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New Treatment Strategies in the Management of Hormone Refractory Prostate Cancer (HRPC): Only Chemotherapy?

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1. Introduction

Prostate cancer progression to androgen ablation refractory stage D3 corresponds to cancer cell escape from androgen withdrawal-induced apoptosis. In this development, enhancement of growth factor stimulation has an essential role in the up-regulation of survival signals and constitutive proliferation [1]. The mainstay of treatment for metastatic prostate cancer is androgen deprivation. Unfortunately, most of men become resistant to hormonal manipulation, developing what is defined as hormone-refractory prostate cancer (HRPC). A decade ago, most clinicians were reluctant to refer these patients for chemotherapy, which was considered to be ineffective and associated with unacceptable toxicity. A review of 26 chemotherapy-based trials revealed an overall response rate of 8.7% with a median survival ranging from 6 to 10 mo [2]. For this reason, it was established that a median expected survival for patients with HRPC is 10 mo.

Therefore, novel therapeutic strategies that target the molecular basis of androgen resistance were required.

The aim of this editorial is to underline two possible strategies: the first, specifically targeted to the role of the neuroendocrine (NE) system in hormone-refractory stage development, and the second, chemotherapy, not target specific and only cytotoxic.

2. NE activity in HRPC: a possible new target

In recent years a marked increase in the number of publications related to NE differentiation in prostate adenocarcinomas has occurred. At least a focal NE differentiation is present in almost all conventional prostate adenocarcinomas. NE activity is considered one of the factors involved in the progression from an androgen-dependent to an androgen-independent state. The NE component of prostate adenocarcinoma is androgen independent and does not produce prostate-specific antigen (PSA). The continuous use of androgen-ablation therapy may produce hyperactivation of the NE system in prostate tissue [3]. NE system products can act as immortalising factors, blocking the apoptotic process in prostate adenocarcinoma cells and then inducing androgen-independent status and progression. Chromogranin A (CgA) is considered the best marker of NE activity in the prostate. In different countries CgA determination started to be used and to be repeated in clinical practice for the evaluation of men with prostate adenocarcinoma.

Several clinical trials have demonstrated impressive efficacy of somatostatin analogues for various hypersecretory disorders resistant to standard therapy. They have also proved useful for the management of symptoms caused by NE diseases. The primary effect of somatostatin analogues is not a direct cytotoxic effect on NE cells, but rather inhibition of the release of peptide hormones

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secreted by NE cells. Clinical trials on somatostatin analogues as monotherapy for prostate cancer have shown negative results [4]. The mechanism of action of these drugs may suggest their use not as monotherapy but rather as combination therapy for prostate cancer. Koutsilieris et al [5] first proposed a combination therapy with dexamethasone and somatostatin analogues in HRPC. The author combined standard luteinising hormone-releasing hormone (LHRH) analogue therapy with somatostatin analogue and dexamethasone. Median overall survival reported in this study was 12 mo, with improvement in performance status and bone pain scores. Di Silverio and Sciarra [6] analysed whether the combination of ethinyloestradiol and lanreotide can offer objective response or symptomatic improvement in patients with D3 prostate cancer. Patients with metastatic HRPC discontinued LHRH analogue and started the combination therapy. The rationale for this combination therapy is: (1) to inhibit the protective antiapoptotic effect of NE system on prostate adenocarcinoma cells (somatostatin analogue); (2) to use a new mechanism of castration (oestrogens); and (3) to add a direct cytotoxic effect on prostate cells (oestrogens). No major related side-effects were reported (gynaecomastia and breast pain). In this phase 2 trial, 95% of cases showed an objective clinical response as demonstrated by at least a 50% PSA decrease from baseline; in all cases the PSA response was accompanied by a significant improvement in Eastern Cooperative Oncology Group (ECOG) performance status and bone pain score; 70% of cases were without disease progression at a median of 16.5 mo of follow-up during therapy. These results suggest the need for a phase 3 trial to confirm the effectiveness of this combination therapy in HRPC.

3. Actual role of chemotherapy in HRPC

In 2004, two pivotal trials of docetaxel-based chemotherapy were reported and, for the first time, a survival benefit was observed for chemotherapy in HRPC. The results from the Southwest Oncology Group (SWOG) 99-16 and TAX 327 studies changed the expectations of treatment outcome in these patients [7,8]. Also these trials demonstrated the need for combination therapies in patients with HRPC. The combination of docetaxel with estramustine increases the thromboembolic risk and necessitates a primary prophylaxis [7,8]. New combination models using docetaxel may represent an exciting investigational field [9]. In particular, less toxic regimens, provided that the activity can be maintained, are more attractive.

Recently, Di Lorenzo et al [9] presented an interesting proposal using a combination of docetaxel, vinorelbine, and zoledronic acid as first-line treatment in patients with HRPC. Vinorelbine is a vinca alkaloid that inhibits the microtubular apparatus in malignant cells and has shown activity in HRPC [9]. The synergism of docetaxel and vinorelbine has been confirmed in preclinical studies and human trials [9]. Moreover, the use of docetaxel in a weekly schedule appears to minimise myelosuppression and has been associated with moderate toxicity [9].

Most HRPC develops bone metastases that are responsible for pain and morbility. Bisphosphonates showed an inhibitory effect on prostate cancer bone metastases by blocking proteolytic activity of the matrix, cell adhesion, and possibly cancer cell growth [9]. Multicentric randomised trials of HRPC with bone metastases showed a significant reduction in skeletal-related events using zoledronic acid [10].

Di Lorenzo et al [9] developed a phase 2 study to evaluate the impact of weekly docetaxel and vinorelbine and monthly zoledronic acid on PSA response, pain improvement, and toxicity profile in 40 men with HRPC. Complete and partial response (PSA reduction) were observed in 18% and 32% of cases, respectively. An objective response (liver, lung, and lymph nodes) was observed in 6 of 15 patients with measurable disease. Stratifying the response in terms of Gleason score, primary treatment, and number of osseous sites, no differences were observed among these groups. No toxic death occurred and the most important grade 3 toxicities included neutropenia (25%). Pain improvement was found in 47.5% of cases. Median progression-free survival was 7 mo, with a median overall survival of 17 mo. The majority of patients received, after progression, a second line of chemotherapy.

The rationale to improve docetaxel efficacy and to reduce the related toxicity using a combination with vinorelbine and zoledronic acid is of great interest. Results in terms of percentage of responding cases and progression-free and overall survival seem to be not different from those obtained using other proposed combination therapies. Multicentric trials with larger populations and phase 3 studies comparing this treatment hypothesis with other strategies are necessary.

4. Conclusion

The management of metastatic neoplasm has traditionally relied on therapeutic modalities, which almost exclusively aim at directly inducing cancer

cell death. However, the in vivo response of malignant cells to anticancer therapies is directly influenced by the local microenvironment in which they reside. Microenvironment factors may attenuate the antitumour activity of several cytotoxic agents on neoplastic cells. In particular, organ sites frequently involved in metastatic advanced disease appear to confer on neoplastic cells protection from anticancer drug-induced apoptosis. Additional emphasis should be placed on the design of novel treatments that can neutralise the protection that the microenvironment and survival factors offer to tumour cells. This neutralisation alone may not induce apoptosis but it can enhance the sensitivity or reverse the resistance of tumour cells to other anticancer strategies with direct cytotoxic effects. The development of therapies targeting NE activity in HRPC progression is an exciting field. The cytotoxic effect of chemotherapy is not target specific and alone does not guarantee a positive efficacy–toxicity profile; it absolutely needs to be supported by other agents, specific to the HRPC cell target.

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