Lee et al. Int J Cancer Clin Res 2016, 3:071
Volume 3 | Issue 6
ISSN: 2378-3419

International Journal of
Cancer and Clinical Research

Case Report: Open Access

Prolonged Use of Aprepitant in Metastatic Breast Cancer and a Reduction in CA153 Tumour Marker Levels

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Abstract

Nausea and vomiting are common problems in patients with advanced cancer [1]. This case report describes a patient whose refractory nausea and vomiting improved significantly with the use of Aprepitant, a highly selective neurokinin 1 receptor antagonist. This improvement led to prolonged daily administration, during which time no chemotherapy or hormone therapy was administered. CA153 tumour markers were noted to have fallen during administration. In-vitro studies have demonstrated anti-tumour activity of NK-1 receptor antagonists on multi cell lineages. This case report may be a witnessed episode of an anti-tumour effect of Aprepitant.

Keywords

Aprepitant, Breast cancer, Chemotherapy, CA153

Introduction

The neuropeptide substance P (SP) shows a widespread distribution in both the central and peripheral nervous system and it is known that after binding to the neurokinin-1 (NK-1) receptors that SP regulate many biological functions which include emesis, and importantly, a role in cancer progression [2]. NK-1 receptors are overexpressed in tumour cells and SP is known to induce proliferation and migration of tumour cells, as well as stimulate angiogenesis [2]. Therefore, the SP/NK-1 receptor complex is an integral part of the microenvironment of cancer and presents a novel therapeutic target [2-4].

Aprepitant is a selective high-affinity antagonist of human NK-1 receptors and is currently licensed for short-term use in chemotherapy-induced nausea and vomiting [5]. It is not routinely used in the palliative care setting. Aprepitant is an oral medication and standard treatment is three days given as an induction dose on day one and 80mg on days two and three. It is highly effective in improving symptoms of acute chemotherapy-induced nausea and vomiting.

Case Presentation

A 27-year-old female was diagnosed with grade 2 invasive lobular breast carcinoma, initially she underwent left mastectomy and axillary clearance. The carcinoma was HER2 negative and ER positive. Tumour activity was monitored with serial CA153 levels.

Thirteen cycles of adjuvant FEC-T chemotherapy were administered with radiotherapy and Tamoxifen was prescribed. Eighteen months later, she presented with persistent headaches, nausea and vomiting. She was diagnosed with leptomeningeal metastasis and acute obstructive hydrocephalus on magnetic resonance imaging. She had a ventriculo-peritoneal (VP) shunt inserted and underwent further chemotherapy but her prognosis remained poor.

At the time of diagnosis of metastatic disease and VP shunt insertion her CA153 was 68. After ten months treatment comprising thirteen cycles of capecitabine this fell to 24. Despite this reduction her clinical condition continued to deteriorate.

Letrozole and goserelin treatment were started but stopped after two months at the patient's request as she was concerned they were contributing to her nausea. Her performance status was 3 and persistent symptoms of intractable nausea and vomiting led to admission at a specialist palliative unit for symptom control. At the time of admission she could mobilise only with the assistance of two nurses and quickly became bedfast. Her CA153 at the time of admission was 187. She was on no form of chemotherapy or hormone therapy and hadn't been for 4 months due to her performance status and progressive disease.

The patient's nausea and vomiting was refractory to all standard antiemetic therapy therefore it was agreed to trial the use of Aprepitant. Maintenance Aprepitant was administered orally daily providing good control of nausea with no noted side effects of treatment. The patient was given 80 mg daily initially for seven months followed by an increase to 120 mg every third day when nausea and vomiting returned, again with good effect. In this time all other antiemetics, except dexamethasone, were withdrawn.

The patient began on a more stable trajectory. Objectively she was noted by nursing staff to be more lucid and although bedfast, could move around her bed with more ease. Her appetite returned and she had an increased oral intake. The patient was hoisted into a wheel chair on several occasions, visited hospice gardens and she started leg exercises in bed.

Improvement in her clinical condition led to re-checking her CA153 level, which had fallen from 187 to 122 during the first six months of Aprepitant use.

Discussion

Published experimental work does show that substance P and its receptors are expressed in a variety of tumour cells. In vitro

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Citation: Lee M, McCloskey M, Staples S (2016) Prolonged Use of Aprepitant in Metastatic Breast Cancer and a Reduction in CA153 Tumour Marker Levels. Int J Cancer Clin Res 3:071

Received: September 12, 2016: **Accepted:** November 14, 2016: **Published:** November 16, 2016

studies have shown that Aprepitant has demonstrated cell growth inhibition in multiple cell lines including glioma, neuroblastoma, pancreas, larynx, gastric and colon carcinomas [6]. This inhibition on cell growth in all of these cell lines has been shown to act in a concentration-dependent manner [6].

Breast cancer has also been shown to express the NK-1 receptor and in a recently published research article all histology sampled expressed the NK-1 receptor and contained SP [7]. Additionally, it has been demonstrated that NK-1 receptors play a role in the tumour progression and promotion of metastasis in breast cancer [4].

There are currently no clinical trials of Aprepitant use as a possible chemotherapeutic agent but in vitro experimental work supports that NK-1 receptor antagonists could provide a novel chemotherapy agent [8]. However most clinical trials have focused on the antiemetic action of Aprepitant in cancer patients treated with chemotherapy [9].

The efficacy of Aprepitant has not been fully tested in other diseases in which the SP/NK-1 receptor system is involved therefore clinical trials are required to see if this association can be further exploited [9]. Available data does include a clinical trial for moderate to severe depression that found that a dose of aprepitant 300mg/day was safe, well tolerated and with side effects similar to placebo [10]. Furthermore, NK1 antagonismhas been shown to significantly reduce tumour associated oedema and blood brain barrier disruption in an in vivo experimental model of brain tumours [11]. In addition, in this study, this treatment was as effective as the treatment in current clinical use, dexamethasone, therefore supporting the development of therapeutics options which target SP [11].

With the knowledge of the role the SP/NK-1 receptor complex plays in tumour activity, it is possible that this case identifies a witnessed chemotherapeutic benefit from Aprepitant and further opens up the possibility of future research trials to explore this.

There are limitations to this case report. The patient detailed was too unwell to transfer for scan at this point in her ongoing care. Therefore we have relied on the objectivity of the fall in CA153 tumour markers and the subjective observations of experienced medical, nursing and physiotherapy staff providing care. Additionally, the pharmacological dosing here, although appearing inconsistent was a pragmatic response to a previously intractable case of nausea and vomiting. Initially 80 mg was given daily due to the length of time the drug was used for. When nausea returned, 120 mg (ie an induction dose) was given every third day to allow an increase in dose and due to the drug strengths and pack sizes available to the hospice at the time.

We believe that Aprepitant may not only have a role as an antiemetic in palliative care but also has the possibility of being a novel broad spectrum chemotherapeutic agent.

Acknowledgements

The patient gave permission for this report to be published.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agencyin the public, commercial or not-for-profit sectors.

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