14 Androgen-Independent Prostate Cancer

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Abstract

Androgen-independent or hormone-refractory prostate cancer (AIPC) is prostate cancer that progresses after primary androgen-ablation therapy—either orchiectomy or a gonadotropin-releasing hormone (LHRH) agonist, followed by addition and subsequent withdrawal of an antiandrogen. In the majority of patients, AIPC appears after a median time of 18 months of hormone deprivation. Patients with AIPC have a median survival between 10 and 20 months and the prognosis can be defined by using nomograms. Standard treatment is continued castration by LHRH agonists in combination with docetaxel-containing chemotherapy. Other treatment options to palliate symptoms are hormones, other chemotherapeutic agents, radioisotopes or radiotherapy and bisphosphonates. New targeted drugs and vaccination strategies are evaluated in the treatment of AIPC.

Epidemiology

Androgen-independent or hormone-refractory prostate cancer (AIPC) is defined as prostate cancer that progresses after primary androgen-ablation therapy by either orchiectomy or a gonadotropin-releasing hormone (LHRH) agonist, followed by addition and subsequent withdrawal of an antiandrogen (Scher et al. 1995).

At diagnosis, AIPC is observed in less than 20% of patients with advanced prostate cancer (Mahler and Denis 1995). In the majority of patients, AIPC appears after a median time of 18 months of hormone deprivation. Patients with AIPC have a median survival between 10 and 20 months.

Pathophysiology

Androgens are the primary regulators of cell growth and proliferation of prostate cancer cells. When androgens are ablated or withdrawn, apoptosis is observed in a proportion of cells, while those that survive remain in the G1 phase of the cell cycle. Clinical progression is the result of regrowth of cells that are primarily resistant to androgen ablation or which, after a period of growth arrest, adapt to the low-androgen environment and resume proliferation (Scher and Sawyers 2005).

Androgen Receptor-Related AIPC

The androgen receptor (AR) plays a critical role in the development of AIPC. The androgen-receptor gene is the only gene that is consistently upregulated during tumor progression in different AIPC experimental models, and it seems that tumor progression despite androgen deprivation is associated with an active AR signaling pathway.

In patients with AIPC, a number of changes in the AR signaling pathway have been described (Scher and Sawyers 2005; Fig. 14.1):

- Changes in the level of ligand(s) in tumor tissue
- Increased levels of the AR protein due to gene amplification or altered messenger (m)RNA expression
- Activating mutations in the receptor that affect structure and function
- Changes in coregulatory molecules including coactivators and corepressors
- Factors that lead to activation of the receptor independent of the level of ligand or receptor by kinase crosstalk

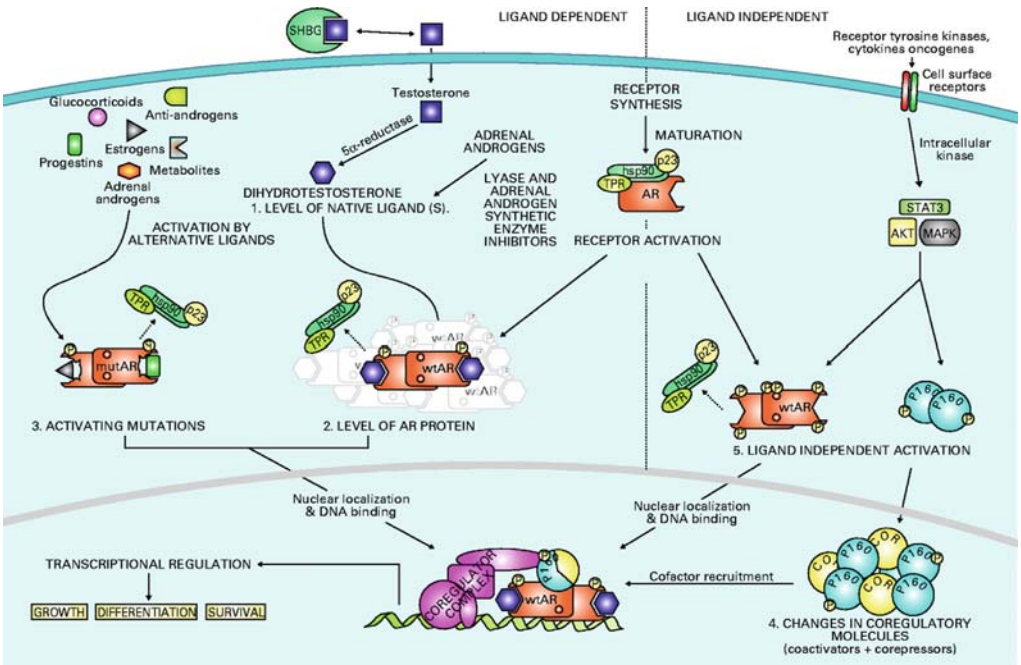

Fig. 14.1 Classification of mechanisms associated with continued signaling through the androgen-signaling axis despite castration

Incomplete Blockade of AR Ligand Production

Medical and surgical therapies that ablate production or androgen action do not result in undetectable androgen levels in tumor tissue. Intratumoral testosterone levels in patients with castration-resistant disease are similar to untreated benign prostatic disease, and the level of dihydrotestosterone is sufficient to maintain AR signaling and expression of prostate-specific antigen (PSA). Intratumoral androgens may come from an adrenal source or from direct synthesis within the tumor by an intracrine mechanism. Therefore, prostate tumors rarely encounter a completely androgen-depleted environment.

Increased Levels of AR Protein Without Mutation

Amplification of the *AR* gene has been documented in 20%–25% of both castration-resistant metastatic and recurrent primary tumors. The increase in AR protein sensitizes prostate cancer cells to respond to low levels of ligand.

AR Mutations

AR mutation rates in human prostate cancer range from 5%–50% depending on tumor status (primary versus metastatic, pre- versus post-androgen ablation) and prior therapy. The majority of mutations are in the ligand-binding domain, and most of the mutations are associated with gains as opposed to a loss of function and produce a receptor that is more sensitive to native ligand, or that can be activated by other steroid hormones and/or by the specific antiandrogen.

Indirect Mechanisms of AR Activation

Coactivators that enhance or corepressors that reduce receptor function mediate the transcriptional activity of the *AR*.

Coactivator proteins such as ARA54 and ARA70 can selectively enhance the activity of the receptor to alternative ligands such as estradiol and hydroxyflutamide, can sensitize the receptor to lower concentrations of native and non-na-

tive ligands, or allow ligand-independent activation by receptor tyrosine kinases (RTKs) such as HER2.

Decreased expression of corepressors such as nuclear receptor corepressor (N-CoR) and silencing mediator of retinoid and thyroid receptors (SMRT), which mediate, in part, the antagonist action of bicalutamide, flutamide, and mifepristone, may contribute to the agonist activity that can be observed with these agents.

A change in the coactivator-to-corepressor ratio can alter AR transactivation activity in the presence of low concentrations of dihydrotestosterone. Conversely, the corepressors SMRT and N-CoR can inhibit AR function in a ligand-dependent manner.

Alterations in the coactivator-to-corepressor ratio can explain the paradoxical agonist effects of antiandrogens and other steroid hormones on prostate cancer growth. Coactivators may play a role in castration-resistant disease.

HER-2/*neu*, a member of the epidermal growth factor receptor (EGFR) family of RTKs is consistently overexpressed at a higher frequency in castration-resistant as opposed to hormone-naïve primary tumors. HER2, and other growth factors such as keratinocyte growth factor, insulin-like growth factor-1, and epidermal growth factor, and cytokines such as interleukin-6, can activate the AR and minimize or possibly even negate the requirement for ligand. HER-2/*neu* is thought to promote DNA binding and AR stability through activation of mitogen-activated protein kinase (MAPK) and Akt, which can also bind directly to the receptor.

Androgen Receptor-Independent Mechanisms

Neuroendocrine cells are present in prostate stem cells and increase in AIPC. Neuroendocrine cells have a low rate of proliferation, which permits them to survive many different types of treatment. In addition, neuroendocrine cells secrete neuropeptides such as serotonin and bombesin, which can increase the proliferation of neighboring cancer cells, thereby allowing progression of AIPC. Neuroendocrine cells are present in 40%–100% of patients with AIPC (Debes and Tindall 2004).

Another pathway that bypasses the AR involves the deregulation of apoptotic genes. The tumor-suppressor gene *PTEN* and the antiapoptotic gene *Bcl-2* play important roles in AIPC. PTEN inhibits the phosphatidylinositol 3-kinase pathway in normal cells. Activation of this pathway stimulates a protein called Akt, which inactivates several proapoptotic proteins, thus enhancing cell survival.

In the normal prostate, PTEN allows cells to undergo apoptosis, whereas in cancer cells and in AIPC the loss of PTEN increases Akt activity and blocks apoptosis. Loss of PTEN function is infrequent in androgen-dependent prostate cancer. Inactivation of PTEN is considerably more likely to occur in AIPC. One of the primary targets of Akt, when it is blocking apoptosis, is Bcl-2. Activated Akt frees Bcl-2 (which is bound to a protein called Bad), allowing it to increase cell survival. Overexpression of Bcl-2 has been implicated in the progression to AIPC (Gleave et al. 2002).

Evaluation

A patient is having AIPC if there is disease progression after treatment with a standard hormonal regimen with androgen-ablation therapy (usually orchiectomy or LHRH agonist), followed by addition and subsequent withdrawal of an antiandrogen. He should be treated with this regimen for at least 4 weeks and his serum testosterone level should be below 30 ng/ml (Small et al. 2004).

Baseline studies should include a complete blood cell count, alkaline phosphatase, serial PSA levels (Bubley et al. 1999; Sartor et al. 1999), lactate dehydrogenase, albumin, testosterone level, chest X-ray, plain radiographs of painful bony sites, bone scan, and imaging of disease (e.g., abdominal CT scan in case of retroperitoneal lymph node metastases).

In addition, quality of life [e.g., European Organisation for Research and Treatment of Cancer (EORTC), QLQ-C32, and a module of ten questions specific for metastatic prostate cancer] and symptom measures (e.g., pain, including present pain intensity, visual analog scale), comorbid conditions and a geriatric assessment should be included in the evaluation of patients with AIPC (Curran et al. 1997).

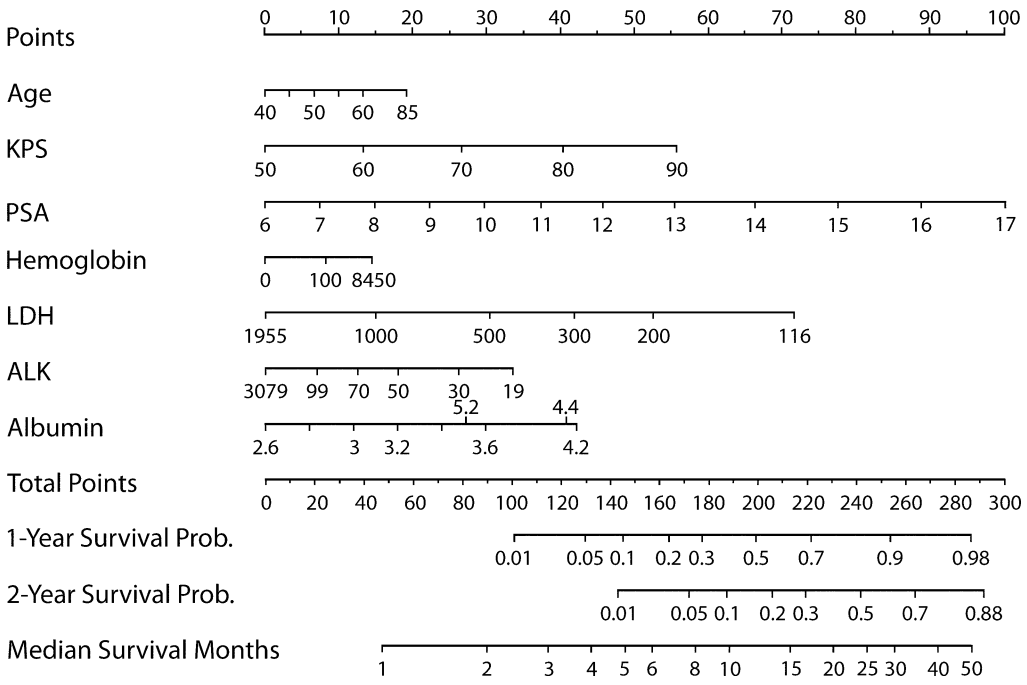

Fig. 14.2 Nomogram for survival of patients with progressive castrate metastatic disease

Prognosis of AIPC

There are several prognostic models that are predictive of survival in men with AIPC.

- In the model of Berry et al., a short survival is seen in patients with an age exceeding 65 years, severe bone pain, poor performance status, presence of soft tissue metastases, anemia, and elevated levels of lactate dehydrogenase (LDH), acid phosphatase, alkaline phosphatase, and prolactin (Berry et al. 1979).
- In the model developed by Emrich et al., identified factors that were predictive of survival in order of importance were previous hormone response, anorexia, elevated acid phosphatase, pain, elevated alkaline phosphatase, obstructive symptoms, tumor grade, performance status, anemia, and age at diagnosis (Emrich et al. 1985).
- Kantoff et al. (1999) identified the following prognostic factors: alkaline phosphatase, LDH, baseline PSA, and hemoglobin.
- Other factors identified in other studies were greater than 50% decline in PSA, changes in PSA after therapy, weight loss, extent of bone metastasis, pretreatment serum testosterone level, and any decline in PSA. Biologic markers such as plasma and urine vascular endothelial growth factor and reverse transcriptase polymerase chain reaction for PSA have been identified as statistically significant predictors of overall survival in patients with AIPC.
- There have also been developed pretreatment nomograms to predict survival in patients with AIPC (Figs. 14.2 and 14.3) (Smaletz et al. 2002; Halabi et al. 2004).

Treatment

Standard treatment options for patients with AIPC include secondary hormonal therapies or chemotherapy. In patients without prior orchiectomy, castration with an LHRH agonist is maintained. The treatment choice depends on the

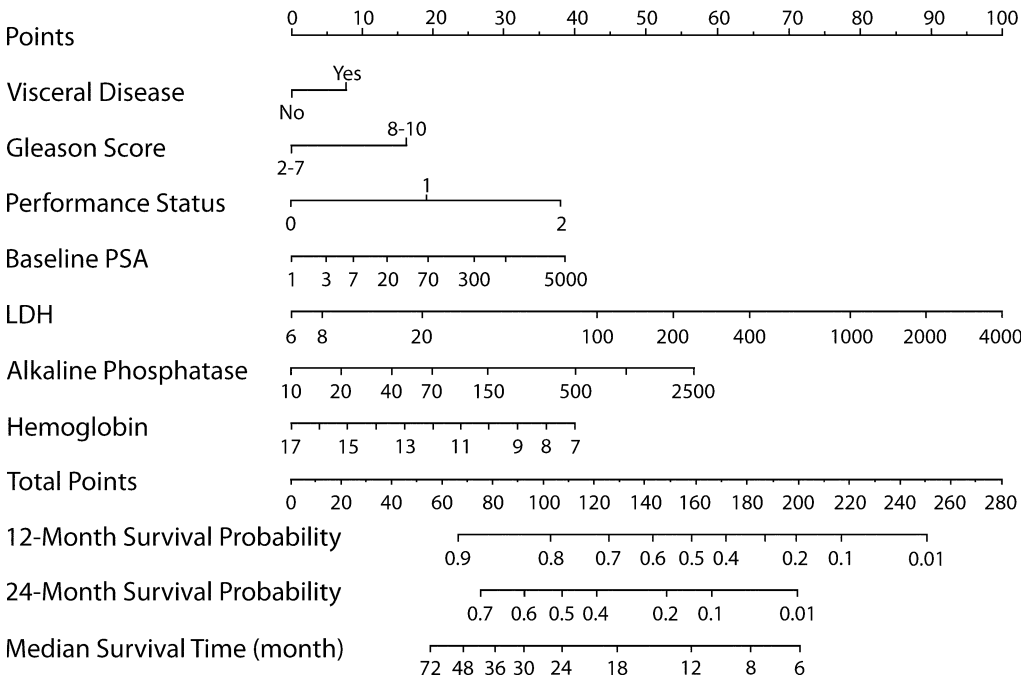

Fig. 14.3 Pretreatment nomogram predicting probability of survival. Instructions to physicians: Please start from the *second top axis* by identifying the disease measurability. Draw a vertical line to the points axis (*top line*) to represent the number of prognostic points the patients will receive for measurable disease. Do the same for the other prognostic variables. Once all prognostic points for the predictors have been determined, add up the prognostic points for each prognostic variable. You can determine the 12-month survival probability by drawing a vertical line down from the "total points axis" (*fourth from the bottom*) to the 12-month survival probability axis (*third line from the bottom*). The same process can be done to estimate the 24-month survival probability

impact of the disease on the quality of life, the expected beneficial effect, and the general condition of the patient.

In patients with painful bone metastases, external radiotherapy, radionucleotides, and bisphosphonates may be beneficial.

Hormonal Manipulation

For patients that progress on both an LHRH agonist and antiandrogen, the withdrawal of antiandrogen therapy results in a response in 25%–50% of patients.

In patients with a frail condition and/or slowly progressing disease, hormonal manipulations may be useful. These hormonal manipulations include prednisone or other glucocorticoids, ketoconazole, and estrogens such as diethylstilbestrol. Although secondary hormonal manipulation may produce a subjective response in approximately 25%–50% of patients, it is short-lived (approximately 4 months).

Prednisone and Dexamethasone

Glucocorticoids may lead to PSA responses or relief of symptoms (or both) in patients with late-stage prostate cancer. Corticosteroids depress adrenocorticotropic hormone secretion leading to suppression of adrenal androgen release. A randomized EORTC phase III study comparing flutamide with prednisone in patients with prostate cancer who were progressing symptomatically after androgen ablative therapy found similar PSA response rates (±20%), and prednisone was superior in terms of pain control

and overall quality of life (Fossa et al. 2001). In most patients who have been treated with first-line chemotherapy, corticosteroids are added; the potential benefit in these patients is therefore probably minimal.

Ketoconazole

Ketoconazole is an inhibitor of steroid synthesis and must be administered with hydrocortisone or prednisone. It may increase the probability of an antiandrogen withdrawal response, although this does not result in improved survival. When used after prior chemotherapy it is associated with occasional PSA responses, although these responses are usually transient (Berthold et al. 2005).

Estrogens

Estrogens, such as oral diethylstilbestrol (DES) have been shown to be associated with PSA responses and improved symptoms in several small trials when used after failure of other hormonal measures. However, they must be used with caution since they may cause thrombosis and cardiovascular events. These side effects are usually not a major problem if the dose of DES is at or below 3 mg/day (Berthold et al. 2005).

Chemotherapy

Several clinical trials have evaluated the role of both single agent and combination chemotherapy in the treatment of AIPC. Some of these trials have demonstrated encouraging results in disease control, PSA response, radiological responses, overall survival, and improvement in quality of life. At the moment, the combination of docetaxel and prednisone is considered as the standard treatment in men with AIPC.

Estramustine

Estramustine is a 17-β-estradiol phosphate derivative linked to a nor-nitrogen mustard molecule and binds to microtubule-associated proteins (MAPs) in the nuclear matrix and inhibits microtubule assembly and disassembly.

As a single agent, estramustine has shown an overall response rate of 14%–48%, with subjective improvements in pain and performance status. The addition of estramustine to other spindle poisons such as vinblastine, vincristine, and paclitaxel improves the response rates compared to these agents alone, although there is no improvement of overall survival. Common side effects of estramustine are nausea, vomiting, and thrombosis secondary to the high estrogen content (Goodin et al. 2002).

Vinca Alkaloids

Vinblastine, an agent that binds to tubulin and prevents microtubule assembly, is active in patients with prostate cancer and has a response rate of 21% when used as a single agent in continuous infusion. In combination with estramustine, the response rate, as measured by PSA, has varied from 40%–54% while several studies showed an improvement in pain control. Vinorelbine, a newer vinca alkaloid, has shown a clinical benefit in 40% of 15 patients in a phase II study. Studies combining vinorelbine with other agents are ongoing (Goodin et al. 2002).

Topoisomerase II Inhibitors

Etoposide is a topoisomerase II inhibitor that acts at the nuclear matrix and has a synergistic effect with estramustine. In phase II studies, a response rate of 39%–50% was seen with this combination, but some of the regimens were associated with major toxicities including grade 3 or 4 leukopenia and nausea in 25% and 29% of patients, respectively.

Doxorubicin is another a topoisomerase II inhibitor; it has a single agent activity of 5%–84% in prostate cancer, depending on response criteria. Combinations of doxorubicin with either ketoconazole (response rate 45%) or cyclophosphamide (response rate 33%–46%) have been reported in phase II trials. These combinations led to substantial hematologic toxicity (Goodin et al. 2002).

Mitoxantrone in combination with prednisone was approved for the treatment of AIPC based on palliative endpoints in randomized phase III trials (Tannock et al. 1996; Kantoff et al. 1999). Patients with AIPC were given prednisone, 10 mg orally each day alone or in combination with mitoxantrone, 12 mg/m² intravenously every 3 weeks. Patients who received mitoxantrone plus prednisone achieved a statistically significant greater palliation of symptoms, including pain, compared with those who received prednisone alone (29% versus 12%, p=0.01) along with a significantly longer duration of symptom palliation (43 versus 18 weeks, p <0.0001). Toxicity was mild, with the exception of a decreased left ventricular ejection fraction in the mitoxantrone group. There was no difference in survival between the groups.

Taxanes

Docetaxel induces apoptosis by interfering with the microtubule formation during mitosis and inhibiting Bcl-2. Docetaxel phosphorylates Bcl-2 at serine residues, which inactivates this protein and leads to the activation of the caspase cascade and apoptosis. Docetaxel also inhibits the growth of Bcl-2-negative tumors by inducing overexpression of the cell cycle inhibitor p27, which is frequently lost in AIPC.

Docetaxel treatment has become the new standard treatment in patients with AIPC, replacing mitoxantrone based on the results of two independent phase III trials showing that taxane-based chemotherapy led to a survival benefit in men with AIPC (Tannock et al. 2004; Petrylak et al. 2004).

In a large international trial, two schedules of docetaxel and prednisone were compared to mitoxantrone and prednisone in 1,006 men with AIPC. They were randomly assigned to docetaxel 75 mg/m² every 3 weeks, docetaxel 30 mg/m² once weekly for 5 weeks, or mitoxantrone 12 mg/m² every 3 weeks. All patients also received 5 mg oral prednisone twice daily. The 3-week schedule of docetaxel increased survival by 24% as compared to mitoxantrone. The median survival was 18.9 months in the every-3-week docetaxel group, 17.4 months in the weekly docetaxel group, and 16.5 months in the mitoxantrone group. Pain reduction was most pronounced in those that received docetaxel every 3 weeks (35% compared with 31% on weekly docetaxel and 22% on mitoxantrone) (Tannock et al. 2004).

Another trial compared docetaxel and estramustine to mitoxantrone and prednisone. Of the 674 patients eligible for the trial, 338 received docetaxel (60 mg/m² every 21 days) and estramustine (280 mg three times daily over 5 days). The other 336 received mitoxantrone (12 mg/m² every 21 days) and prednisone (5 mg twice daily). In an intention-to-treat analysis, the median overall survival was longer for patients receiving docetaxel and estramustine than with mitoxantrone and prednisone, with a 20% reduction in the risk of death in favor of the docetaxel group. Median survival in the docetaxel and estramustine arm was 17.5 months, compared to 15.6 months. The median time-to-progression was 6.3 months compared to 3.2 months. PSA declines of at least 50% occurred in 50% of the patients treated with the docetaxel-based regimen, compared to about 25% of patients in the mitoxantrone group. Grade 3 or 4 neutropenic fever, nausea and vomiting, and cardiovascular events were more common among patients receiving docetaxel and estramustine than among those receiving mitoxantrone and prednisone (Petrylak et al. 2004).

These studies show that a docetaxel-based regimen can improve survival by a median of 2 to 2.5 months and reduce the risk of death by 20% to 24% in comparison to mitoxantrone. In addition to an improvement in survival, docetaxel was linked to an increase in time to disease progression, PSA declines, and quality of life.

Epothilones

Epothilones have significant antitumor activity in *in vitro* and *in vivo* models insensitive or resistant to taxanes. They induce microtubule bundling, formation of multipolar spindles, and mitotic arrest. Although reversible neurotoxicity is the predominant toxicity, an advantage is that no corticosteroid premedication is required.

Ixabepilone is a new epothilone and has potent cytotoxic effects on paclitaxel-sensitive and insensitive cells, and in taxane-resistant tumor cell lines overexpressing P-glycoprotein. It is given in an intravenous dose schedule of 40 mg/m² every 3 weeks and induces PSA responses in patients with AIPC of ±40%.

The response rate increases when ixabepilone is combined with estramustine with responses in ±70% of patients with AIPC. Neutropenia and neuropathy are the main adverse events, with 9% of patients having a grade 3–4 thrombotic event (Berthold et al. 2005).

Platinum Compounds

Several older phase II trials showed a moderate activity of cisplatin and carboplatin as single agents or in combination with other chemotherapeutic agents, with response rates varying between 14%–30%. The newer agent oxaliplatin induced a PSA response rate of 8% with a clinical benefit in 32% of patients.

Satraplatin is an orally bioavailable platinum compound, and in an EORTC Genitourinary Tract Group trial, a PSA decrease of more than 50% was seen in 8.7% on prednisone versus 33.3% on satraplatin, with better progression-free survival on the satraplatin arm (Sternberg et al. 2005).

Based on these data, docetaxel treatment in combination with prednisone should be considered first-line standard treatment in patients with AIPC. Currently, it is unclear how the effectiveness of mitoxantrone is affected when it is used as second-line treatment after docetaxel compared with the results seen in first-line studies.

Overall, the PSA response rate to docetaxel after initial treatment with mitoxantrone seems similar to that achieved with first-line treatment (response rate 44%–85%), whereas a relatively low proportion of patients respond to mitoxantrone after first receiving docetaxel (response rate 6%–15%). Tolerability seems to be somewhat worse than for first-line chemotherapy, with about 45%–65% of patients requiring a delay, dose reduction, or cessation of chemotherapy in the second-line setting (Berthold et al. 2005).

The role of the newer cytotoxic agents should be evaluated in randomized clinical trials.

Targeted Therapies

Several new agents based on translational research are being tested in patients with AIPC.

Oblimersen

Bcl-2 is an important pro-survival regulator of apoptotic cell death. Oblimersen is a phosphorothioate antisense oligonucleotide complementary to the Bcl-2 mRNA and a potent inhibitor of Bcl-2 expression, which in pre-clinical testing can significantly enhance the therapeutic effect of chemo therapy, hormones, and radiation therapy. The antisense oligonucleotide directed to BCL-2, oblimersen sodium (Genasense, Genta, Berkeley Heights) lowers Bcl-2 level (Chi 2005).

Thalidomide

Thalidomide and its analogs modulate the immune system in various ways. Some of these immunomodulatory activities, together with the antiangiogenic, antiproliferative, and proapoptotic properties, are believed to mediate antitumor responses in some tumors. A randomized phase II trial combining docetaxel with thalidomide resulted in an encouraging PSA decline rate. At 18 months, overall survival in the docetaxel plus thalidomide group was 68.2% compared to only 42.9% in the docetaxel alone group (Dahut et al. 2004).

Atrasentan

Endothelin-1, acting via the endothelin-A receptor, has been implicated in metastasis and progression of prostate cancer, particularly in bone.

Atrasentan is a potent, oral, selective endothelin-A receptor antagonist. A meta-analysis of two large randomized placebo-controlled studies of atrasentan in men with metastatic AIPC showed that atrasentan resulted in a significant

reduction in disease progression, attenuation of the rise of the biomarkers PSA and bone alkaline phosphatase, delay in time to biochemical progression, decrease in time to bone pain and incidence of bone pain, and disease-specific quality of life benefit (Vogelzang et al. 2005).

Vaccine Therapy

Prostate cancer cells express many unique differentiation-associated antigens that allow for development of organ-specific targeted vaccines. APC8015 utilizes prostatic acid phosphatase (PAP), which is highly expressed in more than 90% of prostate tumors. It is an immunotherapy cellular product consisting of autologous peripheral blood mononuclear cells enriched for the dendritic cell fraction pulsed with a PAP-GM-CSF construct. Patients with asymptomatic metastatic AIPC were randomized (2:1) to receive APC8015 (n=82) or placebo (n=45) every 2 weeks for 6 weeks, and at 3 years 34% of those vaccinated were alive compared to 11% in the placebo arm. In a subset analysis, treatment with APC8015 resulted in a 6.4-month survival advantage in patients with Gleason scores of less or equal to 7 (Small et al. 2005).

Bisphosphonates

Bisphosphonates act by decreasing the rate of bone turnover, reducing the number of osteoclasts, their recruitment, lifespan, and activity. Bone complications in prostate cancer occur as a result of skeletal metastases, long-term treatment with androgen withdrawal, and radiotherapy. Bisphosphonates have been shown to reduce bone pain in prostatic cancer for 2–3 weeks after a single intravenous infusion, in up to 30% of patients.

Promising results were observed with zoledronic acid, and in phase III trials there were fewer skeletal events compared with placebo (44.2% vs 33.2%, p=0.02) after a 15-min infusion of zoledronic acid every 3 weeks. However, renal function should be monitored carefully, and osteonecrosis of the yaw may occur with the use of bisphosphonates (Goodin et al. 2002).

Radiotherapy

External radiotherapy may be useful for perineal pain, bleeding, or bone pain.

A single fraction of external local radiotherapy is effective for pain relief in symptomatic bony metastases in up to 76% of patients. It may, however, take several weeks for it to take effect.

Hemibody irradiation is utilized where a large treatment field is required, usually encompassing the pelvis and upper femurs. However, this frequently results in diarrhea and nausea.

Strontium-89 is a β-emitter and is used as an intravenous injection for pain control in widespread bone metastases. It may be associated with an initial pain flare, but approximately 10% of treated patients do experience a complete resolution of pain. However, the presence of any critical metastases potentially able to cause spinal cord compression must be excluded, as strontium may cause edema at these sites. In addition, the treatment commonly produces prolonged myelosuppression, particularly thrombocytopenia, and in patients with already depleted marrow reserves, either due to disease or treatment, this can be problematic. It may also limit future use of chemotherapy.

In two randomized phase III studies, strontium-89 was shown to give better and more durable relief of pain than limited field radiotherapy, while in a recent study this effect could not be confirmed (Bauman et al. 2005; Oosterhof et al. 2003).

Newer radiopharmaceuticals e.g., Samarium-159, are being tested for the treatment of painful bone metastases in patients with AIPC.

Conclusions

The evaluation and treatment of patients with AIPC should be performed by an integrated multidisciplinary approach to allow optimal symptomatic control. Recent advances in the understanding of the molecular mechanisms implicated in prostate cancer progression may lead to new therapies.

References

Bauman G, Charette M, Reid R, Sathya J (2005) Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. Radiother Oncol 75:258–270

Berry WR, Laszlo J, Cox E, et al (1979) Prognostic factors in metastatic and hormonally unresponsive carcinoma of the prostate. Cancer 44:763–775

Berthold D, Sternberg C, Tannock I (2005) Management of advanced prostate cancer after first-line chemotherapy. J Clin Oncol 23:8247–8252

Bubley GJ, Carducci M, Dahut W, et al (1999) Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol 17:3461–3467

Chi KN (2005) Targeting Bcl-2 with oblimersen for patients with hormone refractory prostate cancer. World J Urol 23:33–37

Curran D, Fossa S, Aaronson N, Kiebert G, Keuppens F, Hall R (1997) Baseline quality of life of patients with advanced prostate cancer. European Organization for Research and Treatment of Cancer (EORTC), Genito-Urinary Tract Cancer Cooperative Group (GUT-CCG). Eur J Cancer 33:1809–1814

Dahut WL, Gulley JL, Arlen PM, Liu Y, Fedenko KM, Steinberg SM, et al (2004) Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. J Clin Oncol 22:2532–2539

Debes JD, Tindall DJ (2004) Mechanisms of androgen-refractory prostate cancer. N Engl J Med 351:1488–1490

Emrich LJ, Priore RL, Murphy GP, et al (1985) Prognostic factors in patients with advanced stage prostate cancer. Cancer Res 45:5173–5179

Fossa SD, Slee PH, Brausi M, et al (2001) Flutamide versus prednisone in patients with prostate cancer symptomatically progressing after androgen-ablative therapy: a phase III study of the European organization for research and treatment of cancer genitourinary group. J Clin Oncol 19:62–71

Gleave ME, Zellweger T, Chi K, Miyake H, Kiyama S, July L, et al (2002) Targeting antiapoptotic genes upregulated by androgen withdrawal using antisense oligonucleotides to enhance androgen- and chemo-sensitivity in prostate cancer. Invest New Drugs 20:145–158

Goodin S, Rao KV, DiPaola RS (2002) State-of-the-art treatment of metastatic hormone-refractory prostate cancer. Oncologist 7:360–370

Halabi S, Small EJ, Kantoff PW, Kattan MW, Kaplan EB, Dawson NA, Levine EG, Blumenstein BA, Vogelzang NJ (2004) Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. J Clin Oncol 21:1232–1237

Kantoff PW, Halabi S, Conaway MR, et al (1999) Hydrocortisone with or without mitoxantrone in men with hormone refractory prostate cancer: the results of CALGB 9182. J Clin Oncol 17:2506–2513

Mahler C, Denis LJ (1995) Hormone refractory disease. Semin Surg Oncol 11:77–83

Oosterhof GO, Roberts JT, de Reijke TM, Engelholm SA, Horenblas S, von der Maase H, Neymark N, Debois M, Collette L (2003) Strontium(89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation for Research and Treatment of Cancer, Genitourinary Group. Eur Urol 44:519–526

Petrylak DP, Tangen CM, Hussain MH, Lara PNJ, Jones JA, Taplin ME, et al (2004) Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 35:1513–1520

Sartor O, Scher H, Simons J, Sinibaldi V, Small EJ, Smith MR, Trump DL, Wilding G, et al (1999) Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol 17:3461–3467

Scher HI, Sawyers CL (2005) Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. J Clin Oncol 23:8253–8261

Scher HI, Steineck G, Kelly WK (1995) Hormone-refractory (D3) prostate cancer: refining the concept. Urology 46:142–148

Smaletz O, Scher HI, Small EJ, Verbel DA, McMillan A, Regan K, Kelly WK, Kattan MW (2002) Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. J Clin Oncol 20:3972–3982

Small EJ, Halabi S, Dawson NA, Stadler WM, Rini BI, Picus J, Gable P, Torti FM, Kaplan E, Vogelzang NJ (2004) Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583). J Clin Oncol 2004 22:1025–1033

Small EJ, Schellhammer PF, Higano C, Neumanaitis J, Valone F, Herschberg RM (2005) Immunotherapy (APC8015) for androgen independent prostate cancer (AIPC): final survival data from a phase 3 randomized placebo-controlled trial. ASCO Prostate Cancer Symposium, Abstr 264. ASCO

Sternberg CN, Whelan P, Hetherington J, Paluchowska B, Slee P, Vekemans K, et al (2005) Phase III trial of satraplatin, an oral platinum plus prednisone vs. prednisone alone in patients with hormone refractory prostate cancer. Oncology 68:2–9

Tannock IF, Osoba D, Stochler MR, Ernst DS, Neville AJ, Moore MJ, et al (1996) Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone resistant prostate cancer: a Canadian randomized trial with palliative endpoints. J Clin Oncol 14:1756–1764

Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351:1502–1512

Vogelzang NJ, Nelson JB, Schulman CC, Dearnaley DP, Saad F, Sleep DJ, Isaacson JD, Carducc MA (2005) Meta-analysis of clinical trials of atrasentan 10 mg in metastatic hormone-refractory prostate cancer. ASCO Prostate Cancer Symposium, Abstr 4563. ASCO