Management of Peripheral Neuropathy Induced by Nab-Paclitaxel Treatment for Breast Cancer

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Abstract. Nanoparticle albumin-bound paclitaxel (nab-PTX) is a key drug used in breast cancer treatment which often causes chemotherapy-induced peripheral neuropathy (CIPN). No effective approach for CIPN control has been established to date. This study assessed a new approach to CIPN integrating two concepts: compression therapy using stockings and sleeves, and medication therapy using selected prophylactic drugs, including goshajinkigan, which we named the “3S” approach. Fourteen breast cancer patients were divided into a 3S group (n=7) and a control group (n=7), and were treated with 260 mg/m2 of nab-PTX once every three weeks. CIPN initially developed in five control-group patients and one 3S-group patient (p=0.03). Across all cycles, the CIPN grades, as determined by the Common Terminology Criteria for Adverse Events (CTCAE), were significantly lower in the 3S group than in the control group (p<0.001). The mean nab-PTX dose in the 3S group was 77.1 mg/m2/week versus 64.7 mg/m2/week in the control group (p<0.01). By controlling the development and severity of CIPN, 3S treatment appears to support the use of the recommended nab-PTX dosing for breast cancer patients.

Nanoparticle albumin-bound paclitaxel (nab-PTX) is extensively used worldwide, and has become a key drug used in the chemotherapy for breast cancer (1, 2). However, nab-PTX often has adverse non-hematological effects, including peripheral neuropathy (PN) and joint or muscle pain (3, 4). Nonetheless, no effective prophylactic management has so far been established for nab-PTX or for any other drug which can similarly cause PN in breast cancer patients.

With regard to diabetic neuropathy, reports have related the degree of severity to the peripheral skin perfusion (5, 6). Compression therapy, such as wearing stockings and sleeves, is thought to influence the skin perfusion. Goshajinkigan, a well-known traditional Japanese herbal medicine, exhibits effects in alleviating peripheral sensory disturbance and improving the peripheral blood flow (7-9). To address PN due to nab-PTX during treatment of breast cancer, we have investigated a “3S” prophylactic application of two strategies: compression therapy using stockings and sleeves, and medication therapy using selected prophylactic drugs, including goshajinkigan.

Patients and Methods

Patients and management. Fourteen patients with recurrent, metastatic or locally advanced breast cancer were treated with nab-PTX at a dose of 260 mg/m2 once every three weeks at our Hospital from June 2012 to April 2013. The patients were divided into two groups: a prophylactic treatment group (3S group; n=7) and a control group (n=7). In the 3S group, the patients wore stockings (SLIM WALK®, Pip co,. Ltd, Osaka, Japan) and sleeves (Medical Compression Armsleeves, Okamoto Corporation, Osaka, Japan) for 24 h from the beginning of nab-PTX administration and received selected prophylactic drugs over the course of treatment; including goshajinkigan (herbal medicine, 7.5 g/day, Tsumura & Co., Tokyo, Japan), mecobalamin (1,500 μg/day, Eisai Co. Ltd, Tokyo, Japan) and lafutidine (20 mg/day, Taiho Pharmaceutical Co. Ltd, Tokyo, Japan). The two groups were compared for both the grade of peripheral neuropathy evaluated by the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 standards and by the total administered doses of nab-PTX.

Evaluating the grade of peripheral neuropathy. Regarding our Hospital’s evaluation process, various assessments for side-effects, including the PN grade, were first conducted by the pharmacist and subsequently and independently by the physician. If chemotherapy could be applied, patients proceeded to the Ambulatory Treatment
Center where a third set of tests, including an examination of the PN grade, was conducted by the nurse. For the 3S group, the nurse confirmed the patients’ use of stockings and sleeves prior to chemotherapy. For both groups, the nurse administered nab-PTX with side effect monitoring, after which patients could return home if there were no particular reasons for concern.

Statistical analysis. The p-values for Tables I and II were calculated by the Chi-squared method, and the p-value for Figure 1 was calculated by a two-way ANOVA.

The present trial was approved by the Ethics Committee of Nagasaki Harbor Medical Center City Hospital.

Results

There were no significant differences in the following characteristics between the 3S (prophylactic) and control groups: Age, previous treatment with taxanes and treatment lines (Table I).

Following initial treatment with nab-PTX, peripheral neuropathy appeared in five out of the seven patients in the control group and in only one out of the seven patients in the 3S group \( (p=0.03) \) (Table II). After the fourth cycle of nab-PTX, the average grade of PN in the 3S group was better than that observed in the control group \( (p<0.01) \). When the curves were compared across the four cycles, the PN grades in the 3S group remained significantly lower than the grades in the control group \( (p<0.001) \) (Figure 1). The mean dose of nab-PTX in the 3S group was 77.1 mg/m²/week, which was significantly better than that in the control group \( (64.7 \text{ mg/m²/week, } p=0.017) \).

Discussion

Nab-PTX is widely used in the treatment of breast cancer metastasis and recurrence, as well as for adjuvant therapy and preoperative chemotherapy (10-12). In clinical trial for the metastatic setting, the overall response rate for nab-PTX was 33.2%, which was significantly higher than 18.7% with standard paclitaxel \( (p=0.001) \), and nab-PTX was also associated with a significantly improved overall survival \( (p=0.024) \). With respect to adverse effects, the most frequent side-effect is alopecia, followed by peripheral sensory neuropathy, fatigue and neutropenia. PN is experienced by approximately 70% of all nab-PTX patients and 10% of all nab-PTX patients suffer from PN of Grade 3 or higher, compared to 2% of standard PTX patients (3). As side-effects can result in a reduction of doses or in complete discontinuation of the treatment, methods to control side-effects in order to maintain the recommended dose levels are of critical clinical importance.

The mechanism responsible for the development of PN is considered to be related to the disruptive effects of nab-PTX on microtubules, suggesting that the symptoms are caused by damage to the microtubules in the axons of peripheral nerves (13). Attempts using treatments such as the use of a “frozen glove” have been made based on this consideration.
in order to decrease the drug’s ability to reach the skin (14), but there is currently no generally accepted method for addressing PN (15).

Rather than attempting to eradicate PN by an aggressive counter-measure, our approach targeting the above damage mechanism has instead been to prevent the drug from lingering in peripheral tissue nerves, in other words, to raise the drug clearance. Our results suggest that compression therapy applied through the stockings and sleeves supported the protection of the peripheral nerves. In our view, PN may potentially be inhibited by increasing the arteriole flow to the arteriovenous anastomosis, in order to promote the return to the veins, with minimal flow through the capillaries (Figure 2). While the successful results obtained through use of the stockings and sleeves offer a first step towards understanding the benefits of compression therapy, we believe that research to obtain a deeper understanding of why this approach works is urgently required.

The 3S-treatment concept was applied by integrating two approaches: compression therapy, as explained above, plus medication therapy. Certain Japanese traditional herbal medicines, *i.e.* Kampo medicine, have been reported to be effective as medication therapy for PN. Goshajinkigan is especially noted for its effects in patients treated with paclitaxel/carboplatin or oxaliplatin (7, 16), specifically for relief of numbness and improved blood circulation related to aconite root (8, 9). There have also been reports of vitamin-based drugs being used to treat PN. Lafutidine was included in our chemotherapy treatment to help prevent damage to the gastric mucosa, in addition to its apparent reduction of PN (17). Over the course of our comparative study, the current selection of preventive medications appears to have contributed to an overall decrease of PN symptoms. However, the current selection of drugs may be subject to adjustment over time.

The extent of PN was assessed based on the CTCAE standards for classifying a patient’s subjective symptoms. The pharmacists, doctors and nurses involved in the treatment team each conducted the assessments independently to work towards an accurate understanding of each patient’s symptoms.

In conclusion, 3S treatment appears to be able to control the grade of neuropathy and this approach may prove to be supportive for maintaining the total recommended dose of nab-PTX in breast cancer patients.

**Conflicts of Interest**

The Authors declare that there are no conflicts of interest in association with this study.

**References**


Received April 10, 2014
Revised May 31, 2014
Accepted June 2, 2014