Multimodality Treatment in Advanced Prostate Cancer

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1. Introduction

Despite advances in early detection due to the widespread use of prostate specific antigen (PSA) based screening, still about one third of the patients present with locally advanced or micrometastatic disease to the locoregional lymph nodes when diagnosed with prostate cancer (PCA) [1]. The optimal management of locally advanced PCA still remains controversial because the natural history of these tumors is poorly understood, there is a great heterogeneity in patient populations and there are no prospective randomized clinical trials comparing homogenous patient cohorts with different treatment modalities.

Patients with locally advanced PCA following surgery are often at high risk for recurrence due to unfavourable pathological findings associated with systemic micrometastases. Biochemical relapse at 10 years in patients with microscopic lymph node disease is as high as 90% and only about 80% of the patients are free of distant metastasis [2]. Patients with seminal vesicle involvement demonstrate undetectable PSA serum levels in only 37% 10 years after surgery. Therefore, many of the patients undergo immediate adjuvant androgen deprivation since it was shown in rodent animal models that endocrine therapy is most effective when given at a small tumor volume [3,4]. However, as has been shown in several retrospective studies concerning the outcome in Gleason 8 or greater PCA, long-term progression-free rates are poor with only about 50% of the patients remaining without biochemical relapse of metastatic deposits at 8 years despite immediate adjuvant androgen deprivation [5]. If poor Gleason score is combined with additional unfavourable pathological findings such as seminal vesicle invasion or lymph node metastasis, progression-free survival rates are even lower [5,6]. It is thought that the poor long-term response in locally advanced PCA with unfavourable prognosis is due to

the progression of primarily androgen-independent cancer cells escaping hormonal ablation. It, therefore, will be one of the most important challenges to develop new treatment strategies elimanting the whole malignant cell population including androgen-sensitive, androgen-insensitive and hormone refractory PCA cells.

To develop such treatment strategies it will be necessary to better understand the molecular biology of the progression of PCA. In addition, it will be necessary to combine various new treatment modalities in order to select different points of attack such as elimination of androgen sensitive cells by hormonal ablation, eradication of androgen-insensitive PCA cells in lymphatic and visceral organs and elimination of androgen insensitive cancer cells in the bone.

2. Biology of androgen independence

Prostate cancer growth is stimulated by androgens; however, according to the clonal selection model, PCA is a heterogeneous disease soon after malignant transformation due to intrinsic genetic instability. The clonal selection model has been demonstrated by Isaacs et al. [3] with the transplantable Dunning R3327-H rat model when they observed that androgen ablation provides a selective growth advantage for androgen independent cells which will progress and quickly comprise the abundance of the tumor. These data have been confirmed in other animal models such as the androgen-dependent Shionogi carcinoma model demonstrating that recurrent tumors after androgen ablation are mainly composed of androgen-independent stem cells giving rise to androgen-independent cell clones [7,8].

Most probably mutations in the androgen receptor (AR) gene with alterations of the normal androgen signaling play a significant role in the pathogenesis of androgen-independent PCA [9]. It has been shown by several groups that androgen-independent PCA is

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characterized by specific mutations in the steroid binding domain of the AR which were not present in the initial cancer specimens prior to androgen deprivation. Unlike wild-type AR, the mutational variants might be stimulated by other hormones such as progesterone, estrogens and corticosteroids despite castrate levels of serum testosterone. Furthermore, amplifications of the AR responsive to very low levels of circulating testosterone might contribute to PCA progression despite medical or surgical castration.

Besides mere alteration of the androgen signaling pathway, dysregulation of castration triggered apoptosis of prostate glandular epithelial and androgen dependent cancer cells might contribute to cancer progression [10–12]. In this context high expression levels of the anti-apoptotic oncogene bcl-2 are seen with greater frequency as prostate cancer progresses from organ-confined cancer to metastatic androgen-dependent and metastatic androgen-independent PCA [10]. Most probably, the anti-apoptotic effect of bcl-2 is due to stabilization of microtubule integrity [11]. Physiologically, bcl-2 undergoes inactivating phosphorylation as part of the G_2M interphase thereby activating the caspase cascade and facilitating mitosis via the dissolution of laminins and other cell structure proteins [12]. If continuously overexpressed, however, the physiological process of coordinated cell cycle progression is inhibited due to the constant bcl-2 activity resulting in enhanced tumor cell survival.

Once having disseminated from the primary prostate cancer, tumor cells most commonly invade the skeleton and induce unequivocal osteoblastic reactions. Most interestingly, androgen-independent PCA cells acquire osteomimetic properties such as the ability to synthesize and deposit bone matrix proteins (osteopontin, osteocalcin, osteonectin, and bone sialoprotein) explaining the predominance of osseous metastases once the disease progresses [14]. Prior to the development of osseous metastases, these cells must intravasate from the primary cancer to the endothelial cells of adjacent blood vessels, circulate in the blood as emboli, attach to bone marrow endothelium and extravasate to the bone marrow compartment with an affinity to the stromal cells and bone matrix proteins to form metastatic deposits. Although these metastatic deposits mainly formed by androgen-independent cells demonstrate identical anti-apoptotic properties (overexpression of bcl-2, mutated p53) they do not demonstrate long-term responses to taxan-based chemotherapies. It appears to be necessary to apply drugs which more specifically inhibit bone marrow invasion and adhesion to bone extracellular matrices such as bisphosphonates.

Based on the molecular findings being involved in the progression from androgen-dependent non-metastatic PCA to androgen-independent PCA with visceral and/or osseous metastases, it appears to be logical that the primary treatment of advanced prostate cancer following radical surgery should involve a multimodal therapeutic approach considering the distinctive metastatic deposits with their individual specificities:

(1) deposits of androgen-dependent metastatic PCA cells in visceral and osseous organs;
(2) deposits of androgen-independent PCA cells in visceral organs;
(3) depositis of androgen-independent PCA cells in the bone.

Reflecting these complex composition of cancer cells with different molecular properties, a combination therapy of hormonal deprivation, taxanes and bisphosphonates might be most effective as adjuvant therapy in order to improve progression-free and cancer specific survival in locally advanced PCA following radical prostatectomy.

3. Taxanes in the management of prostate cancer

Under normal conditions, microtubules undergo polymerization in the presence of microtubular-associated proteins and GTP interacting with β-tubulin [15]. Taxanes bind to β-tubulin resulting in microtubule assembly with disruption of the normal mitotic process and cell cycle arrest at the G_2M level [16]. Anticancer drugs that inhibit microtubule function also result in phosphorylation of bcl-2 thereby inhibiting its anti-apoptotic function [13,15,16]. Usually, docetaxel arrests cells in the G_2M phase of the cell cycle which, under physiological conditions, exhibit temporary bcl-2 phosphorylation at that stage of cell cycle arrest; docetaxel-induced phosphorylation of bcl-2 results in a continuous activation of the caspase cascade leading to increased apoptosis. Contrary to cytotoxic drugs not interfering with microtubule function such as doxorubicine and cisplatin, taxanes and vinblastine result in significantly higher response rates of longer duration [17].

As we have learned from the management of hormone refractory PCA, docetaxel with or without estramustine phosphate results in high objective PSA response rates (Table 1) in the range of 41% to 85% with a mean time to progression of about 9 to 12 months and a mean survival time of 16 to 18 months [17]. The toxicity of these regimes appeared to be

Table 1
Taxanes and hormone refractory PCA

Author	n	Drug	PSA↓ > 50%
Savarese et al., '99	47	EMP/HC	69%
Sinibaldi et al., '00	35	EMP*	45%
Kosty et al., '00	35	EMP	58%
Petrylak et al., '00	35	EMP	74%
Copur et al., '00	18	EMP	72%
Beer et al., '00	23	Ø	47%
Miller et al., '03	49	EMP	73%
Heidenreich, '03	72	Mitoxantron	65%

acceptable with a low frequency of hematotoxicity (10–15%) and nonhematological toxicities (23% to 33%). At least in elderly patients and in those with a poor performance status, weekly docetaxel in combination with EMP appears to be more suitable than the 3-week regime at higher doses.

Several clinical trials have analysed the efficacy of neoadjuvant weekly docetaxel in patients with high-risk localized PCA [18–20] which was defined as follows: PSA > 20 ng/ml, Gleason score 8–10, invasion of the seminal vesicles or >5 positive biopsies involved with cancer. All patients received docetaxel 36 mg/m^2/week for two consecutive months; if a response could be documented, chemotherapy was continued for another two months followed by radical prostatectomy. In one trial 11 patients were recruited with a PSA response rate of 67% and a significant tumor shrinkage in 40% documented by endorectal MRI [20]. In another trial, El-Rayes et al. [18] recruited 21 patients who were treated with 4 to 6 cycles of docetaxel at 70 mg/m^2 and EMP (280 mg TID) on day 1–3 ever 21 days. In this study all patients demonstrated a positive PSA response, only 3 patients demonstrated positive surgical margins and none of the men had lymph node involvement. The most common toxicity was grade 3/4 neutropenia in 40% and deep venous thrombosis in the first 3 of seven patients before warfarin at 1 mg/day was introduced.

Both trials document the feasibility of neoadjuvant chemotherapy in the clinical setting of high-risk PCA although this concept still has to be tested in prospective randomized trials.

A few studies have used docetaxel for the management of biochemical relapse following definitive therapy for clinically localized/locally advanced PCA. Hussain et al. [21] applied 4 to 6 cycles of docetaxel at 70 mg/m^2 every 21 days in 23 patients with PSA progression following radical prostatectomy, external beam radiation and adjuvant external beam radiation following radical prostatectomy. After four to six cycles the objective PSA response rate was 52% prior to the initiation of total androgen blockade for another

4 months. Treatment was well tolerated with grade 3/4 neutropenia representing the most common toxicity in about 40% of the patients.

In another trial, Taplin et al. [22] combined docetaxel (70 mg/m^2 every 21 days) with EMP (10 mg/kg/die, TID on days 1 to 5) with short-term androgen withdrawal for a total of 15 months. At the completion of 4 cycles of chemotherapy, 12/15 recruited men (80%) achieved a complete response, whereas PSA was still detectable in 3 men. Grade 3/4 hematoxicity developed in 53% of the patients, nonhematologic toxicity was observed in about one third of the patients.

Again, these trials demonstrate clinical efficacy of docetaxel-based chemotherapy in high-risk PCA patients with documented relapse further underlining the potential benefit of a taxan-based adjuvant chemotherapy following radical prostatectomy.

Considering the profile of recurrences following combination with paclitaxel, etoposid and EMP, it has been shown recently that most patients relapse in the bone but not in visceral organs or lymph nodes. These data suggest that taxan-based therapy might be most effective in patients without bone metastases and that other more bone-specific therapies might be necessary to treat or to prevent the development of bone metastases.

4. Bisphosphonates as adjuvant therapy in the prevention of bone metastases

PCA predominantly metastasizes to the bone, however, little is known of the pathogenesis of bone metastases in PCA. Batson et al. [23] described the connection between the vertrebral venous plexus and the bone marrow spaces hypothesizing a retrograde spread allowing metastases from the primary prostatic carcinoma to settle primarily in the lower vertebrae. Later on the concept of cancer cell–bone matrix interaction has been developed with carcinoma cells secreting substances such parathormone-related peptide (PTHrP), prostaglandin E and transforming growth factors that might stimulate tumor growth in the bone marrow by autocrine or paracrine mechanisms and by stimulation of osteoclasts. Specifically in PCA, the deranged and uncoupled bone formation can result in the so-called "bone hunger syndrome" with calcium being entrapped in the bone resulting in low serum calcium levels triggering the development of secondary hyperparathyroidism.

On the molecular level, PC3 cells injected intracardially or into the tibiae of athymic mice induce extensive osteolysis and osteoclastogenesis followed by an increase in bone formation at the same sites.

These mechanisms are due to the expression of bone-resorbing substances such as PTHrP, GM-CSF, Il-1 and Il-6 as well as due to the stimulation of the RANK-ligand ([24], review).

Bisphosphonates (BP) are taken up selectively by the skeleton and suppress bone resorption and bone pain; several BP have been approved for the prevention of skeletal complications due to breast and prostate cancer [25]. Depending on the absence or presence of a nitrogen molecule, BP either exert a direct cellular cytotoxic effect or interfere with specific intracellular pathways in osteoclasts. Nonnitrogen-containing BP such as clodronate, etidronate are metabolized intracellularly to substances toxic to the cell. Nitrogen-containing BP (ibandronate, zoledronate, pamidronate, risedronate) inhibit specific enzymes of the mevalonate pathway inhibiting the synthesis of the isoprenoid geranylgeranyl pyrophosphate and consecutively the prenylation of GTP-binding proteins which is necessary for cytoskeletal integrity and intracellular signaling. Due to BP action osteoclasts become inactive and undergo apoptosis. Since bone metastases due to PCA demonstrate both osteolytic and osteoblastic changes when analyzed histomorphologically, nitrogen-containing BP might be effective in the adjuvant setting following radical surgery to prevent the development of bone metastases.

In patients with high-risk breast cancer three pioneer trials have demonstrated that oral clodronate significantly reduces the incidence of osseous and nonosseous metastases [26–28]; furthermore, benefits with regard to overall and disease-free survival were observed. Contrary to the first study, Powells et al. observed a significant reduction of the incidence of osseous metastases, but the incidence of nonosseous metastases and survival were unaffected.

Of further potential relevance for their use in the prevention of bone metastases in PCA are additional in-vitro and animal in-vivo findings showing an inhibition of adhesion of breast cancer and PCA cells to the bone by various BP. Cell adhesion molecules are most probably involved in the growth and invasion of PCA cells in the bone. As has been shown by Boissier et al. [29] nitrogen containing BP inhibit PCA cell invasion by inhibition of tumor cell migration and by inhibiting the proteolytic activity of metalloproteinases. Furthermore, the same group demonstrated that BP inhibited PCA cell adhesion to mineralized and unmineralized bone extracellular matrices suggesting that BP might be clinically useful to prevent bone metastases in breast cancer or PCA [30–33]. Lee et al. [34] demonstrated that the treatment of various PCA cell lines with pamidronate and zoledronate significantly reduced the growth of all cell lines; whereas pamidronate exerted its effect by induction of cell death, zoledronate induced growth arrest as documented by an accumulation of cells in the G_0–G_1 and S-phase.

Pretreatment with BP in various mouse and rat models effectively prevents the development of bone metastases [35,36]. However, this positive effect can only be achieved within a very limited time frame; once osseous metastases have been established, BP do not exert a preventing effect and none of the BP could induce cell death of metastatic cancer cells.

As has been pointed out in the previous paragraph taxanes appear to be the most effective cytotoxic drugs in the management of hormone refractory PCA. According to recent in vitro studies the combination of BP with taxanes might be of additional clinical value in the prevention of the development of bone metastases [37,38]. Magnetto et al. [37] investigated the effects of ibandronate in combination with paclitaxel or docetaxel on the induction of apoptosis, invasion and adhesion of breast cancer cells to bone. Although ibandronate did not induce apoptosis of breast cancer cells nor did it enhance taxoid-induced apoptosis, it significantly enhanced the antitumor activity of both taxoids against invasion and cancer cell adhesion to bone. Therefore, the combination of ibandronate with docetaxel might be useful for the management of patients with cancer types preferentially metastasizing to the bone such as breast and prostate cancer.

5. Adjuvant chemohormonal therapy in prostate cancer

It has been shown in breast and colon cancer that chemotherapy is not very efficacious when administered in advanced stages of disease, however, it improves survival when used in an adjuvant setting and in early metastatic disease. Since androgen-independent PCA cells exhibit very low proliferation rates, it appears to be logical that even modern chemotherapeutic approaches might only be effective when administered early at a critically small tumor volume [39]. Compared to other solid tumors the evolution of multimodality therapy for PCA has just been started with the development of new chemotherapeutic agents with modest but definite activity in the clinical setting of hormone refractory PCA. The availability of several active chemotherapeutic combinations and the refinements in risk prediction following radical prostatectomy or radiation therapy have resulted in a series of adjuvant therapy trials.

The clinical evulotion of adjuvant chemotherapy following radical prostatectomy or radiation therapy dates back to the National Prostate Cancer Projects 900 and 1000 evaluating the efficacy of cytoxan, estramustine phosphate (EMP) and no therapy for 2 years [40]. At 14.3 years of follow-up, EMP treated patients demonstrated a significantly improved median survival compared to the observation group with 138.9 months and 108.4 months, respectively. The survival benefit was most obvious in patients with locally advanced PCA (pT3/4), poor differentiation (G3) and lymph node metastases.

Pummer et al. [41] demonstrated an improved relapse-free survival in patients with either metastatic or locally advanced PCA randomized to receive either epirubicin and androgen deprivation or hormonal therapy alone. Median relapse-free survival was 18 months and 12 months in the combination arm and the hormonal therapy arm, respectively.

Wang et al. [42] evaluated the clinical efficacy of 4 cycles of mitoxantrone as an adjuvant to complete androgen blockade in patients with metastatic or locally advanced PCA. Patients without obvious metastases receiving chemotherapy not only demonstrated better objective response rates (95% versus 53%, $p = 0.08$) but also a significantly prolonged survival (80 versus 36 months, $p = 0.04$) than patients treated with hormonal therapy alone. The beneficial effect of adjuvant chemotherapy, however, was apparent once metastases had developed.

In another trial, Bagley et al. [43] evaluated the long-term effect of adjuvant chemotherapy added to radiation therapy in 25 patients. All patients exhibited positive seminal vesicles or positive lymph nodes and all men received a combination therapy of vinblastine, doxorubicin and mitomycin along with continuous androgen deprivation. At 10 years, the relapse-free rate determined by undetectable PSA serum levels was 73%, the cancer specific survival was 81%. 82% of the node positive patients were relapse-free at 10 years which is clearly superior to the combination of radiation therapy with adjuvant androgen deprivation.

6. Adjuvant chemotherapy: current trials

Currently, there are four prospective adjuvant clinical trials under way investigating the efficacy of early adjuvant chemotherapy [44,45].

(1) a nonrandomized trial of docetaxel in high-risk patients following radical prostatectomy;
(2) the RTOG-9902 study comparing androgen deprivation with androgen deprivation, EMP, paclitaxel and etoposid following external beam radiation;
(3) an intergroup study comparing goserelin plus bicalutamide with goserelin plus mitoxantron in high-risk patients following radical prostatectomy;
(4) the study of the Association of Urological Oncology (AUO) of the German Cancer Society comparing androgen deprivation versus androgen deprivation plus ibandronate versus androgen deprivation, ibandronate and 4 cycles of docetaxel (Fig. 1)

The latter trial combines the above mentioned in vitro and animal experimental data on the additive and synergistic effects of ibandronate and docetaxel in prostate cancer against the invasion and cellular adhesion of PCA cells to bone. The primary goal of the trial is to reduce the frequency of PSA recurrences by 50% at 5 years; 320 patients at high risk following radical prostatectomy [46] will be prospectively recruited.
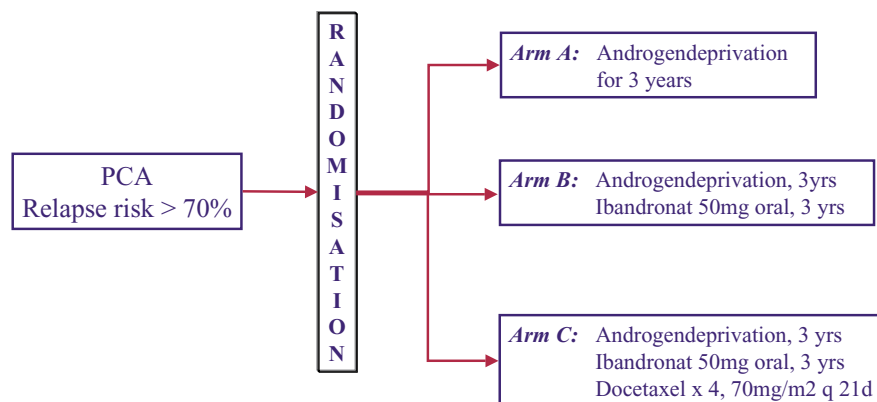

Fig. 1. Prospective randomized trial in patients with high-risk PCA following radical prostatectomy based on postoperative Kattan nomograms.

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