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Management of androgen-ablation refractory prostate cancer. Role for somatostatin analogues?

Abstract

Patients with metastasised prostate cancer survive longer with anti-androgen therapy but eventually all progress into the androgen-ablation refractory (AAR) stage and die. There are only few effective strategies to treat patients with AAR cancers and they include even more effective androgen blockade by for example glucocorticoids or ketoconazole. Some of the tumours differentiate into neuroendocrine tumours and become completely independent of androgen stimulation. It is believed that these tumours over-express somatostatin receptors which may be a new target for the anti-tumour treatment. In this article we present a patient with advanced AAR prostate cancer and intractable retching and vomiting. As the last resort, he was treated with octreotide SC which resulted rapid amelioration of the symptoms and in significantly decreased PSA which could be translated into longer survival. In this article we review rationale for the use of somatostatin analogues in the treatment of patients with hormone-refractory prostate cancer.

Key words: prostate cancer, hormone-refractory prostate cancer, somatostatin analogues, octreotide, lanreotide, vomiting, retching

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Introduction

Despite annual decrease in incidence, prostate cancer is still one of the main causes of cancer related death in the western world [1, 2]. Screening and early detection managed to reduce mortality slightly down, but in many cases lead to overtreatment and loss of quality of life [3, 4]. Disease limited to the prostate has a good chance of cure with resection and radiotherapy, but metastatic disease becomes uncontrollable with an inevitable outcome. Androgen deprivation therapy is used as standard to induce apoptosis of malignant cells [1]. However, eventually the tumour cells become hormone refractory, and progress to hormone-refractory or castration-resistant prostate cancer [5, 6]. Most often this stage becomes apparent when there is a rise in prostate specific antigen (PSA) levels despite adequate androgen deprivation [7, 8]. Once this stage has been reached there are few evidence based medical therapies available to the patients. However, some of them are in development, and appear to be promising [9]. Inhibiting the systemic biosynthesis of androgens with ketoconazole in castration resistant prostate cancer by targeting CYP17 is one of the new therapeutic approach since

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this enzyme catalyses two key steroid reactions involving 17alpha-hydroxylase and C(17,20)-lyase in the androgen biosynthesis pathway [10]. Another approach is to administer glucocorticoids which has some clinical advantages [11]. It is intriguing that some of the prostate cancers may completely bypass the androgen pathway and may differentiate to neuroendocrine cancers which over-express, among others somatostatin (SST) receptors [6]. In this article we present a patient with advanced prostate cancer and intractable retching and vomiting who responded to administration of octreotide and lanreotide. We shall discuss our current knowledge and perspectives of the use of somatostatin analogues (SST-As) both in palliation of the symptom as inhibition of the tumour growth.

Case report

An 80-year-old man was diagnosed with metastatic prostatic carcinoma in 2000, previously treated with androgen deprivation and radiotherapy for his metastasis, was admitted to the hospice in October 2009. Although living at home he was known to the hospice because of problems with sweating. He did have bone pain prior to admission. On admission he was suffering from significant pain despite Tramadol 100 mg tds, had minimal intake and a marked degree of dysphagia. He was also retching and vomiting on a regular basis. No nausea except seconds before vomiting. His PSA had risen from 31 in April 2009 to 500 ng/mL. His pain control was improved with a buprenorphine patch 20 μg/h, as well as 5 mg oral morphine PRN of which he used 1–2 doses per day. After trying multiple avenues to control his retching and vomiting with glucocorticosteroids, metoclopramide, levomepromazine, discontinuation of some medications, zinc sulphate supplements, and acupuncture, he was started on SC octreotide 500 μg/24 hours while continuing with low dose dexamethazone, 2 mg od. His vomiting stopped almost immediately and he was able to eat more and became mobile again. He was discharged to home and seen regularly on an outpatient basis. Just before discharge he was swapped to a lanreotide IM injection (Somatuline®depot, 60 mg once per month) and began a gradual improvement with an increase in appetite, weight gain and better pain control. In February 2010 his PSA had come down to 360 ng/mL. However, by April he was deteriorating again and his PSA had risen again, so the lanreotide was discontinued. By May his PSA was 950 ng/mL, and he was suffering again with loss of mobility and increasing pain. In August he was admitted to the hospice with pain and recurrence of retching and vomiting. He was, again started on SC octreotide 500 μg/24 hours which this time resulted in improvement of retching and vomiting after approximately three weeks. Again, he was swapped to lanreotide and could be discharged in October 2010 to home. He was readmitted in November 2010 for terminal care most probably with the fracture of the lumbar vertebrae. His PSA was than 5600 ng/mL. His retching and vomiting was controlled until death.

Discussion

This case obviously brings up the question of what role somatostatin analogues (SM-As) such as octreotide and lanreotide have to play in the management of metastasized prostate cancer.

Rationale

Somatostatin has a wide range of effects within the body, the main one of which is suppression of growth hormone secretion [12]. Apart from this, its receptors are present in most of the body's tissues to some extent, and is said to serve as the body's 'endocrine off switch.' The possibility of somatostatin analogues being used in the treatment of solid tumours has been known for about 20 years [12]. Although more is known now; it would seem that we are not using this therapy to its full advantage. Somatostatin also had been thought to be effective in pain control, as many peripheral nerve endings express SST receptors [13, 14].

Some hormone-refractory prostate cancers differentiate to neuroendocrine tumours [6]. Neuroendocrine cells are present in 40 to 100 percent of patients with hormone-refractory prostate cancer, depending on the study [6]. These neuroendocrine cells over-express express somatostatin receptors available as a treatment target [15].

Background

Somatostatin is known to bind to 5 different hormone receptors, named $sst_{1\text{-}5}$. Additionally there are two variants of sst_2, known as sst_{2A} and sst_{2B}. Apparently, sst_{2A} seems to be the more active form in humans. Somatostatin itself is not clinically useful as it has a very short half life, but the wide range of effects this hormone has highlights its potential for use in a wide range of clinical conditions [15]. The three SST-As currently licensed for use are octreotide, lanreotide and vapreotide. These bind with high affinity to sst_2 and sst_5, with limited affinity for sst_3 [15].

Apart from having a longer half life than the endogenous hormone, they have very mild toxicity profiles, with the main side effects being GI disturbances and altered glucose metabolism [16].

Pre-clinical evidence

One study looking into the regulation of prostate cancer cells by somatostatin activation showed that in specific androgen dependant prostate cancer cell lines all the sst-s are expressed but sst_4 [17]. Using SST-As with various receptor affinities it was found that all the analogues used inhibited cell proliferation but that sst_1 agonists and the bi-specific compounds which were preferential agonists for sst_2/sst_5 (BIM-23244 and lanreotide) showed the greatest inhibition [17]. Although $sst_{1,2,4 \text{ and } 5}$ all lead to a decrease in proliferation, sst_3 can have a pro-apoptotic effect via induction of the tumour suppressor protein p53 [18], as can sst_2 via a different pathway [19].

Apart from inhibiting cell proliferation BIM-23244 and lanreotide also affect the insulin like growth factor (IGF) system by inhibiting autocrine and paracrine hormones such as epidermal growth factor (EGF), interleukin-6 (IL-6) and tumour growth factors (TGFs), IGF I and II, and by altering the secretory profile of the IGF system [15, 17]. This is of clinical significance as these are known as 'survival factors' whose presence encourages the survival and growth of malignant cells. These are particularly important in prostate cancer as micrometastatic loci are encouraged by such survival factors to develop into macrometastasis [15]. According to this study somatostatin acts to decrease the amount of IGF-I by decreasing production in the tumour microenvironment, by inhibiting growth factors (GFs) release from the pituitary, and by decreasing serum insulin levels. There is also evidence to suggest that tumour size may be regulated by a number of effects on the process of neoangiogenesis.

Furthermore, there is some evidence to suggest that SST activation may re-establish contact inhibition prohibiting tumour growth and also reduce adhesion of some cancer cells to the endothelial basement membrane making metastatic development less likely [20].

Interestingly it has also been shown that many patients treated with SST-As will eventually become refractory to treatment due to tachyphylaxis [15]. There are thought to be a number of mechanisms involved in this process including down regulation of some sst receptors (sst_s in particular) after exposure to SST-As [21], selection of SST-negative tumour cell clones, and SST gene mutations, although the evidence for these processes are relatively weak [22].

Clinical evidence

The idea that prostate cancers may differentiate into neuroendocrine tumours that produce paracrine factors with proliferative properties lies at the basis of this concept. Potential mechanisms of antitumor action include suppression of circulating levels of trophic hormones and growth factors. Various tumours have high concentrations of sst receptors which may be used for their clinical detection with Indium-111 -DOTA-lanreotide [23].

Probably the best investigated are the combinations of SST-As with some other hormonal measures. Dexamethasone plus LHRH analogue together with lanreotide produces objective clinical responses in 10 out of 11 patients with AAR prostate cancers. Besides substantial decrease of the PSA marker, patients also reported improvement of bone pain for a median of 13 months and improvement of performance status [24]. In a systematic analysis of 42 trials with 267 AAR prostate cancer patients, SST-As were found to be effective, particularly when combined with estrogens or corticosteroids. The side effects are mild and related to the gastrointestinal tract [25].

Palliative care perspective

This patient described by us suffered of intractable retching and vomiting which responded to SST-As, first octreotide and later lanreotide. This response was maintained in time. When the disease progressed under lanreotide and this drug was discontinued, retching and vomiting reappeared within months, but was again amenable to the treatment, even when the PSA remained unaffected. Prior to the treatment with octreotide, in November 2009, the patient was informed about poor prognosis and nearing end as his condition deteriorated daily. Effect of octreotide was surprising and certainly affected patients' survival and quality of life. It is unclear whether dexamethazone, continuously administered all this time played here any role or not. However, seen the results of the trials [24] it is very well probable that dexamethazone contributed to this effect. It certainly that dexamethazone alone was unable to control retching and vomiting. Interesting is the report that dexamethasone, LHRH analogues and SST-A were able to decrease the bone pain [24]. Our patient, after he started with SST-As was able for many month maintain good analgesia with only

buprenorphine patch 20 μg/h and practically no other pain controlling measures.

Conclusion

SST-A are expensive and not readily available to all palliative care specialists. We think that SST-As may be useful in advanced prostate cancer, not only for control of the symptoms, but also to improve survival and quality of life until death.

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