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Peripheral neuropathy from paclitaxel: risk prediction by serum microRNAs

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Received 21 May 2019

Revised 29 October 2019

Accepted 10 November 2019

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To cite: Noda-Narita S, Shimomura A, Tanabe Y, et al. *BMJ Supportive & Palliative Care* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bmjspcare-2019-001900

ABSTRACT

Objectives MicroRNAs (miRNAs) have recently been reported as useful diagnostic markers in cancer; however, relationships of miRNAs with adverse events during chemotherapy have yet to be fully described. In this study, we examined the relationship between serum miRNA and the risk of peripheral neuropathy (PN), a common and persistent adverse event induced by paclitaxel, in patients with breast cancer.

Methods A total of 84 serum samples from patients with breast cancer, who received paclitaxel as neoadjuvant or adjuvant chemotherapy, were obtained between January 2011 and September 2013 at National Cancer Center Hospital. Samples were divided, 2:1, into a training cohort and a test cohort, respectively; both cohorts included specimens from patients with severe PN (≥grade 2, PN group) and non-severe PN controls (non-PN group). The training cohort was used to identify miRNAs, and combinations thereof, that could predict PN, which then were validated in the test cohort.

Results Eighty-four patients received paclitaxel: 38 and 46 patients in the PN and non-PN groups, respectively. We identified 15 discriminatory miRNAs with [fold change]>0.5, and 14 combinations of three miRNAs showed the ability to discriminate, with sensitivity, specificity and accuracy of >50%. The most discriminatory miRNA, with the highest [fold change], was miR-451a, which regulates the expression of the drug-transporter protein P-glycoprotein, potentially promoting paclitaxel resistance.

Conclusion MiR-451a could be a predictive marker for PN caused by paclitaxel-containing chemotherapy; however, further investigation of the underlying mechanism is required to determine the role of miR-451a.

INTRODUCTION

Despite advances in systemic chemotherapy and prognosis of breast cancer,

difficulties in controlling adverse events remain. Peripheral neuropathy (PN) induced by paclitaxel is a severe complaint among patients receiving neoadjuvant and adjuvant chemotherapy and often persists for decades after the treatment; however, medication to treat PN is limited, with only duloxetine having moderate evidence for recommendation in an American Society of Clinical Oncology (ASCO) guideline.¹ Although surgical gloves and cold therapy have recently been reported to prevent PN,^{2,3} there are only a few known risk factors for the development of this condition, including age ≥60 years and obesity,^{4–6} and it is difficult to select the patients appropriate to receive these preventive measures.

Serum microRNAs (miRNAs) have recently been reported as useful markers for detecting cancers, with specific combinations of miRNAs effective for detection of early breast cancer.^{7,8} Analysis of miRNA expression levels, both in vitro and in vivo, has identified roles for specific miRNAs in drug resistance and metabolism of anticancer drugs^{9–12}; however, the relationship between miRNAs and adverse events during chemotherapy has yet to be fully investigated, and research for predictive miRNA markers associated with adverse events has just begun to be reported.^{13,14} Those previous studies often suggested potential efficacy of miRNAs grounded on basic research, and only a few of them reported the relationship using patients' samples. As for PN, there were no studies reporting predictive miRNA markers both in basic and preclinical study.

In this study, we estimated the expression of serum miRNAs in patients with breast cancer receiving paclitaxel and examined the relationship between

miRNAs and risk of PN. This is the first study to report the potential efficacy of miRNAs for prediction of PN related to chemotherapy.

PATIENTS AND METHODS

Patients

Eighty-four serum samples were collected from patients with breast cancer before they received paclitaxel as neoadjuvant or adjuvant chemotherapy, between January 2011 and September 2013 in the National Cancer Center Hospital (NCCH), Tokyo, Japan. Patients who had consented to receive detailed medical examination for PN of each extremity in this period were enrolled in the study. We could not estimate the adequate sample size to distinguish the difference of miRNA expression before establishing the study design because the sample collection was retrospectively conducted after the assessment of PN of those patients.

PN was assessed by two physicians in our hospital, according to the Common Terminology Criteria for Adverse Events V.4.0, to confirm the grading. Patients with PN of $\geq$ grade 2 were classified as the severe PN group, and patients without severe PN (grade 0 or 1) were classified as the non-severe PN group (non-PN group). Other clinical data were reviewed manually from electronic medical records. The following data were collected: patient characteristics, including date of birth, sex and Eastern Cooperative Oncology Group performance status at the time of starting the chemotherapy; and characteristics of the primary tumour, including oestrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2) status. ER, PgR and HER2 status were assigned according to the 2010 and 2013 ASCO recommendations and the College of American Pathologists guidelines on the basis of diagnosis by a local pathologist. Treatment regimens were also reviewed and included a combination of HER2-targeted therapy and endocrine regimens. The dates of the first course of chemotherapy, dose reduction and discontinuation of paclitaxel were also recorded.

Analysis of miRNA expression

Serum samples from each patient were stored at -20°C , and total RNA was extracted from a 300 μL aliquot using 3D-Gene RNA Extraction Reagent from a liquid sample kit (Toray Industries, Kanagawa, Japan). Comprehensive miRNA expression analysis was performed using a 3D-Gene miRNA Labeling kit and a 3D-Gene Human miRNA Oligo Chip (Toray Industries), which was designed to detect 2540 miRNA sequences registered in miRBase release 21 (<http://www.mirbase.org/>).

MiRNA was considered to be present if the corresponding microarray signal was more than the (mean $+2 \times \text{SD}$) signal of negative controls, from which the top and bottom 5%, ranked by signal intensity, were

removed. For miRNAs considered present, the mean signal of negative controls was subtracted from the miRNA signal. Signal values negative after background subtraction were replaced by the lowest signal intensity on the microarray by 0.1 on a base-2 logarithmic scale. To normalise the signal across the different microarrays, three preselected internal control miRNAs (miR-149-3p, miR-2861 and miR-4463), which were stably detected in more than 500 serum samples, were used. Each miRNA signal value was standardised using the ratio of the average signal value from the three internal control miRNAs to the preset value.

Statistical analysis

Before the statistical comparisons, samples were randomly divided, 2:1, into a training cohort and a test cohort, independently of PN and non-PN group status. Using the training cohort, only miRNAs with signal values of 2^6 in $>50\%$ of analyses for each clinical group were selected for further analysis. In the training cohort, the two clinical groups were compared using Student's t-test, and Bonferroni-corrected p values of <0.00012 were defined as statistically different. Fold changes were calculated as difference on a base-2 logarithmic scale for each miRNA, and miRNAs with $|\text{fold change}| > 0.5$ were considered significantly differently expressed. Using these miRNAs, Fisher's linear discriminant analysis was conducted in the training cohort, and the diagnostic sensitivity, specificity and

Table 1 Patient characteristics

Characteristic	PN group (n=38)	Non-PN group (n=46)	P value
Age (years)	54 (34–74)	46 (27–73)	0.0379
≥ 65	7 (18)	2 (4)	
< 65	31 (82)	44 (96)	
Body Mass Index (kg/m^2)			0.3249
> 25	7 (18)	5 (11)	
≤ 25	31 (82)	41 (89)	
Hormone receptor status			0.9409
ER+ and/or PgR+	22 (58)	27 (59)	
ER– and PgR–	16 (42)	19 (41)	
HER2 status			0.7123
+	13 (34)	14 (30)	
–	25 (66)	32 (70)	
Perioperative chemotherapy			0.8649
Neoadjuvant	15 (39)	20 (43)	
Adjuvant	23 (61)	26 (57)	
Regimen			0.3867
AC f/b wPTX	25 (66)	26 (57)	
CEF f/b wPTX	13 (34)	20 (43)	

Data are median (range) or number (%).

AC f/b wPTX, doxorubicin and cyclophosphamide followed by weekly paclitaxel; CEF f/b wPTX, cyclophosphamide, epirubicin and fluorouracil, followed by weekly paclitaxel; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; PN, peripheral neuropathy.

accuracy were calculated for each miRNA marker, or a combination of miRNA markers, in both the training and test cohorts.

All analyses were performed using the software packages R V.3.1.2 (R Foundation for Statistical Computing, <http://www.R-project.org>), compute.es V.0.2–4, glmnet V.2.0–3, hash V.2.2.6, MASS V.7.3–45, mutoss V.0.1–10 and pROC V.1.8.

RESULTS

Patient characteristics

A total of 84 serum samples were obtained from patients with breast cancer who received paclitaxel as neoadjuvant or adjuvant chemotherapy between January 2011 and September 2013 at the NCCH. Of these 84 patients, 35 received paclitaxel as neoadjuvant chemotherapy, including 1 patient who had occult breast cancer, and 49 received paclitaxel as adjuvant chemotherapy. Thirty-eight patients had severe PN (5, grade 3; 33, grade 2; PN group), and 46 had non-severe PN (44, grade 1; 2, no symptom; non-PN group). The median age was 54 (range, 34–74) years in the PN group and 46 (range, 27–73) years in the non-PN group, and the PN group was older than the non-PN group ($p=0.04$). Except for age, baseline characteristics were similar in the PN and non-PN groups, including hormone receptor, HER2 status, operation status and chemotherapy regimens (table 1). Of 35 patients who underwent neoadjuvant therapy, 32 received a combination of cyclophosphamide (500 mg/m²), epirubicin (100 mg/m²) and fluorouracil (500 mg/m²), followed by weekly paclitaxel (80 mg/m²), and 48 of 49 patients who underwent adjuvant therapy received a combination of doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²), followed by weekly paclitaxel (80 mg/m²). Among all

84 patients, 11 required reduction or discontinuation of weekly paclitaxel, and for 7 of these, reduction or discontinuation was needed because of PN>grade 2; the remaining patients had reduced or skipped paclitaxel because of neutropenia, oedema, anorexia or pneumocystis pneumonia.

Discriminatory miRNAs and combinations of miRNAs for prediction of PN

In the training cohort, 15 miRNAs with |fold change| values of >0.5 were selected for comprehensive analysis, and the two clinical groups were compared using Student's t-test; however, there were no miRNAs with Bonferroni-corrected p values of <0.00012. The most discriminatory miRNA of those 15 was miR-451a, which showed a |fold change| of 1.01 on a base-2 logarithmic scale (table 2). Although the p value was >0.01, indicating no significant difference, we assumed that miR-451a may be the most discriminatory miRNA in this analysis based on the |fold change| value.

Using Fisher's linear discriminant analysis, we identified discriminatory combinations comprising 1–3 miRNAs, among those 15 identified using the training cohort, and conducted validation analysis in the test cohort. This analysis identified 14 combinations of three miRNAs that showed relatively improved discrimination with sensitivity, specificity and accuracy of >50% in both the training and test cohorts, although the serum samples in each cohort were independent of one another. The diagnostic ability of these 14 combinations is presented in table 3.

Of the 14 combinations shown in table 3, two formulae included miR-451a: (3) $(-0.637557) \times \text{miR-6846-5p} + (1.06691) \times \text{miR-4539} + (-0.201467) \times \text{miR-451a} - 1.52747$ and (4) $(0.599448) \times \text{miR-4718} + (0.730292) \times \text{miR-5008} -$

Table 2 Expression levels of 15 miRNAs in the training cohort

miRNA	Average level in PN group	Average level in non-PN group	Fold change	P value (Bonferroni-corrected)
miR-451a	5.28	6.28	1.01	0.103
miR-6849-5p	5.09	5.96	0.87	0.063
miR-1290	6.00	6.79	0.79	0.040
miR-4476	6.70	6.01	0.69	0.041
miR-204-3p	12.30	11.65	0.65	0.003
miR-23a-3p	5.16	5.81	0.65	0.234
miR-6846-5p	5.20	5.80	0.61	0.223
miR-6870-5p	6.58	5.98	0.60	0.079
miR-5008-5p	6.81	6.21	0.60	0.014
miR-1249-5p	7.48	6.90	0.58	0.022
miR-6806-5p	5.67	5.10	0.57	0.189
miR-4718	7.52	6.96	0.56	0.026
miR-619-5p	7.59	7.06	0.53	0.178
miR-4462	5.72	6.23	0.51	0.192
miR-4539	6.06	5.56	0.50	0.090

Bonferroni-corrected p values <0.00012 were defined as statistically different.

miRNA, microRNA; PN, peripheral neuropathy.

Table 3 Discrimination ability of 14 combinations of three microRNAs

Number	Discriminatory combination	Training cohort (%)			Test cohort (%)		
		Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
1	miR-23a-3p miR-4462 miR-4539	78.6	71.4	75.0	50.0	50.0	50.0
2	miR-204-3p miR-4476 miR-4539	85.7	71.4	78.6	60.0	55.6	57.1
3	miR-451a miR-4539 miR-6846-5p	82.1	75.0	78.6	70.0	50.0	57.1
4	miR-451a miR-4718 miR-5008-5p	64.3	82.1	73.2	60.0	66.7	64.3
5	miR-1249-5p miR-4539 miR-6846-5p	82.1	67.9	75.0	70.0	50.0	57.1
6	miR-1249-5p miR-4718 miR-5008-5p	78.6	67.9	73.2	50.0	83.3	71.4
7	miR-1290 miR-4539 miR-5008-5p	67.9	78.6	73.2	70.0	55.6	60.7
8	miR-4462 miR-4539 miR-5008-5p	89.3	57.1	73.2	50.0	55.6	53.6
9	miR-4462 miR-4539 miR-6806-5p	89.3	64.3	76.8	60.0	72.2	67.9
10	miR-4476 miR-4539 miR-6846-5p	71.4	78.6	75.0	50.0	66.7	60.7
11	miR-4476 miR-4718 miR-6846-5p	64.3	82.1	73.2	70.0	66.7	67.9
12	miR-4539 miR-4718 miR-6846-5p	67.9	85.7	76.8	70.0	83.3	78.6
13	miR-4539 miR-5008-5p miR-6846-5p	82.1	67.9	75.0	60.0	55.6	57.1
14	miR-4539 miR-6846-5p miR-6870-5p	75.0	75.0	75.0	80.0	61.1	67.9

5p+(-0.299362)×miR-451a-7.3612. Formula 3 showed sensitivity, specificity and accuracy in the test cohort of 70.0%, 50.0% and 57.1%, respectively, with values of 60.0%, 66.7% and 66.4% for formula 4. The receiver operating characteristic curves for these formulae are presented in figure 1. Area under the curve values were 0.628 and 0.661 for formula 3 and formula 4, respectively, in the test cohort. Hence, these combinations of miRNAs were promising for prediction of PN.

DISCUSSION

This is the first report to reveal a relationship between the risk of PN caused by chemotherapy and miRNA expression. Although our analysis did not identify a statistically significant discriminatory predictive

marker, miR-451a has promise in this respect, as it showed the highest |fold change| in this study. Further, although the combination formulae comprising three miRNAs were also insufficient to predict PN, and despite the fact that we have concerns regarding possible overfitting in the test cohort, our data indicate that miRNAs may have the potential to predict PNs.

MiR-451a is associated with the metabolism of paclitaxel, through regulation of the expression of the drug-transporter protein P-glycoprotein.¹⁵ P-glycoprotein is a drug efflux pump, which transports anticancer agents from tumour cells to the extracellular side of the plasma membrane, and is known as a multidrug resistance mechanism of some agents, including paclitaxel and doxorubicin.^{16 17} We hypothesise that P-glycoprotein may reduce PN by transporting paclitaxel

Figure 1 Receiver operating characteristic curves for combination formulae containing miR-451a in the training and test cohorts. Combination 3: $(-0.637557) \times \text{miR-6846-5p} + (1.06691) \times \text{miR-4539} + (-0.201467) \times \text{miR-451a} - 1.52747$; combination 4: $(0.599448) \times \text{miR-4718} + (0.730292) \times \text{miR-5008-5p} + (-0.299362) \times \text{miR-451a} - 7.3612$. AUC, area under the curve.

outside the cell membrane, including normal neural cells, and that miR-451a may decrease PN through its positive regulation of P-glycoprotein. Although this hypothesis also suggests a relationship between miR-451a and mechanisms of chemotherapy resistance, it was difficult to compare the outcomes in the PN and non-PN groups in the current study due to an insufficient number of patients.

The roles of the other 14 discriminatory miRNAs in paclitaxel metabolism or neuropathy development are as yet unknown, and it is possible that they may also influence the severity of chemotherapy effects, including those that induce PN, through influencing paclitaxel metabolism or neuronal plasticity. Of those 14 miRNAs, miR-23a-3p is reported to regulate angiogenesis, and miR-1290 is reported to distinguish early-stage pancreatic cancers; however, they require further investigation, and there is no clear link to mechanisms underlying the PN caused by paclitaxel.

There is insufficient evidence to confirm the hypothesis that expression of miR-451a is associated with the risk of PN by promoting P-glycoprotein expression, and there are few studies of the pathway involving miR-451a, P-glycoprotein and paclitaxel metabolism. Furthermore, this study had the limitation that the

discriminant analysis was conducted using data from relatively few patients (a total of 84), which made it difficult to remove the effect of the other risk factors, and none of the predicted markers were statistically significant. We especially have to consider the effect of age as one of the other risk factors of PN in this study. The patient background showed that the PN group was associated with older age, and this was supported by previous studies.^{4,6} It could make spurious associations as a confounding factor.

Extensive further investigations, including in vitro studies using neuron cell lines and in vivo studies, are needed to determine the importance of miRNAs for the prediction of PN. Further, examination of miR-451a expression in prospectively collected serum samples may also demonstrate the reliability of our results. Moreover, the relationships of miRNAs with other adverse events may be a fruitful subject for investigation.

CONCLUSION

This is the first study to evaluate the relationship between the expression of miRNAs and the risk of chemotherapy-induced PN. MiR-451a was the most discriminatory miRNA in this study; however, it was

not statistically significant as a predictive marker. MiRNAs are potential biomarkers for prediction of not only the efficacy of chemotherapy, but also the risk of adverse events, and extensive further investigation is warranted to reveal the role of miRNAs in responses to systemic chemotherapy.

Acknowledgements The authors thank Tomomi Fukuda, Takumi Sonoda, Hiroko Tadokoro, Megumi Miyagi, Tatsuya Suzuki and Kamakura Techno-Science for performing the microarray assays; Makiko Ichikawa and Satoshi Kondou for technical support; Noriko Abe for the management of serum samples; Michiko Otori for the management of personal information; Hitoshi Fujimiya for developing in-house analytical tools; and Kazuki Sudo for independent confirmation of participant eligibility. Some of the samples were obtained from the National Cancer Center(NCC) Biobank, which is supported by NCC Research and Development Fund.

Contributors SN-N, AS, CS and TO conceived the study and designed the experiments. SN-N, AS, YT, CS and KT participated in the data collection. SN-N, AS, JK, ST and YA conducted the experiments. JK, JM and ST performed the statistical analysis. SN-N, AS and JM interpreted the data and wrote the manuscript. All authors have read and approved the submission of the manuscript.

Funding This study was financially supported through a 'Development of Diagnostic Technology for Detection of miRNA in Body Fluids' grant from the Japanese Agency for Medical Research and Development.

Competing interests JK and ST are employees of Toray Industries, Inc, the provider of the 3D-Gene system. YA is an employee of Dynacom Co., Ltd, the developer of the statistical script used for selecting the best miRNA combination. All the other authors have no conflict of interest to declare.

Patient consent for publication Obtained.

Ethics approval The present study involving human subjects was approved by the National Cancer Center Hospital Institutional Review Board (2016–120, G2009-005) and the Human Tissue Samples Ethics Committee for R&D, Toray Industries (HC2018-2). Written informed consent was obtained from each subject.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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