Prostate cancer
Multidisciplinary approach: a key to success

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Accepted 8 July 2008

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Abstract

Diagnosis and treatment of prostate cancer has improved in the last few years, in part due to a multidisciplinary approach between urologists, oncologists, radiotherapists, radiologists, pathologists, basic and translational researchers for a successful management. The TAX 327 study is the paradigm of a smooth communication between expert physicians that led to the approval of docetaxel in metastatic hormone-resistant prostate cancer (HRPC). Survival benefit with docetaxel in HRPC was confirmed in an updated survival analysis reported this year. A nomogram to predict survival in metastatic HRPC treated with chemotherapy was established based on the TAX 327 study. Unfortunately in early prostate cancer, some of the phase III clinical trials with chemotherapy had to be closed due to lack of sufficient accrual, due to, at least in part, an unsuccessful collaboration between urologists, medical oncologists and radiotherapists. In earlier phases of prostate cancer, a successful multidisciplinary approach has led to important advances in genomics, biomarkers and imaging techniques that have created big excitement for future improvements in the management of prostate cancer. An example is the validation of novel molecular diagnosis tests such as PCA3 or TMPRSS2 – ETS in urinary samples. Importantly, we should not forget that the key for a successful future development in the management of prostate cancer will require the expertise of all disciplines to provide optimal care.

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Keywords: Prostate cancer; Multidisciplinary approach; Chemotherapy; Molecular diagnosis

1. Introduction

The natural history of prostate cancer from asymptomatic organ-confined disease to locally advanced, metastatic hormone dependent and hormone-refractory disease reflects the complexity of the biology of this tumor and justifies the need for a fluid collaboration between expert physicians including...
urologists, oncologists, pathologists and radiologists for a correct management of this cancer. Diagnosis and treatment of prostate cancer has rapidly improved in the last few years, with the development of new genetic and molecular valid tools and technologies. Nevertheless, a key factor to success is the optimization of a multidisciplinary approach that includes different disciplines for a global management of this biologically complex tumor. In other tumor types, such as breast or colon cancer there is a long tradition of well-organized effective Tumor Board and Functional Units where different specialized physicians interact to carefully assess the stage of patient’s illness and set the best individual treatment [1,2]. Moreover, a multidisciplinary team has been shown to be a basic requirement for good planning, quality, conduct and high accrual of patients in clinical trials [1,2]. A multidisciplinary approach including basic, translational researchers and physicians is also crucial for a successful development of new therapeutic and diagnostic tools from the preclinical to the clinical setting. Therefore, in prostate cancer, all efforts should be made to promote a multidisciplinary approach where urologists, oncologists, radiotherapists, radiologists, pathologists, basic and translational researchers work together for a better quality of the management of prostate cancer patients, reflected in a better design, conduct and higher accrual in clinical trials and an effective development of new therapies and diagnostic tools.

2. Chemotherapy in metastatic hormone-resistant prostate cancer. A successful multidisciplinary approach

An example of a successful multidisciplinary approach is the TAX 327 study [3]. In this study, both oncologists and urologists collaborated to reach an excellent accrual and conduction of the study. This study included 1006 men with metastatic hormone-resistant prostate cancer (HRPC) that were randomized 1:1:1 to receive docetaxel administered every three weeks, weekly docetaxel or mitoxantrone, each with prednisone. The primary endpoint of the study was overall survival, and secondary endpoints were pain, prostate-specific antigen (PSA) levels, and quality of life. Results of the study showed statistically significant better survival and response rates for pain, PSA and quality of life for men treated with prednisone plus docetaxel every three weeks when compared with weekly docetaxel or mitoxantrone. Men treated with docetaxel every three weeks had a hazard ratio for death of 0.76 (p = 0.009) and those given weekly docetaxel had a hazard ratio for death of 0.91 (p = 0.36), as compared with the men in the mitoxantrone group. The median overall survival was 2.5 months higher in the docetaxel every three weeks group, with a survival of 16.5 months in the mitoxantrone group, 18.9 months in the group treated with docetaxel every three weeks and 17.4 months in the group given weekly docetaxel.

At the time of the initial report, 557 deaths had occurred. An updated survival analysis by March 2007 included data on 310 additional deaths [4]. The analysis showed that the survival benefit of docetaxel every three weeks had persisted with extended follow-up (p = 0.004). Importantly, similar survival improvement for docetaxel every three weeks was reported in men greater than and less than 68 years of age, in both symptomatic and asymptomatic patients, as well as for those with baseline PSA greater and less than 115 ng/mL. Even if the trial was not initially designed to address these subgroups analysis, these results raise several questions. The first point would be whether to treat elderly patients. Considering the similar benefit among subgroups, age alone should not discount a patients from receiving chemotherapy, even if one should take into account the increased risk of neutropenia seen in this population and therefore a closer monitoring of blood counts would be appropriate with or without growth factor support. The second question to be addressed is whether treating asymptomatic patients or waiting for symptomatic progression. Taking into account the fact that symptomatic response is less frequent than PSA response and that pain-free patients had a better tolerance of 10 cycles of chemotherapy than patients with pain, it seems reasonable to offer treatment to symptomatic patients as well as to patients with high risk of developing symptoms in the near future, mainly based on PSA doubling time. Although a lead time bias needs to be taken into account, asymptomatic patients had a median survival of 21.3 months comparing favorably to symptomatic patients (median survival of 14.2 months).

Based on the TAX 327 study, a multivariate prognostic model incorporating PSA kinetics has been developed to predict survival at 1, 2 and 5 years in metastatic HRPC men treated with chemotherapy [5]. This novel model identified new independent clinical prognostic factors including PSA doubling time (PSA-DT) and others such as baseline pain, mode of progression and the number of metastatic disease sites. A statistically significant better overall survival was reported in patients with PSA ≥ 114 ng/mL and PSA-DT lower than 55 days. The nomogram showed internal validity and is therefore a clinically applicable nomogram that includes simple and easily obtainable clinical variables to predict survival in metastatic HRPC treated with chemotherapy. This nomogram is a helpful tool to stratify patients for further docetaxel-based trials.

Based on these data, we have now robust evidence that supports the use of chemotherapy in men with HRPC, although there is less evidence on when it should be started. Men with HRPC should be treated with docetaxel every three weeks in all symptomatic cases, all cases with bone scan progression and based on the recently reported results, PSA kinetics also need to be considered. Cases of PSA only progression should be considered for further hormonal manipulations when PSA kinetics are favorable.
3. Chemotherapy in early stage prostate cancer: Not yet a successful multidisciplinary approach

The 2.5 months improvement in median survival of docetaxel over mitoxantrone in metastatic HRPC as well as the encouraging results of several phase I and II clinical trials of docetaxel in earlier stages of prostate cancer clearly supports the need of large randomized phase III studies to define the role of docetaxel in earlier stages of prostate cancer [6,7]. In early stage clinical studies, a good communication between urologists, pathologists and medical oncologists is important for a successful accrual and management of the patients included in these trials. Several randomized studies in early stage prostate cancer patients have failed to meet their accrual goals and have been closed, in part due to an unsuccessful multidisciplinary approach. The first study is the RTOG 0014 study (www.clinicaltrials.gov) which included androgen-dependent prostate cancer men that had a PSA relapse after local therapy. Patients were randomized to receive hormonal therapy versus chemotherapy plus hormonal therapy for 4 cycles followed by hormone therapy. The primary endpoint was overall survival and the planned number of patients was 1050. However, in May 2007 the study had to be closed due to higher toxicity in the chemo-hormonal therapy arm. The second study, the ECOG 1899 (www.clinicaltrials.gov) randomized androgen-independent prostate patients without metastases to receive ketocanazole plus hydrocortisone versus docetaxel plus estramustine. With a primary endpoint of progression free survival, the study had to be closed also due to lack of accrual. The third study is the TAX 3501 that included post-radiotherapy patients with high-risk criteria according to the Kattan nomogram. Patients were randomized between immediate treatment either hormonal therapy alone or in combination with chemotherapy (docetaxel) and a deferred arm where at progression patients could receive either hormonal therapy alone or in combination with chemotherapy (docetaxel). Again, poor accrual led to a premature closing of the study. A better multidisciplinary collaboration between urologists, oncologists, radiotherapists, radiologists and pathologists in early phases of the disease would probably have led to a more successful conduction of these trials.

4. Multidisciplinary approach in the near future: a key to success

Important improvements in genomics, biomarkers, targeted therapies and imaging techniques are creating great expectations in the diagnosis and treatment of prostate cancer. Some examples of success based on a multidisciplinary approach have taught us that close collaboration between basic research physicians, urologists, oncologists and pathologists is possible and necessary for the correct development from the bench to the clinics of new therapeutic and diagnostic tools.

4.1. Therapeutics: from the bench to the clinics

Oncogene addiction seems to underlie the success of many targeted therapies in several tumors such as gefitinib or erlotinib in lung cancer, imatinib in chronic myeloid leukemia and trastuzumab in breast cancer [8,9]. While the complexity of prostate cancer biology adds difficulty in the search for biologic therapies, it also offers a wide range of potential targets for therapeutic inhibition. A proposed genetic model for prostate cancer has identified different genetic alterations arising in the different stages of prostate cancer tumorigenesis from benign histology to PIN, localized, metastatic and hormone-refractory cancer. Importantly, GSTP1 would be involved in the transition from benign to PIN lesions, catenin, E-cadherin and PTEN play an important role in the development of metastatic disease and androgen receptors mutation or amplification in the acquisition of hormonal independence [10]. Interestingly, changes in gene expression after castration and during androgen-independent progression, identified Bcl-2 and clusterin as negative prognostic markers of androgen independence and resistance to treatment in HRPC [11]. Preclinical studies with Genasense, a phosphorothioate antisense oligonucleotide complementary to the bcl-2 mRNA open reading frame, and OGX-011, a 2′-Methoxyethyl Phosphorothioate Antisense to Clusterin showed significant activity [12]. Phase I clinical trials of both drugs in combination with chemotherapy were encouraging, however genasense failed to show the endpoints of the study in a randomized phase II EORTC trial [13–15].

4.2. Diagnostic biomarkers: from the bench to the clinics

Some initial improvements in the field of early diagnosis have been obtained based on genomic advances. Serum PSA is widely used as a screening biomarker for prostate cancer. However, the specificity of serum PSA as a diagnostic marker for prostate cancer is poor. Men with serum PSA levels between 3–10 ng/mL have a localized disease in only 27% of the cases, meaning that approximately 80% do not have prostate cancer and will be receiving unnecessary diagnostic biopsies [16]. It is therefore of high priority to characterize more specific diagnostic biomarkers as well as biomarkers that distinguish between aggressive and more indolent forms of prostate cancer. DD3(PCA3) is a highly overexpressed gene in prostate cancer that shows no expression in other normal adult tissues [17]. Preclinical exploratory studies showed that PCA3 accurately discriminates between malignant and non-malignant prostate tissues, which implies that a minority of malignant cells in a background of non-malignant cells is sufficient to discriminate cancer from non-cancer. These studies set the rationale for a molecular PCA3-based analysis of urinary sediments after extended digital rectal exam (DRE) [18]. The test is a simple non-invasive method where after DRE, a first catch urine specimen is transported into a 2 mL tube and sent in cold directly to the laboratory where PCA3 mRNA is detected [19]. Several studies using quan-
titative PCA3 assay for diagnosis of prostate cancer show consistent results, with a sensitivity of 51–69% and a specificity of 66–83% [18–21]. Importantly, the PCA3 score in low volume/low grade prostate cancer is significantly lower than in high volume/high grade prostate cancer (>0.5 mL volume/Gleason score >6) [22]. Moreover, the higher the PCA3 score the greater the likelihood of a positive biopsy, with the greatest diagnostic utility occurring at a cut-off of 35 in the Progensa® PCA3 test.

Current efforts are being made to find novel biomarkers to optimize the sensitivity of the PCA3 test, and new complementing biomarkers are in clinical evaluation. The discovery of a recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer had potential important implications in the molecular diagnosis of this tumor [23]. The sensitivity to detect prostate cancer of a test that combines TMPRSS2-ERG detection and PCA3 in urinary analysis is 73% [24]. These novel biomarkers should have a significant impact on the diagnosis and staging of prostate cancer in a near future.

4.3. Imaging technologies

A multidisciplinary approach is also partially responsible for the improvement in imaging technologies that is aiming to facilitate the management of prostate cancer patients. Exploring new imaging techniques such as iron nanoparticle MR tumor may contribute to a better treatment of prostate cancer. Moreover, image guided therapy, sharper beams and brachytherapy may help to focally boost to high doses. Technology can be used to improve tumor targeting by reducing the number of fractions, increasing the dose to certain parts of the prostate and reducing morbidity. In general, physicians need to remember that these improvements are time-consuming, costly and most importantly require a multidisciplinary collaboration for an efficient development.

5. Conclusions

The future of prostate cancer patients relies in a successful multidisciplinary collaboration between experienced physicians, which has already led to important advances such as the approval of chemotherapy for HRPC patients or the validation of novel molecular diagnostic tests such as PCA3 in urinary samples.

One of the main future goals in prostate cancer is to avoid overtreatment in men with indolent disease and to achieve a good stratification of patients with non-indolent disease according to their biology. In this sense, the real promise is the development of biomarkers based on genetic and epigenetic changes which has already brought promising results such as TMPRSS2-ERG.

While there is a lot of excitement in the development of new diagnosis and treatment tools for prostate cancer, we should not forget that success is based in the development of new ways of working were collaboration between urologists, oncologists, pathologists, radiologists and researchers is key to success.

Conflict of interest statement

All authors disclose that there is no conflict of interest.

References


