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Review Article

Hylonome

Cancer and bone repair mechanism: Clinical applications for hormone refractory prostate cancer

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Abstract

It is a long-standing clinical observation that the bone corresponds to the prevalent site for metastatic growth of prostate cancer. In addition, bone metastases of this malignancy produce a potent blastic reaction, in contrast to the overwhelming majority of other osteotropic neoplasms, whose metastases are generally associated with an osteolytic reaction. Osteoblastic metastases represent almost always the first and, frequently, the exclusive site of disease progression to hormone refractory stage, stage D3. Moreover, the number of skeletal metastatic foci is the most powerful independent prognostic factor associated with a limited response to hormone ablation therapy and poor survival of advanced prostate cancer. It is noteworthy that disease progression to hormone refractory stage occurs almost always in osteoblastic metastases. These clinical observations suggested that the osteoblastic reaction is possibly not an innocent bystander of the metastatic prostate tumour growth, simply suffering its consequences, but it may in fact facilitate the efforts of metastatic cells to expand their population. An extensive line of research in the pathophysiology of osteoblastic metastases has established that the local blastic reaction involves the uPA/plasmin/IGF/IGFBP-3/TGFbs bioregulation system which can stimulate both the growth of osteoblasts and prostate cancer cells. Furthermore, we were the first to characterize osteoblast-derived "survival factors" able to rescue metastatic prostate cancer cells from chemotherapy-induced apoptosis. These data resulted in the development of a novel concept of an anti-survival factor therapy, namely an anti-IGF-1 therapy, which has provided encouraging preliminary data in a phase II clinical trial with terminally-ill hormone/chemotherapy-resistant prostate cancer patients.

Keywords: Prostate Cancer, Bone Metastases, IGF-1, Bone-Derived Survival Factors

Pathophysiology of the osteoblastic metastasis and bone-derived survival factors for metastatic cancer cells

The therapeutic management of metastatic prostate cancer represents a major challenge, especially in regards to patients who, despite an initial objective response to androgen ablation therapy, eventually progress to hormone refractory stage (stage D3). This development is associated with poor prognosis[1]. The median survival of stage D3 prostate cancer patients is 12 months and salvage chemotherapy has not offered substantial amelioration in the overall survival of such patients[2,3]. It is a long-standing clinical observation that the bone corresponds to the prevalent site for metastatic growth of prostate cancer[4]. In addition, bone metastases of this malignancy produce a potent blastic reaction, in contrast to the overwhelming majority of other osteotropic neoplasms, whose metastases are generally associated with an osteolytic reaction[5]. Osteoblastic metastases represent almost always the first and, frequently, the exclusive site of disease progression to hormone refractory stage, stage D3[6,7]. Moreover, the number of skeletal metastatic foci is the most powerful independent prognostic factor associated with limited response to hormone ablation therapy and poor survival of advanced prostate cancer[7-9]. It is noteworthy that, frequently, disease progression to hormone refractory stage occurs only in the osteoblastic metastases, despite of the fact that hormone ablation therapy still provides an adequate and sustained control of disease at the primary site[7-12]. These clinical observations have suggested that the osteoblastic reaction is possibly not an innocent bystander of the metastatic prostate tumour growth, simply suffering its consequences, but it may in fact facilitate the efforts of metastatic cells to expand their population. An extensive line of research in the pathophysiology of osteoblastic metastases

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has established the notion that the bone constitutes a favorable microenvironment for the homing of metastatic prostate cancer cells[13-14]. It is now evident that this is secondary to local production of growth factors with mitogenic properties upon both the osteoblasts and prostate cancer cells. These intercellular interactions serve both the establishment of a local osteoblastic reaction and the support of the growth of metastatic prostate cancer cells, locally[13-17]. Within this context, a novel line of investigation has been following the tenet that metastatic prostate cancer cells to the bone are also enjoying a preferential protection from apoptosis, while under attack from anti-cancer therapies. Therefore, research attempts have been focused on the presence of osteoblast-derived survival factors that can rescue metastatic cancer cells from chemotherapy-induced apoptosis[18-20]. Herein, we are reviewing the data which confirmed the presence of osteoblast-derived survival factors and their relationship with known bone growth factors implicated in the osteoblastic reaction. In addition, we are analyzing the mechanisms of survival factor actions and the possible role of survival factors in the development of hormone-refractory and chemotherapy-resistant metastatic prostate cancer growth. We are also discussing the molecular mechanisms that can be targeted in order to achieve, with therapeutic intent, control of the bioavailability of survival factors and, consequently we present the concept of a novel adjuvant anti-survival factor therapy, basically an anti-insulin-like growth factor-1 (anti-IGF-1) therapy, which has provided encouraging preliminary data in the setting of a phase II clinical trial with terminally-ill hormone-refractory/chemotherapy-resistant prostate cancer patients.

Application of the anti-survival factor (ASF) therapy in hormone refractory/chemotherapy resistant prostate cancer

In our institution, the concept of ASF therapy is currently investigated, as an adjuvant therapeutic strategy aiming at the reduction of tumour protection against currently available anti-cancer therapies, in a phase II study. Herein it is important to clarify that ASF therapy is not an anti-cancer therapy per se, but a modality designed to enhance the effectiveness of existing therapeutic regimens. Neutralizing the protection of cancer cells from apoptosis does not activate apoptosis. Therefore, the novel concept of combination therapy shall include ASF therapy plus anti-cancer therapy. Consequently, in our phase II trial, the novel concept of ASF therapy was tested in combination with hormone ablation therapy, employing terminally-ill prostate cancer patients who had progressed to stage D3 while on complete androgen blockade (CAB; GnRH-A plus flutamide) and had failed to respond to salvage chemotherapy.

Our ASF therapy included administration of dexamethasone (4 mg, qD, per os) plus somatostatin analog (somatuline; lanreotide; 30 mg, im, q14D) in combination with hormone ablation therapy [(GnRH-A; triptorelin, 3,75 mg, im, q28D) with or without antiandrogen (flutamide 250, tid, per os) depending whether these stage D3 patients have shown antiandrogen withdrawal syndrome]. The four initial cases of this trial are published, in a form of case series, in the Prostate[11,8]. Up until today, ten (10) patients have entered this trial and have been followed up for more than 4 months. All of them have experienced an objective clinical response; two (2) have experienced a complete clinical response, as assessed by the normalization of PSA values within 2-3 months (PSA < 4.0 ng/ml) followed by a remarkable improvement of their performance status. This has been lasting for up to 6 and 9 months, respectively. Four others have experienced partial response, as documented by decreasing PSA values below 50% while they have experienced a definite improvement of performance status. Unfortunately, one of them presented with local disease progression, namely bladder invasion and obstruction of the ureters. The patient refused any surgical intervention/ hospitalization and passed away, after 9 months of ASF therapy (renal failure). The other three patients with partial responses continue to experience an improved performance status, without disease progression, after 4, 6 and 8 months, respectively, on ASF.

The remaining 4 patients who received ASF therapy in combination with hormone ablation, have experienced a stable response as documented by decreasing PSA to less than 50% of their initial values while have improved their performance status. One (1) of them, while on stable response, has suddenly passed away (no autopsy was performed) while the other three patients with stable responses have been followed from 6 up to 8 months. Herein, we present the PSA responses of two such patients, receiving ASF therapy in combination with hormone ablation therapy. The median survival of hormone refractory patients, even if there is an initial response to salvage chemotherapy, is 12 months[1, 2]. Therefore, the ability of ASF therapy to produce clinical responses, some of them extraordinary, in patients who had progressed to stage D3 and had failed salvage chemotherapy is very encouraging. In addition, we neither observed nor expected the ASF therapy to cause severe side effects in these patients. The objective clinical response, which was sustained for more than 6 months, re-introducing practically clinical response to hormone ablation therapy in terminally-ill stage D3 patients, is quite remarkable. Conceivably, this novel concept of combination therapy using ASF therapy and hormone ablation therapy is of clinical significance. We believe that these data call for the testing of this therapy with regards to efficacy, efficiency and quality of life, in comparison to salvage chemotherapy, early on at progression to stage D3, through a randomized clinical trial.

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