International Congress on Hormonal Steroids and Hormones and Cancer

Endocrine/paracrine/autocrine survival factor activity of bone microenvironment participates in the development of androgen ablation and chemotherapy refractoriness of prostate cancer metastasis in skeleton

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Abstract

Bone is the most frequent site of metastases of prostate cancer and is almost always the first and frequently the only site of metastases where disease will progress to stage D3. In addition, the number of skeletal metastatic foci is the most powerful independent prognostic factor of limited response to hormone ablation therapy and poor survival of patients with advanced prostate cancer. Furthermore, disease progression frequently occurs in the osteoblastic metastases, even though androgen ablation therapy still provides adequate and sustained control of disease at the primary site. Notably, the management of metastatic disease onto bones has traditionally relied on therapeutic modalities, which almost exclusively aim at directly inducing cancer cell death. However, accumulating pieces of evidence, from both the clinical and the basic research front, point to major limitations of this conventional approach. The in vivo response of malignant cells to anticancer therapies is directly influenced by the local microenvironment in which they metastasize. In particular, organ sites frequently involved in metastatic diseases, such as the bones, appear to confer to metastatic cells protection from anticancer drug-induced apoptosis. This protection is mediated by soluble growth factors and cytokines released by the normal cellular constituents of the host tissue microenvironment. The characterization of bone microenvironment-related survival factors has led to the development of a novel hormone manipulation which can re-introduce clinical responses in patients with stage D3 prostate cancer.

Introduction

Androgen ablation therapy (surgical or pharmaceutical orchietomy) almost always produces an objective clinical response in newly diagnosed advanced stage prostate cancer (PCAs). However, the disease will eventually progress to the final androgen ablation refractory stage (stage D3). The median survival of patients in stage D3 disease is approximately 10 months (9–12 months) and salvage chemotherapy cannot improve the overall survival of such patients (Dowling & Tannock 1985, Yagoda & Petrylak 1993, Small & Vogelzang 1997, Oh 2000, Small & Harris 2002). At this stage, to improve quality of life physicians have to choose from various treatment options (which unfortunately are not well standardized as yet although they are well known and quite popular as second-line hormonal therapies) which
include high-dose bicalutamide, ketoconazole, low-dose corticosteroids, and estrogen-based therapies (Petrylak 2002). Ongoing clinical phase II trials looking at prostate specific antigen (PSA) reduction, palliative response (reduction in consumption of pain killers and pain relief) and radiographic measurable endpoints have suggested that a significant proportion of patients with stage D3 androgen-insensitive PCa may benefit from these regimens. However, the appropriate timing and order of application of such therapies in stage D3 disease remain unclear. In general, the goal of these treatments is to relieve the pain of patients and to slow, if possible, cancer progression using drugs of minimal toxicity (Small & Harris 2002).

Regarding the application of cytotoxic chemotherapy in stage D3 PCa, reviews of clinical trials conducted before 1991 have reported an overall response rate of 4.5% to 8.7% (Eisenberger et al. 1985, Yagoda & Petrylak 1993). More recent phase III trials have reported similar response rates for measurable disease from 6% to 7% (Hudes et al. 1999, Kantoff et al. 1999). If patients with bone-only metastases are excluded from the analysis, the response rate increases to as high as 27% (Hudes et al. 1999). Phase II trials of taxane-based regimens have reported measurable disease response rates from 10% to 25% if all patients are included, or 11% to 58% if patients with only measurable soft tissue metastases are included. These trials reported a <50% decrease in the level of serum PSA from baseline in 45% to 74% of patients (Petrylak et al. 2000, Sinibaldi et al. 2000, Athanasiadis et al. 2001, Beer et al. 2001, Hudes et al. 2001, Copur et al. 2001, Kotsy et al. 2001, Savarese et al. 2001). In addition, chemotherapy in the form of estramustine phosphate and mitoxantrone plus prednisone has objectively shown a modest palliative effect especially on bone pain but no survival benefit in randomized clinical studies (Gilligan & Kantoff 2002). Furthermore, therapeutic regimens that may include taxanes (paclitaxel or docetaxel) and estramustine phosphate appear to be more active in palliative features but have greater toxicity. These regimens are currently being tested against mitoxantrone plus prednisone with regard to any survival advantage in hormone refractory PCa (Petrylak 2002). However, comparing recent and older prostate cancer chemotherapy trials must be done with caution. In the pre-PSA testing era, response rates were based on reductions in tumor burden, as determined by radiological studies. However, prostate cancer spreads predominantly to bone, and bony metastases and their response to treatment are difficult to quantify radiographically (Smith et al. 1990, Sabbatini et al. 1999). Using PSA as a surrogate endpoint has been justified by the demonstration of an association between longer survival and a decrease of <50% after therapy. A multivariate analysis in a contemporary retrospective study showed inferior survival for those patients who were no longer receiving luteinizing hormone releasing-hormone analogs (LHRH-A), suggesting the continuation of androgen ablation therapies even at stage D3 disease (Small & Harris 2002).

**Bone microenvironment participates in the development of androgen ablation and chemotherapy refractoriness of bony metastasis**

Bone is the most frequent site of metastases of prostate cancer and is almost always the first and frequently the only site of metastases where disease will progress to stage D3 (Belliveau & Spencer 1975, Koutsilieris et al. 1986a, Koutsilieris 1993). Spinal cord compression and pathological fracture occur in approximately one-third of cases with stage D3 disease, and anemia, cachexia, bone pain, and sepsis are common complications in such prostate cancer patients (Koutsilieris 1995, Small & Harris 2002). In addition, the number of skeletal metastatic foci is the most powerful independent prognostic factor of limited response to hormone ablation therapy and poor survival of patients with advanced PCa (Koutsilieris et al. 1986a, Crawford et al. 1989, Koutsilieris et al. 1990, 1994a, Koutsilieris 1995). Furthermore, disease progression frequently occurs in the osteoblastic metastases, even though androgen ablation therapy still provides adequate and sustained control of disease at the primary site (Tolis et al. 1985, Koutsilieris et al. 1986a, Koutsilieris & Ackman 1987, Koutsilieris et al. 1990, 1996, Behrakis & Koutsilieris 1997).

Notably, the management of metastatic disease onto bones has traditionally relied on therapeutic modalities, which almost exclusively aim at directly inducing cancer cell death. However, accumulating pieces of evidence, from both the clinical and the basic research front, point to major limitations of this conventional approach (Koutsilieris 1995). The in vivo response of malignant cells to anticancer therapies is directly influenced by the local microenvironment in which they metastasize. In particular, organ sites frequently involved in metastatic diseases, such as the bones, appear to confer to metastatic cells protection from anticancer drug-induced apoptosis. This protection is mediated by soluble growth factors and cytokines released by the normal cellular constituents of the host tissue microenvironment (Dimitriadou & Koutsilieris 1997, Choki et al. 1998, Reyes-Moreno et al. 1998, Koutsilieris et al. 1999, 2000).

A prime example of the role of the metastatic microenvironment in protecting tumor cells from anticancer therapies is within the setting of hormone refractory (stage D3) metastatic prostate cancer. A recent article has reviewed the line of investigation on the molecular mechanisms of resistance to combined androgen blockade (Mitsiades & Koutsilieris 2001). For years, it has been a widely accepted notion that resistance to hormonal therapy is an outcome exclusively determined at the generic level and involving mutations/
chromosomal abnormalities that neutralize pro-apoptotic intracellular pathways and/or constitutively activate anti-apoptotic ones. That this resistance can also be conferred by epigenetic, non-genetically determined mechanisms is not well documented. Among others, the most intriguing anti-survival pathway appears to be the type I insulin-like growth factor (IGF) receptor-induced activation of phosphatidylinositol 3-kinase (PI-3K)/Akt-mediated phosphorylation of the androgen receptor (AR) and the type I IGF receptor-mediated activation of nuclear factor kappa B (NF-κB) survival pathway (Fig. 1). Apparently, growth factor pathways, such as IGF-I, interleukin-6 (IL-6), and transforming growth factor β1 (TGFβ1) can activate the transcriptional targets of AR, even in the setting of major suppression of androgenic activity, which is produced by the use of the combined androgen blockade (a combination of either chronic administration of LHRH-A or orchiectomy plus anti-androgen). Obviously, the development of survival factor-mediated resistance to anticancer therapy-induced apoptosis of prostate cancer cells is a major hurdle preventing long-lasting clinical responses to conventional or investigational therapies (Koutsilieris 1995, Koutsilieris et al. 1999, 2000).

Survival mechanisms of prostate cancer cells are produced by the interactions of the tumor cells with the local microenvironment of the host tissue, thus explaining why the bone metastases are the almost exclusive sites for the development of androgen ablation refractoriness in advanced prostate cancer (Koutsilieris 1995, Choki et al. 1998, Reyes-Moreno et al. 1998, Koutsilieris et al. 1999). A major mediator of this rescue from anticancer drug apoptosis of metastatic prostate cancer is the increased IGF-I bioavailability in the bone microenvironment of metastasis (Fig. 2). Metastatic prostate cancer cells release urokinase-type plasminogen activator (uPA), which binds to its receptor (uPA-R) on the surface of osteoblasts. This binding activates proteolytic activity at sites adjacent to the osteoblasts and leads to local increase of proteinolysis. The IGF-binding proteins (IGFBPs) are molecules that have higher activity for IGFs than the type I IGF receptor (type I IGF-R), thereby acting as controllers of extracellular IGF bioavailability.

**Figure 1** Growth factor receptor-mediated signal transduction pathways, such as those activated by the receptors of transforming growth factor beta 1 (TGFβ1), interleukin 6 (IL-6) and insulin-like growth factor I (IGF-I), can interfere with androgen receptor (AR) transcription activity, stimulating AR function even in the absence of ligand (androgen), thereby inhibiting directly or indirectly apoptosis of prostate cancer cells. This survival factor activity of growth factors can explain the inhibition of androgen ablation-induced apoptosis (development of refractoriness) of prostate cancer cells at the metastatic sites of high content for such growth factor activity (bone microenvironment-derived IGF-I, TGFβ1, IL-6, etc.), TGFβ1,-R, TGFβ2 receptor, IL-6R, IL-6 receptor; MAPK, MAP kinase; ARE, androgen response element.
Figure 2 Schematic presentation of the urokinase-type plasminogen activator (uPA)-mediated increase of IGF-I at the sites of osteoblastic metastasis. Prostate cancer cells produce large amounts of uPA, which hydrolyze IGF binding protein 3 (IGFBP-3), the main carrier protein both of GH-dependent IGFs activity in the circulation and of local osteoblast-derived IGF activity, resulting in a remarkable increase in IGF bioavailability in the bone metastasis microenvironment.

(Koutsilieris & Polychronakos 1992). Consequently, uPA-mediated limited proteolysis of the IGFBPs (mainly of IGFBP-3) produces a local increase in IGF bioavailability which, in turn, stimulates the proliferation of osteoblasts and tumor cells, locally leading to the development of an osteoblastic reaction at the sites of bony metastases from prostate cancer (Koutsilieris et al. 1986a, 1987ab, Polychronakos et al. 1991, Koutsilieris 1992, Koutsilieris & Polychronakos 1992, Koutsilieris et al. 1993, 1994b). The outcome of these self-amplifying molecular loops is that the locally increased bioavailability of IGF-I activates, via its type I IGF-R on prostate cancer cells, several proliferative and anti-apoptotic mechanisms which can alter the biology of metastatic prostate cancer cells (Mitsiades & Koutsilieris 2001).

The effort to define pharmacological agents which can control IGF-I bioavailability in the bone metastasis microenvironment, has been greatly facilitated by ex vivo studies on the molecular constituents of the uPA/plasmin/IGF-I pathway. Analysis of the promoter regions of the uPA and IGF-I genes for putative transcription factor consensus binding sites reveals the presence of glucocorticoid receptor (GR) binding sites, suggesting that glucocorticoids can regulate transcription of these particular genes (Chen et al. 1991, Koutsilieris 1992). This indicated that modulation of the GR is a potential target for anti-survival factor (ASF) strategies. However, it had to be confirmed that the GR is functional in both prostate cancer cells and osteoblasts and that its transcriptional activity does indeed serve to down-regulate both uPA and IGF-I transcripts (and protein levels) (Koutsilieris et al. 1992, 1993, Delany & Canalis 1995, Boulanger et al. 1995, Reyes-Moreno et al. 1995, Reyes-Moreno & Koutsilieris 1997). Further studies did confirm the presence and functional integrity of GR in human and rat prostate cancer cells (Koutsilieris et al., 1992, Reyes-Moreno et al. 1995) and confirmed that GR function can play a major role in modulating the cell–cell interactions between the prostate cancer cells and osteoblast-like cells (Delany & Canalis 1995, Boulanger et al. 1995, Reyes-Moreno & Koutsilieris 1997). Indeed, dexamethasone decreased the osteoblast-derived IGFs (Boulanger et al. 1995) and also down-regulated prostate cancer cell expression of uPA (Koutsilieris et al. 1997, Reyes-Moreno & Koutsilieris 1997), subsequently reducing the uPA/uPA-R/plasmin-mediated degradation of extracellular matrix and the uPA-mediated hydrolysis of IGFBPs (Fig. 3). Consequently, the bioavailability of IGFs to both prostate cancer cells and osteoblasts was greatly diminished, while the pro-apoptotic effect of IGFBP-3 upon prostate cancer cells was increased (Rajah et al. 1997). The aforementioned converging molecular mechanisms explained the ability of glucocorticoids to inhibit the proliferation of androgen-insensitive rat PA-III and human PC-3 prostate cancer cells in vitro. These effects were also confirmed by the dexamethasone-induced...
GR FUNCTION IN BONE METASTASIS

GR FUNCTION

↑ IGFBP-3 ⇐ ↓ uPA production of prostate cancer cells

↓ IGF-I production of osteoblasts

REDUCTION OF IGF-I BIOAVAILABILITY IN OSTEOBLASTIC METASTASIS

Figure 3 Schematic presentation of the glucocorticoid receptor (GR) function in the bone metastasis microenvironment. GR function down-regulates urokinase-type plasminogen activator (uPA) production by the prostate cancer cells and the IGF-I production by the osteoblasts. In addition, dexamethasone reduction of uPA expression in prostate cancer cells decreases IGFBP-3 hydrolysis, resulting in increased IGFBP-3 activity, which reduces further IGF-I bioavailability locally.

regression of PA-III prostate tumors onto rat bones (Reyes-Moreno & Koutsilieris 1997, Kruit et al. 1999).

However, IGF-I is abundantly present in the peripheral blood where the major source is the growth hormone (GH)-dependent, mainly liver-derived, IGF-I (Davies et al. 1998). Glucocorticoids can locally down-regulate osteoblast-derived IGF-I, but this effect is eventually neutralized by the incoming influx to the bone of circulating, GH-dependent IGF-I and the systemic (blood) IGFBP-3/IGF complexes (Villafuerte et al. 1992, Giustina & Veldhuis 1998). Therefore, dexamethasone administration is necessary to sustain the suppression of local uPA-mediated IGF-I production, but it cannot neutralize extraskeletal bioavailability of IGFs, unless the appropriate blockade of GH-dependent IGF production is attempted (Fig. 4).

Anti-survival factor approach in stage D3 prostate cancer: translation from ex vivo studies to clinical applications

Since no specific inhibitors of the IGF-I signal transduction pathways are currently available for clinical use, the crucial step in designing therapeutic approaches against the survival factor effect of IGF-I is to define clinically applicable methodologies of down-regulating the local IGF-I concentration at the metastatic sites in the skeleton. Preclinical studies on the effect of glucocorticoids against the bone metastases of prostate cancer indicated the clear merit of this approach in suppressing uPA-mediated IGF-I production (Koutsilieris et al. 1997). However, a more comprehensive suppression of IGF-I concentrations has to be sought, with particular emphasis on simultaneous suppression of systemic GH-dependent, mainly liver-derived, IGF-I production. The use of somatostatin analogs (SM-A) is an effective clinical strategy to suppress systemic IGF-I production. It has been applied for years in the setting of GH-secreting pituitary adenomas. Octreotide or other SM-A and, more recently, long-acting SM-A, such as lanreotide and octreotide, have offered remarkable clinical improvement, associated with a decrease in circulating, GH-dependent, IGF-I (Davies et al. 1998) and an increase in circulating IGFBP-1 (Ezzat et al. 1992, Villafuerte et al. 1992). The toxicity profile of these compounds has been very favorable with only minimal side effects, such as abnormal oral glucose tolerance test, increased blood glucose, moderate elevations of blood pressure, cholestasis, constipation, etc., all of which were well-managed medically (Davies et al. 1998). These data prompted us to incorporate both dexamethasone and SM-A into our therapeutic protocol aiming at decreasing IGF-I bioavailability to prostate cancer cells (Fig. 4). However, the
The concept of anti-survival factor (ASF) therapy, combining dexamethasone and somatostatin analog (SM-A). The aim of this regimen is to reduce IGF-I bioavailability at osteoblastic metastasis. SM-A administration reduces the GH-dependent IGF production ('endocrine', mainly liver-derived, IGF bioavailability) and dexamethasone administration reduces the urokinase-type plasminogen activator (uPA)-mediated increase in IGF bioavailability (local GH-independent 'paracrine/autocrine' IGF production).

Development of an anti-survival factor therapy (ASF regimen) would have to be combined with an appropriate pro-apoptotic regimen, namely androgen ablation therapy. Conceivably, this would allow the latter regimen to achieve a more potent induction of tumor cell death as a result of the suppressed protective effect of the cancer cell survival factor i.e. IGF-I.

In metastatic prostate cancer, an appropriate stage for the establishment of such an approach is in patients in whom both combined androgen blockade (CAB) and anti-androgen withdrawal have failed. The latter manipulation can yield objective (yet mostly transient) responses in patients with a mutated androgen that is paradoxically activated by anti-androgens (Dupont et al. 1993). Although there is no conclusive evidence that cytotoxic chemotherapy can significantly prolong the overall survival or improve the quality of life of stage D3 patients, the first clinical applications of the ASF approach involved patients who had also failed salvage chemotherapy. Consequently, all patients enrolled in the trial of the ASF were refractory to every available conventional modality.

This approach is novel as instead of attempting directly to induce cancer cell apoptosis, it aims at neutralizing the protective effect conferred upon cancer cells by the survival factor(s) derived from the local microenvironment. This neutralization per se may not necessarily induce apoptosis, but it can enhance the sensitivity and/or reverse the resistance of tumor cells to other anticancer therapeutic strategies (Santor 2002). Therefore, a combination of dexamethasone and long-acting SM-A can decrease the circulating and locally released IGF-I bioavailability (Fig. 4).

The concept of ASF therapy is currently under investigation in an investigator-driven phase II study in prostate cancer patients with: (1) disease progression to stage D3 while on combined androgen blockade (CAB; LHRH-A plus anti-androgen, e.g. flutamide); (2) relapse from CAB therapy and progression-free survival of < 12 months, which is an important adverse prognostic indicator for overall survival; (3) no response to anti-androgen withdrawal manipulation or relapse after an initial response to it; (4) failure to respond to salvage chemotherapy; and (5) more than six foci of skeletal metastases, which is yet another powerful adverse prognostic indicator.

The treatment schedule includes administration of oral dexamethasone (4 mg daily for the first month of treatment, followed by 2 mg daily within 2 months and a maintenance dose of 2 mg daily thereafter) plus long-acting SM-A (lanreotide or octreotide as i.m. injections) in combination with androgen ablation therapy (using i.m. injections of the LHRH-A). Dexamethasone was chosen for use in this combination therapy because it is the most potent agonist of the GR that is available for clinical use (having 30 times more activity than prednisolone).
potent glucocorticoid activity than cortisol) and has no mineralocorticoid activity. Currently, 65 patients have entered this trial, with 40 patients being evaluated at this stage (follow-up more than 6 months; M Koutsilieris, C Mitiadies, J Bogdanos, T H Dimopoulos, A Sourla, C Milathianakis, E Zagoras, A Tsintavis, manuscript in preparation).

In a preliminary report of the initial 6-month follow-up of the first four patients receiving the ASF therapy, a major improvement in bone pain and analgesic requirements, reduction in PSA and alkaline phosphatase (AP) levels and significant improvement in performance status were reported (Koutsilieris et al. 1999). These initial responses to ASF have been confirmed in a larger cohort of patients, where we documented major and sustained responses of serum PSA and AP, as well as prolonged improvements in performance status and bone pain control (Koutsilieris et al. 2001).

Conclusive proof that the combination of the ASF regimen with LHRH-A can prolong the survival of these patients will require further clinical trials. Definitive conclusions regarding the efficacy of this regimen in comparison with conventional strategies, e.g. combination chemotherapy, can be drawn only after the completion of randomized controlled clinical trials which are currently under way. However, results from the first clinical applications of the ASF therapy reveal several very encouraging features. First, this is a well-tolerated regimen, with no life-threatening side effects. The combination of dexamethasone and SM-A may contribute to insomnia (10%), psychotic syndrome (0.5%), myopathy (15%), and elevated blood glucose levels (20%) primarily in those with a prior history of diabetes. However, these side effects were transient and were resolved upon tapering of the dexamethasone dose or were effectively controlled with appropriate lifestyle (e.g. diet) modifications, or adjustments in insulin dosage. Secondly, the ASF approach has led to a major improvement in the parameters of quality of life, such as bone pain and performance status (Koutsilieris et al. 2001, 2002). Thirdly, although almost all patients that have been followed up for > 12 months have relapsed, their post-relapse performance status and bone pain were still significantly improved compared with their baseline status, even months after progression. Fourthly, in metastatic prostate cancer patients who develop resistance to CAB, their overall survival has been in the range of 10 months, even when salvage chemotherapy is administered. The patients enrolled in the clinical trials of the combination of LHRH-A with SM-A plus dexamethasone had already undergone anti-androgen withdrawal and salvage chemotherapy and failed both. However, in the initial cohort of patients receiving the combination therapy the median overall survival surpassed 10 months (Koutsilieris et al. 2001, 2002).

Ongoing studies are expected to define the exact extent to which IGF-I suppression can account for the activity of the ASF-based combination. The currently available data suggest that IGF-I is a main target for this therapy and that if other mechanisms of action exist they play a supporting role to that of IGF-I down-regulation (Koutsilieris et al. 2001). Other mechanisms that might contribute to the activity of the ASF-based combination include various other known growth and survival factors locally produced by the bone microenvironment, such as IL-6 or fibroblast growth factors (FGFs). IL-6, a multifunctional cytokine produced by multiple sources in the bone microenvironment e.g. bone marrow stromal cells (Calligaris-Cappio et al. 1991, Treon & Anderson 1998), osteoclasts (Battaille et al. 1991) or osteoblasts (Calligaris-Cappio et al. 1992), can also confer resistance against cisplatin and etoposide-induced cell death in PC-3 and DU-145 prostate cancer cells (Borsellino et al. 1995). Serum IL-6 levels are significantly elevated in hormone-refractory prostate cancer patients compared with earlier stages of the disease or with benign prostate hyperplasia patients (Drachenberg et al. 1999). The fact that glucocorticoids can also down-regulate IL-6 production from osteoblasts (Hierl et al. 1998, Manolagas 1998, Swolin-Eide & Ohlsson 1998) might suggest a role for IL-6 as an additional potential target for the ASF-based combination therapy. However, it must be noted that serum IL-6 levels in advanced prostate cancer are much lower than those of IGF-I (Drachenberg et al. 1999). Basic FGF (bFGF), an angiogenic cytokine associated with in vitro epigenetic resistance to a wide range of cytotoxic drugs (Song et al. 2000), could potentially be a target of the ASF-based combination. Similar to IL-6, bFGF levels in the serum or bone marrow aspirates of patients with prostate cancer (Meyer et al. 1995, Cronauer et al. 1997) or various ostetotropic neoplasias (Di Raimondo et al. 2000) are again considerably lower than those of IGF-I. This further reinforces the notion that the role, if any, of growth/survival factors other than IGF-I in the mechanism of action of the ASF-based combination therapy appears to be less significant (Koutsilieris et al. 2002).

Despite the encouraging and durable responses to the ASF-based regimen, almost all patients that have been followed up for > 12 months do eventually progress. Even though their performance status and overall quality of life remains significantly improved for several months post-relapse in comparison with their baseline at the onset of the ASF combination therapy, it is worth addressing the molecular mechanisms responsible for the resistance. Such efforts may lead to clinically applicable methodologies to extend the response to ASF therapy and the overall survival of patients. It is currently unclear why patients relapse from ASF and it is possible that this event has multi-factorial aetiology. Obviously, up until now all patients enrolled on the clinical trial of the ASF combination were at far advanced stages of their disease, having failed all available conventional treatment options. In these patients, the metastatic prostate cancer cells are likely to have a more aggressive biological behavior in comparison with earlier disease stages, which may, in turn, contribute to genetic events promoting growth and survival despite major suppression of IGF-I.
There are no clear cut answers as to which of these mechanisms may be more relevant or more important for relapse from ASF. In any event, the future clinical and basic research efforts in this exciting field will have to take all of these aspects into proper consideration. In its true sense, the ‘ASF therapy’ concept is neither confined to only one survival factor (e.g. IGF-I) nor matter how significant its role is for tumor refractoriness, nor should it be focused entirely on a simple strategy to neutralize each survival factor’s activity. Instead, the application of the ASF concept should involve the targeting of multiple potential survival factors at multiple levels of their mechanisms of anti-apoptotic action (Koutsilieris et al. 2002). To address the former goal, further research will be required to fully characterize the array of paracrine/autocrine and/or endocrine survival factors for prostate cancer originating from both osteoclasts and osteoblasts (Fig. 5).

Therefore, future clinical applications of the ASF therapeutic strategy may have to be individualized to distinct patterns of genomic abnormalities in each patient’s tumor cells. This task will, in time, become progressively more feasible, thanks to the major progress that has recently been achieved in the fields of high-throughput global analysis of the genomic, transcriptomic and proteomic make-up of tumor cells.

**Conclusions**

In hormone refractory prostate cancer, IGF-I (either GH-dependent or GH-independent) can protect tumor cells from apoptosis, despite the significant suppression of androgenic stimuli. The application of the ASF therapeutic concept in this setting involves the combination of dexamethasone (which suppresses ‘autocrine-paracrine’, GH-independent IGF-I) and SM-A (which suppresses ‘endocrine’, GH-dependent IGF-I) with the pro-apoptotic effect of androgen ablation therapy. In hormone refractory prostate cancer patients the ‘ASF-based’ combination achieved durable objective responses and major symptomatic improvement, paving the way for future applications of this concept, in an effort to increase the sensitivity or reverse the resistance of tumors to conventional or investigational anticancer therapies. The ASF-based combination therapy also illustrates a novel paradigm in cancer treatment: anti-tumor treatment strategies may be aimed not only directly at inducing cancer...

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**Figure 5** Evolution of anti-survival factor (ASF) therapy by the inclusion into the ASF regimen (dexamethasone and somatostatin analog) of an inhibitor of osteoclast-mediated bone resorption. Conceivably, bisphosphonates can contribute both to the tapering of the local bone reaction, neutralizing osteoclast-derived survival factors, and to the anti-tumor actions, which are otherwise mainly exerted by hormone ablation therapy in stage D3 prostate cancer. PTHrP, parathyroid hormone-related peptide; Chemo, chemotherapy.
cell apoptosis but can also target the tumor microenvironment and neutralize the protection it offers to metastatic cancer cells. The low toxicity profile of this novel therapeutic approach calls for its testing in a randomized controlled setting in metastatic prostate cancer and, conceivably, in other IGFI-1-responsive malignancies.

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