD/PDL-1 and FGF-2 inhibition).

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References

The Role of Androgen Deprivation in Prostate Cancer: What Setting? Can It Harm?

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Androgen Deprivation Therapy (ADT) is the mainstay systemic treatment of prostate cancer because of the androgen dependence of the disease. Although ADT has long been used to manage prostate cancer, its use continues to evolve as data from clinical trials mature and long-term effects are recognized. For patients with localized disease and high-risk features, short and long courses of ADT as neoadjuvant/adjuvant therapy have been shown to improve survival when used with radiation therapy, but this has not been demonstrated with radical prostatectomy. The role of ADT with salvage radiotherapy after radical prostatectomy continues to be defined. Lifelong ADT in patients with node-positive disease after surgery or with radiation is also associated with increased survival. Increasingly though, the adverse effects of ADT that go beyond those on libido and hot flashes are being acknowledged. The metabolic effects on lipids, glycemic control, and bone loss from ADT can lead to an increased risk of cardiovascular events and osteoporosis, which needs to be considered when deciding to initiate and treat patients with ADT. Large, randomized trials comparing intermittent to continuous ADT have now been reported. Although the hope for improved cancer outcomes with intermittent therapy has not come to realization, an interrupted approach to therapy may help mitigate some of the negative effects of ADT in selected patients by allowing for off-treatment intervals.

It has been over 70 years since the initial description of prostate cancer androgen dependence by Huggins and Hodges leading to androgen deprivation becoming a mainstay treatment for the disease. Despite this long history, the use of androgen deprivation therapy (ADT) in the management of prostate cancer continues to evolve and be defined across multiple parameters: disease status, long-term adverse effects, optimal timing of initiation, duration of therapy, and schedule of treatment. The purpose of this review is to update the reader on the current status and latest developments on the use of ADT for patients with localized and recurrent prostate cancer.

ADT as NeoAdjuvant/Adjuvant Therapy for High-Risk Disease

Short-Course ADT and Radiation Therapy for Intermediate- and High-Risk Localized Disease

A short course (4 to 6 months) of neoadjuvant and concurrent ADT has been shown to improve overall survival when added to conventional-dose radiation in men with mainly intermediate- and high-risk clinically localized disease. In the Dana-Farber 95–096 randomized trial, 206 men with cT1b-T2b and a PSA level greater than 10, a Gleason score of 7 or higher, or MRI evidence of extracapsular extension were treated with 70 Gy of external radiation with or without 6 months of combined androgen blockade. Overall survival was 74% versus 61% at 8 years favoring ADT (p = 0.01).1 Similarly, the RTOG 94–08 trial found that 4 months of combined androgen blockade added to 66 Gy of radiation for men with cT1b-T2b and a PSA level of less than 20 improved 10-year overall survival (62% vs. 57%, p = 0.03). An unplanned postrandomization analysis suggested that the benefit was limited to men with intermediate-risk disease, and that among high-risk men, 4 months of ADT was not associated with an improvement in overall survival (p = 0.47).2 This may reflect a lack of power in the high-risk group (who represented only 11% of the study), or alternatively it is possible that at least 6 months of ADT is needed to improve survival for high-risk disease and 4 months was truly not adequate. The latter notion is somewhat supported by the TROG 96.01 trial that found that for men with cT2b-T4 disease treated with 66 Gy of radiation, 6 months of ADT improved overall survival compared with 0 months (hazard ratio (HR) 0.63, p = 0.0008), but 3 months of ADT did not (HR 0.84, p = 0.18).3 Currently, the TROG 03.04 RADAR trial is testing whether 18 months of ADT could further improve prostate-cancer–specific survival compared with 6 months of ADT when added to radiation for men with mostly cT2 and a Gleason score of 7 or higher and...
A PSA level of 10 or higher, and survival results are expected in 2014.

**Long-Course ADT Plus Radiation Therapy for High-Risk Localized/Locally Advanced Disease**

Two randomized trials have demonstrated the benefits of longer-duration ADT for mainly locally advanced disease. The randomized RTOG 92–02 trial treated men with cT2c-T4 and a PSA level lower than 150 to 65 to 70 Gy of radiation with either 4 months or 28 months of ADT, and found that long-course ADT improved prostate-cancer–specific survival from 84% to 89% at 10 years (p = 0.0042), but not overall survival (p = 0.36). However, a hypothesis-generating postrandomization analysis found that overall survival was improved among the men with a Gleason score of 8 to 10 (45% vs. 32%, p = 0.0061). Similarly, the European Organisation for Research and Treatment of Cancer ran a noninferiority trial of radiation plus either 6 months or 36 months of ADT in men with mainly cT2c-T4 disease and found that short-course ADT had inferior survival. At 5 years, long-course ADT reduced overall mortality by 3.8%, from 19.0% to 15.2%. Although both of these trials establish long-course ADT as the standard of care for men with locally advanced disease, it should be noted that neither trial specifically addresses whether long-course is needed for men with high-risk clinically localized disease (e.g., cT1c with a Gleason score of 8), and it is possible that a shorter course of ADT may be adequate for select men with these tumor characteristics.

**Lifelong ADT for Node-Positive Disease**

Two randomized trials demonstrated an improvement in overall survival from lifelong ADT for men with node-positive disease. The RTOG 85–31 randomized trial included 977 men with T3 or N1 disease administered radiation with or without lifelong ADT and found that lifelong ADT improved 10-year overall survival (49% vs. 39%, p = 0.002). A post-randomization subgroup analysis limited to the 173 pathologically node-positive suggested on multivariable analysis that node-positive men treated with radiation alone had a higher all-cause mortality (relative risks (RR) 1.62, p = 0.03). For surgically treated men, the ECOG/EST 3886 randomized trial by Messing et al. treated 98 men with pathologically node-positive disease after prostatectomy to lifelong ADT versus observation, and found that lifelong ADT improved overall survival (HR for mortality 1.84, p = 0.04).

**Salvage ADT Plus Radiation Therapy for Rising PSA after Prostatectomy**

The RTOG 96–01 randomized trial evaluated whether 2 years of antiandrogen therapy using bicalutamide 150 mg could improve outcomes when added to salvage radiotherapy for men with pT3 or pT2 margin-positive disease and a rising PSA after prostatectomy. Initial results in abstract form with a median follow-up of 7.1 years found that antiandrogen therapy reduced metastases at 7 years from 12.6% to 7.4% (p < 0.04), and overall survival was 91% versus 86%, but no statistical test was performed on this difference as the study had not yet reached the prespecified number of events. Because bicalutamide 150 mg is generally not used in the United States or Canada, some clinicians extrapolate from the results of the RTOG study and substitute a gonadotropin-releasing hormone (GnRH) agonist for the bicalutamide. Whether a shorter course of hormone therapy could achieve the same result is one of the questions being asked in the United Kingdom/Medical Research Council/NCIC RADICALS randomized trial that includes men receiving either adjuvant or salvage radiation to either no hormones, 6 months of hormones, or 2 years of hormones. The hormone therapy in that study can either be bicalutamide 150 mg or combined androgen blockade. Also, the RTOG 05–34 trial is randomly assigning over 1,700 men with a rising PSA after prostatectomy to prostate bed radiation, prostate bed radiation with 4 to 6 months of ADT, or pelvis and prostate bed radiation and 4 to 6 months of ADT. The trial will also help clarify whether short-course ADT would be a viable alternative to 2 years of bicalutamide.

**Neoadjuvant ADT before Prostatectomy**

At least eight randomized trials have evaluated the role of a 3-month course of neoadjuvant ADT before prostatectomy. A recent meta-analysis of these trials found that neoadjuvant ADT was associated with a significant reduction in positive margins (RR 0.49, p < 0.00001), increase in organ-confined disease (RR 1.63, p < 0.0001), and reduction in lymph node positivity (RR 0.66, p = 0.02), but this did not translate into a benefit in disease-free survival (RR 1.04, p = 0.48), disease-specific survival (RR 1.00, p = 0.77), or overall survival (RR 1.00, p = 0.95). Interest in neoadjuvant ADT before prostatectomy has been renewed with the presentation at the
2012 ASCO Annual Meeting of a randomized phase II study by Taplin et al. of 58 men with high-risk prostate cancer randomly assigned to 3 months of neoadjuvant GnRH agonist alone followed by 3 months of GnRH agonist plus abiraterone acetate versus 6 full months of neoadjuvant GnRH agonist plus abiraterone acetate. At prostatectomy, 4% versus 10% in each arm achieved a pathologic complete response (p = 0.33) and 15% versus 34% in each arm received a total or near-total pathologic complete response (p = 0.09).13

**TABLE 1. Potential Complications from ADT from the Patient Perspective**

<table>
<thead>
<tr>
<th>What Physicians Commonly Tell You</th>
<th>What You Feel</th>
<th>What You See</th>
<th>What You Don’t See</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of libido</td>
<td>Fatigue or loss of energy, initiative</td>
<td>Weight gain</td>
<td>Loss of bone mineral density</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Aches and pains</td>
<td>Loss of muscle mass and strength</td>
<td>Changes in lipids</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Low spirits, depression</td>
<td>Increased subcutaneous tissue, especially hips and thighs</td>
<td>Glucose intolerance, diabetes</td>
</tr>
<tr>
<td></td>
<td>Emotional liability</td>
<td>Gynecomastia</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Cognitive changes</td>
<td>Decrease in testicular size and penile length</td>
<td>Increased cardiovascular risk</td>
</tr>
</tbody>
</table>

excess cardiovascular deaths at median follow-up times of 7.6 to 13.2 years. Importantly, men with unfavorable risk disease had improved prostate-cancer–specific (RR 0.69, p < 0.001) and overall survival (RR 0.86, p < 0.001). A subsequent analysis by the same group retrospectively evaluated over 14,500 patients with a history of congestive heart failure or myocardial infarction before treatment with brachytherapy for localized prostate cancer. After a median of only 4 months of ADT and median follow-up of 4.3 years, all-cause mortality was greater in those who received ADT compared with those treated only with radiation (5-year estimates of all-cause mortality of 22.71% for ADT compared with 11.62% for no ADT, log-rank < 0.0001). As discussed previously, although the addition of ADT to radiation should benefit those with high-risk prostate cancer in terms of overall survival, this study suggests that a subgroup of men with known congestive heart failure or myocardial infarction could be harmed by the addition of ADT.

Intriguing new data was recently presented suggesting that the risk for cardiovascular events and death from any cause during the first year of treatment is 50% lower in men with pre-existing cardiovascular disease who were treated with the LHRH antagonist degarelix compared to those treated with a pre-existing cardiovascular disease who were treated with the LHRH agonist buserelin. Prospective trials with the primary endpoint of cardiovascular events are clearly needed.

### ADT Effects on Bone
Hypogonadism is also associated with loss of bone mineral density (BMD) and increased risk for fractures and, in addition to alcoholism and glucocorticoid therapy, is one of the most common causes of osteoporosis in men. Hip fractures in men account for one-third of all hip fractures worldwide. Compared with women, men who suffer hip fractures are more likely to die within the year and are less likely to return to independent living. Hence, osteoporosis and/or fractures can cause significant morbidity and mortality in men.

ADT causes a rapid loss of BMD in the first 6 to 12 months of treatment and continues thereafter at a slower rate. In addition to direct effects on BMD as a risk factor for fracture, the effects of ADT on lean body mass and strength also contribute to the risk for falling and fracture. In a retrospective, population-based study of over 50,000 men with prostate cancer, the incidence of fracture at 5 years from diagnosis was higher in the ADT-treated men compared with those who were not treated (19.4% compared with 12.6%). The mortality rate for those who sustained a fracture was double that of those who did not have a fracture.

Recommendations for baseline assessments are listed in Table 3. These are common sense approaches based on what is known about the side effects of ADT and also incorporate recommendations from specialty groups. Educating the patient about the potential side effects of ADT at the outset empowers patients to be active participants in their own care and to better understand the importance of engaging in healthy behaviors, including exercise. It is well recognized that exercise plays a significant role in overall good health and has been shown to improve survival in patients with breast and colorectal cancer. In addition, exercise can abrogate many of the side effects of ADT. At the present time, however, the optimal exercise regimen for men treated with ADT is not clear. Resistance exercises are important in several phase III trials but the advantage of adding aerobic exercise is unclear. Further research is indicated to better define the appropriate combination of resistance, aerobic, and balance training.

If baseline studies indicate a history of hip or vertebral fracture, osteoporosis by T-score, or osteopenia by T-score plus the World Health Organization’s Fracture Risk Assessment Tool (FRAX) estimates the 10-year probability of hip fracture is 3% or higher or major osteoporosis-related fracture is 20% or higher, initiation of bone-directed therapy to prevent or treat osteoporosis and fracture should be considered. FRAX is an online assessment tool that incorporates age, body mass index, and other clinical risk factors to calculate the 10-year probability of a hip fracture and the 10-year probability of a major osteoporosis-related fracture. Because the sensitivity of the dual-energy X-ray absorptiometry (DXA) scan with respect to predicting fractures is low (many patients who suffer fractures have BMD values above the osteoporotic threshold of T-score of −2.5 SD), results of the FRAX can help stratify patients who may not have frank

### TABLE 2. Features of Hypogonadism versus ADT

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hypogonadism</th>
<th>ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition by T level</td>
<td>T &lt;325 ng/dL (11.3 nmol/L)</td>
<td>T &lt;50 ng/dL (1.7 nmol/L) or &lt;20 ng/dL (0.7 nmol/L)</td>
</tr>
<tr>
<td>Time to reach low T levels</td>
<td>Years</td>
<td>Hours to days</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Insulin resistance/diabetes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Obesity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lipid abnormalities</td>
<td>Yes</td>
<td>Triglycerides increased</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cardiac death increased</td>
<td>Yes&lt;sup&gt;38&lt;/sup&gt;</td>
<td>No&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Increased all cause mortality</td>
<td>Yes&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Yes in selected high risk: previous hx CHF, MI&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: T, testosterone; Hx, history; CHF, congestive heart failure; MI, myocardial infarction.

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osteoporosis but who are at risk for fracture and might benefit from drug therapy. When using FRAX, it is not necessary to have the DXA results but the answer to “secondary osteoporosis” should be answered “yes” in men who are on or about to start ADT.

Options for bone-directed therapy include bisphosphonates (pamidronate, zoledronic acid, alendronate, risedronate), denosumab, a RANKL inhibitor, and selective estrogen-receptor modulators or SERMs (raloxifene, toremifene) result in increased BMD and decreased markers of bone turnover in men treated with ADT. Fracture risk was reduced only in the denosumab and toremifene trials.25

The frequency of follow-up studies varies. Weight and blood pressure should be recorded at each visit. The fasting glucose should be followed as outlined in Fig. 1. The DXA scan should be repeated at one year from baseline and as indicated thereafter. The fasting lipid panel should also be followed annually. Other studies suggested can be followed as clinically indicated.

In addition to strategies that address individual side effects, use of intermittent androgen deprivation is another approach to minimizing the effects of ADT. A detailed discussion of recent data comparing intermittent ADT to continuous ADT follows below.

**INTERMITTENT OR CONTINUOUS HORMONE THERAPY?**

The preclinical rationale for intermittent hormone therapy arose 20 years ago from the work of Bruchovsky et al. in androgen-dependent cancer models demonstrating a delay in the time to development of androgen-independent growth when tumors were re-exposed to androgens.26,27 The underlying hypothesis was that cancer stem cells would remain sensitive if re-exposed to androgens rather than undergoing adaptive changes to a treatment-resistant phenotype in an androgen-deprived environment.28,29 Several phase II trials and case series have reported on the clinical feasibility of this approach in patients of various stages of their disease with demonstration of sometimes prolonged off-treatment intervals during which a recovery of testosterone and a decrease in side effects related to androgen deprivation were documented.30,31 Thus, the promise of intermittent therapy held several potential benefits: improved cancer outcomes by

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**TABLE 3. Baseline Assessments before Starting ADT**

<table>
<thead>
<tr>
<th>History</th>
<th>Physical Exam</th>
<th>Laboratory</th>
<th>Bone Density and Fracture Risk</th>
<th>Nutrition Assessment</th>
<th>Physical Therapy Evaluation</th>
<th>Additional Considerations</th>
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</thead>
<tbody>
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<td>Cardiac disease</td>
<td>Height</td>
<td>Fasting glucose</td>
<td>DXA scan¹</td>
<td>Weight loss recommendations</td>
<td>Calcium and vitamin D intake</td>
<td>Drug therapy (statin, low dose aspirin, antihypertensive, metformin etc.)</td>
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<tr>
<td>Congestive heart failure</td>
<td>Weight</td>
<td>Fasting lipids</td>
<td>FRAX²</td>
<td>Calcium 1200 mg/d</td>
<td>Resistance exercise</td>
<td>Psychologist/counselor</td>
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<td>Myocardial infarction</td>
<td>Blood pressure</td>
<td>HgbAlc</td>
<td>Urinary N-telopeptide</td>
<td>Low glycemic diet if indicated</td>
<td>Core/balance exercise</td>
<td>Sex therapist</td>
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<td>Other vascular</td>
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<td>Vitamin D level</td>
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<td>Stretching</td>
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<td>Exercise habits</td>
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<td>Osteoporosis and fracture</td>
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**FIG 1. Strategy to monitor for diabetes in men receiving ADT.**

Adapted with permission from Shahani et al 2008 (reference 16)
Recently reported trials have compared intermittent versus continuous androgen deprivation therapy (ADT). Several randomized studies comparing intermittent versus continuous ADT have been reported. The largest and most recently reported trials were those led by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the Southwest Oncology Group (SWOG). The NCIC CTG PR7 study enrolled 1,386 patients with rising PSA after primary or salvage radiotherapy and no metastases, and randomly assigned them to continuous hormone therapy or intermittent therapy based on an 8 month treatment cycle with luteinizing hormone-releasing analogs and a minimum of 4 weeks of nonsteroidal antiandrogen therapy. The primary endpoint was overall survival and designed to test for equivalence, with an interim analysis for noninferiority if there was 95% certainty that the absolute difference in overall survival was less than 8% (HR < 1.25, 95% CI < 1.00, < 1.25). At the interim analysis, the HR for death for intermittent therapy versus continuous therapy was 1.02 (95% CI 0.86, 1.21) with a p value for noninferiority of 0.009, and the study was stopped at the recommendation of the Data and Safety Monitoring Board. After a median follow-up of 6.9 years, the median overall survival was 8.8 years for intermittent therapy and 9.1 year for continuous therapy. Notably, the majority of deaths (59%) were unrelated to prostate cancer. Disease-specific survival was in favor of continuous therapy but this was nonsignificant (HR 1.18, 95% CI 0.90, 1.55, p = 0.24) and balanced by a greater number of deaths unrelated to prostate cancer in the continuous therapy group. There was no differential treatment effect for Gleason score. Quality-of-life assessments were performed at fixed time points and thus did not necessarily reflect on- and off-treatment phases for patients on the intermittent therapy arm. Nevertheless, differences were observed in favor of intermittent therapy for hot flashes, sexual activity, urinary symptoms, and a trend for improved fatigue. Consistent with phase II studies, patients on the intermittent arm received considerably less therapy, receiving a median of 15.4 months of therapy with a cumulative off-treatment time of 37.6 months, and the continuous treatment arm received a median of 43.9 months of treatment on study.

Results of the SWOG 9346 study were reported at the 2012 ASCO Annual Meeting. Patients with hormone-sensitive metastatic prostate cancer were treated with 7 months of goserelin and bicalutamide with those achieving a PSA level of 4 ng/mL or less randomized to continuous or intermittent therapy. Patients with a PSA level higher than 4 at this time point have been previously shown to have a poor prognosis. The study was designed as a noninferiority trial, with the intermittent therapy arm considered not inferior if the 95% CI for the HR excluded 1.2. 3,040 patients were accrued and 1,535 assigned treatment. Patients on intermittent therapy were on an off-treatment interval approximately 50% of the time. Median overall survival from time of randomization was 5.1 years for those on intermittent therapy and 5.8 years for patients on continuous therapy (HR = 1.09, 95% CI 0.95, 1.24). Because the upper boundary of the 95% CI exceeded 1.2, the authors concluded that intermittent therapy was not proven to be noninferior. This interpretation is controversial, however, as the 95% CI lower boundary crossed unity (and thus a benefit of intermittent therapy cannot be ruled out), making the results inconclusive for noninferiority. No interaction with therapy was significant except for a suggestion with disease extent: patients with extensive disease had a median overall survival of 5.0 years with intermittent therapy versus 4.4 years on continuous therapy (HR = 0.96, 95% CI 0.80, 1.16, p = 0.64) while those with minimal disease resulted with a HR of 1.23 (95% CI 1.02, 1.49, p = 0.035). This somewhat counter-intuitive finding may reflect a false-positive result or be related to the way disease extent was defined, which might not have truly reflected high-burden disease. Preliminary quality-of-life data from questionnaires taken at baseline and 3-months post-randomization demonstrated differences for the two arms with patients on continuous therapy reporting statistically significantly more impotence (p < 0.01) and less libido (p < 0.01) than those on intermittent therapy, and emotional functioning was also better for the intermittent therapy arm (p < 0.01).

So what can we take away from these studies to inform our practice? First, it can be assumed that the medication costs would be substantially less for an intermittent approach particularly in patients without evidence of metastases, although a formal cost analysis has not been reported and the increased monitoring required would likely blunt this benefit. Second, preliminary quality-of-life data supports the anecdotal and single-arm study evidence of decreased side effects, better sexual function, and improved well-being associated with the off-treatment periods of intermittent therapy. Lastly, despite the promise of improved cancer outcomes, there is no benefit on survival with intermittent therapy. But neither does there appear to be substantial harm. In patients without clinical metastases, the NCIC CTG PR7 study demonstrates intermittent therapy as noninferior, but carries with it the caveat that these patients could have had a delayed approach and spared treatment altogether. The SWOG 9346 study in patients with metastases is inconclusive for noninferiority, but there is a trend to worse outcomes with intermittent therapy. Additionally, any quality-of-life benefits of intermittent therapy in this population are mitigated by the relatively fewer number of treatment cycles and shorter time off therapy. The optimal schedule of intermittent therapy (e.g., duration of therapy before interruption, when to reinitiate treatment) and criteria for patients to proceed with treatment interruption (e.g., disease extent, PSA value) is unknown. Thus, in patients starting hormone therapy for recurrent prostate cancer, continuous therapy remains a standard treatment. However, patients that are motivated to have an off-treatment interval time and the quality-of-life benefits associated with that, particularly in those without metastases and with a good response to induction therapy, should be given the opportunity for an intermittent therapy approach provided careful follow-up and reinstitution of treatment is carried out in a defined manner. 
Disclosures of Potential Conflicts of Interest


References


