Table 5 The results of factor analysis of the disease management activities: factor loadings after Promax rotation and Cronbach's alpha coefficients ($N = 330$)

	Factor 1	Factor 2	Factor 3
Muscle training and weight management activities $\alpha = 0.69$			
I do muscle training	*0.70*	−0.01	0.01
I do stretching	*0.67*	0.02	−0.06
I do exercise to prevent weight gain	*0.63*	−0.05	0.03
I am careful with my diet to avoid weight gain	*0.31*	0.25	0.07
Activities to prevent load on hip $\alpha = 0.63$			
I use a cane or hold a handrail when necessary	−0.04	*0.59*	0.01
I do not choose shoes with high heels or hard soles	−0.04	*0.55*	−0.03
I try not to lift heavy objects	0.07	*0.48*	0.18
Activities to aid careful walking $\alpha = 0.66$			
I am careful about the walking distance and speed in daily life	0.00	0.09	*0.53*
I try not to remain standing for long periods of time	−0.03	0.18	*0.54*
Total contribution 38%			

Table 6 Related factors of the disease management activities

$N = 330$	Muscle training and weight management activities		Activities to prevent load on hip			Activities to aid careful walking		
	r[a]	*P*-Value	r[a]	*P*-Value		r[a]	*P*-Value	
Age	0.07	0.22	0.38	<.001	***	0.17	0.00	***
Duration of osteoarthritis	−0.02	0.78	0.00	0.98		−0.04	0.46	
Disease stage	0.02	0.76	0.51	<.001	***	0.18	0.00	***
BMI	−0.05	0.34	0.13	0.02	*	0.07	0.22	
JOA score								
Range of motion	0.08	0.15	−0.33	<.001	***	−0.09	0.11	
Pain	0.03	0.60	−0.32	<.001	***	−0.14	0.01	**
Walk	−0.04	0.45	−0.46	<.001	***	−0.22	<.001	***
ADL	0.04	0.48	−0.49	<.001	***	−0.24	<.001	***
Difficulty in their daily life[b]								
There are no local medical specialists for disease management	0.03	0.60	0.25	<.001	***	0.14	0.01	**
I find it difficult to maintain my body weight appropriately	−0.07	0.18	0.18	0.00	***	0.12	0.03	*
I have a hard time controlling pain in daily life	0.01	0.91	0.25	<.001	***	0.08	0.16	
I am reluctant to use a walking stick	−0.07	0.18	0.02	0.76		0.08	0.13	
I have a hard time moving joints as I wish	−0.02	0.68	0.41	<.001	***	0.22	<.001	***
It difficulty to choose a treatment method	−0.01	0.85	0.20	0.00	***	0.11	0.05	*
I feel that I am putting burdens on my family or friends	0.04	0.47	0.30	<.001	***	0.20	0.00	***
I have a hard the sleeping well due to pain	0.03	0.64	0.16	0.00	***	0.07	0.19	

[a] r are expressed as Spearman's coefficients. *P*-value $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

[b] Difficulty in their daily life using answers graded from 1 to 5 which ranged from "I feel exactly the same" to "I do not feel any at all".

statistically significant, it is likely that the patients performed the management activities out of necessity because they had problems caused by OA symptoms.

Since weight loss and muscle training can relieve the pain of OA and improve the range of motion (van Baar et al., 1998) and exercises including stretching and muscle training are expected to slow the progression of OA (Hochberg et al., 1995; Anon., 2000), we consider it necessary to advise patients at an earlier stage of the disease to perform the management activities and to develop a program to link the advice to actual performance of the activities.

In terms of muscle training and weight management activities, a small number of patients performed half of its items. Also, stages of the disease did not affect motivation of patients' training performance. These two facts are considered to be the reasons why there were no related factors.

Caution is required when generalizing this result since the present study focused on the patients of an orthopaedic outpatient service specializing in hip joints at one university hospital. Also, we used the answers from the patients to determine whether they performed the disease management activities, and did not verify whether they actually did or did not. Since it is important to continue the management activities, we consider it necessary to study temporal change of the result in addition to the present cross-sectional survey at a specific point in time.

Conclusions

The present study clarified the status of the disease management activities of the patients who were having conservative treatment. We consider it necessary to advise patients at an earlier stage of the disease to perform the management activities and to develop a program to link the advice to actual performance of the activities.

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Attitude of outpatients with neuromuscular diseases in Japan to pain and use of analgesics

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Abstract

The prevalence of pain and its impact on outpatients with neuromuscular disease, and their attitude towards the use of analgesics were studied. Seventy-eight outpatients at the university hospital, Tokyo, diagnosed with Parkinson's disease, spinocerebellar degeneration, amyotrophic lateral sclerosis, or multiple sclerosis were asked whether they had experienced pain in the preceding week. The Brief Pain Inventory, Japanese version was used to interview participants reporting pain, about its intensity and interference with activities, the way they dealt with it, attitudes to pain and use of analgesics, and desire for treatment. Forty-six participants experienced pain in the preceding week (59%). The mean pain intensity was 4.1 out of 10, and 20% of participants reported that the degree of interference with mobility was at least 6 out of 10. Most participants dealt with their pain without medication, by changing posture frequently or massage. Approximately 80% of participants regarded pain as something they should endure. Half of the participants wanted more information on methods for pain relief. Approximately 80% of participants were anxious about adverse reactions of analgesics. These findings suggest that medical staffs should provide appropriate information and educate their patients.

Keywords: Attitude to pain; Attitude to use of analgesics; Interference with activities by pain; Neuromuscular disease; Pain intensity; Prevalence of pain

1. Introduction

In Japan, the number of patients with Parkinson's disease (PD), spinocerebellar degeneration (SCD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) was approximately 80,000, 15,000, 7000, and 10,000, respectively, in 2005 [1]. PD, SCD, and ALS are progressive neurodegenerative diseases, while MS is a demyelinating disease with a variable natural course [2]. Therapies for complete remission against these diseases have not yet been established. However, because of improvements in medical treatment and the prevention of infectious complications, the prognosis of patients with these diseases has improved. Therefore, long-term disease and symptom management is needed.

Symptoms of neuromuscular diseases vary with the disease and the phase of disease. Pain is one of the common symptoms [3]. Pain is an unpleasant symptom and is a factor that reduces the patient's activity [3,4]. Although, the origin of pain varies with each disease, most previous studies have reported that analgesics and adjuvant analgesics such as antidepressants are effective to relieve pain in neuromuscular diseases. For pain that is not reduced by analgesics, physiotherapy or psychotherapy are effective [3,5]. Nevertheless, it has been reported that the prevalence of pain in neuromuscular diseases is approximately 10–60% in the

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USA and Europe, and many patients feel that pain interferes with their daily activities [6–14]. In Japan, there have been few studies on this subject.

From the clinical point of view, pain relief is an important goal of treatment and care, in order to maintain the patient's comfort and activities of daily living (ADL). Medical staffs need to know the prevalence and the impact of pain. Relief from pain depends not only on medical specialists' knowledge about methods of pain relief, but also on the patient's knowledge and cooperation with the medical staff [15]. Some previous studies suggest that the pain threshold depends on culture, education level, and the healthcare and health insurance systems [16]. From these findings, it seems that patients' attitudes to pain and relief from pain differ among different cultures. The United Nations points out that the consumption of opioids in Japan is less than that in Western countries [17]. The Pharmaceutical Society of Japan says that the consumption of analgesics such as nonsteroidal inflammatory drugs (NSAIDs) is also less [18]. Little is known about the reasons for the low consumption of analgesics in Japan; however, it is possible that patients do not desire to use analgesics and that physicians are reluctant to prescribe them, being afraid of overuse.

To achieve relief from pain, it is necessary to clarify the characteristics of pain in neurological diseases and patients' attitudes to pain and relief from pain. For the maintenance of pharmacotherapy, it is also helpful to know the patient's attitude to the use of analgesics. Therefore, the first aim of this study was to investigate the prevalence and characteristics of pain in several representative neurological diseases: PD, SCD, ALS, and MS. The second aim was to investigate patients' attitudes to pain in neurological diseases and to relief from this pain. The third aim was to compare attitudes to the use of analgesics in people with and without pain.

2. Methods

2.1. Participants

Participants were outpatients at the University of Tokyo Hospital. Patients were included if they were more than 20 years old, had been diagnosed with PD, SCD, ALS, or MS, and were able to communicate in Japanese. The exclusion criterion was cognitive impairment.

2.2. Procedure

Data were collected in face-to-face interviews with participants in a room where privacy was ensured. First, participants were asked to complete the Hasegawa Dementia Scale-Revised (HDS-R) [19] to confirm the absence of cognitive impairment. The HDS-R is widely used in Japan to assess cognitive function, with a cutoff point of 20 or 21 out of 30. The HDS-R score is reported to be positively correlated to the score on the Mini-Mental State Examination (MMSE), which is popular in the USA and European countries [19]. When the HDS-R score was higher than 21, the participant was asked about their experience of pain in the preceding week. If the participant had experienced pain in the preceding week, they were further asked about the intensity and other characteristics of the pain. Data such as "time since disease diagnosis" were collected by reviewing the medical records.

This study was approved by the University of Tokyo institutional ethical review board and informed consent was obtained from each participant.

2.3. Measures

2.3.1. Prevalence of pain

All participants were asked about the presence or absence of pain in the preceding week.

2.3.2. Pain intensity and its interference with activities

Participants who had experienced pain in the preceding week were asked to assess the intensity of their pain and the extent to which it had interfered with their ADL, using the Japanese Brief Pain Inventory (BPI-J) [20]. The BPI was initially developed to assess pain severity and interference in persons with cancer in the USA [21,22] and has been validated for people with cancer and noncancer pain. BPI was translated into Japanese in 1998 and has been used to assess pain intensity and its interference with ADL in Japan. The BPI-J includes ratings for worst pain, weakest pain, and average pain in the preceding week, and current pain, on a 0–10 numerical rating scale (NRS), where 0 is no pain and 10 is pain as bad as can be imagined.

Interference with ADL by pain was assessed in seven domains of life–general activities, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life–using a 0–10 NRS, with 0=does not interfere and 10=completely interferes.

2.3.3. How participants dealt with their own pain and its effect

Participants who had experienced pain in the preceding week were asked about the way they had dealt with their pain. Additionally, they were asked whether the means they had used to deal with their pain had any effect.

2.3.4. Attitude to their pain

Participants who had experienced pain in the preceding week were asked questions to discover if they thought they had to bear the pain and that whether they felt it was only they who had to face an unpleasant experience such as pain.

2.3.5. Desire for treatment

Participants who had experienced pain in the preceding week were asked three questions regarding the treatment for the pain relief: whether they were satisfied with the current treatment of pain, wished to be prescribed analgesics and

requested to be given more information about the methods of pain relief.

2.3.6. Use of analgesics

All participants were asked whether they used analgesics.

2.3.7. Attitude to use of analgesics

All participants were asked whether they would want to use opioids or analgesics other than opioids, or would not like to use any analgesics. Additionally, they were asked whether they had any anxiety for adverse reactions to analgesics and whether they thought that the effect of an analgesic decreased with continuous use.

2.3.8. Background

Background data on participants were collected by interview and medical record review, including age, gender, marital status, whether the participant was living with someone or had a caregiver, employment status, education level, use of health-care services, diagnosis, time since diagnosis, the worst symptoms, the number of medications, and activities of daily living (ADL). ADL was measured with the Barthel index (BI) [23], with a score ranging from 0 to 100. A BI score of 100 implies full functional independence.

2.4. Data analysis

Continuous data, such as age, other participant characteristics, and the BPI-J score, were expressed as mean and standard deviation (SD). Categorical data on the participant's characteristics, the way the patients dealt with their pain, attitudes to pain, etc., were expressed as frequency and percentage. The prevalence of pain in the preceding week was calculated. If the BPI-J score of pain intensity and interference with activities by pain was 6 or greater, this was categorized as "moderate to severe pain" and "moderate to severe interference."

Data on the use of analgesics and attitude to the use of analgesics were calculated as frequency and percentage and were analyzed with the chi-square test for the "with pain" and "without pain" groups. The worst symptom was analyzed with Fisher's exact test. Continuous data, such as age, time since diagnosis and the number of medications were analyzed with the *t*-test. All tests were two-tailed and considered significant at p level of 0.05. All statistical tests were undertaken using SAS version 9.1 (SAS Institute, Cary, NC).

3. Results

3.1. Response rate

Of the 81 patients invited to participate in the study, 80 accepted and one declined to participate in. One patient had a low HDS-R score and one patient was not eligible for other reasons, leaving 78 patients who completed the study (response rate was 96%).

3.2. Participant characteristics

The average age of participants was 61.2±10.1 years, and 53% were male (Table 1). Approximately 80% of participants lived with their family and had one or more caregiver available when care was needed. The number of unemployed participants was 50 (64%). Eighteen participants were educated to at least college or graduate school level. The number of participants with diagnosis of PD, SCD, ALS, and MS was 46 (59%), 14 (18%), 7 (9%), and 11 (14%), respectively. The mean time since diagnosis was 9.6± 8.9 years. The worst symptoms were mobility disturbance (59%) and pain (24%). The mean number of medications that participants were prescribed was 5.1±3.3. The average BI score was 92.9/100.

Table 1
Characteristics of participants (N=78)

	n	(%)
Age [mean (SD)]	61.2 (10.1)	
Gender		
Male	41	(53)
Female	37	(47)
Marital status		
Married	50	(64)
Single/divorced/widowed	28	(36)
Live		
With family	62	(79)
Single/with friend	16	(21)
Caregivers, number of		
One or more	61	(78)
None	17	(22)
Employment status		
Employed	28	(36)
Unemployed	50	(64)
Education		
College graduate or beyond	18	(23)
Junior high school/high school graduate	60	(77)
Use of health-care services		
Used	20	(26)
Not used	58	(74)
Diagnosis		
PD	46	(59)
SCD	14	(18)
ALS	7	(9)
MS	11	(14)
Time since diagnosis, years [mean (SD)]	9.6 (8.9)	
Worst symptom		
Motility disturbance	46	(59)
Pain	19	(24)
Fatigue, weakness	13	(17)
Number of medications [mean (SD)]	5.1 (3.3)	
HDS-R [mean (SD)]	28.4 (1.6)	
BI [mean (SD)]	92.9 (17.0)	

PD, Parkinson's disease, SCD, spinocerebellar degeneration, ALS, amyotrophic lateral sclerosis, MS, multiple sclerosis, HDS-R, Hasegawa's Dementia Scale — Revised (a scale of cognitive function with scores 0–30; a score <20 indicates the presence of cognitive impairment), BI, Barthel index (BI score 100 implies full functional independence).

3.3. Prevalence of pain

Of 78 participants, 46 responded that they had experienced pain in the preceding week. The prevalence of pain was 59%. Thirty-one of 46 patients with PD, 4 of 7 patients with ALS, 5 of 14 patients with SCD and 6 of 11 patients with MS experienced pain.

3.4. Pain intensity and its interference with activities

The mean pain intensity of the worst pain in the preceding week was 5.6 (SD=2.2) and 17 participants (37%) responded that the worst pain was moderate to severe. The mean pain intensity in the preceding week was 4.1 (SD=19) and 8 participants (17%) responded that the average pain was moderate to severe (Table 2).

The mean level of interference of pain in walking ability, normal work, general activities, and enjoyment of life was 4.3 (SD=3.9), 3.2 (SD=3.4), 2.8 (SD=3.3) and 2.5 (SD=3.4), respectively. For these four domains, over 20% of participants responded that pain interference in the preceding week was moderate or severe.

3.5. How participants dealt with the pain and its effects

The ways patients dealt with the pain were, in percentage order, enduring the pain (78%), changing posture frequently (50%), and use of analgesics (33%). More than half of the participants reported that the following 5 ways of dealing with their pain were effective: use of analgesics (93%), massaging/having massage (90%), cooling (89%), changing posture frequently (83%), and warming up (67%). Enduring the pain was considered effective by 39% of participants (Table 3).

Table 2
Intensity of pain and its interference with activities (N=46)

	Mean (SD)	Moderate to severe [a] n (%)
Intensity of pain [b]		
Worst pain in the preceding week	5.6 (2.2)	17 (37)
Average pain in the preceding week	4.1 (1.9)	8 (17)
Interference of pain in activities [c]		
General activities	2.8 (3.3)	11 (24)
Mood	2.5 (2.6)	6 (13)
Walking ability	4.3 (3.9)	17 (37)
Normal work	3.2 (3.4)	12 (26)
Relations with other people	2.2 (3.2)	8 (17)
Sleep	1.6 (3.2)	6 (13)
Enjoyment of life	2.5 (3.4)	9 (20)

[a] 6 or more on numerical rating scale.
[b] 0–10 numerical rating scale, where 0 is no pain and 10 is pain as bad as can be imagined.
[c] 0–10 numerical rating scale, where 0 is does not interfere and 10 is completely interferes.

Table 3
How patients dealt with their pain and its effect (N=46; multiple choice)

	n (%)	Effective n (%)
Enduring the pain	36 (78)	14 (39)
Changing posture frequently	23 (50)	19 (83)
Massaging or having massage	21 (46)	19 (90)
Warming up	18 (39)	12 (67)
Cooling	18 (39)	16 (89)
Use of analgesic	15 (33)	14 (93)
Others [a]	17 (37)	15 (88)

[a] Moxibustion, exercising, drinking warm green tea, and magnetic treatment.

3.6. Participants' attitude to pain and desire for treatment

More than 80% of participants, who experienced pain in the preceding week, considered that they had to endure the pain within their tolerance and that they had to endure it as a symptom of the disease. Half of the participants who experienced pain questioned why only he or she had to face an unpleasant experience such as pain (Table 4).

Fifty-two percent of participants who experienced pain in the preceding week asked their physician or nurse to provide information on methods of relief from pain. Eleven percent of participants were satisfied with their present treatment, while 11% wanted their physician to prescribe analgesics, to increase the analgesics presently prescribed, or to change the analgesic prescribed.

3.7. Use of analgesics and attitude to analgesics use

The number of participants in the "with pain" group who took analgesics regularly or only when they experienced pain was 13 (18%; not significantly different from the "without pain" group statistically; p=0.10) (Table 5).

Thirty-six (78%) of participants in the "with pain" group thought that the effect of analgesics decreased with regular use and 78% feared adverse reactions of analgesics.

Table 4
Participants' attitude to pain and desire for treatment (N=46; multiple choice)

	n	(%)
Attitude to participants' own pain		
Must endure pain if it is tolerable	41	(89)
Must endure pain because it is a symptom of their disease	37	(80)
Questions why only the participant has to face such an unpleasant experience	23	(50)
Desire for treatment		
Desires to be given information on methods of pain relief by physician or nurse	24	(52)
Desires to have analgesics or more analgesics prescribed, or to have a different analgesic prescribed	5	(11)
Satisfied with present treatment	5	(11)

Table 5
Use of analgesics and attitude to use of analgesics ($n=78$)

	With pain ($n=46$)		Without pain ($n=32$)		p
	n	(%)	n	(%)	
Use of analgesics					
Regular use or single use	13	(28)	3	(9)	0.10
Not used	33	(72)	29	(78)	
Thinks the effect of analgesics decreases with regular use	36	(78)	25	(78)	1.00
Fears adverse reaction of analgesics	36	(78)	22	(69)	0.49
Desires to use analgesics only when external medicine or massage does not relieve pain	30	(65)	23	(72)	0.71
Desires to use analgesics other than opioids when pain is experienced	28	(61)	24	(75)	0.29
Desires to use opioids when pain is experienced	9	(20)	19	(59)	<0.01**
No desire to use analgesics	21	(46)	9	(28)	0.18

**$p<0.01$.

Corresponding percentages in the "without pain" group were 78 and 69, respectively. There were no significant differences between the groups ($p=1.00$ and $p=0.49$ for the two variables, respectively). Thirty participants (65%) in the "with pain" group and 23 (72%) in "without pain" group responded that they desired to use analgesics only when external medicine or massage would not relieve pain ($p=0.71$). Twenty-eight participants (61%) in the "with pain" group and 24 (75%) in the "without pain" group responded that they desired to use analgesics other than opioids ($p=0.29$). The number of participants who responded that they desired to use opioids when they experienced pain was 9 (20%) in the "with pain" group and 19 (59%) in the "without pain" group ($p<0.01$). Twenty-one participants (46%) in the "with pain" group and 9 (28%) in the "without pain" group reported that they did not wish to use any analgesic ($p=0.18$).

4. Discussion

We investigated the prevalence of pain, its intensity, and interference with daily living in outpatients with neuromuscular disease, the ways in which patients dealt with their pain, and their attitude to the pain. Our findings on the use of analgesics show considerable variation in attitude to achieve relief from pain.

Fifty-nine percent of the participants had experienced pain in the preceding week and the prevalence of pain of PD, ALS, SCD, and MS was 67%, 57%, 36%, and 55% respectively. In Japan the prevalence of pain in neuromuscular disease is greater than that of chronic pain in the general population (13%) [24]. This suggests that pain is common in neuromuscular disease and is not relieved sufficiently.

The percentages of the pain intensity for the worst and average pain in preceding week were moderate to severe and similar to those reported in previous research [9]. However, in previous research, 58.5% of the participants took analgesics or adjuvant analgesics such as steroids, anticonvulsants, antidepressants, and muscle relaxants. In contrast, in this study, only 28% (13 of the 46 participants with pain) of the participants with pain use analgesics. This suggests that the appropriate use of analgesics or adjuvant analgesics might relieve pain, although therapies other than pharmacotherapy might also reduce pain.

Interference with mobility (walking ability, normal work, general activities, and enjoyment of life) was moderate to severe in more than 20% of the participants. Interference in mood, relations with other people, and sleep was moderate to severe in more than 10%. This suggests that pain interferes in a wide range of aspects of daily life, and needs to be relieved. Some studies point out that a decline in daily activities leads to depression or low quality of life (QOL) [25]. Pain has been shown to prevent people from continuing physiotherapy [3]. Thus, maintenance of activities with the proper use of analgesics and physiotherapy may also prevent a decline in QOL.

Many participants dealt with pain without the use of analgesics, such as by changing their posture frequently and by massaging themselves or having a massage. This may not only be due to negative aspects of the image of analgesics, but also be due to the belief that an individual should accept pain as a companion in their life, and as something that they should endure [24]. However, most of the participants who used moxibustion, exercised, drank warm green tea and used magnetic treatment, did experience pain relief. More information needs to be obtained about the alternative methods of pain relief.

Many participants regarded their pain as something they should endure. A previous study on health-seeking behavior for acute pain suggested that Japanese people tend to delay health-seeking behavior because they think that the symptoms will go away and that the symptoms are not serious [26]. The participants in the present study might have thought that their own pain would go away or was not serious. In addition, patients might regard the reporting of pain to their physician or asking their physician to prescribe analgesics as complaining behavior in a negative sense.

While half of the participants who had experienced pain asked their physician or nurse to provide information about methods of pain relief, only 11% of participants requested to be prescribed analgesics. Participants want to relieve pain, but might not want to take analgesics for fear of their adverse reactions. It is important that the physician and nurse explain the necessity of relief from pain and give information about the methods for pain relief. They should additionally encourage the patients to deal with pain through physical therapy and other means. It is also important that medical specialists try to allay patients' anxiety about analgesics.

The shorter time after diagnosis for the patients who reported pain suggests that pain may occur at any time after diagnosis. Thus, physicians and nurses need to assess pain in their patients from an early phase of their disease [3]. While

72% of the participants with pain did not use any analgesics, 28% of the participants who took analgesics regularly or on a single occasion responded that they had experienced pain in the preceding week. This suggests that it may be difficult to relieve pain in these patients or that their analgesics may not have been appropriate for the relief of their pain [3,10]. The intention of using analgesics was not generally different in participants with or without pain. One possible reason is the negative image of analgesics and adverse reactions or the fear of a decrease in effect with regular use. A second reason may be that most of the participants wanted causal treatment rather than symptomatic treatment [24]. A third reason may be that the patients underestimate their own pain or regarded it as untreatable. To achieve relief from pain, the negative image of analgesics must be removed, and physicians and nurses must educate patients about appropriate methods for pain relief. It is also important to clarify the reasons why patients have a passive attitude to the use of analgesics and the attitudes of physicians and nurses to pain relief.

4.1. Study limitations

There are several limitations of this study. Because of the small number of participants, generalization of the results is difficult. The cause of the pain in these participants is not considered, so we cannot say whether the pain experienced by the participants was related to their neuromuscular disease. Finally, because the reliability and validity of the BPI-J for use in neuromuscular diseases have not yet been established, pain intensity and its interference in the participants' activities may have been under- or overestimated.

5. Conclusion

This study revealed that the prevalence of pain in outpatients with neuromuscular disease (PD, ALS, SCD, or MS) was 59%. The percentage of patients in whom the intensity of the worst and average pain in the preceding week was moderate to severe was 37% and 17%, respectively. Pain had moderate to severe interference with mobility in more than 20% of participants. Although analgesic use was the most effective means of relieving pain, only 33% of participants used analgesics and many participants dealt with pain by other means. Patients want more information about methods of relief from pain other than the use of analgesics. It is important for medical staffs to provide more information to patients actively. It is required in future to clarify the reason why patients are reluctant to use analgesics.

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Case Report

A CASE SERIES OF CHILDREN WITH HIGH-RISK METASTATIC NEUROBLASTOMA TREATED WITH A NOVEL TREATMENT STRATEGY CONSISTING OF POSTPONED PRIMARY SURGERY UNTIL THE END OF SYSTEMIC CHEMOTHERAPY INCLUDING HIGH-DOSE CHEMOTHERAPY

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□ *The aim of this study was to clarify the feasibility of a novel treatment strategy consisting of postponed primary surgery till the end of systemic chemotherapy including HDC without interruption by local therapy for neuroblastoma patients at a high risk for relapse. After induction chemotherapy, patients received double conditioning HDC consisting of thiotepa and melphalan. Radical surgery was applied to local lesions. Irradiation was not applied to any lesions. Eleven consecutive pediatric neuroblastoma patients were treated according to this strategy. Seven of 11 patients remained in complete remission for 21[171 months. This treatment strategy seems feasible and a further study is warranted.*

Keywords delayed primary surgery, high-dose chemotherapy, high-risk neuroblastoma, melphalan, thiotepa

Advanced neuroblastoma is a systemic disease that spreads to the whole body, including the bone marrow, liver, lymph nodes, and bones. Morphologic or radiologic methods only detect metastases larger than a certain size. This indicates that high-risk neuroblastoma should be considered as a

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systemic disease and that an increase of chemotherapy intensity is a premise for the improvement of treatment outcome. Indeed, the only method that has been proven to significantly improve survival is strengthening of chemotherapy intensity, including high-dose chemotherapy (HDC) with stem cell rescue. Thus, HDC with stem cell salvage following intensive induction chemotherapy has been widely accepted as being required for neuroblastoma treatment in high-risk groups, and treatment results have improved [1–5]. However, the 5-year event-free survival (EFS) rate is 30–40% and remains unsatisfactory despite various intensive efforts [3–5].

Neuroblastoma cells acquire resistance to chemotherapy in the early stages of treatment: it is therefore a premise for attaining a cure to eradicate tumor cells before they acquire chemotherapy resistance. We therefore assumed that interruption of systemic chemotherapy and/or reduction of dose intensity by surgery and radiotherapy might promote acquisition of drug resistance by malignant cells and clonal evolution. We also assumed that intensive chemotherapy combined with potent HDC might enable us to postpone local therapy until after the completion of all systemic chemotherapies. Based on this hypothesis, we postponed local therapy until the completion of all systemic chemotherapies, which made it possible to administer intensive chemotherapy in a shorter period of time and increase chemotherapy intensity without interruption of chemotherapy. As local therapy, surgery for the primary focus and residual metastases was finally performed at completion of treatment and response to chemotherapy was then evaluated pathologically.

With respect to local therapy, no difference has been observed in the EFS rate between gross total resection and partial resection in prospective studies despite a decrease in local recurrence rate with gross total resection [6, 7]. In a similar manner, local radiotherapy has been clearly shown to reduce local recurrence [8], but its contribution to the improvement of EFS has not been proven [9, 10]. Thus, though extensive local therapy reduces the local recurrence rate, it does not significantly contribute to increased survival. Since we assumed the significance of local surgery might increase under sufficient control of systemic disease, gross total resection was attempted in all patients. Radiotherapy was not performed because of the acute adverse effects and late complications following intensive chemotherapy. We report the results of this novel treatment approach in a consecutive series of 11 children (1992–2005) with high-risk abdominal neuroblastoma.

PATIENTS AND METHODS

Patients

Eleven consecutive pediatric patients with abdominal and mediastinum neuroblastoma at high risk for relapse were treated according to the

current treatment strategy. The high-risk category includes International Neuroblastoma Staging System (INSS) stage 4 for patients aged ≥1 year and $MYCN^+$ stage 4 for those aged <1 year. Table 1 summarizes the clinical data for the 11 patients (6 males; 1 aged <1 year; age range 6–64 months (median, 33 months)). Amplification of the MYCN gene was analyzed in primary tumors at first surgery in 8 patients and in bone marrow samples for the other 3. Six patients had MYCN amplification and 5 had no amplification by fluorescence in situ hybridization analysis. Seven of 8 patients who underwent biopsy of primary tumor or metastatic lymph nodes had unfavorable histopathological findings. Eight patients had poorly differentiated neuroblastoma and 1 had undifferentiated neuroblastoma according to the International Neuroblastoma Pathology Classification. Three patients (#6, #8, and #11) did not undergo biopsy at the outset but histological confirmation was performed in patient 6 at final surgery.

Induction Chemotherapy

For induction chemotherapy, we basically employed the new A1 regimen (cyclophosphamide (CPA) 1.2 g/m^2, etoposide (VP-16) 100 mg/m^2 × 5, tetrahydropyraniyl-adriamycin (THP-ADR) 40 mg/m^2, and cisplatin (CDDP) 90 mg/m^2) or the 98A3 regimen (CPA 1.2 g/m^2 × 2, CDDP 90 mg/m^2, THP-ADR 40 mg/m^2, and vincristine (VCR) 1.5 mg/m^2). We administered newA1 or 98A3 regimen every 4 weeks. Three patients received carboplatin (CBDCA) instead of CDDP because of insufficient renal function. Irinotecan was additionally administered to 4 patients [11]. Induction chemotherapy was administered for 3–6 courses, principally until normalization of tumor markers (neuron-specific enolase (NSE), vanillylmandelic acid (VMA), and homovanillic acid (HVA)) and disappearance of distant metastases. The disappearance of metastasis was evaluated by computed tomography, technetium-99 bone scan, bilateral bone marrow aspiration, and iodine-123 metaiodobenzyl-guanidine scan.

High-Dose Chemotherapy

After induction chemotherapy, patients received a double-conditioning regimen of 2 cycles of high-dose chemotherapy (HDC) consisting of thiotepa and melphalan [12]. Patients aged ≥2 years received 800–1000 mg/m^2 of thiotepa and 280–300 mg/m^2 of melphalan, and patients aged <2 years at HDC received 32 mg/kg of thiotepa and 6 mg/kg of melphalan. This HDC regimen consisted of 2 cycles of administration of thiotepa and melphalan with a 1-week interval; thiotepa (140–200 mg/m^2/day) and melphalan (50–75 mg/m^2/day) were administered on days −11, −10, -4 and −3. When creatinine clearance (Ccr) was <90 mL/min/1.73m^2 in

TABLE 1 Characteristics of Patients with Stage 4 Neuroblastoma

Patient	Age (mo.)	Gender	Primary site	INSS stage	Metastatic site at diagnosis	MYCN	Histology	
							INPC	Shimada
1	25	F	Adrenal	4	LN, B, BM	no amp	Poorly diff. NB	UH
2	53	M	Adrenal	4	LN, B	no amp	Poorly diff. NB + GN	UH
3	20	M	Adrenal	4	LN, B, BM, Lu	14	Undiff. NB	UH
4	19	M	Adrenal	4	LN, B	>20	Poorly diff. NB	UH
5	6	M	Adrenal	4	LN, BM, L	12	Poorly diff. NB	FH
6	48	F	Adrenal	4	LN, B, BM	20	N.E	N.E
7	29	F	Adrenal	4	LN, B, BM	>10	Poorly diff. NB	UH
8	33	M	Adrenal	4	LN, B, BM	>10	N.E.	N.E.
9	54	M	Retroperitoneum	4	LN, B, BM	no amp	Poorly diff. NB	UH
10	64	F	Retroperitoneum	4	LN (mediastinum)	no amp	Poorly diff. NB	UH
11	49	F	Mediastinum	4	B, BM	no amp	N.E.	N.E.

Note. B, bone; BM, bone marrow; F, female; FH, favorable histology; GN, ganglioneuroblastoma; INPC, International Neuroblastoma Pathology Classification; L, liver; LN, lymph node; Lu, lung; M, male; N.E., not evaluable; Poorly diff. NB, poorly differentiated neuroblastoma; UH, unfavorable histology; Undiff. NB, undifferentiated neuroblastoma.

TABLE 2 Induction Chemotherapy and Preconditioning Regimens

Patient	Conventional protocol	Chemotherapy (no. of courses)	Time to HDC from onset (days)	Time of stem cell harvest (course)	Stem cell source	Conditioning regimen	
						Thiotepa (mg/m^2)	Melphalan (mg/m^2)
1	new A1[a]	3	120	3	Auto-BM	1000	300
2	new A1	5	130	2	Auto-PB	800	280
3	new A1[a]/ CPT-11	6		N.D.	N.D.		
4	new A1[a]	5	167	3	Auto-BM	1000	280
5	98A3 / CPT-11	6	185	N.D	u-CB	26[c]	6[b,c]
6	98A3 / CPT-11	5	165	N.D	u-CB	760[b]	210[b]
7	98A3→98A3/ CPT-11	4	139	2 (PB) and 4 (BM)	Auto-PB, BM	800	280
8	98A3	5	167	5	Auto-BM	800	280
9	98A3	4	167	2	Auto-PB	720[d]	252[d]
10	98A3	4	132	1	Auto-PB	720[d]	252[d]
11	98A3	4	148	3 (PB) and 4 (BM)	Auto-PB, BM	570[d]	200[d]

Note. Auto-BM, autologous bone marrow; Auto-PB, autologous peripheral blood; CBDCA, carboplatin; CDDP, cisplatin; CPT-11, irinotecan N.D., not done; u-CB, unrelated cord blood.

[a]CBDCA was administered instead of CDDP.

[b]Drug dose was reduced because of transplantation from allogeneic donors.

[c]Drug was administered in terms of body weight (mg/kg).

[d]Drug dose was reduced to 70–90% of the prescribed dose according to renal function.

patients aged ≥2 years, dosage was adjusted according to the following formula: given dose (mg/m^2) = (Ccr/100) × 800 mg/m^2 (thiotepa) or 280 mg/m^2 (melphalan). In the case of allogeneic transplantation, doses of these drugs were reduced, because of severe gastrointestinal toxicity due to these alkylating agents. Peripheral blood stem cells (PBSCs) and bone marrow cells were used as salvage stem cells in 4 and 3 patients, respectively. Because PBSC count was insufficient for stem cell rescue in 2 patients, bone marrow cells were also transfused with PBSCs. Autologous bone marrow was used in the patients in whom PBSCs could not be harvested: this was performed at the end of induction chemotherapy. PBSCs were harvested after the 1st to 4th course of induction chemotherapy, after morphologic disappearance of tumor cells from bone marrow. In the 2 patients in whom disappearance of tumor cells from bone marrow was delayed, unrelated umbilical cord blood was used (Table 2).

Local Therapy

After all courses of chemotherapy including HDC, radical surgery was finally applied to remove tumor tissue in local lesions when bone marrow function was acceptably recovered for surgery. Total resection for primary tumor as well as lymph node metastases was attempted. All lesions where the primary tumor and local lymph node metastases existed in onset of the disease were explored and if any suspected tumor tissue was existed, then resection was performed.

CT scan was performed after surgery to confirm no residual tumor in local lesions in all cases. Irradiation was not applied to any local lesions.

RESULTS

Response to Induction Chemotherapy

In 1 patient (#3), tumors did not respond to induction chemotherapy and he showed progressive disease. He died from progression of pulmonary metastatic tumors 6 months after diagnosis before HDC. After 3–6 courses (median, 5 courses) of induction chemotherapy, 10 patients received HDC. Time from initial diagnosis to HDC was 4–6 months (median, 5 months). With respect to metastases at initial diagnosis in patients who received HDC, these were detected in bone ($n = 8$), bone marrow ($n = 7$), lymph node ($n = 9$), and liver ($n = 1$)and evaluated by computed tomography, technetium-99 bone scan, bilateral bone marrow aspiration, and iodine-123 metaiodobenzyl-guanidine scan. After induction chemotherapy, the bone marrow metastases disappeared in all patients, but liver and bone metastases each remained in 1 patient, respectively. Primary tumors and regional lymph node metastases remained in all patients. Tumor marker levels were

normalized in all patients. At HDC, 7 patients attained PR and 2 VGPR according to International Neuroblastoma Response Criteria.

Response to High-Dose Chemotherapy

Nine patients received HDC at PR or VGPR. The size of one primary tumor did not change. After HDC, residual bone metastases disappeared in 1 patient. Liver metastases persisted in 1 patient. Five primary tumors that decreased to below 50% after conventional chemotherapy decreased to below 10% and the sizes of primary tumors did not change dramatically, but metastatic lymph nodes disappeared in 2 patients. With respect to adverse reactions observed during HDC, fungal osteomyelitis was observed in 1 patient who received allograft. In addition, gastrointestinal tract mucositis with bloody stools was observed in 1 patient and NCI-CTC grade III mucositis was noted in all patients.

Surgery and Pathological Evaluation of Tumors

Radical surgery was performed in each patient, resecting all recognizable lesions, including the primary tumor and affected lymphatic tissues. The timing of surgery was 2 months after the initiation of HDC in most patients who received autologous stem cell transplantation, and it was prolonged to 4 months in the patients who underwent allogeneic transplantation and/or had HDC-related complications (Table 3).

We evaluated the effect of chemotherapy including HDC by comparing tumor specimens resected at outset and second-look surgery in 6 patients, according to the histologic criteria for the effects of anticancer therapy for pediatric solid malignant tumors in Japan (Table 4) [13]. We were not able to evaluate the remaining 4 patients as insufficient amounts of pretreatment specimen were available. Necrotic or fibrous lesions were seen in one-third to two-thirds of the area of tumor tissues (Ef1b) of 1 patient. In the 4 cases, prominent necrosis and loss of tumor cells were observed in more than two-thirds of the tumor area and was associated with fibrosis and calcification (Ef2). On histological examination, the specimens from almost all, except one (#11), resected primary tumors had some degree of residual tumor tissue and in occasional cases viable tumor tissue was recognized in concurrently resected lymph nodes. However, residual tumor tissue consisted of scattered nests of neuroblastic cells in degenerative fibrous tissue, occasionally associated with Schwannian cell proliferation. Neuroblastic cells were more differentiating with abundant neutrophil formation as compared to pretreatment tumors. The preoperative induction chemotherapy and HDC produced remarkable cytotoxic effects and induced differentiation toward ganglionic cells. Examples of the histopathologic changes resulting from treatment are shown in Figures 1 and 2.

TABLE 3 Response to Treatment and Outcome

Patient	Response to induction chemotherapy			Response to induction chemotherapy and HDC			Time to surgery		Post therapy histology classification[a]	Outcome from diagnosis (mo.)
	Response	Residual site	VMA,HVA (mg/mg_{Cr})[c]	Response	Residual site	VMA, HVA (mg/mg_{Cr})[c]	From HDC (days)	From onset (days)		
1	PR	P/LN	≦20, ≦20	PR	P/LN	≦20, ≦20	96	216	N.E.	EFS (171)
2	PR	P/LN	N.E.[d]	VGPR	P	N.E.[d]	79	209	N.E.	EFS (104)
3	PD	–		–	–		––	––	–	PD (3[b])
4	PR	P/LN/B	N.E.[d]	VGPR	P	N.E.[d]	68	235	Ef1b	EFS (159)
5	PR	L/LN	≦20, ≦20	PR	L/LN	≦20, ≦20	106	291	Ef2	EFS (73)
6	PR	P/LN	N.E.[d], ≦20	VGPR	P	N.E.[d] ≦20	99	264	N.A	EFS (57)
7	PR	P/LN	N.E.[d], ≦20	VGPR	P	N.E.[d], ≦20	52	191	Ef2	Relapse in LN (24)
8	VGPR	P	≦20, ≦20	VGPR	P	≦20, ≦20	83	250	N.E.	EFS (38)
9	VGPR	P	≦20, ≦20	VGPR	P	≦20, ≦20	85	252	Ef2	Relapse in multiple sites (20)
10	PR	P	≦20, ≦20	VGPR	P	≦20, ≦20	50	182	Ef2	Relapse in LN (18)
11	PR	P	≦20, ≦20	PR	P	≦20, ≦20	55	203	Ef3	EFS (21)

Note. B, bone; CR, complete response; EFS, event-free survival; HDC, high-dose chemotherapy; L, liver; LN, lymph node; NR, no response; P, primary; PD, progressive disease; PR, partial response; VGPR, very good partial response. HVA, urine homovanillic acid; VMA, urin vanillylmandelic acid.

[a]Pathological classification according to the Committee on Histological Classification of Childhood Tumors, Japanese Society of Pathology (see Table 4).

[b]Decreased.

[c]The level of VMA and HVA are revised by urin creatinin. Normal levels of VMA and HVA are below under 20 mg/mg Cr in our institute for every age.

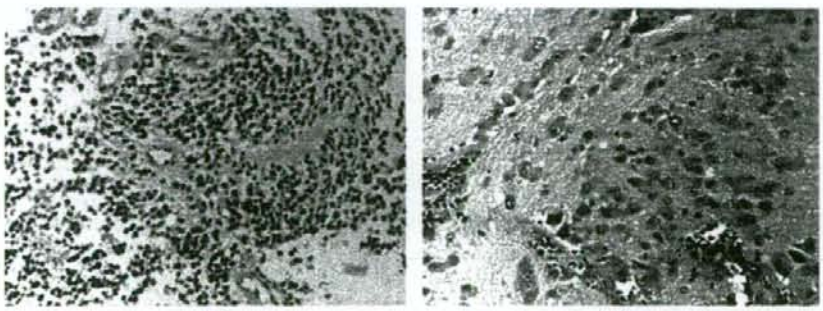
[d]Normal levels of cathecholamine at onset.

TABLE 4 Pathological Classification of Treatment Effect According to the Committee on Histological Classification of Childhood Tumors, Japanese Society of Pathology

Ef0	No effect
Ef1a	Necrosis of tumor cells in less than one-third of tumor area
Ef1b	Necrosis of tumor cells in less than two-thirds and in more than one-third of tumor area
Ef2	Necrosis and disappearance of tumor cells plus calcification and fibrosis in more than two-thirds of tumor area
Ef3	All tumors are affected by obvious necrotic tissue and no tumor cells are seen

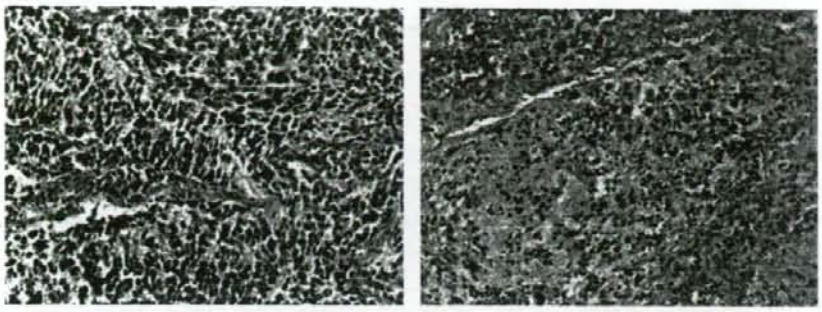
Outcome

Altogether, 10 of 11 patients received HDC and 7 patients have remained in remission for 21–171 months (median, 73 months). In 2 patients (#7 and #10), the tumor relapsed in regional abdominal and thoracic lymph nodes after 24 and 18 months, respectively, from initial diagnosis. In patient #9, relapse was observed in multiple sites including bone, bone marrow, and lymph nodes 20 after from diagnosis. After gross total resection of the tumors, patient #7 received salvage chemotherapy, consisting of irinotecan and topotecan, and local irradiation. Finally, allogeneic stem cell transplantation preconditioned with fludarabine and busulfan was performed. She has been in remission for 21 months after relapse. The other 2 patients are currently undergoing treatment.



(a) (b)

FIGURE 1 Histological findings for primary tumor is from patient 4: (a) before treatment—poorly differentiated subtype with low mitosis karyorrhexis index (MKI); and (b) after HDC—residual tumor nests of differentiating neuroblastic cells.



(a) (b)

FIGURE 2 Histological findings for lymph node metastasis from patient 5: (a) before treatment—poorly differentiated subtype with low mitosis karyorrhexis index (MKI); and (b) after HDC—extensive necrosis with residual differentiating neuroblastic cell nests.

DISCUSSION

Primary surgery is generally and traditionally performed between induction chemotherapy and HDC. It might be possible that tumor cells become more sensitive to chemotherapy after mass reduction, but the rationale of the timing of local therapy is unclear. In this case series, we performed primary surgery after completion of induction chemotherapy and HDC based on the hypothesis that consecutive conventional and high-dose chemotherapies without interruption by local therapy can eradicate systemically spread tumor cells before acquisition of resistance to cytotoxic drugs and clonal evolution of resistant clones. The disadvantage of this treatment strategy is the increased risk for metastasis of tumor cells residing in the local tumors and emergence of resistant clones in these. Among 11 consecutive high-risk patients with stage 4 neuroblastoma, except 1 patient whose tumors were primarily refractory to induction chemotherapy, none displayed progressive disease before local surgery; 7 patients remain in event-free survival; and systemic relapse was observed in only 1 patient.

The disadvantage of performing surgery during chemotherapy appears to be related to the interruption of systemic therapy. Furthermore, when intraoperative/postoperative complications occur, discontinuation of systemic chemotherapy may be prolonged and this may cause systemic relapse. In performing surgery after all courses of chemotherapy, the timing of surgery can be selected under conditions of sufficient tumor control. Surgery was safely performed after recovery of hematopoiesis in this series.

In this treatment strategy, HDC plays a key role, since less potent HDC may allow progression of the local tumor. For HDC, we employed a double-conditioning regimen consisting of thiotepa and melphalan, as previously reported [12]. These agents were chosen for the treatment of neuroblastoma, as they show efficacy as high-dose, single-agent therapy for

neuroblastoma and are not used for conventional chemotherapy prior to HDC [4, 14, 15]. This HDC regimen consisted of 2 cycles of administration of thiotepa and melphalan with a 1-week interval: this interval facilitated combination therapy at the maximum tolerated dose of a single agent without severe complications. The major adverse effect of this regimen is gastrointestinal mucositis and narcotic drugs are frequently required. However, life-threatening complications such as veno-occlusive disease and renal insufficiency are not observed.

In this case series, the effect of chemotherapy was pathologically validated in primary tumors. No residual tumor cells were observed except in one patient. Scattered viable tumor cells were detected in other resected tumor specimens, though the number of these cells was small and they were embedded in the connective tissue. Similar findings were observed in regional lymph nodes. These scattered cells are tightly embedded in fibrous tissue and might possibly proliferate, contributing to relapse. Thus, it was shown that even HDC rarely totally eradicates tumor cells of the primary tumors.

Concerning local therapy, gross total resection was eventually performed after completion of all systemic chemotherapies. No conclusion has been drawn concerning the role of gross total resection. With our treatment strategy, systemic disease seemed to be controlled sufficiently, and under such conditions the significance of the local therapy may increase. Radiation therapy was not performed in this case series and local recurrence was observed in 2 patients without recurrence in other sites. This might suggest that radiotherapy is beneficial to selected patients who undergo gross total resection. To identify these patients, histopathological evaluation of chemotherapy outcome may provide useful information, in addition to the extent of local disease at initial diagnosis and the extent of surgery. Although the relationship between histopathological findings and clinical outcome was unclear in this series, recruitment of additional patients may assist in drawing some conclusions.

This novel treatment strategy consisting of the postponement of local surgery until the end of chemotherapy combined with intensive induction and consolidation chemotherapy seems feasible. A multicenter phase II study is being planned in Japan to confirm the utility of this strategy.

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