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# Chemotherapy-related polyneuropathy may deteriorate quality of life in patients with B-cell lymphoma

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**Abstract**
*Purpose* This prospective study was performed to evaluate the effect of chemotherapy-related neurotoxicity on quality of life (QOL) of patients with lymphoma.
*Methods* Thirty-two patients with diffuse large B-cell or follicular lymphoma without prior evidence of neuropathy were enrolled. Patients underwent the evaluations based on neuropathy symptom and disability score, nerve conduction studies, and SF-36 questionnaire for QOL assessment. They received six cycles of chemotherapy every three weeks, and all evaluations were repeated during and after the completion of 6th cycle.
*Results* Sensory neuropathy-associated symptoms were observed in 27 patients (84.4%), and polyneuropathy was confirmed by nerve conduction study in 14 patients (43.8%). These patients with polyneuropathy showed worse QOL in domains mainly associated with physical health status including "physical function" compared to patients without polyneuropathy. There was a significant association of neuropathy symptom and disability scores with "bodily pain" and "vitality" of QOL domains. The serial evaluations of patients with neuropathy showed a worsening of QOL and neuropathy symptom scores during chemotherapy, then improvement of these values after chemotherapy. Thus, the final nerve conduction study confirmed the decrease in polyneuropathy compared to the 2nd evaluation ($P = 0.032$).
*Conclusion* Chemotherapy-related polyneuropathy may deteriorate QOL of patients with lymphoma, mainly physical health-associated QOL.

**Keywords** Neuropathy · Chemotherapy · Lymphoma · Quality of life

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## Introduction

Advances in the treatment of B-cell non-Hodgkin lymphoma (NHL) such as the use of rituximab for diffuse large B-cell or follicular lymphoma have greatly improved the survival of patients [1, 2]. This advance in treatment allows a focus on the psychological well-being and quality of life (QOL) of lymphoma survivors. Chemotherapy-induced toxic effects are considered as an important factor in health-related QOL [3–6]. In response, most recent studies evaluating efficacy and safety of new treatment protocols have adopted patient self-reported QOL as a relevant outcome measure [7]. Among the various toxic effects related to chemotherapy, peripheral neuropathy is a common, dose-limiting complication [8]. Combination regimens, such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) or rituximab, cyclophosphamide, vincristine, and prednisolone (R-CVP), include vincristine, which frequently induces peripheral neuropathy. Almost every patient with diffuse large B-cell or follicular lymphoma receiving these chemotherapies suffers from vincristine-induced neuropathy. Neuropathy symptoms usually begin during active chemotherapy and may become worse for some time, even after cessation of treatment. However, unlike more immediate toxicities that affect the gastrointestinal tract and bone marrow, physicians may give less attention to peripheral neuropathy, as it is rarely life-threatening. In addition, some patients may minimize reporting of symptoms in an effort to prevent dose reduction or chemotherapy holidays. While previous studies have addressed the impact of chemotherapy toxicity on QOL, no study has addressed the relationship between neuropathy-specific symptoms and QOL. We hypothesize that chemotherapy-induced neuropathy has a major impact on QOL. We conducted this prospective study in patients with diffuse large B-cell lymphoma or follicular lymphoma who were treated with R-CHOP or R-CVP.

## Methods

### Patients

Consecutive patients diagnosed with diffuse large B-cell or follicular lymphoma in a university-affiliated hospital were recruited between March 2006 and December 2007. For the study period, 58 patients were diagnosed as diffuse large B-cell and follicular lymphoma. After screening, 17 patients were excluded because they had a history of pre-existing peripheral nerve or muscle disease, a neuromuscular junction disorder, spine surgery for herniated nucleus pulposus or cervical spondylosis, or a medical condition associated with peripheral neuropathy, such as diabetes mellitus, alcohol abuse, metabolic disorders, or long-term drug use. Thus, 41 patients who satisfied the inclusion and exclusion criteria completed the baseline study. The baseline nerve conduction study revealed that four patients had polyneuropathy, even though they did not have neuropathic symptoms, so they were excluded from further study because of the possibility of neurolymphomatosis with the involvement of peripheral nerves. Of 37 patients who had no evidence of neuropathy according to clinical examination including nerve conduction study, five patients declined further study because of the pain associated with the nerve conduction study. These all five patients denied the development of symptoms or signs suggestive of a polyneuropathy.

Finally, 32 patients (22 men and 10 women; mean age 55.9, range 21–79 years) who completed the follow-up study during chemotherapy were enrolled for final analysis. Twenty-two patients with diffuse large B-cell lymphoma and ten patients with follicular lymphomas were analyzed, and the characteristics of the patients at diagnosis are summarized in Table 1. Of the 32 patients, 3 (including 1 with polyneuropathy) died before completing the study. Another five declined to complete the study after chemotherapy because they did not experience any symptoms related to polyneuropathy. Twenty-four patients completed the full study, and for the last visit evaluation, 18 among 24 patients completed the study within 2 months after chemotherapy. These 24 patients with complete data were not significantly different from 17 patients who did not complete the study due to aforementioned reasons in terms of baseline characteristics including age, sex, stage, and so on. Written informed consent was obtained from all participants, and this study was reviewed and approved by our institutional review board.

### Evaluation

All patients were treated with six cycles of chemotherapy at 3-week intervals. Patients with diffuse large B-cell lymphoma were treated with R-CHOP, and patients with follicular lymphoma were treated with R-CVP. Before starting the chemotherapy schedule, all patients were evaluated using the neuropathy symptom score and the neuropathy disability score [9]. Nerve conduction study was performed to evaluate peripheral nerve function. In addition, all patients were asked to complete the SF-36 self-questionnaire for QOL measurement. All evaluations were repeated at the 2nd visit during chemotherapy and on the last visit after the 6th chemotherapy session. The 2nd visit evaluations were performed immediately before chemotherapy infusion on one of the visits for the 3rd–5th cycles of chemotherapy. The last visit was conducted after 1 month but before 6 months after the 6th chemotherapy

**Table 1** Characteristics of patients

| Characteristics | No. of patients | No. of patients with neuropathy | *P* value |
|---|---|---|---|
| Gender | | | |
| Male | 22 | 10 | 0.773 |
| Female | 10 | 4 | |
| Age (years) | | | |
| <60 | 19 | 5 | 0.029 |
| ≥60 | 13 | 9 | |
| ECOG Performance status | | | |
| <2 | 22 | 7 | 0.062 |
| ≥2 | 10 | 7 | |
| Extranodal involvements | | | |
| <2 | 23 | 9 | 0.453 |
| ≥2 | 9 | 5 | |
| Ann Arbor stage | | | |
| I/II | 0/14 | 4 | 0.165 |
| III/IV | 12/6 | 10 | |
| Serum lactate dehydrogenase (IU/l) | | | |
| Normal | 18 | 7 | 0.721 |
| Increased | 14 | 7 | |
| B symptoms | | | |
| Present | 14 | 6 | 0.607 |
| Absent | 18 | 8 | |
| Serum b2 microglobulin (ug/ml) | | | |
| Normal | 20 | 8 | 0.581 |
| Increased | 12 | 6 | |
| Bone marrow involvement | | | |
| Yes | 6 | 3 | 0.540 |
| No | 26 | 11 | |
| International prognostic index | | | |
| Low/Low-intermediate | 14/7 | 1/6 | 0.012 |
| High-intermediate/High | 6/5 | 4/3 | |

cycle. The National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 was used for grading the toxicity at each patient visit.

### Nerve conduction study

The nerve conduction study was performed using standard electrodiagnostic equipment (Viking IV; Nicolet Biomedical, Madison, WI, USA). Each patient's skin temperature was confirmed to be at or above 31°C on the dorsum of the hand and foot. Motor nerve conduction and F-wave studies were performed on the median, ulnar, peroneal and posterior tibial nerves, and sensory nerve conduction studies were performed on the median, ulnar, superficial peroneal and sural nerves. H-reflexes were obtained for both posterior tibial nerves with stimulation at the popliteal fossa.

### Quality of life measurement

All participating patients completed the SF-36 survey without assistance except seven patients (21.9%) among elderly patients more than 60 years old. However, no researchers were involved in completing the questionnaire. The eight domains of the SF-36 were as follows: (1) general health perceptions, (2) physical function, (3) general mental health, (4) role function as limited by physical problems, (5) role function as limited by emotional problems, (6) bodily pain, (7) vitality, and (8) social function. These data were then used to compute physical component summary and mental component summary scores using the equation provided by the Medical Outcomes Study [10]. The score was commuted as norm-based score when the score of normal healthy people are assumed as 50 with standard deviation of 10. A royalty-free license agreement was obtained for academic use and publication from QualityMetric.

### Statistical analysis

The frequencies of neuropathy confirmed by nerve conduction study among visits were compared using McNemar's test. The relationship of clinical characteristics with neuropathy was assessed by chi-square analysis. Repeated measures ANOVA was used to analyze the effect of chemotherapy and development of neuropathy on the QOL scores and neuropathic symptom scales. The baseline QOL scores were compared using an independent *t*-test between patients with and without neuropathy. Bonferroni's method was used to adjust inflated type I error rates in the multiple comparisons of the baseline, 2nd, and final visits. The correlation between neuropathic symptom scales and QOL scores was analyzed using correlation analysis. *P* values <0.05 were considered statistically significant. Statistical analyses were performed using the SPSS software (release 12.0; SPSS, Inc., Chicago, IL, USA).

## Results

### Polyneuropathy

At the 2nd visit evaluation, 27 patients (84.4%; $P < 0.001$) complained of a new onset distal symmetric sensory disturbance of varying severity, and 14 patients (43.8%; $P < 0.001$) had polyneuropathy confirmed by the nerve conduction study. Among patients ≥60 years old, nine patients (69.2%, 9/13) had neuropathy confirmed by nerve conduction study during chemotherapy, while five patients <60 years old (26.3%, 5/19) had neuropathy. Ten men (45.5%, 10/22) and four women (40%, 4/10) had

neuropathy. The other clinical variables including tumor stage and bone marrow involvement were not significantly associated with the occurrence of neuropathy. The comparison of neuropathy frequencies according to the clinical variables was summarized in Table 1. Although substantial number of patients experienced symptoms associated with sensory neuropathy, none had motor weakness or disturbance in activities of daily living.

Among the 24 patients completed the final visit evaluation (1–6 months after chemotherapy), five patients (20.8%, 5/24) still complained of distal sensory symptoms. But only two patients had neuropathy confirmed by nerve conduction study among them (8.3%, 2/24; compared to 2nd visit, $P = 0.032$; compared to baseline, $P = 0.250$; McNemar's test using Bonferroni's correction). This might represent the recovery of neuropathy after the completion of chemotherapy. Consistent with these findings, the mean neuropathy symptom score increased from 0.44 at the baseline visit to 2.84 at the 2nd visit during chemotherapy, and reverted to 0.5 at the last visit after chemotherapy ended. The mean neuropathy disability score also showed similar changes; specifically, 0.1 at baseline, 0.97 at the 2nd visit, and 0.21 at the last visit. After we dichotomized patients according to the presence of neuropathy, we compared patients in terms of neuropathy symptom score and neuropathy disability score. The mean neuropathy symptom score of patients with neuropathy was significantly higher than patients without neuropathy ($P = 0.019$, Table 2). However, the mean neuropathy disability score was not significantly different between patients with neuropathy and without neuropathy ($P = 0.709$, Table 2).

## Quality of life

The mean score of each domain of the SF-36 at baseline was in the normal range ($> 40$) within one standard deviation (10) of an average score of 50. However, among the total of 32 patients, the baseline mental component summary score of 9 patients was less than 40, and this means these patients had decreased in mental health status before chemotherapy. In the aspect of physical health status, only one patient had a physical component summary score less than 40 at the baseline before chemotherapy. When the QOL was assessed at the 2nd visit evaluation, 8 patients revealed the mental component summary score less than 40. However, the final evaluation of QOL showed the improvement of mental component summary score, thus only two patients remained as being decreased in the mental health status, which means less than 40 after the completion of chemotherapy.

The serial change of the physical component summary score showed that of twelve patients decreased to less than 40 at the 2nd visit evaluation. Consistent with the mental health status, the impaired of physical health status recovered after chemotherapy, so five patients still had the physical component summary score less than 40 after the completion of chemotherapy. When we compared the SF-36 data between the group of neuropathy and non-neuropathy, the baseline values of all domains were not significantly different between them. However, the mean scores of most domains were decreased after chemotherapy started especially in patients with neuropathy. Thus, the physical function, role function as limited by physical problems, vitality, and physical component summary score significantly decreased in patients with neuropathy compared to patients without neuropathy (Table 3). A paired comparison of scores between the baseline and the 2nd visit in patients with neuropathy showed a trend of worsening in the domains of QOL including the physical function, role function as limited by physical problems, bodily pain, vitality, social function, and physical component summary score. However, only the worsening of vitality domain at the 2nd visit compared to the baseline was statistically significant ($P = 0.036$; paired $t$-test using Bonferroni's correction).

When we assessed the chemotherapy-induced toxicity according to the scale of 0–4 in CTCAE version 3, the fatigue ($P = 0.031$) and neuropathy ($P = 0.002$) was changed during chemotherapy. Thus, the mean grade of fatigue increased from 0.25 at baseline to 1.03 at the 2nd

**Table 2** Neuropathic symptom scales in patients with and without neuropathy

| | Baseline evaluation | 2nd evaluation | Final evaluation | $P$ value |
|---|---|---|---|---|
| NSS | | | | |
| Non-neuropathy ($n = 18$) | 0.15 ± 0.38 | 2.23 ± 2.42 | 0.23 ± 0.59 | 0.019 |
| Neuropathy ($n = 14$) | 0.67 ± 1.23 | 4.33 ± 2.64 | 0.75 ± 1.14 | |
| NDS | | | | |
| Non-neuropathy ($n = 18$) | 0.00 | 1.08 ± 0.99 | 0.33 ± 0.89 | 0.709 |
| Neuropathy ($n = 14$) | 0.17 ± 0.58 | 1.17 ± 1.03 | 0.33 ± 0.89 | |

Data are presented as mean ± standard deviation; Repeated measures ANOVA was used for analysis

*NSS* neuropathy symptom score, *NDS* neuropathy disability score

**Table 3** Quality of life scores in patients with and without neuropathy

| | Baseline evaluation | 2nd evaluation | Final evaluation | *P* value |
|---|---|---|---|---|
| Physical function | | | | |
| Non-neuropathy (18) | 52.93 ± 4.65 | 44.06 ± 9.73 | 49.26 ± 6.42 | 0.026 |
| Neuropathy (14) | 48.16 ± 9.34 | 38.24 ± 13.72 | 40.57 ± 11.78 | |
| Role function as limited by physical problems | | | | |
| Non-neuropathy (18) | 52.44 ± 6.57 | 38.89 ± 10.23 | 51.20 ± 6.01 | 0.047 |
| Neuropathy (14) | 47.06 ± 12.77 | 36.73 ± 13.34 | 42.82 ± 11.28 | |
| Bodily pain | | | | |
| Non-neuropathy (18) | 58.06 ± 7.15 | 56.50 ± 8.07 | 56.73 ± 8.14 | 0.982 |
| Neuropathy (14) | 60.33 ± 6.66 | 51.49 ± 15.25 | 59.62 ± 4.99 | |
| General health perception | | | | |
| Non-neuropathy (18) | 44.56 ± 9.77 | 43.53 ± 8.85 | 50.03 ± 8.53 | 0.133 |
| Neuropathy (14) | 44.66 ± 9.05 | 40.71 ± 9.07 | 42.62 ± 6.39 | |
| Vitality | | | | |
| Non-neuropathy (18) | 50.99 ± 11.24 | 44.63 ± 10.03 | 54.97 ± 8.00 | 0.003 |
| Neuropathy (14) | 48.07 ± 13.38 | 36.25 ± 8.43 | 41.02 ± 9.82 | |
| Social function | | | | |
| Non-neuropathy (18) | 51.66 ± 9.44 | 37.76 ± 11.90 | 49.29 ± 8.76 | 0.63 |
| Neuropathy (14) | 50.61 ± 10.44 | 38.54 ± 15.80 | 45.44 ± 12.91 | |
| Role function as limited by emotional problems | | | | |
| Non-neuropathy (18) | 51.60 ± 9.67 | 44.86 ± 14.28 | 54.68 ± 3.42 | 0.981 |
| Neuropathy (14) | 51.43 ± 7.75 | 48.93 ± 10.79 | 50.57 ± 12.41 | |
| General mental health | | | | |
| Non-neuropathy (18) | 48.88 ± 13.89 | 45.78 ± 12.16 | 57.37 ± 8.09 | 0.765 |
| Neuropathy (14) | 50.00 ± 12.54 | 49.40 ± 13.16 | 49.49 ± 14.64 | |
| Physical component summary score | | | | |
| Non-neuropathy (18) | 53.25 ± 5.68 | 45.88 ± 8.83 | 49.88 ± 7.36 | 0.024 |
| Neuropathy (14) | 49.92 ± 8.25 | 38.53 ± 11.81 | 44.47 ± 6.35 | |
| Mental component summary score | | | | |
| Non-neuropathy (18) | 49.16 ± 13.66 | 43.37 ± 12.85 | 55.95 ± 5.56 | 0.819 |
| Neuropathy (14) | 50.15 ± 10.48 | 47.27 ± 11.54 | 48.89 ± 13.76 | |

Data are presented as mean ± standard deviation; Repeated measures ANOVA was used for analysis

visit then decreased to 0.59 at the final. The mean neuropathy grade increased from 0.03 at baseline to 0.97 at the 2nd visit, and then decreased to 0.72. Correlation analysis between neuropathy-related symptom scales and SF-36 domains showed that neuropathy symptom score had a significant negative correlation with bodily pain ($r = -0.436$, $P = 0.013$) and vitality ($r = -0.371$, $P = 0.037$). Neuropathy disability score also had a significant negative correlation with bodily pain ($r = -0.369$, $P = 0.038$) and vitality ($r = -0.366$, $P = 0.039$).

## Discussion

Approximately 85% of patients ($n = 27$) had symptoms suggestive of polyneuropathy, and this frequency was relatively higher than previous reports [11, 12]. This may be related with the chemotherapy regimens we used in this study because CHOP and CVP regimens have included vincristine, a neurotoxic agent. However, the majority of patients got recovered from neuropathy-associated symptoms after they finished their chemotherapy, and it was confirmed by nerve conduction study. Consistent with this, the chemotherapy-induced worsening of neuropathy symptom and disability scores improved after the completion of chemotherapy (Table 2). But the comparison of patients with neuropathy and non-neuropathy showed that the neuropathy disability score was not significantly different between them although the neuropathy symptom score was different according to the presence of neuropathy. Thus, to assess the impact of neuropathy on the QOL of patients, we used the SF-36, which is a widely applied health-related status assessment instrument for QOL measurement instead of applying the alternative,

condition-specific instruments for chemotherapy, cancer, and neuropathy. The application of an instrument for various disease conditions can reduce redundancy, data collection, and the burden related with analysis [13]. In addition, the SF-36 has norm-based scores that are useful for comparing scores of each patient to the normal population.

In this study, nine patients showed abnormally decreased mental component summary scores in view of the norm-based score at the baseline evaluation before chemotherapy. However, these patients did not show the worsening of the value after starting chemotherapy. Furthermore, seven patients showed the improvement of the mental component summary score after chemotherapy among these patients who had the decreased mental component summary score at the baseline. Thus, this initial decrease in the mental component summary score can be interpreted as being associated with lymphoma itself because lymphoma alone may act as a stressor to impair the mental health status. The successful completion of chemotherapy might give patients hope, resulting in an improvement in the mental component summary score. That may be the reason why patients with initial decrease in mental component summary score showed the improvement of mental health status. In contrast, the physical component summary scores were in the normal range in all but one patient at baseline, but 12 had decreased scores during chemotherapy. These findings may be related to chemotherapy-induced toxic effects.

When we compared the mean scores of the SF-36 domains between patients with and without neuropathy, the scores of several domains including physical function, role function as limited by physical problems, vitality, and physical component summary were lower in the group of neuropathy than non-neuropathy (Table 3). Considering these domains are mainly associated with physical health, chemotherapy-induced neuropathy may mainly affect the physical health status rather than mental health in patients receiving chemotherapy. This finding is also supported by that the worsening of mean neuropathy symptom score in patients with neuropathy compared to non-neuropathy (Table 2).

When we evaluated the serial changes of QOL in patients with neuropathy, the majority of patients showed a trend of the worsening of QOL domains including the physical function, role function as limited by physical problems, bodily pain, vitality, social function, and physical component summary during treatment. Furthermore, the correlation analysis showed a significant association of neuropathy symptom and disability scores with bodily pain and vitality of SF-36 domains. This was consistent with the worsening of chemotherapy-associated toxicity including fatigue and neuropathy grades during chemotherapy. Although only the worsening of vitality at the 2nd visit compared to the baseline was statistically significant ($P = 0.036$), this finding strengthens the importance of polyneuropathy as a key factor in the deterioration of QOL in patients undergoing chemotherapy. In addition, the final assessment of QOL in patients with neuropathy after the completion of chemotherapy revealed that the improvement of physical health represented by physical function, role function as limited by physical problems, vitality, and physical component summary scores seemed to be relatively slow while the improvement of neuropathic symptom score and nerve conduction study findings rapidly improved. This suggests that more attention may be paid to the negative effects of polyneuropathy on the QOL during the follow-up of patients after chemotherapy.

In conclusion, the negative impact of chemotherapy-induced polyneuropathy on the QOL, especially the physical functioning aspects in patients with diffuse large B-cell or follicular lymphoma with long-term survival was presented in this study. However, the size of study population was too small to draw a firm conclusion. In addition, the long-term follow-up should be required to show the change of QOL in long-term survivors of lymphoma. Thus, further study with a larger study population should be warranted in the future.

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