Sympathomimetic Amine Therapy Markedly Improves Severe Fatigue That Diminishes Quality of Life in Patients with Cancer – A Case Report

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ABSTRACT

One of the main morbidities of patients with cancer is severe fatigue. It is especially prominent in patients receiving chemotherapy or radiotherapy. Unfortunately, there is not a pharmaceutical agent that has been approved for treatment of cancer related fatigue. There are data that off-label use of dextroamphetamine sulfate has provided marked improvement in the chronic fatigue syndrome. However, the efficacy of this therapy has not been established for treating the severe fatigue of patients with cancer, especially while undergoing chemotherapy, immunotherapy, or radiotherapy. A 64-year-old woman, with stage IV breast cancer, had a good response to a combination of chemotherapy and immunotherapy and hormonal therapy. However, she suffered from incapacitating fatigue. She was treated with a small dosage of dextroamphetamine sulfate while continuing immunotherapy and hormonal therapy and demonstrated a dramatic improvement in her fatigue. She actually claimed her fatigue was completely eradicated and she resumed normal activity, which included a daily 3-mile power walk and 100 push-ups. Dextroamphetamine sulfate is very well tolerated, with no serious long-term risks. This treatment should be considered for patients with cancer related fatigue.

Keywords

Advanced cancer, Cancer related fatigue, Dextroamphetamine sulfate, Dopamine.

Introduction

Lolas Radbruch et al, stated that “80% of cancer patients, and in up to 99% of patients following radio or chemotherapy, complain of severe fatigue” [1]. In a 2017 palliative case update, Eduardo Bruera and Sriram Yennurajalingam stated that for severe fatigue, bed rest and relaxation was the most common treatment recommendation (37%) [2]. In fact, 40% of patients were not offered any recommendations [2].

Unfortunately, there are no pharmaceutically approved medications for the treatment of this fatigue. However, anecdotally, off-label treatment with sympathomimetic amines, e.g., dextroamphetamine sulfate, has been demonstrated to markedly improve the chronic fatigue syndrome [3].

At the 2017 International Conference on Palliative Care & Hospice Nursing, held in Philadelphia, PA, Check, DL et al., presented data on a prospective study of the efficacy of dextroamphetamine sulfate therapy in treating unexplained chronic fatigue syndrome. A questionnaire was completed by patients 6 months from initiation of therapy (9.4 mg. to maximum of 37.6 mg dextroamphetamine sulfate), which asked was their chronic fatigue: 1) worse, 2) stable but no better, 3) slightly better, 4) moderately better, or 5) markedly better? There were 48 of 50 (96%) responding markedly better, and 2 of 50 (4%) moderately better [4].

Dextroamphetamine sulfate is included in a group of pharmacologic agents known as psychostimulants. These drugs include methylphenidate, pemoline, modafinil, armodafinil, along with dextroamphetamine sulfate. There had been 6 randomized clinical controlled (RCT's) studies evaluating methylphenidate and 1 evaluating modafinil in patients with cancer suffering from severe fatigue [5-7]. Only one study showed some benefit, in women, who completed chemotherapy for breast or ovarian cancer

[5]. Another large randomized controlled study did not find any improvement over placebo using a long-acting methylphenidate preparation [8].

Modafinil is a centrally acting non-amphetamine central nervous stimulant and has a different mechanism of action than amphetamines. The exact mechanism is not known. However, a large randomized controlled trial of 850 patients receiving chemotherapy, evaluated modafinil for cancer related fatigue, but failed to show significant differences compared to placebo [7]. Nevertheless, there are some data to suggest that patients with cancer complaining of severe fatigue, may benefit from these drugs [5-8].

Over the 40 years of treating non-cancer patients with symptoms of the increased cellular permeability syndrome, which frequently includes chronic fatigue syndrome, we have experienced patients taking methylphenidate for attention deficit disorder (ADD), yet suffering from one of the many manifestations of this disorder, besides ADD, who have demonstrated dramatic improvement when treated with dextroamphetamine sulfate [9-11]. Based on our very positive experience in treating chronic fatigue syndrome, not related to cancer or chemotherapy, despite the less than enthusiastic data from RCT's involving other psychostimulants, we treated a woman who developed extremely severe fatigue following chemotherapy for breast cancer, with dextroamphetamine sulfate [3,4].

Case Report

A 64-year-old woman was diagnosed with stage IV breast cancer. There was extensive involvement of the chest, abdomen, and pelvis. The primary tumor was quite large filling the entire left breast, and extended posterior to the chest wall. The tumor invaded the chest wall, including the sternum. There was significant metastatic disease in the liver, and extensive lymph node involvement of tumor throughout the entire chest, the upper abdomen and retroperitoneum, with extension to the left pelvis as determined by PET/CT.

The biopsy found the tumor to be estrogen receptor positive, progesterone receptor negative, and was HER2 positive. She was treated with docetaxel, paraplirin and trastuzumab.

The patient, despite having extensive stage IV breast cancer, denied significant fatigue before her diagnosis. Her profound fatigue and edema developed after her second infusion of chemotherapy/immunotherapy, two months after her initial diagnosis. The fatigue progressively worsened with each chemotherapy infusion, with no improvement between infusions. She was forced to lead a very sedentary life, with limited daily activity. Two months from last chemotherapy her fatigue did not abate. She remained on immunotherapy (trastuzumab and pertuzumab) and hormonal therapy (letrozole). Her PET/CT 4 months after chemotherapy and immunotherapy showed a dramatic response. The hyper-metabolism within the left breast, lower neck, axilla, chest, abdomen, and pelvis had mostly resolved. However, her fatigue remained incapacitating.

She was then started on 10 mg immediate release amphetamine salt tablets (6.2 mg dextroamphetamine sulfate), once daily, for the first week followed by twice daily (upon arising and noon). She was rewarded within 2 weeks of treatment with a marked increase in energy, and dissipation of marked edema that had persisted after chemotherapy. In fact, now after three months of treatment with dextroamphetamine sulfate, she states that she has no fatigue, as evidenced by full resumption of daily activities, including a 3-mile power walk and 100 push-ups per day. Though a side effect of pertuzumab can be fatigue, her fatigue markedly improved following dextroamphetamine therapy despite her continuance of pertuzumab.

One of the other complications from her cancer therapy that this patient had was marked edema, which is known to be a manifestation of the increased cellular permeability syndrome [10]. In fact, because edema was so common in the increased cellular permeability syndrome, previously the condition was named the sympathetic neural hyperalgesia edema syndrome [11,12]. The edema was believed to be related to insufficient release of dopamine at the capillary level, which would increase capillary permeability, especially related to the increase in hydrostatic pressure in the sitting or standing position [12]. The increased capillary permeability allows fluid to move from intracellular to extracellular space causing edema [10-12]. Dextroamphetamine amine sulfate was found to be far more effective in reducing edema, and subsequent weight gain, than diuretic therapy [12].

Discussion

The theoretical mechanism of action of dextroamphetamine sulfate, in improving fatigue, is by releasing dopamine from sympathetic nerve fibers, which in turn, corrects a permeability defect in the muscle mitochondrial [9-11]. According to the hypothesis, the fatigue was related to infusion of unwanted chemicals into muscle mitochondria, leading to dysfunction [9-11]. The defect may also cause smooth muscle dysfunction, leading to gastrointestinal muscle disorders, or urinary incontinence which has also responded to dextroamphetamine sulfate therapy [13-16].

Dextroamphetamine sulfate has also been used to treat bone pain, resulting from treating estrogen receptor positive breast cancer with aromatase inhibitors [15].

Based on dramatic improvement in fatigue demonstrated by the patient reported here, it is hoped that a large prospective study could be initiated, similar to the study performed on unexplained chronic fatigue syndrome, in patients with a variety of cancers and treatments [4].

There is little question that treatment with dextroamphetamine sulfate markedly improved this patient with extreme fatigue following therapy, to a state of no fatigue, whatsoever, in a very short time. This indicates that dextroamphetamine sulfate can improve cancer or chemotherapy related fatigue, in some circumstances. However, only a large controlled trial can demonstrate how effective is it in a large number of patients with cancer. Was the

benefit demonstrated the exception, rather than the rule? Other questions need to be answered include: will it prove effective for just certain types of cancer, or certain types of chemotherapy?

One thing is clear from this case report and the previous RCTs using other psychostimulants (that were not especially effective); any future RCTs should use dextroamphetamine, to evaluate its efficacy for treating cancer related severe fatigue [1-8].

Since the chemotherapy seemed to cause not only fatigue, but also marked edema, and both responded to dextroamphetamine treatment, perhaps the mechanism of how chemotherapy causes fatigue may be by inducing changes in sympathetic tone causing insufficient dopamine release. This could explain other manifestations of complications following anticancer therapy, e.g., fibromyalgia, that may be associated with aromatase inhibitors [17,18].

The majority of patients with advanced cancers will not be cured. Thus, treatment considerations should be focused on palliation. One of the major morbidities of current treatments is extreme fatigue, precluding a functional life while they are still alive. Dextroamphetamine sulfate treatment should be considered for patients with advanced cancers suffering from severe fatigue, even before a large prospective study confirms the finding of this anecdotal report. Thus, dextroamphetamine sulfate, which is extremely well tolerated, without serious immediate, or long-term risks, should be considered for patients experiencing cancer related fatigue.

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