In this issue of ONCOLOGY, Davis et al provide a succinct overview of the contemporary management of high-risk prostate cancer patients. As the authors point out, the introduction and widespread implementation of prostate-specific antigen (PSA) as a tumor marker has driven a remarkable stage migration in how patients present with prostate cancer, yet a significant number of men continue to present with features placing them at high risk for local treatment failure, development of prostate cancer metastases, and ultimately, death.

With these tools, clinicians are better able to predict patient outcome, improve patient counseling, and help patients make better treatment decisions. By identifying patients at high risk for progression, one would hope that these predictions will assist the clinician in deciding whether to implement adjuvant therapy. But this premise is based on the presumption that an effective adjuvant therapy exists. Despite the advances in our ability to identify, counsel, and prognosticate, what is most striking about the material covered in this review is the utter lack of effective treatment options available for these patients. Contemporary treatment options for clinically localized prostate cancer include radical retropubic prostatectomy and radiotherapy given by either external beam or transperineal interstitial permanent implant, or a combination of both. It is somewhat distressing, therefore, that it is these identical treatment modalities that are available for high-risk patients, albeit with the use of dose escalation or adjuvant hormonal deprivation therapy-a noncurative treatment modality in use for over 50 years. This situation is rapidly changing with the development of new technologies that enable researchers to gain insights into the biology of prostate cancer and metastasis. Men die not from localized prostate cancer, but from the development of androgen-independent, metastatic prostate cancer. Metastasis is a multistep process in which a cancer cell escapes from the primary tumor, enters either the lymphatic or hematogenous circulation, takes up residence in a distant tissue or organ, develops a new blood supply, and activates other mechanisms that permit it to survive in a foreign environment. Because many steps are involved, it may be possible to block the metastatic process at one or more of these steps.

**Hormone-Refractory Prostate Cancer**

Progression to hormone-refractory prostate cancer remains a major obstacle to effective control of metastatic disease. The treatment of choice for palliation of patients with advanced prostate cancer is withdrawal of androgen by continuous androgen blockade. However, androgen ablation fails to eliminate the entire malignant cell population. Androgen-independent variants acquire alternative...
growth mechanisms that allow survival of prostate cancer cells and proliferation during androgen deprivation therapy. Understanding the molecular mechanisms and alternative growth pathways induced by androgen deprivation will be crucial before a more rational strategy for the management of prostate cancer can be developed and androgen-independent cell growth can be prevented. Data suggest that the molecular mechanisms underlying the progression of disease during hormonal therapy involve numerous adaptive mechanisms including cell growth, apoptosis, and the development of alternative, non-androgen-based growth-signaling pathways, and that androgen-independent propagation of prostate cancer cells arises as a consequence of the development or upregulation of these alternative autocrine/paracrine growth signal transduction pathways. It has been demonstrated that a number of growth factors are capable of directly activating the androgen receptor in the absence of the androgen ligand, bypassing normal activation of the hormone-signaling pathway. These changes in the pattern of expression of growth factors and their ligands as prostate cancer progresses from localized androgen deprivation to metastatic androgen-independent disease suggest that inhibition of these autocrine growth factors may be important in the treatment of hormone-refractory prostate cancer.

**Targeted Therapies**

New technologies are promising a new era of "targeted therapies" for targeted patient populations. With tools such as gene expression profiling and proteomics that can identify what is different in the cancer cell and identify aberrantly expressed genes and proteins being expressed in an individual patient's tumor, the possibility of choosing the best targets for therapy and the best patients to receive a targeted therapy is increasingly becoming a reality. This new paradigm is best exemplified by new pharmaceutical agents such as trastuzumab (Herceptin), a monoclonal antibody targeted against HER2/neu that works only in the 30% of patients whose breast tumors are HER2/neu-positive, and imatinib mesylate (Gleevec), a tyrosine-kinase inhibitor that blocks the function of the Bcr-Abl protein, an abnormal fusion protein expressed by the Philadelphia chromosome that contributes to the rapid reproduction of white blood cells in patients with chronic myelogenous leukemia. These new agents are used in an attempt to disrupt pathways unique to cancer cells, while theoretically leaving normal cancer cells alone and avoiding the toxic side effects commonly associated with chemotherapy and radiation. Clinical trials of targeted therapies in men with high-risk prostate cancer are under way. One such study involves oral CCI-779 in newly diagnosed prostate cancer patients undergoing radical prostatectomy who are at high risk for disease relapse. CCI-779 inhibits translation of several key proteins that regulate the G1 phase of the cell cycle by binding to the intracellular cytoplasmic protein FKBP-12. The complex of CCI-779 and FKBP-12 blocks the activity of a kinase-the mammalian target of rapamycin (mTOR)-and subsequently inhibits key signaling pathways, including those regulated by p70S kinase and 4E-BP1, thereby blocking the G1 phase of the cell cycle. This pathway is downstream from the tumor-suppressor gene PTEN, and mutations of PTEN have been implicated in several cancers, including prostate cancer.

Preliminary in vitro studies in a number of tumor types, including prostate cancer, have demonstrated a correlation between PTEN loss and sensitivity to growth inhibition by CCI-779. This study is designed to evaluate the effect of CCI-779 in men with PTEN normal vs PTEN-mutated prostate cancer tumors. Conclusions

Davis et al aptly summarize the contemporary management of high-risk prostate cancer patients, focusing on currently available standards of care. Yet wider surgical margins, escalation of radiotherapy dose, and use of adjuvant hormonal deprivation therapy can only be expected to incrementally improve the outcome in high-risk prostate cancer patients. The management of these patients remains an extraordinary clinical challenge, but advances in technology and an increased understanding of tumor biology have opened the door to a new paradigm for their treatment.

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