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.

Preclinical data in prostate cancer shows upregulation of a wide variety of growth factors and their receptors such as PDGF, EGF, IGF, FGF, and VEGF suggesting efficacy of agents targeting these pathways. Data on the use of growth signal targeting in prostate cancer by tyrosine kinase inhibitors and monoclonal antibodies alone, and in combination with chemotherapy and/or radiotherapy seem to be promising in prostate cancer.

Antisense oligonucleotide therapy: One of the most important pathways that bypasses the androgen receptor involves the deregulation of apoptotic genes. Bcl-2, which regulates apoptosis (programmed cell death), is expressed in most human cancers and is an important contributor of resistance to therapy. Bcl-2 protein is a critical regulator of apoptosis in many tissues and is over expressed in the majority of patients with HRPC. Bcl-2 may mediate resistance to androgen ablation and chemotherapy and appears to have a critical role in the transition from androgen-dependent to androgen-independent growth. Antisense oligonucleotide therapy is currently under evaluation.

Bone targeted therapy: HRPC is often associated with the development of painful bone metastases. Newer generation bisphosphonates may relieve pain caused by bone metastases, prevent treatment-related loss of bone mineral density, possibly slow the growth of metastases, and reduce skeletal complications. They are effective for the treatment of both osteolytic and osteoblastic metastases.

Targeting the Endothelin Receptor: Endothelin A plays a role by inhibition of apoptosis, stimulation of proliferation, stimulation of osteoblasts and has pain nociceptive effects. In HRPC there are increased plasma concentrations of Endothelin-1 (ET-1), decreased clearance of endothelin and increased endothelin A expression. Endothelin axis deregulation triggers a series of events that lead to a profound deregulation in cancer cells, including key tumorigenic cellular events such as proliferation, invasion, escape from programmed cell death, new vessel formation, abnormal osteogenesis and the alteration of nociceptive stimuli. Atrasentan is a potent, oral, selective endothelin-A receptor antagonist. Two large randomized studies of atrasentan have been performed in metastatic HRPC. A meta-analysis demonstrated a reduction in the risk associated with disease progression, attenuation of the rise of biomarkers, delay in time to biochemical progression, decrease in time to bone pain and incidence of bone pain, and disease-specific quality of life benefit.

Targeting Angiogenesis: Vascular endothelial growth factor (VEGF) is a growth factor that is essential for pathological neoplastic angiogenesis, tumor growth and metastasis. Antiangiogenesis is a relatively new antitumor strategy that has been employed in the treatment of many malignancies. As prostate cancer is likely dependent on angiogenesis for its growth and progression, it would logically serve as a good target for this modality. Initially met with great enthusiasm, antiangiogenic drugs have seen only limited success when used as single agents. This has been attributed to many possible etiologies including lack of cytotoxicity and use in situations of large tumor burden. In order to overcome these problems, antiangiogenic agents are also being used in combination with more traditional cytotoxic chemotherapy regimens.

The tumor-associated stroma may also produce significant amounts of VEGF via tumor-associated induction of the VEGF gene promoter. Inhibition of VEGF signaling with several strategies, including monoclonal antibodies to VEGF and tyrosine kinase inhibition are currently under clinical development. The combination of docetaxel and thalidomide an anti-angiogenic agent has demonstrated activity in HRPC.

Other drugs inhibit several raf kinases and other tyrosine kinase targets including VEGFR-2, PDGFR-b, FLT-3 (flit 3) and c-KIT, which may inhibit both angiogenesis and cell signaling.

The outline of our present and future focus in the study of HRPC is becoming clearer with an increasing understanding of therapeutic targeting based on the biologic sub setting and novel therapeutics targeting several different hallmarks of cancer.

Scientific Symposium
The challenge of implementing intensity modulated radiotherapy in the clinic

78 INVITED

Target volume definition and organ motion for IMRT

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Intensity-modulated radiotherapy (IMRT) can shape the radiation dose distribution with high precision, such that we can treat irregularly shaped tumor target volumes with therapeutic doses while sparing the surrounding healthy tissues. However, setup errors and motion of the patient or the inner organs during the treatment can result in a geographical miss and have a negative effect on the outcome, if the dose is conformed too closely to the clinical target volume. For this reason, the target volume definition is very important and is described by the International Commission on Radiation Units and Measurements (ICRU) Reports 50 and 62. These recommendations clearly define the Gross Tumor Volume (GTV), the Clinical Target Volume (CTV), the Internal Target Volume (ITV), and the planning target volume (PTV). The GTV is the volume of known tumor. The CTV is the volume of suspected microscopic spread. The ITV encompasses the motion of the CTV and is formed by adding a margin [Internal Margin (IM)] to the CTV. The PTV is the volume necessary to account for patient motion and is formed by adding a Setup Margin (SM) to the ITV. Although these recommendations are widely used, they have some practical limitations because the ITV or IM is only defined for some organs like prostate, pancreas and rectum. However for prostate cancer, the IM was differently reported by several investigators (e.g.: the anterior-posterior motion of the prostate ranges from 2.7 to 4.5 mm [1 standard deviation (SD)]. The ITV has also been defined for lung cancer but the ITV is different according to the location of the tumor in the lung. Another problem is the deformation of the ITV caused by motion during the CT. Other pitfalls in the ITV definition are the bladder filling or the bowel motion. A full bladder during simulation can be requested but previous research showed that it was difficult for the patient to be treated with a full bladder. Also the variation of bowel inside the pelvis can be large and differ from day to day: an anterior-posterior motion of the rectum up to 10 mm (1SD) was found. Many techniques are developed to reduce the internal margin or setup margin because a smaller PTV combined with an IMRT technique often results in a dose reduction to the organs at risk. Examples of these techniques that reduce the set up margin are patient immobilization using molds, casts, or other restraining devices and on- or offline portal imaging protocols. Some of the techniques that reduce internal margin are abdominal compression, deep inspiration breathing training, active breathing control and target tracking with markers placed in the tumor. With this last technique the CTV to PTV margin (IM+SM) can be reduced from 10 mm to 1 mm.

79 INVITED

The challenge of implementing IMRT planning

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Ideally, the IMRT planning system creates a desired dose distribution as a sequence of treatment machine-states and monitor unit values (often called control point sequence). In reality, the present IMRT planning systems are not yet capable to achieve this goal autonomously. The systems are interactive and many machine parameters have to be set upfront by a skilled planner. Also, the desired dose distribution may be impossible to achieve and the systems then need expert guidance to achieve an *acceptable dose distribution* as a realistic goal. We define as acceptable; a dose distribution that differs from the desired dose distribution 1) within preset limits of dose and 2) only in regions where the desired dose distribution cannot be physically achieved.

For IMRT planning, the dose provisional prescription guidelines in a protocol often need to be complemented by additional parameters to obtain suitable dose objectives for planning. Procedures to obtain these parameters will be discussed including i) PTV-fragmentation, relaxing the dose objectives and securing flash to deal with build-up and in-air PTV regions, ii) priority ranking, fragmentation and weighting of importance factors to deal with PTV and PRV/OAR overlap volumes and with conflicting dose objectives and iii) dose constraints to the UIV (Unspecified Imaged Volume); the creation of virtual critical structures, pseudo-OARs and shells and the use of stepwise constraints with distance from PTV to avoid dose littering and hot spots outside PTV and PRV/OAR.

Finally, future directions will be discussed including i) the use of probability distributions of the CTV and OAR location based on models for anatomical deformation that will make the concepts of PTV and PRV obsolete and will solve many of the problems associated with build-up, flash and overlap; ii) the incorporation of biological and functional imaging in IMRT planning; iii) voxel-based instead of contour-based IMRT planning and iv) the use of biological- instead of dose-objectives in IMRT planning.

80 INVITED

Treatment delivery

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This review will be about the developments during the last 10 years in delivery of intensity modulated radiation therapy a.k.a. IMRT. The techniques can in short be divided in

- tomotherapy or fan based and
- multi-leaf collimator, MLC or cone based methods.