The medical management of prostate cancer: a multidisciplinary team approach

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INTRODUCTION

For many years the benefit of chemotherapy in patients with prostate cancer was thought to be limited to palliation of late-stage disease, and thus medical oncologists only became involved in patient care towards the end of the disease process, if at all. However, two recent landmark phase-III trials with docetaxel-based therapy (TAX 327 and Southwest Oncology Group, SWOG, 9916) have shown a survival benefit with chemotherapy for patients with metastatic androgen-independent prostate cancer (AIPC), prompting a change in patterns of care [1,2].

The consequent change in treatment has increased the need for closer collaboration between urologists, medical oncologists, and radiation therapists to benefit patient management. With clinical trials for new drugs and new indications (neoadjuvant therapy, adjuvant therapy, increasing PSA levels after local treatment, and hormone-sensitive cancer) planned or underway, it is crucial that solid foundations are laid for a dynamic relationship between the physicians responsible for the care of patients with prostate cancer, as this relationship is likely to become even more important over time.

The aim of this review is to facilitate the medical management of patients with AIPC by assessing the treatment of prostate cancer within the context of a multidisciplinary team. It encompasses a broad range of topical issues, including the definition of hormone resistance, opportunities for introducing chemotherapy at earlier stages of the disease, and how urologists, medical oncologists, and radiation therapists can work together to identify these opportunities.

IMPROVING COLLABORATION BETWEEN UROLOGISTS, MEDICAL ONCOLOGISTS, AND RADIATION THERAPISTS

Education and further training will be required to optimize the relationship between specialists such as urologists, medical oncologists, and radiation therapists. This should include early interaction at the training level (urology and oncology fellowships). In general, urologists are further along in the process of obtaining the relevant subspecialty training, as exemplified by the recognition of urological oncologists in some countries. In medical oncology departments, the availability of expert experience in the treatment of urological cancers is currently often based on individual interest and needs to be provided in a structured way in the future. It will be important to ensure that urologists and radiation therapists do not feel that they are ‘losing’ their patients by collaborating with oncologists; instead, they should be encouraged to see it as gaining access to physicians who are experienced in administering systemic therapy and can thereby improve the overall treatment results with their complementary skills. Some of the barriers to successful collaboration between urologists, oncologists, and radiation therapists are:

• Absence of interaction between urologists and medical oncologists in the past.
• Chemotherapy for prostate, testicular, and bladder cancer is given by urologists in some departments.
• Late referral of patients with prostate cancer to oncologists after the use of most therapeutic options.
• Lack of feedback from oncologists to urologists in some cases.
• Difference of opinion between urologists and oncologists as to what constitutes a beneficial survival advantage from a drug.

CURRENT TREATMENT OF PATIENTS WITH INCREASING PSA LEVELS AFTER LOCAL THERAPY

An increasing PSA level in this situation is defined as PSA progression after a nadir following definitive local treatment. Varying thresholds have been used as the exact value for the PSA nadir, with 0.2 or 0.4 ng/mL both being accepted in the context of prostatectomy. Risk factors for metastases and prostate cancer-related death subsequent to an increasing PSA level after surgery or radiation therapy include a high preoperative PSA level, a high Gleason score, positive margins, seminal vesicle involvement, extracapsular extension, a short PSA doubling time of <10 months and a disease-free interval of <3 years between local treatment...
and increasing PSA [3–5]. A rising PSA-doubling time of <3 months is associated with a substantial decrease in survival, with the mortality rate 5 years after PSA failure estimated to be 31% (95% CI 17–45%) for patients with a PSA-doubling time of <3 months, vs only 1% (95% CI 0–2%) for patients with a PSA-doubling time of ≥3 months [6]. Other factors influencing for risk of biochemical recurrence are age, race, percentage of positive biopsy cores, DNA ploidy, and bcl-2 expression [7–9].

Patients with an increasing PSA level after initial therapy with curative intent and who are at low risk of developing metastases (PSA doubling time >10 months, low or intermediate Gleason score, prolonged time to PSA relapse) should either be monitored or, in some after surgery, receive salvage radiotherapy, in accordance with the best estimate of the possibility of having disease isolated to the pelvis. The quality of life is usually of paramount importance to the patient at this stage.

Patients at high risk of developing metastases after a radical prostatectomy (RP) and a subsequent PSA relapse might benefit from either local or systemic treatment. These patients include those with a PSA doubling time of ≤10 months, a Gleason score of ≥8, or increasing PSA levels within 2 years of curative treatment. Nomograms have been devised to assess which patients might benefit from radiation therapy [10]. Importantly, while risk groups are becoming increasingly well characterized, prospective intervention studies that show a sustained clinical benefit with early intervention in these high-risk patients have not been conducted.

Further local therapy after RP, as radiotherapy, is most often used when there are positive surgical margins or the stage is ≥pT3a [11]. However, more detailed guidance is available about the patients most likely to benefit and (in addition to surgical margin status) typically includes covariates such as the Gleason score, PSA doubling time, and absolute serum PSA level.

In high-risk patients whose tumours have negative margins and with a Gleason score of ≥8, or who have other characteristics which define them in the high-risk category, early use of systemic therapy might be considered. This usually involves the use of a LHRH analogue with or without bicalutamide or, in the context of a clinical trial, might imply chemotherapy. However, there are no randomized data defining the optimum timing for initiating androgen deprivation therapy or chemotherapy. In the absence of a clinical trial, most physicians tend to start hormonal treatment before the development of visible metastases, at an arbitrary time based on PSA levels alone.

Chemotherapy, intermittent hormone therapy, and chemohormonal therapy might all have a future role in this setting, but well-designed clinical trials are required to show acceptable efficacy and safety profiles before their use is recommended. Planned and ongoing trials with chemotherapy are discussed later.

SECONDARY HORMONAL MANIPULATIONS

AIPC is defined as prostate cancer that has progressed despite continued androgen ablation under castrate levels of testosterone. Stringent definitions are required for entry into clinical trials [12]. These criteria vary and include the presence of progressive metastatic measurable disease according to Response Evaluation Criteria in Solid Tumors, biochemical progression (two consecutive increases in PSA level; the absolute minimum for this is not established but >5 ng/mL or >10 ng/mL are commonly used), castrate testosterone <50 ng/mL (<20 ng/mL is also commonly used), or progression despite cessation of any antiandrogen (up to 4–6 weeks earlier).

Although second-line hormonal therapy is considered to be an active approach to therapy, it has not been shown to affect overall survival. Therefore, with secondary hormonal manipulations, the objective of therapy must be considered, whether this is a PSA response, objective response, or, most often, improved quality of life. Antiandrogen withdrawal can be effective in 15–30% of patients who have been on combined androgen blockade [13]. Using an antiandrogen for second-line therapy (as monotherapy or an element of combined androgen blockade) can also produce PSA responses in 20–30% of patients [14–16].

Other second-line therapies include diethylstilbestrol and other oestrogens, ketoconazole, and corticosteroids. Each of these can be associated with PSA response rates of 20–50%, and a median duration of response of 3–6 months [17].

Several key issues remain to be resolved about when to commence secondary hormonal therapy or chemotherapy, and in which patients secondary hormonal manipulation, chemotherapy, and novel targeted therapy should be considered. A reasonable approach is to consider the use of such secondary hormonal manipulations in patients with earlier asymptomatic or minimally symptomatic AIPC.

CHEMOTHERAPY FOR AIPC

Since the publication of the results of the TAX 327 and SWOG 9916 studies, which for the first time showed a survival benefit with docetaxel-based therapy in patients with metastatic AIPC [1,2], urologists and medical oncologists have sought to incorporate the latest data into their guidelines. Docetaxel is now recognized in many guidelines as the accepted standard for treating this stage of the disease (e.g. the European Society of Medical Oncologists, the European Association of Urologists, and the WHO).

Clinical trials of agents for the second-line chemotherapeutic treatment of AIPC are of interest, as this represents a clear unmet medical need, and as currently available drugs, such as mitoxantrone, vinorelbine, and oral cyclophosphamide, have only minimal activity in this setting, with response rates of ≈10% [18]. No large-scale trials have yet addressed the question of the sequence of therapy, although the results of a few small phase II trials were presented and suggested that docetaxel is as effective as both first- or second-line therapy [18].

Outcomes are awaited with agents such as satraplatin, an orally bioavailable platinum compound with activity against a variety of solid tumours. The SPARC (Satraplatin and Prednisone Against Refractory Cancer) trial has just finished accrual of 912 patients randomized to satraplatin and prednisone or prednisone alone as second-line chemotherapy [19].

Epothilones have antitumour activity in in vitro and in vivo models insensitive or resistant to taxanes, with reversible neurotoxicity being the predominant toxicity [20]. Epothilones are being evaluated in the second-line setting, and phase III trials of
comparisons with mitoxantrone and prednisone will be initiated shortly. Other potential avenues include the use of antiangiogenic and novel targeted agents.

As yet, no prospective randomized trial has systematically addressed the optimum timing of chemotherapy in AIPC (the two randomized phase III docetaxel trials accrued patients with progressive metastatic AIPC, whether symptomatic or not). Increasingly, it is recognized that AIPC is a heterogeneous disease, and hence individualized risk-adapted approaches appear to be appropriate in the absence of definitive evidence. Chemotherapy can be appropriate for both symptomatic and asymptomatic metastatic AIPC but should perhaps be individualized in patients with limited asymptomatic metastases. Presently, chemotherapy is not indicated in patients who do not have clinically evident metastases, whether they have androgen-dependent or -independent prostate cancer, or biochemical progression only (increasing PSA level).

FUTURE DEVELOPMENTS IN THE MEDICAL TREATMENT OF PROSTATE CANCER

NEW WAYS OF USING CHEMOTHERAPY IN AIPC

Preliminary phase II data have shown that intermittent chemotherapy, rather than treatment until disease progression, might be a promising approach to reduce treatment-related toxicity. Re-treatment with calcitriol plus docetaxel (subsequent to a PSA increase after a chemotherapy rest period) was successful in eight patients who had responded initially, and there was a statistically significant improvement in fatigue between the periods of chemotherapy (median duration 20 weeks between treatment periods) [21]. Some of the patients were eligible for multiple cycles of intermittent chemotherapy and the median time to treatment failure was 26.5 months [22]. In a larger phase II study, 75 patients received a sequence of three once-weekly cycles of docetaxel-based therapy and further sequences of chemotherapy upon doubling of their PSA levels (based on the previous nadir) [23]. Treatment was active and well tolerated. These studies show that intermittent treatment warrants further investigation vs the traditional continuous therapy model.

NEW APPLICATIONS OF CHEMOTHERAPY IN AIPC

The positive results obtained in phase III trials with docetaxel in metastatic AIPC have stimulated interest in the potential application of chemotherapy at earlier stages of the disease, including patients with rising PSA levels after attempted curative therapy for localized disease, and those at high risk of disease progression. This further underlines the need for a strong, effective partnership between cancer physicians in a multidisciplinary team, to offer patients optimal care from the most appropriate specialist at a given time.

HIGH-RISK LOCALIZED PROSTATE CANCER

ADJUVANT THERAPY

The effect of adjuvant docetaxel in high-risk prostate cancer has been investigated in a pilot phase II study [24]. Docetaxel was administered weekly for 6 months to high-risk patients within 3 months of RP. The median time to PSA relapse had not been reached at a median follow-up of 17 months. This study showed the feasibility of this approach but did not address efficacy.

Three ongoing adjuvant studies are comparing chemotherapy with or with no hormonal therapy or observation after RP. The SWOG 9921 study (1360 men) aims to investigate adjuvant hormonal therapy compared with the combination of hormonal therapy with mitoxantrone and prednisone in high-risk patients after RP, with a primary endpoint of a 30% improvement in overall survival. This trial has accrued over 800 patients to date. The TAX 3501 study (1696 men), a phase III multicentre trial, is comparing immediate vs deferred treatment with an LHRH analogue, with or without docetaxel (Fig. 1). Patients considered to be at high risk of relapse after RP for localized prostate cancer are selected on the basis of Kattan’s postoperative predictive probability nomogram [25]. The primary endpoint is progression-free survival. A Veterans’ Administration Cooperative Group Trial (700 men) will randomize patients with T3, G7–10, N0 disease after RP to 4 months of docetaxel and prednisone, vs surveillance alone.

Another ongoing trial will evaluate the addition of docetaxel to hormonal therapy in patients receiving radiation therapy. In Radiation Therapy Oncology Group Study 0521, 600 patients with clinically localized high-risk prostate cancer will receive the combination of androgen suppression and radiotherapy followed by (a) androgen suppression or (b) docetaxel/prednisone and androgen suppression. The planned primary endpoint of the study is overall survival.

NEOADJUVANT THERAPY

Neoadjuvant therapy has the advantage that the vasculature is intact and the in vivo biological effects of therapy can be assessed. Thus far, neoadjuvant androgen ablation has shown no clear benefit in cancer-specific or progression-free survival in randomized trials of surgically treated patients [26].

To date, there has been insufficient positive evidence to recommend neoadjuvant therapy.
with either hormones or chemotherapy in prostate cancer. A phase II study showed that there were no pathological complete responses in patients with high-risk localized prostate cancer who received docetaxel for 6 months before surgery [27]. However, any longer-term impact of neoadjuvant therapy in this study is not yet known.

In Study 05–043, a multicentre randomized trial, overall survival after either neoadjuvant and concurrent docetaxel plus 6 months of androgen ablation and radiotherapy, or androgen ablation and radiotherapy, will be evaluated in 350 patients with high-risk localized or locally advanced prostate cancer. In the Groupe d’Etudes des Tumeurs Uro-Génitales (GETUG) 12 study, 250 patients with high-risk localized or locally advanced prostate cancer will receive neoadjuvant hormonal therapy with or without 3 months of neoadjuvant docetaxel/estramustine before local treatment. Hormonal therapy will continue for 3 years in both arms. The primary endpoint is biochemical and clinical progression-free survival at 8 years. Of interest is the Cancer and Leukaemia Group B (CALGB) 90203 study of 720 patients, which seeks to show whether the combination of androgen deprivation therapy and docetaxel used for 6 months before surgery will affect the 5-year disease-free survival in patients at high risk of progression. Until the results of these trials become available, neoadjuvant therapy in prostate cancer cannot be recommended outside a clinical trial. In the future, it will be essential to establish reliable endpoints for neoadjuvant trials, such as biomarkers, pathological complete response, clinical response rate, PSA response, and progression-free survival.

There is no consensus as to whether neoadjuvant or adjuvant treatment strategies are best. It is clear that there is a developing definition of advanced prostate cancer to include earlier-stage disease that is destined to become metastatic. Nomograms and PSA kinetics are increasingly being used to identify patients at high risk, but the role of neoadjuvant or adjuvant treatment regimens remains to be established. Results of large-scale clinical trials are awaited with interest so that evidence-based recommendations can be made. Undoubtedly urologists, radiation therapists, and medical oncologists must work closely together in assessing patients for clinical trials, and in establishing the best treatment for patients with high-risk prostate cancer.

### ANDROGEN-DEPENDENT, RECURRENT PROSTATE CANCER

It is accepted that the use of hormonal therapy will ultimately lead to hormone-insensitive prostate cancer. It has been tempting to try to tackle the problems of both hormone-sensitive and -insensitive prostate cancer by adding chemotherapy to the well-established therapeutic tools, especially for patients with an increasing PSA level where the tumour burden is fairly small.

In patients who have an asymptomatic PSA increase with no metastatic disease after local treatment, therapy is controversial. Two phase II studies were published showing that docetaxel induced a PSA response in >40% of patients with biochemical progression (increasing PSA level) [28,29]. In the study by Hussain et al. [29], although only 49% of patients had a PSA response with docetaxel alone, there was a PSA response in all patients with subsequent complete androgen blockade. Results are eagerly awaited for the R-PSA study (ARTIC/GETUG), in which 252 patients with high-risk prostate cancer with an increasing PSA level after surgery or radiation therapy will receive hormonal therapy for 1 year with or without six cycles of docetaxel. The primary endpoint is biochemical progression-free survival. Another ongoing study is assessing cycling androgen stimulation and docetaxel; PSA and survival data are pending but there is no early sign of a sustained effect on PSA suppression [30].

### NOVEL TARGETS AND DRUGS IN PROSTATE CANCER MANAGEMENT

Several pathways have been identified as potential targets for prostate cancer treatments; these include (but are not limited to) receptor-signalling, angiogenic, and survival pathways. Some of the most interesting potential approaches are listed in Table 1. There are many possible new targets, and several randomized phase III large-scale trials that seek to improve upon the results with docetaxel in AIPC are planned or underway. Some key studies investigating docetaxel in novel combinations with other drugs for the treatment of AIPC are shown in Table 2.

### CONCLUSIONS

In AIPC, the importance of a successful partnership between urologists, radiation therapists, and medical oncologists as part of a multidisciplinary team cannot be over-emphasized. Recent data on the survival...
benefit associated with docetaxel in metastatic AIPC has prompted changes, not just in drug choice, but in ways of working together. The results of these trials have renewed interest and enthusiasm concerning a further role for non-hormonal drug therapy, including alternative applications of docetaxel and the clinical development of other drugs.

A strong partnership between urologists, radiation therapists, and medical oncologists will therefore be the cornerstone of using new developments in the treatment of prostate cancer to their fullest potential. In this review we explored some of the contentious points and barriers to success and, it is hoped, took a step along the path toward a new standard in multidisciplinary prostate cancer care.

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Abbreviations: AIPC, androgen-independent prostate cancer; CALGB, Cancer and Leukaemia Group B; GETUG, Groupe d’Etudes des Tumeurs Uro-Génitales; RP, radical prostatectomy; SWOG, Southwest Oncology Group.