important not only for causing prostate cancer, but also for permitting or inhibiting prostate tumor cells to respond to therapeutic interventions. Clinical trials have shown different responses to various therapies that correlate with molecular alterations. Biological determinants related to treatment response and markers aimed at individualized therapies are being defined and implemented. It is expected that the newly developed high-throughput methods, such as expression profiling by microchip technology, will complement our armamentarium of predictive tools needed to address the molecular complexity that characterizes prostate cancer.
In addition to molecular genetics, a new "systems pathology" approach is being developed. Systems pathology can be defined as a discipline that integrates clinical variables with histological and cellular features, as well as molecular profiles. This is achieved through the application of novel technologies in the areas of object-oriented image analysis, pattern recognition, and quantitative biomarker multiplexing. The obtained complex data-sets are analyzed by distinctive supervised mathematical approaches, including machine learning algorithms and neural networks. Our working hypothesis is that by using this approach we could significantly improve the accuracy of predictive tools, such as individualized nomograms already developed for the management of prostate cancer.
The practice of conventional histopathology based on light microscopy changed and was in part complemented in the second half of the twentieth century by three technological advances: ultrastructure, immunohistochemistry, and molecular diagnostics. The first two represented incremental gains in diagnostic power and efficiency, but did not force substantial changes in the practice of morphological studies. However, "molecular medicine" is profoundly changing the approach to tissue analyses. Perhaps more importantly, molecular medicine is altering the pathway for advancement. In the recent years the elucidation of the molecular pathogenesis of neoplastic diseases and the multistep nature of cancer progression has directly led to the discovery and application of molecular tumor markers. The diagnosis and prognosis have in many cases been enhanced by the use of the marker(s), and finally the marker may constitute a therapeutic target (e.g. Her-2/neu and Herceptin, Bcr-Abl and Gleevec). With the advances in biotechnology and bioinformatics, the integration of these approaches made sense. More over, the preceding sequence of events can be predicted to accelerate. Rather than elucidating a molecular pathway, we will have a complete view of the molecular genetics and protein profile of a given tumor. This comprehensive understanding will lead to the development of specific therapies and to the rational selection of therapeutic modalities for a specific patient. Integrated tests will allow an accurate assessment of the response and modification of therapy when required. The detailed morphologic and molecular knowledge of the natural history of tumors will yield markers for inherited and acquired risks, tumorigenesis and tumor progression. These will in turn make early diagnosis and cancer monitoring a reality.

75 Abstract not received

76 INVITED

The evolving role of chemotherapy in prostate cancer

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Clinical results of chemotherapy in androgen independent prostate cancer have been disappointing for many years. Objective responses reported in single agent chemotherapy studies conducted in the 1980s were scarce. In the 1990s, changes in prostate-specific antigen (PSA) levels were demonstrated to correlate with response, and these levels have served as a surrogate endpoint for evaluable disease. Also, "palliative measurement scales" were developed by Canadian investigators, which measure pain and analgesic consumption. By using these criteria, randomized studies have shown mitoxantrone plus either prednisone or hydrocortisone to provide symptom improvement, but there was no impact on survival.
In parallel, phase I and II studies were conducted to test new agents, including the taxanes, paclitaxel and docetaxel. The studies used weekly and 3-weekly schedules, with and without concomitant estramustine. Substantial activity in terms of pain responses, PSA decreases and median survivals of 16–24 months were demonstrated, that warranted the initiation of two randomized phase 3 studies; TAX 327 and study SWOG 99-16.
TAX 327 investigated the regimen of docetaxel 75 mg/m^2 every 3 weeks plus prednisone (10 mg daily), and the weekly regimen of docetaxel 30 mg/m^2 (5 of 6 weeks) plus prednisone, versus the accepted regimen of mitoxantrone 12 mg/m^2 every 3 weeks plus prednisone [1]. The primary endpoint was overall survival. Secondary endpoints were pain, PSA levels and QL. From March 2000 through June 2002, 1006 patients were randomized. The docetaxel every 3 weeks regimen resulted in significantly superior survival and higher PSA and pain response rates compared with mitoxantrone. The survival was 18.9 vs 16.5 months, the reduction in the HR of death was 0.76 (0.62–0.92). Also, during the course of chemotherapy improvements in quality of life were significantly more frequently obtained in patients on docetaxel as compared with mitoxantrone (22% vs 13%, P = 0.009). Docetaxel every 3 weeks was well tolerated, with few cases of neutropenic fever (3%). There were no treatment-related deaths. Grade 3/4 non-hemotologic toxicities were rare.
SWOG 99–16 was built on the prejuidice that the combination of docetaxel plus estramustine had the greatest therapeutical potential and was the compator against mitoxantrone plus prednisone [2]. Also in this study the median overall survival was superior in the group receiving the docetaxel regimen, 17.5 vs 15.6 months, HR 0.80 (0.67–0.97). The incorporation of estramustine in the docetaxel regimen, however, was characterized by increased gastrointestinal and cardiovascular toxicity (mostly thromboembolic complications).
In view of this increased toxicity profile on the one hand and the apparent lack of improved effectiveness as compared with the similar survival benefit as obtained with docetaxel every 3 weeks plus prednisone in TAX 327 on the other, there appears no further role for the use of estramustine as an add-on to docetaxel [3].
These study results have also prompted studies to test the use of chemotherapy earlier in the course of the disease, such as the International trial TAX 3501, investigating immediate adjuvant hormonal treatment plus docetaxel vs hormonal treatment alone vs deferred therapy by the same therapeutical options in patients prostate cancer at high risk of relapse after radical prostatectomy. In the setting of androgen independent disease, studies will be aimed to investigate the addition of new active agents to docetaxel. Ongoing and planned randomised studies are employing the addition of high-dose calcitriol, DN-101 (International Industry sponsored trial), the addition of bevacuzimab (CALGB/ECOG/NCIC), astrasentan (SW0G) and the bisphosphonate risedronic acid (Netherlands).

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77 INVITED

Targeted therapy in androgen-independent prostate cancer

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Most currently available hormonal therapies, interfering with the androgen receptor axis are considered to be palliative, since hormone unresponsiveness eventually develops. Hormonal resistance occurs as cells become self sufficient, insensitive to anti-growth signals, invade and metastasize with limitless replicative potential. There is sustained angiogenesis and they are able to evade apoptosis and programmed cell death. Understanding of the biology of prostate cancer and hormonal resistance has grown. Strategic information as to how prostate cancers arise and progress has led to identification of novel therapeutic targets.
The combination of docetaxel chemotherapy and prednisone has been shown to be effective in improving survival in two large phase III randomized trials. Can one improve upon the results with docetaxel chemotherapy in hormone refractory prostate cancer (HRPC)? How much is an incremental gain in survival worth in terms of quality of life? What is the role of investigational treatments such as tyrosine kinase growth factor inhibitors, antisense oligonucleotides, endothelin antagonists, anti-angiogenesis agents in lieu of or in addition to traditional hormones and chemotherapy? And, what makes an ideal therapeutic target?
An ideal therapeutic target should theoretically be present in the majority of patients and have a causative relationship to tumor genesis. It should have an essential function in tumor cells, but not be essential for normal cellular function.
Growth Factor Receptor Inhibition: A number of tyrosine kinase growth factor receptors have been cloned which transmit an intracellular signal. This signal can be increased by overexpression of the receptors or by increased ligands or ligand binding (which increases signal transduction). All of the tyrosine kinase receptors have differences in their extracellular ligand binding domain and differences at the level of the tyrosine kinases. There is an increasing knowledge of the intracellular domain and knowledge that mutations in these domains may determine whether or not a signal is important and whether or not an inhibitor may function. Overexpression of the extracellular receptors can also produce amplification in the intracellular signal transduction.