Perspectives

A New Therapy Paradigm for Prostate Cancer Founded on Clinical Observations

Eleni Efstathiou1,2 and Christopher J. Logothetis2

Abstract

Efficacy equivalent to that reported in other common adult solid tumors considered to be chemotherapy-sensitive has been reported with Docetaxel in patients with castrate-resistant prostate cancer. However, in contrast to other cancers, the expected increase in efficacy with the use of chemotherapy in earlier disease stages has not been reported to date in prostate cancer. On the basis of these observations, we speculated that the therapy development paradigm used successfully in other cancers may not apply to the majority of prostate cancers. Several lines of supporting clinical and experimental observations implicate the tumor microenvironment in prostate carcinogenesis and resistance to therapy. We conclude that a foundation to guide the development of therapy for prostate cancer is required. The therapy paradigm we propose accounts for the central role of the tumor microenvironment in bone and, if correct, will lead to microenvironment-targeted therapy. Clin Cancer Res; 16(4); 1100–7. ©2010 AACR.

Recent clinical observations compel a reassessment of the framework used to develop therapy for patients with prostate cancer. The therapeutic paradigm used in the development of chemotherapy for solid tumors has been to first optimize new therapies in the advanced disease setting, followed by the gradual integration of those therapies into treatment for disease at earlier stages, with the expectation of increased survival. However, recently reported results of clinical trials suggest that this approach, despite its proven success in other common adult solid tumors, does not apply to prostate cancer. This unexpected finding prompts the search for a better understanding of the underlying biology of prostate cancer.

In this Perspectives, we present a conceptual biological framework that proposes the tumor microenvironment as the key aspect of prostate cancer evolution. The properties of the microenvironment are likely to account for the stage-dependent chemotherapy-response profile of the disease. Experimental observations and clinical-pathologic associations suggest that prostate cancer progresses through a microenvironment-dependent state (which for the purpose of this discussion will be called paracrine state) and on to a microenvironment-independent state (epithelio-centric; and here called autocrine state) during its clinical evolution. The progression of prostate cancer to this autocrine state may explain why more advanced prostate cancer is chemotherapy-responsive. This may account for a direct relationship between prostate cancer progression and chemotherapy responsiveness (theraphy-response profile) and distinguish prostate cancer from other cancers (Fig. 1).

Clinical Evidence Supporting the Importance of the Microenvironment in the Biology and Progression of Prostate Cancer

Chemotherapy response by disease state. The development of chemotherapy for prostate cancer was initially hampered by the perception that elderly patients would have limited tolerance to chemotherapy. Moreover, in the era before prostate-specific antigen concentration was used to detect prostate cancer, the absence of measurable disease or some other acceptable surrogate to measure treatment outcome resulted in great skepticism about the merits of chemotherapy (1). However, chemotherapy became an accepted part of the treatment strategy for advanced prostate cancer when prospectively conducted and properly controlled studies showed palliation (2), and, later, modest prolongation of survival with chemotherapy (2, 3).

These promising results prompted efforts to integrate chemotherapy into the treatment of prostate cancer at earlier stages of disease progression. These efforts were based on a theoretical framework similar to that used for treating other solid tumors. First, various combinations of agents were developed and studied (4–6). Chemotherapy was then used in combination with androgen ablation for earlier-stage disease (i.e., castration-naive disease; refs. 7, 8),
or in combination with molecularly targeted therapies (9, 10). Last, trials of neoadjuvant therapy were conducted (11–17). Despite the strong rationale for this approach, the reported results to date have been disappointing. Reported studies have not shown improved outcomes with initial androgen ablation and chemotherapy for most men with prostate cancer. Studies combining chemotherapy with androgen ablation for the initial treatment of patients with metastatic prostate cancer have, thus far, revealed no survival benefit in unselected patients (7, 8). Adjuvant treatment with docetaxel is still being studied (Table 1A), and only two relatively small adjuvant chemotherapy studies have been reported to date (18, 19). Preoperative studies integrating chemotherapy, alone or in combination with androgen ablation, failed to achieve a degree of cytoreduction analogous to that observed in other common solid tumors (11–17). Phase II neoadjuvant studies have, in fact, been characterized by a striking absence of meaningful pathologic regression of primary cancers. Two phase III studies are under way (Table 1B).

The data reported thus far, although not conclusive, predict that earlier use of chemotherapy in prostate cancer will not result in improved efficacy similar to that observed with other cancers. A modest increase in efficacy may yet be observed, but the likelihood that such efforts will have a major effect on survival is small.

These unexpected findings have profoundly affected our view of prostate cancer. The view emerging from these clinical observations serves as the impetus for further investigation. The goal of future studies will be to confirm and understand the paradoxical clinical observation that earlier-stage prostate cancer may be more resistant to chemotherapy than are advanced castrate-resistant cancers. Given that chemotherapy predominantly affects tumor cells, the insensitivity of earlier-stage prostate cancer to chemotherapy supports that tackling tumor cells per se is not sufficient to inhibit prostate cancer progression.

Organ-specific disease spread and targeting. The clinical presentation of patients with advanced prostate cancer is characterized by a high frequency of bone-homing and bone-forming metastases. Furthermore, complications due to bone metastases (pain, fractures, paralysis due to spinal cord compression, and cranial nerve root involvement) are frequent sources of suffering for these patients. Thus, clinicians have been focused on developing specific strategies to therapeutically target bone metastases.

A long-standing empiric treatment approach adopted by oncologists is to target sites of preferred metastasis for cancers with a predictable pattern of spread, such as pulmonary resection for selected patients with sarcomas and hepatic perfusion or resection for patients with colon cancer. This strategy has been extended to prostate cancer with the use of bone-homing radiopharmaceutical agents. We and others have exploited the properties of these radiopharmaceuticals for palliating symptoms and treating patients in the hope of prolonging their survival. Indeed, initial studies with $^{89}$Sr revealed symptom relief and perhaps delayed disease progression to new metastatic sites (20, 21). Since then, similar effects have been observed.
by others using various radiopharmaceutical agents both alone and in combination with chemotherapy (22, 23). Randomized studies are currently under way to prospectively confirm these findings.

These clinical observations indirectly support the concept that targeting organ-specific microenvironment implicated in disease progression may alter disease outcome. The nonrandom localization of tumor to specific anatomical sites suggests a strong dependence of tumor on the specific organ environment.

Experimental evidence linking the prostate cancer microenvironment to disease progression in bone and resistance to Therapy. The lack of enhanced efficacy with the earlier introduction of chemotherapy in prostate cancer progression previously described, along with the organ-specific progression of prostate cancer, led us to consider that properties of the bone microenvironment, shared in part with the prostate (24, 25) may be central to the observed stage-dependent chemotherapy-response profile (Fig. 1).

Experimental data support the view that the properties of the microenvironment affect the epithelial components of cancers in diverse ways (26–29). For instance, physiologic prostate-derived microenvironments induce cellular differentiation of normal prostate glandular formations, whereas cancer-associated microenvironments promote carcinogenesis (30–34). Recent reports raise the possibility of an alternative explanation and suggest paracrine support of prostate cancer in bone may be primarily mediated by stromal elements (34–37). This concept is also supported by the observation that prostate stromal cells, harvested from sites adjacent to cancer, have growth-promoting effects on malignant epithelial cells (35). Others have shown that in vivo, in bone metastases, osteoblasts promote prostate cancer progression, including castrate-resistant disease progression (24, 25, 33). These data further support the concept that cancer growth promotes crosstalk between prostate cancer cells in bone and is central to prostate cancer progression. More recently, analogous findings were reported from studies using a prostate cancer xenograft-a mixed-species model of bone development in which the epithelial compartment is human and the mesenchymal compartment is murine (36). These experimental observations reported in the literature infer that the tumor microenvironment, and therefore stromal-epithelial-interacting pathways, play a critical role in disease progression. Taken together, these observations provide the rationale for prioritizing the microenvironment as a therapy target.

## Paracrine Pathways in the Prostate Tumor Microenvironment

An increasing number of stromal-epithelial-interacting pathways have been associated with prostate cancer progression and likely account for many of its clinical features. Several lines of evidence indicate that pathways integral to bone or prostate development, as well as homeostasis, are implicated in prostate cancer progression when aberrantly activated. The concept that prostate cancer usurps these normal developmental and functional programs in carcinogenesis and progression provides a basis for the rational prioritization of these pathways for further study.

Androgen signaling was identified more than half a century ago as a principal contributor to prostate cancer progression and therefore as a legitimate therapy target. More recent findings suggest that androgen signaling may have a dual role: directly on the epithelium and indirectly through the stroma. Preclinical data have shown that the stromal androgen receptor in both the prostate gland and the bone also functions as a tumor promoter (37). Other data also support the concept that androgen receptor-expressing stromal cells are capable of supporting and stimulating the growth of androgen receptor-negative epithelial cells (37).

Clinical data from ongoing studies of new agents suggest that there is a hierarchy among stromal-epithelial-interacting pathways and that optimum suppression of

### Table 1. Docetaxel-based trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Randomization</th>
<th>Primary endpoint</th>
<th>Planned accrual status</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Adjuvant phase III trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPG-12 (NCT003767)92</td>
<td>Docetaxel × 6 vs. observation</td>
<td>bPFS</td>
<td>396</td>
</tr>
<tr>
<td>SWOG 9921 (NCT00004124)</td>
<td>Mitoxantrone × 6 cycles + prednisone + ADT × 2 y</td>
<td>bPFS</td>
<td>Closed early</td>
</tr>
<tr>
<td>TAX3501 (Sanofi -Aventis)</td>
<td>Docetaxel + prednisone × 6 cycles + ADT alone</td>
<td>bPFS</td>
<td>Closed early</td>
</tr>
<tr>
<td>VA CSP (NCT00132301)</td>
<td>Docetaxel + Prednisone × 6 cycles vs. observation</td>
<td>bPFS</td>
<td>636</td>
</tr>
<tr>
<td>B. Neoadjuvant phase III trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB 90203 (NCT00430183)</td>
<td>Docetaxel × 6 + ADT × 18/24 wk vs. RP alone</td>
<td>bPFS</td>
<td>700</td>
</tr>
<tr>
<td>GETUG 12 (NCT0055731)</td>
<td>Docetaxel + Estramustine prior to RP or RT and ADT</td>
<td>bPFS</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td>× 3 y vs. local and ADT × 3 y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: bPFS, biochemical progression-free survival; ADT, androgen deprivation therapy.
androgen signaling is a necessary component of molecularly targeted therapy for some patients. The importance of androgen signaling can be inferred from the efficacy of further androgen blockade with CYP-17 inhibition (38) in cancers previously considered androgen-independent, which contrasts with the lack of reported efficacy of molecularly targeted therapies (9, 39, 40). CYP-17 (C17-20 lyase, C17 hydroxylase) is a key enzyme in the biosynthetic route of androgens enabling the conversion of precursors to androstenedione. CYP-17 inhibition thus blocks androgen production not only from the gonads but the adrenals as well. There is also recent evidence to support intratumoral production of androgens and presence of CYP-17 expression.

Besides androgen signaling, several signaling pathways central to prostate and bone development are associated with or implicated in prostate carcinogenesis (41). These include but are not limited to fibroblast growth factor, hedgehog, transforming growth factor-beta (TGF-beta), integrins, Src, Wnt, and Notch (Table 2; refs. 39, 40, 42–55). These associations are consistent with the hypothesis that the paracrine pathways common to prostate and bone development are also involved in prostate carcinogenesis. The hedgehog signaling pathway, for example, plays critical

### Table 2. Tumor microenvironment targeting

<table>
<thead>
<tr>
<th>Microenvironment targeting strategy</th>
<th>Molecular target</th>
<th>Agent</th>
<th>Class</th>
<th>Clinical development status/Trial phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-angiogenesis</td>
<td>VEGF</td>
<td>Bevacizumab</td>
<td>mAb</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Afibercept</td>
<td>Recombinant fusion</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aflibercept</td>
<td>Recombinant fusion</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib</td>
<td>Small-molecule inhibitors of RTKs</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>VEGFR (and other RTKs like PDGFR)</td>
<td>Sunitinib</td>
<td>Small-molecule inhibitors of RTKs</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arzoxifene</td>
<td>Small-molecule inhibitors of RTKs</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vatalinib</td>
<td>Small-molecule inhibitors of RTKs</td>
<td>III</td>
</tr>
<tr>
<td>Integron signaling networks</td>
<td>αβ3 integrin</td>
<td>Thalidomide</td>
<td>Not clarified-Immunomodulators</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lenalidomide</td>
<td>Thalidomide analog-iMids</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>αβ3 integrin</td>
<td>MEDI-522 (Abekrin or Vitaxin)</td>
<td>Humanized mAb</td>
<td>III</td>
</tr>
<tr>
<td>Developmental pathways</td>
<td>Src-family kinases</td>
<td>Dasatinib</td>
<td>Small molecule kinase inhibitor</td>
<td>III</td>
</tr>
<tr>
<td>Bone development-related pathways</td>
<td></td>
<td>AZD0530</td>
<td>I/II</td>
<td></td>
</tr>
<tr>
<td>RANK ligand</td>
<td>Denosumab</td>
<td>mAb</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>Endothelin receptor</td>
<td>Atrasentan</td>
<td>Selective antagonist</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>Hedgehog signaling</td>
<td>Zibotentan</td>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGF family</td>
<td>GDC-0449</td>
<td>Smoothened antagonist</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>Notch</td>
<td>TK258</td>
<td>FGF receptors</td>
<td>I/II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MK0752</td>
<td>NOTCH</td>
<td>I/II</td>
<td></td>
</tr>
<tr>
<td>Androgen signaling</td>
<td>CYP17</td>
<td>Abliraterone acetate</td>
<td>Irreversible inhibitor of CYP17</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>MDV3100</td>
<td>Small molecule AR antagonist</td>
<td>I/II</td>
<td></td>
</tr>
<tr>
<td>Signaling cross-talk with AR</td>
<td>mTOR</td>
<td>Temsirolimus</td>
<td>Rapamycin analogs</td>
<td>II</td>
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<td></td>
<td></td>
<td>Everolimus</td>
<td>Rapamycin analogs</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deforolimus</td>
<td>Rapamycin analogs</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>EGFR</td>
<td>Gefitinib</td>
<td>EGFR tyrosine kinase inhibitor</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>IGF Receptor</td>
<td>CP-751,871</td>
<td>mAb</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IMC-A12</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>TGF-beta</td>
<td>TGF-beta</td>
<td>AP-11014, AP12009</td>
<td>mAb</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

Abbreviations: mTOR, mammalian target of rapamycin; RTK, receptor tyrosine kinase.
roles during prostate development and was found to be activated and support cancer cell survival during prostate cancer progression (40, 41). The clinical relevance of these observations in preclinical models can be inferred from evidence that thalidomide, an agent with anti-angiogenesis activity, exhibited clinical efficacy likely through inhibition of sonic hedgehog signaling in prostate cancer (45, 46). This clinical observation, although implied by association, supports the idea that this bone- and prostate-development program may also be central to prostate cancer progression.

Overall conceptual framework of paracrine pathways in prostate cancer. Deciphering the role of the paracrine pathways implicated in the tumor microenvironment will lead to improved understanding of prostate cancer progression and resistance to therapy. In the model we propose, prostate cancer usurps pathways involved in development and function of prostate and bone in progression and resistance to therapy. We therefore reason that knowledge of developmental biology and physiology will contribute to the understanding of prostate cancer progression and resistance to chemotherapy and thus provide valuable insight into prostate cancer treatments.

Our conceptual framework is based on the hypothesis that the properties of the prostate cancer microenvironment are important determining features in the clinical disease phenotype and its response to therapy. The evolution of prostate cancer—from a lesion with the morphologic features of cancer but with limited potential for progression to the potentially lethal form of the disease—has been attributed to a series of molecular events operating through adaptation and selection. For the purpose of this discussion, stroma comprises all nonepithelial components of the microenvironment. Paracrine interactions within the organ microenvironment ensure homeostasis in physiologic conditions: During early stages of carcinogenesis, the microenvironment contributes to the normal organ function and serves as a functional barrier to prostate carcinogenesis. Early disease lesions have the morphologic features of cancer but with limited potential for progression to the potentially lethal form of the disease. On disseminated disease progression, however, aberrant paracrine-pathway activation serves tumor growth, and the predominant microenvironment effect is to assist tumor survival. It is at those later stages of prostate cancer progression, when the tumor epithelium has become self-supporting and the pathways supporting its growth are sufficiently regulated within cancer cells, that the disease is indeed “epitheliocentric” (Fig. 2).

As we previously mentioned, our proposed two-compartment model suggests that prostate cancer progresses through a paracrine, i.e., microenvironment-dependent phase to an autocrine phase that occurs later in the clinical course. This two-compartment model is able to account for the clinical observations described earlier in this discussion, given that progression through a paracrine phase (“microenvironment dependent”) precedes the autocrine phase of disease.

Our working hypothesis differs from the epitheliocentric view, i.e., autocrine, which attributes most aspects of progression, bone homing, and response and resistance to therapy to the malignant epithelial cells. Improved understanding of the stromal-epithelial-interacting signaling networks will be required to develop and apply effective combinations of molecularly targeted therapies. One possible explanation is that the molecular therapy is applied late in the progression of the disease when the heterogeneity of autocrine progression may be driving the biology.

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**Fig. 2.** Progressive exchanges in the tumor microenvironment (paracrine) interactions from the regulation of homeostasis, to the maintenance of this function in early nonneoplastic or preneoplastic lesions, through early invasion, to tumor-promoting effect in bone, and autonomous autocrine- (epitheliocentric-) driven progression not limited or restricted by a specific microenvironment.
For instance, this may account for the limited patient benefit observed with the endothelin 1 receptor antagonist (39). A second possibility is that persistent paracrine androgen signaling contributes to the clinically observed resistance to inhibition of alternative signaling pathways. The latter could be addressed by developing markers reflecting the specific biology of disease in a particular patient. Addressing these possibilities will require earlier introduction of therapy with parallel monitoring of biomarkers that reflect the microenvironment. Understanding the heterogeneity of stromal-epithelial interactions will lead to the development of individualized microenvironment-targeting therapies. For example, preliminary evidence suggests that blockade of both platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) can produce tumor remission (56). In addition, encouraging results with the use of the Src inhibitor dasatinib that blocks Src family kinases in both the epithelial and stromal compartments in combination with chemotherapy have been reported (57). These preliminary observations are consistent with the hypothesis that the use of combinations of agents that target stromal-epithelial-interacting pathways earlier in disease progression will be more efficacious. These two treatment options are being evaluated in ongoing phase III studies.

Proposed Therapy Paradigm and Implementation Strategy

Implementation of this therapy paradigm will require the development of biomarkers for disease state-specific therapies. This strategy will also provide a framework for prioritizing candidate therapies targeting the tumor microenvironment. For example, in early disease states, the paradigm would provide the rationale for inhibiting progression by maintaining the functional barrier of the prostate microenvironment, a step we term "secondary prevention." According to our hypothesis, cancers that exhibit evidence of microenvironmental remodeling are transitioning to a potentially lethal phenotype, and thus intervention with surgery or radiation may be effective in treating disease at this stage. Two examples of this are a decrease in the ratio of E-cadherin to matrix metalloproteinase expression in the malignant epithelium and an increase in the vascular density in the microenvironment, both of which have been strongly associated with disease progression (55).

Cancers that have transitioned to more aggressive forms, i.e., by developing a bidirectional paracrine interaction, will be dependent on the microenvironment for their survival and proliferation. In comparison to other common solid cancers, the state at which prostate cancer becomes dependent on the microenvironment seems to persist longer. On the basis of clinical observations of treatment responses, the autocrine progression in other common solid cancers may occur much earlier, thus the microenvironment has a lesser role in defining the phenotype in those cancers.

The current understanding of the role of tumor microenvironmental factors in prostate cancer progression is limited and has prevented the development of successful therapy strategies for patients with advanced and castrate-resistant prostate cancer. Bone-homing radiopharmaceuticals that target both tumor cells and the bone microenvironment palliate patients' symptoms and may affect the survival time of patients with metastases. Unfortunately, although the molecularly targeted therapies tested to date, including the selective endothelin A receptor antagonist atrasentan, the PDGF blocker imatinib, and the bone-resorption inhibitor zoledronic acid, were able to modify the bone microenvironment (as reflected by serial measurements of bone-turnover markers), they have not changed the course of the disease, at least in respect to serum concentrations of prostate-specific antigen (9, 39, 40, 56).

According to our hypothesis, combinations of agents targeting multiple factors that modulate the networks of signaling pathways involved in bone development should be prioritized for therapy development. Given that some signaling pathways are common to locally advanced cancers and early bone metastases, the therapeutic rationale may be extendable to subsets of patients with localized prostate cancer (17).

Prompted by encouraging experimental data and preliminary results from ongoing phase II studies of inhibition of VEGF and Src (54), we have initiated phase III studies of this combinatorial strategy. The success of therapy based on this hypothetical paradigm will depend on the validation of specific biomarkers that reflect the microenvironment and will guide the development and application of this and other combinatorial molecular-targeting therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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23. Tu S, Jones D, Mathew P, Logothetis CJ. Phase I study of concurrent weekly docetaxel (Tax) and repeated $^{153}$Sm-leiodrion (Sam) in androgen-independent prostate cancer (AIPC). J Clin Oncol 2008;26:5132.


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