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SHORT REPORT

Melatonin, a Promising Role in Taxane-Related Neuropathy

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Abstract

Purpose: Melatonin has neuroprotective effects in animal studies and has been suggested to decrease adverse reactions of chemotherapy including neuropathy. This pilot trial aimed at assessing whether melatonin, given during taxane chemotherapy for breast cancer, will decrease the incidence and/or severity of neuropathy.

Methods: Twenty two consecutive patients beginning chemotherapy for breast cancer with paclitaxel, or docetaxel were enrolled. Patients received melatonin 21 mg daily at bedtime. Incidence and severity of neuropathy were assessed using neurological examinations, toxicity assessment per NCI-CTC 3.0 scale and FACT-Taxane quality of life questionnaire.

Results: Neuropathy was seen in 45% (n = 10) of patients, 23% (n = 6) grade 1 and 22% (n = 5) Grade 2 neuropathy. No grade 3 neuropathies were reported. The majority (55%) of all patients reported no neuropathy. Compliance with melatonin (>60% of dose) was seen in most patients (86%) No patient reported daytime sedation. The median FACT-Taxane quality of life end of study score was 137, with only a 0.5 median decline from baseline**.**

Conclusion: Patients receiving melatonin during taxane chemotherapy had a reduced incidence of neuropathy. Melatonin may be useful in the prevention or reduction of taxane-induced neuropathy and in maintaining quality of life. Larger trials are warranted to further explore the role of melatonin in neuropathy treatment and prevention.

Keywords: neuropathy, taxane, melatonin, quality of life

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Introduction

Taxane-related neuropathy remains a challenging clinical problem causing treatment delays and worsening of quality of life. Taxane-based cytotoxic chemotherapeutic agents are among the most potent agents for the treatment of a variety of types of cancers including breast, lung, and ovarian cancers.[1,2] Taxanes are standard components of many therapeutic regimens in both early stage and metastatic breast cancer. These medications, by inhibiting microtubules, are known to cause neurotoxicity which can decrease the quality of life in many patients and may necessitate discontinuation of chemotherapy.[3–7]

The high incidence of toxic neuropathy is a significant limiting factor in patients receiving taxanes. Agents that could reduce the incidence or severity of taxane related neurotoxicities are urgently needed. Multiple medications have been evaluated for that purpose.[8,10,11] However, no therapy has been consistently successful and there is no current approved medication to prevent neuropathy or decrease its severity in this setting.

Melatonin, a pineal hormone has been suggested to exert a neuroprotective effect in preclinical and clinical studies.[12–15] At this time it is not clear if melatonin is effective in the reduction of the incidence or severity of taxane-induced neuropathy. In this study, we aim to assess the effect of melatonin on taxane-induced neuropathy in consecutive patients diagnosed with breast cancer at a single University affiliated cancer. We plan to determine whether melatonin given during taxane chemotherapy may decrease the incidence of neuropathy.

Patients and Methods

Design

This is an open label, phase II pilot study using melatonin to evaluate its effect on preventing neuropathy or decreasing its severity in breast cancer patients initiating taxane chemotherapy with standard paclitaxel, albumin bound paclitaxel, or docetaxel. The study was approved by the local review board and each patient signed an informed consent form prior to her enrolment.

Patients' demographics and study characteristics

Women with biopsy-proven breast cancer were recruited from three breast oncology clinics at a University affiliated cancer center after being scheduled for treatment with paclitaxel, nab-paclitaxel, or docetaxel for early stage or advanced breast cancer. Patients with known preexisting neuropathy, or history of exposure to drugs known to cause neuropathy including taxanes were excluded. No concurrent treatment with other therapy for neuropathy was allowed during protocol treatment. Twelve patients (54%) have received previous non- taxane chemotherapy. The treatments received were as follows: twenty (90%) patients received paclitaxel with a median dose of 750 mg/m^2 delivered (range 450–1350 mg/m^2). The majority (54%) received paclitaxel on a weekly schedule and 36% on an every 2 or 3weeks schedule. Two patients (9%) received docetaxel at the standard dose of 75 mg/m^2 given every 3 weeks for 6 doses. The median length of taxane treatment was 52.5 days (range 21–105 days). Patients with nonmetastatic breast cancer received surgery and radiation therapy per standard clinical practices.

On the first day of chemotherapy every participant received one batch containing a supply of melatonin 3 mg tablets for 28 days. Participants were asked to take 7 tablets (21 mg) daily at bedtime. Patients were asked to return their bottles of melatonin to assess compliance every 28 days. Melatonin was given for the duration of taxane chemotherapy in the adjuvant, neoadjuvant setting or metastatic setting. Once taxane chemotherapy was discontinued, patients continued to take melatonin for an additional 28 days. Final evaluation was done 28 days after discontinuation of taxane or 6 months after initiation of melatonin if the patient continues taxane chemotherapy for longer than 6 months.

Evaluation of neurotoxicity

Prior to the initiation of the first chemotherapeutic cycle, each participant underwent a complete neurological examination and a neuropathy evaluation per National Cancer Institute's Common Toxicity Criteria (NCI-CTC) 3.0 scale. According to the NCI-CTC, peripheral neuropathy may be graded on a scale of 1 to 5.[17] A grade of 1 indicates asymptomatic chemotherapy induced peripheral neuropathy (CIPN), 2 indicates symptomatic CIPN, 3 denotes CIPN that interferes with activities of daily living (ADL), 4 signifies disabling CIPN, and 5 indicates death. The patients also completed a Functional Assessment of Chronic Illness Therapy (FACT) -Taxane quality

Table 1. FACT-Taxane (Version 4): detailed questionnaire and scoring system. Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
Physical well-being						
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
Social/family well-being						
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section					
GS7	I am satisfied with my sex life	0	1	2	3	4
Emotional well-being						
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
Functional well-being						
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4
Additional concerns						
NTX1	I have numbness or tingling in my hands	0	1	2	3	4
NTX2	I have numbness or tingling in my feet	0	1	2	3	4
NTX3	I feel discomfort in my hands	0	1	2	3	4
NTX4	I feel discomfort in my feet	0	1	2	3	4
NTX5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX6	I have trouble hearing	0	1	2	3	4
NTX7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX8	I have trouble buttoning buttons	0	1	2	3	4

(*Continued*)

Table 1. (*Continued*)

		Not at all	A little bit	Some-what	Quite a bit	Very much
NTX9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
Tax1	I feel bloated	0	1	2	3	4
Tax2	My hands are swollen	0	1	2	3	4
Tax3	My legs or feet are swollen	0	1	2	3	4
Tax4	I have pain in my fingertips	0	1	2	3	4
Tax5	I am bothered by the way my hands or nails look	0	1	2	3	4

of life assessment questionnaire (Table 1). The participants were clinically re-evaluated at 28 days interval while receiving taxane chemotherapy. They underwent complete neurological examinations and were assessed per NCI-CTC 3.0 scale for neuropathy by answering specific questions regarding the presence of tingling, numbness, pain, muscle weakness and motor activities. Four weeks after completion or discontinuation of taxane or 6 months after initiation of melatonin (if the patient continues taxane chemotherapy for longer than 6 months), they underwent a final neurological examination, a final assessment of the incidence and severity of neuropathy using the NCI-CTC 3.0 scale for neuropathy, and completed the FACT-Taxane quality of life assessment questionnaire.

Statistical design and analysis

The primary objective was to assess taxane-related neuropathy (any grade) in patients receiving melatonin during taxane chemotherapy and compare it with hitstorical controls. The trial was designed to be conducted as a pilot study, intended to detect a trend in favor of melatonin supplementation, that would justify its expansion to a subsequent placebo controlled randomized trial. Descriptive statistics are reported. The incidence of neuropathy, severity of neuropathy, and changes in quality of life were assessed using neurological examinations, NCI-CTC 3.0 scale for neuropathy, and FACT-Taxane questionnaire, conducted by the treating oncologists and verified by the P.I (neurological examinations) and investigators on the trial (NCIC-CTC 3.0 scale, and FACT-Taxane questionnaires). The FACT-Taxane Scoring Guidelines were obtained based on the scoring and administration procedures outlined in the FACT manual.[18]

Results

Twenty three consecutive patients were recruited; one patient declined participation. Twenty—two patients were suitable for final analysis as shown in Table 2. The mean age was 49 years (range 33–68 years). The stages were distributed as follows: Stage IIA: 4 (18%); stage IIB: 3 (14%); stage IIIA: 5 (23%); stage IIIB: 4 (18%); stage IIIC: 2 (9%); and stage IV: 4 (18%). Neuropathy (all grade) was seen in 46%(n = 10) of all patients (Table 3). No patient developed Grade 3 or 4 neuropathy per NCI-CTC 3.0; 27% (n = 5) had grade 1 and 23% (n = 5) had grade 2 neuropathies. Fifty five percent of all patients (n = 11) reported no neuropathy (Grade 0). Other severe adverse events were reported as follows: 3 patients had grade 3 nausea or vomiting, and one patient had grade 3 fatigue. Two patients withdrew from the study due to grade 3 nausea and progressive disease, respectively. Compliance with melatonin (>60% of dose) was seen in the majority of patients (86%). Two patients reported nighttime sedation. No patient reported daytime sedation.

Table 2. Patient characteristics.

Characteristics	Result
No. of patients (%)	22 (100)
Mean age, years	49
Race	
White	20 (90)
African American	1 (5)
Asian	1 (5)
Stages	
II	7 (32)
III	11 (50)
IV	4 (18)
Taxane	
Paclitaxel	20 (91)
Docetaxel	2 (9)

Table 3. Neurotoxicity grading as per NCI-CTC 3.0.

Symptom	No. of patients (%)
Neurotoxicity (any grade)	10 (46)
Grade 1	5 (23)
Grade 2	5 (23)
Grade 3 or more	0 (0)

All patients completed baseline FACT-Taxane quality of life questionnaire but only 11 patients completed the final (post-treatment) one. The median baseline score was 137 in the whole group and 137.5 in those who completed both surveys. The median end of study score was 137, with only a 0.5 median decline from baseline, indicating no significant change in quality of life overall. Among patients who completed both questionnaires, most patients reported some symptoms attributed to neuropathy like numbness or tingling in hands or feet, discomfort in hands or feet, joint pain or muscle cramps, trouble buttoning or feeling the shape of small objects , pain in fingertips or walking but less than 40% of all patients reported those symptoms as severe (Table 4).

Discussion

Taxane-related neuropathy remains a challenging clinical problem; it occurs 24–72 hours after administration of taxanes, but may occur at different times during chemotherapy courses, and it may be irreversible. Patients are at increased risk if they have received previous neurotoxic drugs. The mechanism of taxane induced neuropathy is thought to be due to aggregation of intracellular microtubules in neuronal cells. It is also thought that taxanes cause intrinsic toxicity and injury to cells. However, the exact mechanism of neurotoxicity is not known at this time.[1,2] Types of neuropathy caused by taxanes include peripheral neuropathy, motor weakness, myalgias, and arthralgias. About 60%–90% of patients receiving taxanes develop mild-moderate neuropathy[3–7] and a many as 30% of treated patients will develop a disabling sensory neuropathy.[5]

The reported incidence of neurotoxicity with these agents varies depending on patient characteristics, chemotherapy regimen, dose of chemotherapy, and administration method. At doses used in patients receiving adjuvant treatment for breast cancer, up to 90% of

Table 4. FACT-Taxane (Neuropathy-related).

Symptom	Final n = 11 (100%)
Numbness or tingling in hands	
Little bit/somewhat (Mild 1/2)	2 (18)
Quite a bit/very much (Severe 3/4)	4 (36)
Numbness or tingling in feet	
Little bit/somewhat (1/2)	2 (7)
Quite a bit/very much (3/4)	3 (27)
Discomfort in hands	
Little bit/somewhat (1/2)	0
Quite a bit/very much (3/4)	5 (46)
Discomfort in feet	
Little bit/somewhat (1/2)	1 (10)
Quite a bit/very much (3/4)	4 (36)
Joint pain or muscle cramps	
Little bit/somewhat (1/2)	6 (55)
Quite a bit/very much (3/4)	1 (10)
Feels weak all over	
Little bit/somewhat (1/2)	6 (55)
Quite a bit/very much (3/4)	1 (10)
Trouble hearing	
Little bit/somewhat (1/2)	1 (10)
Quite a bit/very much (3/4)	0
Ringing or buzzing in ears	
Little bit/somewhat (1/2)	4 (36)
Quite a bit/very much (3/4)	0
Trouble buttoning buttons	
Little bit/somewhat (1/2)	0
Quite a bit/very much (3/4)	4 (36)
Trouble feeling shape of small objects	
Little bit/somewhat (1/2)	2 (18)
Quite a bit/very much (3/4)	1 (10)
Trouble walking	
Little bit/somewhat (1/2)	3 (28)
Quite a bit/very much (3/4)	0
Feel Bloated	
Little bit/somewhat (1/2)	3 (28)
Quite a bit/very much (3/4)	1 (10)
Hands are swollen	
Little bit/somewhat (1/2)	3 (28)
Quite a bit/very much (3/4)	1 (10)
Legs or feet are swollen	
Little bit/somewhat (1/2)	2 (8)
Quite a bit/very much (3/4)	0
Pain in fingertips	
Little bit/somewhat (1/2)	1 (10)
Quite a bit/very much (3/4)	0
Bothered by the way hands or nails look	
Little bit/somewhat (1/2)	4 (36)
Quite a bit/very much (3/4)	1 (10)

patients receiving paclitaxel experience mild-moderate neurotoxicity, around 20% of whom may require chemotherapeutic dose reduction.[3,4] As many as 30% of treated patients will develop a disabling sensory neuropathy.[5] A randomized clinical trial in metastatic breast cancer compared docetaxel and paclitaxel. The incidence of neuropathy was 64% of 222 in patients receiving docetaxel and 59% in those receiving paclitaxel.[6] In other trial Seventy-one percent of 229 patients with metastatic breast cancer receiving paclitaxel protein bound as a single agent experienced neuropathy.[7]

Possible strategies to decrease the incidence of neuropathy include avoiding paclitaxel doses greater than 200 mg/m^2, avoiding cumulative doses greater than or equal to 250 mg/m^2, and giving taxanes as continuous infusions over 24 hours.[8,9] Addition of medications including glutamine, amitriptyline, gabapentin and acetyl-L-carnitine have been evaluated to reduce the incidence of neuropathy.[8,10,11] However, no therapy has been consistently successful. Melatonin decreases peripheral nerve injury and motoneuron loss on melatonin-treated axotomized rats.[12] It was suggested that it exerts a neuroprotective effect that would attenuate the neuropathological changes in the vagal ganglia following a severe hypoxic insult.[13] Clinical studies have evaluated the role of melatonin for counteracting chemotherapy-toxicity, particularly myelosuppression and immunosuppression.[14–16] Melatonin has been found to inhibit the production of free radicals, which play a part in mediating the toxicity of chemotherapy.[14,15] In a pilot study conducted by Lissoni and colleagues,[14] 80 patients with a variety of metastatic solid tumors received chemotherapy with or without melatonin 20 mg daily. Thrombocytopenia, malaise, asthenia, stomatitis, and neuropathy were less frequent in patients treated with melatonin. The effectiveness of chemotherapy was not altered by the addition of melatonin. In another study, 70 patients with non-small cell lung cancer using cisplatin (20 mg/m^2/day intravenously for 3 days) and etoposide 100 mg/m^2/day for 3 days received melatonin 20 mg daily or chemotherapy alone. The frequency of myelosuppression, neuropathy, and cachexia was significantly lower in the melatonin group.[15] Investigators found that the incidence of neuropathy with melatonin was 0/34 patients compared to 5/36 patients who received chemotherapy alone. In addition there was no impact on the effectiveness of the chemotherapy regimen. Tumor response was seen in 10/34 patients receiving melatonin and 6/36 patients receiving chemotherapy alone. The one year survival for patients receiving melatonin was 15/34 compared to 7/36 in chemotherapy alone patients (P = 0.05). Other studies specifically evaluating the myeloprotective effect of melatonin when administered with chemotherapy failed to show decrease in the incidence of neutropenia.[16]

Melatonin has been used safely in previous trials assessing its use in cancer and other patients.[14–16,19–24] In the two trials by Lissoni and colleagues, there were no adverse effects documented that had increased incidence in patients receiving chemotherapy plus melatonin compared to patients receiving chemotherapy alone.[14,15] The frequency of myelosuppression, neuropathy, and cachexia was significantly lower in the melatonin group.[15] In our trial, patients receiving melatonin during taxane chemotherapy had a reduced incidence of all grade neuropathy (46%) compared to historical controls (around 60%). We recognize that this study included a limited number of patients and lacked the power to detect statistically significant differences for the various parameters. However, based on the mere trend of decreased incidence of severe neuropathy and attenuated severity of symptoms, with no major changes in FACT-Taxane quality of life, the possibility that melatonin may be useful in the prevention or reduction of taxane-induced neuropathy and in maintaining quality of life seems likely. Larger trials are warranted to further explore the role of melatonin in taxane-related neuropathy treatment and prevention.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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