The prognosis of patients with acute promyelocytic leukaemia (APL), a distinct subtype of acute myeloid leukaemia (AML) (Grignani *et al*, 1994), has been improved dramatically by the introduction of differentiation induction therapy with all-*trans* retinoic acid (ATRA) (Fenaux *et al*,1999; Tallman *et al*, 2002; Sanz *et al*, 2004). However, recent clinical trials with ATRA and anthracycline-based chemotherapy found that recurrent disease posed a major problem, especially for high-risk patients. (Sanz *et al*, 2000, 2009).

Childhood APL, which consists of only 7–10% of all patients, is often associated with risk factors such as hyperleucocytosis (Guglielmi *et al*,1998; Mann *et al*, 2001); however, few studies of paediatric patients have specifically examined its long-term prognosis. In those studies, the complete remission (CR) and overall survival (OS) rates have been improved to >80%, but event-free survival (EFS) remains at around 70–80% because of increased cumulative incidence of relapse (CIR). (de Botton *et al*, 2004; Ortega *et al*, 2005; Testi *et al*, 2005) In addition to frequent relapse in the bone marrow, extramedullary (EM) relapse involving mostly the central nervous system (CNS) occurs at incidence of 1–5%. (Ko *et al*, 1999; de Botton *et al*, 2006; Chow & Feusner, 2009) The therapeutic effectiveness of cytarabine added to anthracycline-based consolidation therapy has been reported for high-risk adult patients(Adès *et al*, 2006, 2008), but the efficacy of cytarabine in addition to the combination of ATRA and anthracyclines in consolidation remains unknown for paediatric patients.

More recently, there has been increasing concern regarding long-term adverse effects, including cardiotoxicity and secondary malignancy, for children with leukaemia. The cumulative dosage of anthracyclines may be related to the risk of late cardiotoxicity as well as therapy-related myelodysplastic syndrome (t-MDS)/AML for childhood malignancies (Nysom *et al*,1998; Le Deley *et al*, 2003). Although such effects of anthracyclines are yet undetermined for APL, the cumulative dosage of anthracyclines may be an important perspective of the long-term prognosis of children with APL.

This report describes the outcome of a prospective study for childhood APL, AML99-M3, in which patients received therapy with cytarabine in addition to ATRA and anthracyclines. The improved outcome of this study suggests that the combination of cytarabine, ATRA and anthracyclines may have useful implications in the perspective of long-term prognosis and late adverse effects for childhood APL.

Patients and methods

Patients

Between August 1997 and March 2004, 58 children with *de novo* APL (31 males and 27 females; median age of 11 years [range:11 months – 16 years] were enrolled in the AML99-M3 study of the Japanese Childhood AML Cooperative Study Group, and a follow-up survey was performed in May 2010 (Table I). Three patients with APL were not recruited to this study: two had already started another chemotherapeutic regimen for AML when APL was diagnosed; the other died of intracranial haemorrhage (ICH) at diagnosis. The relevant institutional review board approved the protocol. Written informed consent was obtained from the parents of all patients. APL was diagnosed according to the French–American–British (FAB) criteria (Bennett *et al*, 1982); the involvement of t(15;17) translocation was examined cytogenetically. APL patients with t(15;17) translocation or *PML-RARA* chimaeric gene confirmed through examinations with fluorescence *in situ* hybridization (FISH) or reverse transcription–polymerase chain reaction (RT-PCR) were registered to this study.

Treatment protocol

In remission induction therapy, ATRA was initiated (45 mg/m^2, until CR) and then daunorubicin (45 mg/m^2 per d, days 6–8) and cytarabine (200 mg/m^2, days 6–12) were added (Fig 1). For patients with a white blood cell (WBC) count $>10 \times 10^9$/l at diagnosis or after the initiation of ATRA therapy, chemotherapy was started before day 6. Consolidation

Table I. Characteristics of patients with APL (N = 58).

Characteristics	Median	Range	No. (%)
Age, years	11	0·9–16	
<5			9 (16)
5 to 10			14 (24)
>10			35 (60)
Sex			
Male			31 (53)
Female			27 (47)
WBC, $\times 10^9$/l	4·3	0·7–171	
<10			36 (62)
≥10			22 (38)
Haemoglobin, g/l	91	37–131	
<10			44 (76)
≥10			14 (24)
Platelets, $\times 10^9$/l	2·3	5–233	
<40			48 (83)
≥40			10 (17)
FAB subtype			
Typical			53 (91)
Variant			5 (9)
Cytogenetics			
t(15;17)			47 (81)
t(15;17) + others			9 (15)
Normal			1 (2)
Unknown			1 (2)
PML-RARA			
Examined			47 (81)
Long isoform (bcr1)			21
Short isoform (bcr3)			8
bcr not determined			18
Not examined			11 (19)

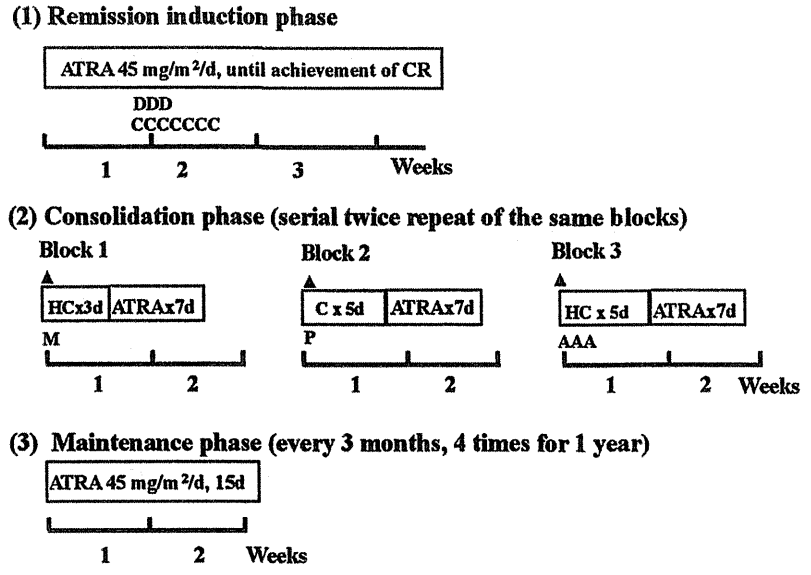

Fig 1. Scheme of AML99-M3 protocol. In remission induction, oral administration of ATRA (45 mg/m^2 per d) was combined with daunorubicin (D) (45 mg/m^2) and cytarabine (C) (200 mg/m^2). In consolidation, administration of ATRA (45 mg/m^2 per d for 7 d) was combined with mitoxantrone (M) (10 mg/m^2 per d, day 1) and high-dose cytarabine (HC) (3 g/m^2 × 2/d, days 1–3) in Block 1, with pirarubicin (P) (45 mg/m^2 per d, day 1) and cytaratibine (C) (200 mg/m^2 per d, days 1–5) in Block 2, and with aclarubicin (A) (30 mg/m^2 per d, days 1–3) and high-dose cytarabine (HC) (3 g/m^2 per d, days 1–5) in Block 3. For CNS prophylaxis, intrathecal injection (▲) of methotrexate, cyatarbine and hydrocortisone at day 1 of every consolidation block in age-adjusted doses as described in Methods. In maintenance therapy, ATRA (45 mg/m^2 per d, days 1–15) was administrated every 3 months for 1 year.

therapy consisted of six courses of block treatment (Blocks 1, 2 and 3), in which each block was performed every month and the same block was repeated serially twice. In respective blocks, chemotherapy with cytarabine and each of the different anthracycline agents was administrated respectively and then ATRA (45 mg/m^2 per d, 7 d) was administrated consecutively. Block 1 consisted of mitoxantrone (10 mg/m^2 per d × day 1) and cytarabine (3 g/m^2 × 2/d × days 1–3), Block 2 of pirarubicin (45 mg/m^2 per d × day 1) and cytarabine (200 mg/m^2 per d × days 1–5), and Block 3 of aclarubicin (30 mg/m^2 per d × days 1–3) and cytarabine (3 g/m^2 per d × days 1–5). On the first day of each consolidation block, patients received intrathecal (IT) therapy with methotrexate (3 mg for <3 months; 6 mg for 3 months to <1 year; 7·5 mg for 1 year; 10 mg for 2 years; 12·5 mg for 3 years or older), cytarabine (6 mg for <3 months; 12 mg for 3 months to <1 year; 15 mg for 1 year; 20 mg for 2 years; 25 mg for 3 years or older) and hydrocortisone (10 mg for <3 months; 10 mg for 3 months to <1 year; 15 mg for 1 year; 20 mg for 2 years; 25 mg for 3 years or older). In maintenance therapy, ATRA alone (45 mg/m^2 per d) for 15 consecutive days was given every 3 months, for a total of four times during 1 year.

Adverse effects

Retinoic acid (RA) syndrome was diagnosed based on clinical signs, including fever, respiratory distress, pulmonary infiltration, pleural and pericardial effusion and renal failure. (Ko *et al*, 1999) When RA syndrome was diagnosed or strongly suspected, ATRA therapy was stopped and the patients received administration of dexamethasone (8 mg/m^2 per d, i.v. in two doses) unless they clinically improved. Disseminated intravascular coagulopathy (DIC), bacterial infections, and other adverse effects were summarized in each phase of treatment. Long-term adverse effects, including cardiotoxicity and secondary malignancy, were surveyed through followe-up analysis. For evaluation of the potential risk of cardiotoxicity, cumulative doses of anthracyclines were converted to equivalent doses of daunorubicin using ratios in 1:3–1:5 for idarubicin/mitoxantrone, 1:1·6 for pirarubicin, and 1:0·2 for aclarubicin (Warrell, 1986; Lenk *et al*, 1990; Sakata-Yanagimoto *et al*, 2004).

Minimal residual disease (MRD) monitoring

For MDR monitoring, the *PML-RARA* chimaeric mRNA in marrow samples was detected using RT-PCR as described (Suzuki *et al*, 2001). Serial evaluation of MRD monitoring was performed every 3 months for 17 patients whose bone marrow samples were sent to the reference laboratory.

Statistical analysis

The OS and EFS were calculated from the beginning date of induction therapy to the date of events; failure to achieve CR, relapse or death of any cause. The OS and EFS were analyzed

using the Kaplan–Meier method. Statistical analyses used the Statistical Package for the Social Sciences (SPSS) software, version 16 (SPSS Japan Inc., Tokyo, Japan), estimated by the log-rank test and considered to be significant when a P value is <0·05. For patients who achieved CR, cumulative incidence functions of relapse as well as death without relapse were calculated using the competing risk method with the cmprsk software package (http://biowww.dfci.harvard.edu/~gray), ver.2.1-5 on R ver.2.10.1.

Results

Patient characteristics

The median follow-up period of 58 patients was 86 months (range: 16 d–12·1 years) (Table I). The median age of patients was 11 years (range: 11 months–16 years); 35 (60%) patients were over 10 years old; 31 patients were male and 27 were female. The WBC counts at diagnosis were 0·9–171 × 10^9/l (median: 4·3 × 10^9/l) and 22 patients (38%) had WBC counts >10 × 10^9/l. The proportion of these high-risk patients was comparable to that (35–48%) reported by other studies for childhood APL (de Botton *et al*, 2004; Ortega *et al* 2005; Testi *et al*, 2005). Haemoglobin levels were 37–131 g/l (median: 91 g/l). Platelet counts were 5–233 × 10^9/l (median: 23 × 10^9/l) and 48 patients (83%) had a platelet count <40 × 10^9/l at diagnosis. Haematological examination identified FAB:M3 morphology in 53 patients and five others exhibited the microgranular FAB: M3v morphology. No patient showed leukaemic infiltration in the cerebrospinal fluid obtained by lumbar puncture performed for CNS prophylaxis at the beginning of consolidation therapy.

Cytogenetic examination revealed that 47 patients had t(15;17) translocation abnormality alone, nine had t(15;17) with additional chromosomal abnormalities, one with normal karyotype, and one with no result. In the latter two patients, the involvement of *PML-RARA* chimaeric gene was confirmed using RT-PCR. Examinations for *PML-RARA* were performed in 47 patients. RT-PCR detected *PML-RARA* in 29 patients, 21 of whom showed the long type (bcr1) isoform; eight showed the short type (bcr3) isoform. Eighteen patients had *PML-RARA* detected by FISH analysis without differentiation of the isoform types. No patient had ATRA-insensitive fusion genes, such as the *ZBTB16-RARA* caused by the t(11;17) chromosomal translocation.

Clinical course and statistical analysis

In induction therapy, two patients (3·4%) died from ICH and pulmonary bleeding after 16 and 24 d respectively. CR was achieved in 56 patients (96·6%), two of whom exhibited relapse at bone marrow; one relapsed at 15 months and died of ICH, the other relapsed at 19 months and remains in second CR after treatment with marrow transplantation. For patients who achieved CR, the period of ATRA administration in induction was a median of 29 d (range 14–60 d), during which 13 patients temporarily discontinued the administration of ATRA for a median 4 d (range 1–31 d). Overall, four patients died: two of DIC with haemorrhage during induction, one of sepsis and meningitis in remission, and one of ICH after relapse. Consequently, the OS and EFS rates at 7 years were respectively, 93·1% (95% confidence interval [CI], 86·5–99·7%) and 91·4% (95% CI, 84·0–98·4%) (Fig 2A). No significant difference was found in the OS and EFS rates between patients with or without haematological risk factors, such as WBC count >10 × 10^9/l or platelet count <40 × 10^9/l. (Sanz *et al*, 2000) (Figs 2B, C) The CIR was 3·6% (95%CI: 0–8·5%) at 7 years, while the cumulative incidence of death without relapse, one of the competing events, was 1·8% (95%CI: 0–5·3%) at 7 years (Fig 2D).

Adverse effects and events

Table II presents the incidence of adverse effects and the duration of neutropenia. In induction therapy, DIC was observed in 10 patients (17%) and four of these patients (7%) showed haemorrhagic complications including retinal haemorrhage in two patients and ICH and/or pulmonary haemorrhages in the other two who died. RA syndrome, which occurred in 7% of cases, was resolved with cessation of ATRA and administration of dexamethasone, the incidence of which was comparable to those (7–19%) reported by other studies of childhood APL (de Botton *et al*, 2004; Ortega *et al* 2005; Testi *et al*, 2005).

Bacterial infection was the major adverse effect in induction and consolidation, and sepsis with documented microbes was determined at a higher incidence during consolidation than induction. Although one patient died in remission of pseudomonas sepsis and meningitis after Block 2 consolidation, all other patients recovered from sepsis with treatment. A proportional relationship was apparent between the periods of neutropenia (<0·1 × 10^9/l) and the incidence of whole infections at any sites, including gingivitis, stomatitis, bronchopneumonia, enteritis, or cellulites during neutropenia, and herpes zoster only in maintenance. Other complications included impaired consciousness or convulsion associated with pseudotumour cerebri and aclarubicin-related dysuria in consolidation Block 3. Severe headache/nausea associated with ATRA therapy was experienced at an incidence of 8–22% throughout treatment.

Table III shows the characteristics of five patients with early death or relapse, two of whom exhibited at least one of the following: WBC count >10 × 10^9/l, M3v morphology, *PML-RARA* bcr3 isoform. The proportion of these patients was not significantly different from that of the whole population of 58 patients. Because of adverse effects, Block 3 consolidation was omitted or reduced in dosage at the physician's discretion in five patients, including two with WBC count >10 × 10^9/l, of whom all remained in remission for 4·9–8·9 years.

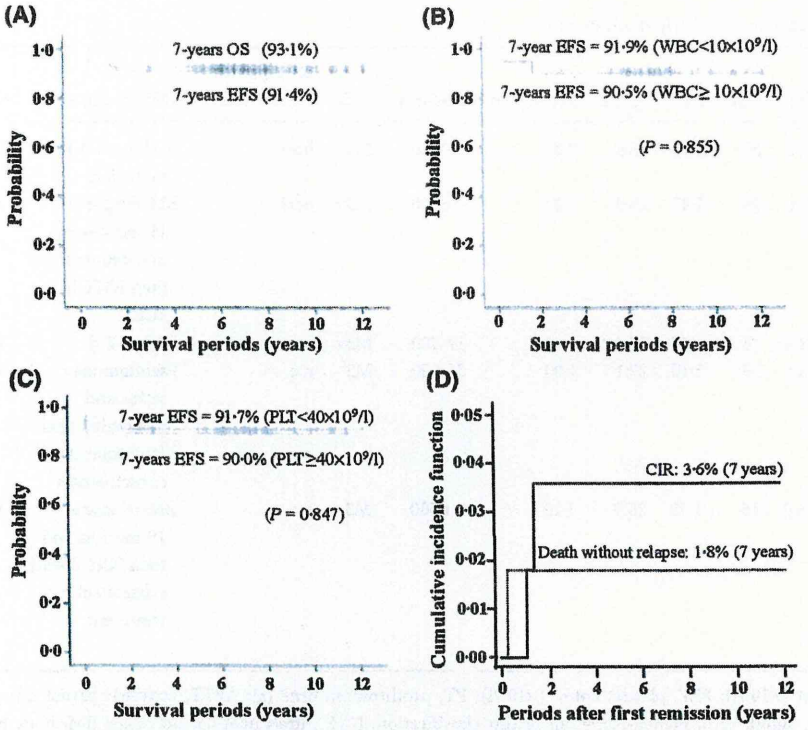

Fig 2. Analysis of the rates of OS, EFS and cumulative incidence functions of CIR and death without relapse in patients treated with the AML99-M3 protocol. (A) OS and EFS rates of total patients; (B) EFS rates of patients with WBC count > 10 × 10^9/l or <10 × 10^9/l at diagnosis; (C) EFS rates of patients with a platelet (PLT) count <40 × 10^9/l or >40 × 10^9/l at diagnosis. No significant difference was found in the EFS rates of patients with and without these risk factors. (D) the cumulative incidence functions of CIR (solid line) and death without relapse (dotted line). [Correction added on 1 October 2010, after first online publication: The data in Figure 2B was amended.]

Table II. Incidence of adverse effects and periods of neutropenia.

		Consolidation			
	Induction	Block 1	Block 2	Block 3	Maintenance
No of assessed patients	55	54	54	53	49
Deterioration of DIC with serious haemorrhages, %	7·2	0	0	0	0
Sepsis, %	1·8	9·2	10·9	5·6	0
Infection of any site, %	10·8	14·5	14·8	15·9	10·2
RA syndrome, %	7	0	0	0	0
Consciousness impairment and/or convulsion, %	3·6	1·8	0	0	0
Severe headache or nausea, %	23·6	11·1	12·9	13·2	8·1
Dysuria, %	0	0	0	3·7	0
Duration of ANC < 0·5, days	17·2	14·3	16·1	16·1	0
Duration of ANC < 0·1, days	6·3	10	10·3	10·9	0

DIC, disseminated intravascular coagulopathy, RA syndrome, retinoic acid syndrome; ANC, absolute neutrophil count, ×10^9/l.

In the evaluation of late cardiotoxicity, echocardiography and electrocardiogram were performed in 18 patients, of whom one patient showed asymptomatic prolongation of the QTc interval in the electrocardiogram. Except for this patient, no clinical symptoms of late cardiotoxicity was seen in other patients including those who did not receive examinations. As of May 2010, no patient had developed t-MDS/AML.

MRD monitoring

In 17 patients, including six with WBC count > 10 × 10^9/l, MRD monitoring was performed at the initial onset and subsequently every 3 months; the monitoring period was an average of 13·6 months. As a result, MRD levels became undetectable (lower than 10^{-3}–10^{-4}) after consolidation Block 1 in 16 patients (94%) and another PCR-positive patient

Table III. Characteristics of patients with early death or relapse.

Patients	Age (years)	Sex	WBC	PLT	PT	APTT	Fibrinogen	D-dimer	FAB	Breakpoint of *PML-RARA*	Clinical course	Outcome
1	15	M	1·2	55	1·25	28·6	0·65	65 300	M3	bcr1	ICH at 15 d in induction	Death at 24 d
2	4	F	171·0	28	1·47	25·9	1·02	6200	M3v	bcr3	BM relapse at 15 months in maintenance and then BMT in 2CR	Alive at 83 months
3	14	M	62·4	4	1·46	30·4	0·79	17 400	M3v	n.e.	ICH at 2 d	Death at 16 d
4	11	F	2·1	39	1·10	27·1	1·00	35 000	M3	n.e.	Pseudomonas sepsis and meningitis after four courses of consolidation	Death at 5 months
5	12	M	1·8	16	1·45	26·9	1·10	6500	M3	n.e.	BM relapse at 19 months and then ICH during subsequent treatment	Death at 24 months

WBC, white blood cell count ($\times 10^9$/l); PLT, platelet count ($\times 10^9$/l); PT, prothrombin time (s); APTT, activated partial thromboplastin time (s) Fibrinogen, mg/dl; D-dimer, μg/ml. FAB, French-American-British classification; ICH, intracranial haemorrhage; BM, bone marrow; BMT, bone marrow transplantation; 2CR, 2nd complete remission; n.e., not evaluated.

became PCR-negative after 6 months of therapy. No patient that was monitored for MRD exhibited re-conversion to PCR-positivity.

Discussion

APL with the *PML-RARA* chimaeric gene is more homogenous than other types of AML and, for infrequent childhood APL, therapy has been often considered together with that of adult patients. However, for paediatric patients, who typically have physiological differences from adults, it has not been thoroughly understood whether the combination of cytarabine with ATRA and anthracyclines would be effective in terms of long-term prognosis.

As shown in Table IV, recent clinical studies of childhood APL, in which patients were enrolled from the mid-1990s to the early 2000s and followed up for median periods of 36 months or longer, were compared to our study (de Botton *et al*, 2004; Ortega *et al*, 2005; Testi *et al*, 2005). In all of these studies, induction therapy with administration of ATRA and anthracyclines with or without cytarabine achieved CR rates at >90% and incidence of early death at <10% respectively. In the state-of-the-art treatment guidelines (Sanz *et al*, 2009), anthracyclines should start together with ATRA (or as soon as possible) in high-risk patients. Regarding drug dosages and clinical parameters, the adjusted cumulative dosage of anthracyclines of our study (375–415 mg/m^2) was lower than other studies (390–750 mg/m^2), while that of cytarabine varied to a large extent among studies. Regarding long-term survival, other three studies presented EFS rates of 71–82% despite OS rates at around 90%, whereas our study achieved a 7-year EFS of 91·4% (Table IV). Accordingly, the 7-year CIR of our study (3·6%) was lower than reported by other studies (15·6–27%) (Table IV). Moreover, none of our patients suffered EM relapse, whereas the other studies reported five patients with EM relapse (skin, middle ear or CNS; Table IV). In our study, one patient exhibited asymptomatic prolongation of QTc interval, which may be associated with late effects of anthracyclines. One other study (Testi *et al*, 2005) reported that two patients developed t-MDS after 36 and 80 months from diagnosis.

In post-remission therapy studies including chemotherapy-based consolidation without ATRA, recurrent disease might develop late in the course, such as seven clinical relapses that occurred over 4–36 months in the APL93 study (de Botton *et al*, 2004) or 14 haematological and five molecular relapses at the median of 26 and 31 months respectively, in the AIDA (ATRA and idarubicin) study (Testi *et al*, 2005). The PETHEMA (Programa para el Estudio y Tratamiento de las Hemopatias Maligna) group reinforced the consolidation therapy of LPA96 study with single anthracycline agent by adding ATRA and increased dosage of idarubicin for intermediate and high-risk patients (LAP99 study). (Ortega *et al*, 2005) These reports indicated that addition of ATRA to anthracycline-based consolidation therapy improved the prognosis of APL patients, especially those with risk factors,

Table IV. Comparison of AML99-M3 with recent studies on childhood APL.

Reports	de Botton *et al*	Testi *et al*	Ortega *et al*	Imaizumi *et al*
Protocol	APL93	AIDA	LPA96/LPA99	AML99-M3
Year	2004	2005	2005	This study
Period of enrollment	1993–1998	1993–2000	1996–2004	1997–2004
Median follow-up time	67 months	79 months	38 months	86 months
No. of patients	31	110	66	58
Proportion of patients with WBC $\geq 10 \times 10^9$/l	48%	35%	39%	38%
Therapy				
Induction	1) ATRA → DNR + CA* 2) ATRA+DNR + CA*	ATRA + IDA	ATRA + IDA	ATRA + DNR + CA
Consolidation	1) DNR + CA 2) DNR + HCA	1) IDA + HCA 2) MIT + VP-16 3) IDA + CA + 6TG	1) IDA + ATRA† 2) MIT + ATRA† 3) IDA + ATRA†	1) ATR + MIT + HCA‡ 2) ATRA + THP + CA‡ 3) ATRA + ACM + HCA‡
Maintenance	(−) or ATRA ± MP/MTX§	ATRA or MP/MTX§	ATRA + MP/MTX	ATRA alone
Dosage of anthracyclines (mg/m^2)	DNR (495)	IDA (80), MIT (50)	IDA (80–100), MIT (50)	DNR(135), MIT(20), THP(90), ACM(180)
Anthracycline dosage converted to DNR (mg/m^2)¶	495	390–650	390–750	375–415
Cumulative dosage of cytarabine (mg/m^2)	10800	6250	0	68000
Cumulative dosage of ATRA (mg/m^2)	1350–6750	750–6150	3750–4875	5940
Incidence of headache/ pseudotumour cerebri (%)	39/16	13/9	30/6	24/5
Clinical outcome				
Early death (%)	3	3·6	7·5	3·4
CR rate (%)	97	96	92	96·6
CIR (%)	27 (5 years)	NA	17 (5 years)	3·6 (7 years)
Extramedullary relapse (sites)	1 (skin)	2 (middle ear)	2 (CNS)	0
Overall survival rate (%)	90 (5 years)	89 (10 years)	87 (5 years)	93·1 (7 years)
Event-free survival rate (%)	71 (5 years)	76 (10 years)	82 (5 years)	91·4 (7 years)
Late cardiotoxicity	No	No	No	1**
Secondary malignancy	No	2 (tMDS)	No	No

DNR, daunorubicin; IDA, idarubicin; MIT, mitoxantrone; THP, pirarubicin; ACM, aclarubicin; CA, cytarabine; HCA, high-dose CA; MP, mercaptopurine; MTX, methotrexate; CR, complete remission; CIR, cumulative incidence of relapse; CNS, central nervous sytem; tMDS, therapy-related myelodysplastic syndrome; NA, not available.

*Patients with WBC $\leq 0{\cdot}5 \times 10^9$/l were randomized to 1) or 2), and those with WBC $>0{\cdot}5 \times 10^9$/l assigned to 2).

†In LPA96 anthracyclines alone; in LPA99 ATRA was combined and IDA dose was increased for intermediate and high-risk patients.

‡Each course was repeated twice.

§Patients were randomized.

¶Equivalent DNR doses were converted using ratios in1:3–1:5 for IDA/MIT, 1:1·6 for THP and 1:0·2 for ACM.

**One patient with asymptomatic prolongation of QTc interval in the examination with electrocardiogram.

although the trial to add cytarabine to ATRA and anthracycline-based consolidation remains undetermined.

In our study, which combined cytarabine with ATRA and anthracyclines both in induction and consolidation, the long-term outcome was improved and showed a low CIR level. Moreover, by adopting prarubicin (Lenk *et al*, 1990) and aclarubicin (Warrell, 1986), two agents of anthracyclines with relatively low acute cardiotocicity, the cumulative doses of anthracycllines were lowered to levels that did not exceed moderate dosages (approximately 300–550 mg/m^2). Late abnormalities of left ventricular performance were uncommon with cumulative anthracycline doses <300 mg/m^2, but late cardiotoxicity might be an important concern in patients with moderate or higher dosages.(Sorensen *et al*, 1997; Nysom

et al, 1998) However, our study included one patient who showed asymptomatic electrocardiographic changes of QTc prolongation which may be associated with late effects of anthracyclines (Bagnes *et al*, 2010) and, therefore, cautious observation might be important for children with a long prospect of survival.

It is to be noted, however, that our regimen with six reinforced courses of consolidation led to increased risks of infectious complications attributable to the prolonged duration of neutropenia. The incidence of sepsis in our study (5·6–10·9% in each consolidation block) was higher than that (3·3–6·6% of incidence) reported by the PETHEMA study (Ortega *et al*, 2005). Although all but one of patients in remission recovered from sepsis with treatment, the compliance of the regimen was decreased in five patients with inevitable omission or dose-reduction of Block 3 consolidation because of chemotherapy-related toxicities. On the basis of the decreased MRD shown during this combined consolidation therapy, the intensity of consolidation therapy should be adjusted to ensure safety. In the ongoing trial in Japan that succeeded AML99-M3, the intensity of consolidation therapy has been reduced from six to four courses, and the effects of this will be compared to AML99-M3.

Recently, the European APL Group suggested the possibility of additional cytarabine to reduce the chance of relapse for patients with APL.(Adès *et al*, 2006) More recently, in the comparative analysis between APL2000 trial with additional cytarabine and LPA99 trial without cytarabine, the 3-year OS and CIR of high-risk patients were respectively, 91·5% vs. 80·0% and 9·9% vs. 18·5%.(Adès *et al*, 2008) Furthermore, the PETHEMA group also demonstrated that the risk-adapted treatment with ATRA, idarubicin and cytarabine for high-risk patients significantly improved the 3-year CIR (11%) when compared to that (26%) of their previous study.(Sanz *et al*, 2010) These findings suggest an importance of risk-adapted treatment and additional cytarabine for high-risk patients.

While EM relapse involving mostly CNS occurs at an incidence of 1–5% (Liso *et al*, 1998; Ko *et al*, 1999; Specchia *et al*, 2001; Breccia *et al*, 2003), at least one in 10 relapses of APL have a CNS component (Sanz *et al*, 2009). For 81 children with relapse reported in the literature, six patients (7·4%) had CNS involvement and the incidence of isolated CNS of good risk patients was as low as 2/218 (0·92%).(Chow & Feusner, 2009) In a European study, which reported 169 relapses (23%) in 740 patients (de Botton *et al*, 2006), the 3-year cumulative incidence (5·0%) of EM relapse was more frequent in patients with WBC count $> 10 \times 10^9$/l, suggesting that high-risk patients may benefit from IT therapy for CNS prophylaxis. Accordingly, IT therapy was performed for high-risk patients (Sanz *et al*, 2005; Adès *et al*, 2008), whereas IT therapy for CNS prophylaxis is not currently recommended for low-risk patients (Chow & Feusner, 2009). As high-dose cytarabine could have contributed to the prevention of CNS relapse because of a high penetration property into the CNS, TI therapy for low-risk patients would be omitted in our regimen while holding CIR at low levels.

Secondary malignancy is another emerging problem, even if at low levels, for APL patients as their survival is prolonged. The PETHEMA LPA99 study, with 560 subjects, identified nine patients with second malignancies, including six t-MDS/AML, at a median interval of 41 months.(Sanz *et al*, 2008) More recently, the European APL group reported the very long-term outcome of 578 patients with a median follow-up of 10 years, in which the cumulative incidence of secondary tumours and t-MDS was 1·4% and 0·2% at 5 years respectively, and 2·7% and 1·1% at 10 years respectively.(Adès *et al*, 2010) It is of note that the risk of t-MDS/AML may be increased by exposure to moderate or high cumulative doses of anthracyclines, which act by inhibiting DNA topoisomerase II, for children with malignant tumours.(Zunino & Capranico, 1990; Le Deley *et al*, 2003) Although the risk of secondary malignancy may not be thoroughly understood with regard to the use of anthracyclines for APL, the cumulative dosage of anthracyclines may be an important perspective of the long-term outcomes and adverse effects for childhood APL.

Recently, therapy with arsenic trioxide, which induces differentiation as well as apoptosis of APL cells, has been shown to be effective for patients not only with relapsed but also with newly diagnosed APL (Ferrara, 2010). With accumulating evidence for the efficacy and safety of therapy with arsenic trioxide alone or in combination with other agents, it would be a promising approach for treatment of childhood APL in the near future (Zhang *et al*, 2008) (Zhou *et al*, 2010).

In conclusion, although this study, without risk-adjusted stratifications or randomized approaches, is insufficient to make definite conclusions, the improved outcome of paediatric APL patients in this study may provide useful implications in the perspective of long-term prognosis and late adverse effects of childhood APL. Further investigations are needed.

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References

Adès, L., Chevret, S., Raffoux, E., de Botton, S., Guerci, A., Pigneux, A., Stoppa, A.M., Lamy, T., Rigal-Huguet, F., Vekhoff, A., Meyer-Monard, S., Maloisel, F., Deconinck, E., Ferrant, A., Thomas, X., Fegueux, N., Chomienne, C., Dombret, H., Degos, L. & Fenaux, P. (2006) European Acute Promyelocytic Leukemia Group. Is cytarabine useful in the treatment of acute promyelocytic leukemia?

Results of a randomized trial from the European Acute Promyelocytic Leukemia Group. *Journal of Clinical Oncology*, **24**, 5703–5710.

Adès, L., Sanz, M.A., Chevret, S., Montesinos, P., Chevallier, P., Raffoux, E., Vellenga, E., Guerci, A., Pigneux, A., Huguet, F., Rayon, C., Stoppa, A.M., de la Serna, J., Cahn, J.Y., Meyer-Monard, S., Pabst, T., Thomas, X., de Botton, S., Parody, R., Bergua, J., Lamy, T., Vekhoff, A., Negri, S., Ifrah, N., Dombret, H., Ferrant, A., Bron, D., Degos, L. & Fenaux, P. (2008) Treatment of newly diagnosed acute promyelocytic leukemia (APL): a comparison of French-Belgian-Swiss and PETHEMA results. *Blood*, **111**, 1078–1084.

Adès, L., Guerci, A., Raffoux, E., Sanz, M., Chevallier, P., Lapusan, S., Recher, C., Thomas, X., Rayon, C., Castaigne, S., Tournilhac, O., de Botton, S., Ifrah, N., Cahn, J.Y., Solary, E., Gardin, C., Fegeux, N., Bordessoule, D., Ferrant, A., Meyer-Monard, S., Vey, N., Dombret Degos, H.L., Chevret, S. & Fenaux, P. (2010) European APL Group. Very long-term outcome of acute promyelocytic leukemia after treatment with all-trans retinoic acid and chemotherapy: the European APL Group experience. *Blood*, **115**, 1690–1696.

Bagnes, C., Panchuk, P.N. & Recondo, G. (2010) Antineoplastic chemotherapy induced QTc prolongation. *Current Drug Safety*, **5**, 93–96.

Bennett, J.M., Catovsky, D., Daniel, M.T., Flandrin, G., Galton, D.A., Gralnick, H.R. & Sultan, C. (1982) Proposals for the classification of the myelodysplastic syndromes. *British Journal of Haematology*, **51**, 189–199.

de Botton, S., Coiteux, V., Chevret, S., Rayon, C., Vilmer, E., Sanz, M., de La Serna, J., Philippe, N., Baruchel, A., Leverger, G., Robert, A., San Miguel, J., Conde, E., Sotto, J.J., Bordessoule, D., Fegueux, N., Fey, M., Parry, A., Chomienne, C., Degos, L. & Fenaux, P. (2004) Outcome of childhood acute promyelocytic leukemia wit all-trans-retinoic acid and chemotherapy. *Journal of Clinical Oncology*, **22**, 1404–1412.

de Botton, S., Sanz, M.A., Chevret, S., Dombret, H., Martin, G., Thomas, X., Mediavilla, J.D., Recher, C., Ades, L., Quesnel, B., Brault, P., Fey, M., Wandt, H., Machover, D., Guerci, A., Maloisel, F., Stoppa, A.M., Rayon, C., Ribera, J.M., Chomienne, C., Degos, L., Fenaux, P.; European APL Group & PETHEMA Group. (2006) Extramedullary relapse in acute promyelocytic leukemia treated with all-trans retinoic acid and chemotherapy. *Leukemia*, **20**, 35–41.

Breccia, M., Carmosino, I., Diverio, D., De Santis, S., De Propris, M.S., Romano, A., Petti, M.C., Mandelli, F. & Lo-Coco, F. (2003) Early detection of meningeal localization in acute promyelocytic leukaemia patients with high presenting leucocyte count. *British Journal of Haematology*, **120**, 266–270.

Chow, J. & Feusner, J. (2009) Isolated central nervous system recurrence of acute promyelocytic leukemia in children. *Pediatric Blood & Cancer*, **52**, 11–13.

Fenaux, P., Chastang, C., Chevret, S., Sanz, M., Dombret, H., Archimbaud, E., Fey, M., Rayon, C., Huguet, F., Sotto, J.J., Gardin, C., Makhoul, P.C., Travade, P., Solary, E., Fegueux, N., Bordessoule, D., Miguel, J.S., Link, H., Desablens, B., Stamatoullas, A., Deconinck, E., Maloisel, F., Castaigne, S., Preudhomme, C. & Degos, L. (1999) A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. *The European APL Group Blood*, **94**, 1192–1200.

Ferrara, F. (2010) Acute promyelocytic leukemia: what are the treatment options? *Expert Opinion on Pharmacotherapy*, **11**, 587–596.

Grignani, F., Fagioli, M., Alcalay, M., Longo, L., Pandolfi, P.P., Donti, E., Biondi, A., Lo Coco, F., Grignani, F. & Pelicci, P.G. (1994) Acute promyelocytic leukemia: from genetics to treatment. *Blood*, **83**, 10–25.

Guglielmi, C., Martelli, M.P., Diverio, D., Fenu, S., Vegna, M.L., Cantù-Rajnoldi, A., Biondi, A., Cocito, M.G., Del Vecchio, L., Tabilio, A., Avvisati, G., Basso, G. & Lo Coco, F. (1998) Immunophenotype of adult and childhood acute promyelocytic leukaemia: correlation with morphology, type of PML gene breakpoint and clinical outcome. A cooperative Italian study on 196 cases. *British Journal of Haematology*, **102**, 1035–1041.

Ko, B.S., Tang, J.L., Chen, Y.C., Yao, M., Wang, C.H., Shen, M.C. & Tien, H.F. (1999) Extramedullary relapse after all-trans retinoic acid treatment in acute promyelocytic leukemia – the occurrence of retinoic acid syndrome is a risk factor. *Leukemia*, **13**, 1406–1408.

Le Deley, M.C., Leblanc, T., Shamsaldin, A., Raquin, M.A., Lacour, B., Sommelet, D., Chompret, A., Cayuela, J.M., Bayle, C., Bernheim, A., de Vathaire, F., Vassal, G., Hill, C. & Société Française d'Oncologie Pédiatrique. (2003) Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines: a case-control study by the Société Française d'Oncologie Pédiatrique. *Journal of Clinical Oncology*, **21**, 1074–1081.

Lenk, H., Tanneberger, S., Wiener, N., Giesske, H., Gärtner, S., Geyer, J. & Rotte, K.H. (1990) Phase II study of pirarubicin (THP-adriamycin) in metastatic breast cancer patients. *Oncology*, **47**, 97–100.

Liso, V., Specchia, G., Pogliani, E.M., Palumbo, G., Mininni, D., Rossi, V., Teruzzi, E., Mestice, A., Coppi, M.R. & Biondi, A. (1998) Extramedullary involvement in patients with acute promyelocytic leukemia: a report of seven cases. *Cancer*, **83**, 1522–1528.

Mann, G., Reinhardt, D., Ritter, J., Hermann, J., Schmitt, K., Gadner, H. & Creutzig, U. (2001) Treatment with all-trans retinoic acid in acute promyelocytic leukemia reduces early deaths in children. *Annals of Hematology*, **80**, 417–422.

Nysom, K., Holm, K., Lipsitz, S.R., Mone, S.M., Colan, S.D., Orav, E.J., Sallan, S.E., Olsen, J.H., Hertz, H., Jacobsen, J.R. & Lipshultz, S.E. (1998) Relationship between cumulative anthracycline dose and late cardiotoxicity in childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology*, **16**, 545–550.

Ortega, J.J., Madero, L., Martín, G., Verdeguer, A., García, P., Parody, R., Fuster, J., Molines, A., Novo, A., Debén, G., Rodríguez, A., Conde, E., de la Serna, J., Allegue, M.J., Capote, F.J., González, J.D., Bolufer, P., González, M., Sanz, M.A. & PETHEMA Group. (2005) Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. *Journal of Clinical Oncology*, **23**, 7632–7640.

Sakata-Yanagimoto, M., Kanda, Y., Nakagawa, M., Asano-Mori, Y., Kandabashi, K., Izutsu, K., Imai, Y., Hangaishi, A., Kurokawa, M., Tsujino, S., Ogawa, S., Chiba, S., Motokura, T. & Hirai, H. (2004) Predictors for severe cardiac complications after hematopoietic stem cell transplantation. *Bone Marrow Transplantation*, **33**, 1043–1047.

Sanz, M.A., Lo Coco, F., Martín, G., Avvisati, G., Rayón, C., Barbui, T., Díaz-Mediavilla, J., Fioritoni, G., González, J.D., Liso, V., Esteve, J., Ferrara, F., Bolufer, P., Bernasconi, C., Gonzalez, M., Rodeghiero, F., Colomer, D., Petti, M.C., Ribera, J.M. & Mandelli, F. (2000) Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. *Blood*, **96**, 1247–1253.

Sanz, M.A., Martín, G., González, M., León, A., Rayón, C., Rivas, C., Colomer, D., Amutio, E., Capote, F.J., Milone, G.A., De La Serna, J.,

Román, J., Barragán, E., Bergua, J., Escoda, L., Parody, R., Negri, S., Calasanz, M.J., Bolufer, P. & Programa de Estudio y Traitmiento de las Hemopatías Malignas. (2004) Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. *Blood*, **103**, 1237–1243.

Sanz, M.A., Tallman, M.S. & Lo-Coco, F. (2005) Practice points, consensus, and controversial issues in the management of patients with newly diagnosed acute promyelocytic leukemia. *Oncologist*, **10**, 806–814.

Sanz, M.A., Montesinos, P., Vellenga, E., Rayón, C., de la Serna, J., Parody, R., Bergua, J.M., León, A., Negri, S., González, M., Rivas, C., Esteve, J., Milone, G., González, J.D., Amutio, E., Brunet, S., García-Laraña, J., Colomer, D., Calasanz, M.J., Chillón, C., Barragán, E., Bolufer, P. & Lowenberg, B. (2008) Risk-adapted treatment of acute promyelocytic leukemia with all-trans retinoic acid and anthracycline monochemotherapy: long-term outcome of the LPA 99 multicenter study by the PETHEMA Group. *Blood*, **112**, 3130–3134.

Sanz, M.A., Grimwade, D., Tallman, M.S., Lowenberg, B., Fenaux, P., Estey, E.H., Naoe, T., Lengfelder, E., Büchner, T., Döhner, H., Burnett, A.K. & Lo-Coco, F. (2009) Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European Leukemia Net. *Blood*, **113**, 1875–1891.

Sanz, M.A., Montesinos, P., Rayón, C., Holowiecka, A., de la Serna, J., Milone, G., de Lisa, E., Brunet, S., Rubio, V., Ribera, J.M., Rivas, C., Krsnik, I., Bergua, J., González, J., Díaz-Mediavilla, J., Rojas, R., Manso, F., Ossenkoppele, G., González, J.D. & Lowenberg, B. (2010) Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. *Blood*, **115**, 5137–5146.

Sorensen, K., Levitt, G., Bull, C., Chessells, J. & Sullivan, I. (1997) Anthracycline dose in childhood acute lymphoblastic leukemia: issues of early survival versus late cardiotoxicity. *Journal of Clinical Oncology*, **15**, 61–68.

Specchia, G., Lo Coco, F., Vignetti, M., Avvisati, G., Fazi, P., Albano, F., Di Raimondo, F., Martino, B., Ferrara, F., Selleri, C., Liso, V. & Mandelli, F. (2001) Extramedullary involvement at relapse in acute promyelocytic leukemia patients treated or not with all-trans retinoic acid: a report by the Gruppo Italiano Malattie Ematologiche dell'Adulto. *Journal of Clinical Oncology*, **19**, 4023–4028.

Suzuki, H., Imaizumi, M., Sato, A., Yoshinari, M., Rikiishi, T., Endo, M., Takano, T., Shimizu, T., Hatae, Y., Fujimoto, T., Hayashi, Y. & Iinuma, K. (2001) Monitoring of minimal residual disease in children with acute promyelocytic leukemia by RT-PCR detecting PML/RARalpha chimeric gene: a retrospective study of clinical feasibility. *Tohoku Journal of Experimental Medicine*, **193**, 127–139.

Tallman, M.S., Nabhan, C., Feusner, J.H. & Rowe, J.M. (2002) Acute promyelocytic leukemia: evolving therapeutic strategies. *Blood*, **99**, 759–767.

Testi, A.M., Biondi, A., Lo Coco, F., Moleti, M.L., Giona, F., Vignetti, M., Menna, G., Locatelli, F., Pession, A., Barisone, E., De Rossi, G., Diverio, D., Micalizzi, C., Aricò, M., Basso, G., Foa, R. & Mandelli, F. (2005) GIMEMA-AIEOPAIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood*, **106**, 447–453.

Warrell, Jr, R.P. (1986) Aclacinomycin A. clinical development of a novel anthracycline antibiotic in the haematological cancers. *Drugs Under Experimental and Clinical Research*, **12**, 275–282.

Zhang, L., Zhao, H., Zhu, X., Chen, Y., Zou, Y. & Chen, X. (2008) Retrospective analysis of 65 Chinese children with acute promyelocytic leukemia: a single center experience. *Pediatric Blood & Cancer*, **51**, 210–215.

Zhou, J., Zhang, Y., Li, J., Li, X., Hou, J., Zhao, Y., Liu, X., Han, X., Hu, L., Wang, S., Zhao, Y., Zhang, Y., Fan, S., Lu, C., Li, L. & Zhu, L. (2010) Single-agent arsenic trioxide in the treatment of children with newly diagnosed acute promyelocytic leukemia. *Blood*, **115**, 1697–1702.

Zunino, F. & Capranico, G. (1990) DNA topoisomerase II as the primary target of anti-tumor anthracyclines. *Anti-Cancer Drug Design*, **5**, 307–317.

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HEALTH AND QUALITY OF LIFE OUTCOMES

RESEARCH Open Access

Validation of the Japanese version of the Pediatric Quality of Life Inventory (PedsQL) Cancer Module

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Abstract

Background: The PedsQL 3.0 Cancer Module is a widely used instrument to measure pediatric cancer specific health-related quality of life (HRQOL) for children aged 2 to 18 years. We developed the Japanese version of the PedsQL Cancer Module and investigated its reliability and validity among Japanese children and their parents.

Methods: Participants were 212 children with cancer and 253 of their parents. Reliability was determined by internal consistency using Cronbach's coefficient alpha and test-retest reliability using intra-class correlation coefficient (ICC). Validity was assessed through factor validity, convergent and discriminant validity, concurrent validity, and clinical validity. Factor validity was examined by exploratory factor analysis. Convergent and discriminant validity were examined by multitrait scaling analysis. Concurrent validity was assessed using Spearman's correlation coefficients between the Cancer Module and Generic Core Scales, and the comparison of the scores of child self-reports with those of other self-rating depression scales for children. Clinical validity was assessed by comparing the on- and off- treatment scores using Kruskal-Wallis and Mann-Whitney U tests.

Results: Cronbach's coefficient alpha was over 0.70 for the total scale and over 0.60 for each subscale by age except for the 'pain and hurt' subscale for children aged 5 to 7 years. For test-retest reliability, the ICC exceeded 0.70 for the total scale for each age. Exploratory factor analysis demonstrated sufficient factorial validity. Multitrait scaling analysis showed high success rates. Strong correlations were found between the reports by children and their parents, and the scores of the Cancer Module and the Generic Core Scales except for 'treatment anxiety' subscales for child reports. The Depression Self-Rating Scale for Children (DSRS-C) scores were significantly correlated with emotional domains and the total score of the cancer module. Children who had been off treatment over 12 months demonstrated significantly higher scores than those on treatment.

Conclusions: The results demonstrate the reliability and validity of the Japanese version of the PedsQL Cancer Module among Japanese children.

Background

In the last 50 years, long-term survival rates of children with cancer have dramatically improved and 70 to 80% of patients can now be cured in developed countries [1]. However, 20 to 30% of patients who are diagnosed with advanced-stage neuroblastoma, soft tissue sarcoma, brainstem tumors, or relapsed tumors do not survive. For this reason, pediatric oncologists have 2 missions. For curable disease, we need to optimize anti-cancer treatment by reducing toxicity and preventing late complications without reducing the survival rate [2-6]. For fatal diseases, we have to balance the benefit and toxicity of anti-cancer treatment to maximize the quality of life remaining for the patients. To achieve both missions, we need to be able to measure the quality of life

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of childhood cancer patients. However, there has been no standardized measurement scale to do this in Japan.

The World Health Organization defined health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' [7]. Therefore, a health-related quality of life (HRQOL) instrument should include physical, mental, and social health dimensions [8,9]. Moreover, a pediatric HRQOL measurement needs to consider the cognitive development of the child and integrate child self-reports and parent proxy-reports [10]. Taking these points into account, the PedsQL [11] is thought to be suitable. This scale has been used in many countries to measure HRQOL in children and adolescents aged 2 to 18 years. Evaluation is conducted by both children and parents; children aged 5 to 18 years are asked to evaluate their own HRQOL (child self-report) and the parents of children aged 2 to 18 years are asked to evaluate their child's HRQOL (parent proxy-report). The PedsQL was designed using a modular approach to integrate the advantages of generic and disease-specific approaches [12,13]. Generic core scales enable the comparison of HRQOL of healthy children with those of ill children. In Japan, Kobayashi and her colleagues have developed the Japanese version of the PedsQL 4.0 Generic Core Scales [14]. We could have used this scale to assess HRQOL for children with cancer, but the instrument was not developed specifically for oncology patients. To enhance the measurement sensitivity for these patients, a cancer-specific module is necessary.

The PedsQL 3.0 Cancer Module was designed to measure HRQOL dimensions optimally for children with cancer. This instrument has already been validated in English [6], German [15], Portuguese [16], and Chinese [17]. However, until now, validation of the Japanese version has not been conducted.

The aim of this study was to demonstrate the reliability, validity, and feasibility of the Japanese version of the PedsQL 3.0 Cancer Module and compare scores by treatment status. As a result, Japanese children will be able to join international clinical trials and contribute to improvement of HRQOL of childhood cancer patients.

Methods

Scale development

Before starting this validation study, we obtained permission from Dr. James W. Varni (JWV) to translate the PedsQL 3.0 Cancer Module into Japanese using a standardized validation procedure [18]. Two Japanese translators competent in English independently translated PedsQL into Japanese. After discussion among translators and the authors, these forward translations were unified into a single version that was a conceptually equivalent translation of the original English version. Then, a professional bilingual translator (Japanese and English) performed backward translation of the first version from Japanese to English. Comparing the back-translated and original versions, minor changes were made to the first version. Then, we conducted pilot testing by using this modified version.

This Japanese version was tested on children and their parents (a total of 16 children and 20 parents). Then the researchers (NT or NK) looked at the responses on each questionnaire, checked how long it took to complete, and asked the subjects how well they understood the questions.

A final version of the Japanese version of the PedsQL Cancer Module was produced after modification of the pilot version. All translation procedures were reported to JWV, who reviewed the equivalence between the final Japanese version and the original English version.

Study population

This validation study was developed in Japan from September 2006 through June 2010. We recruited children with cancer and their parents from 9 hospitals in Japan. Children were excluded from this study if they had comorbid disease or major developmental disorders. Families who did not agree to join this study were also excluded. Children aged 5 to 18 years who were diagnosed with cancer were included in this study, and the parents were included if their child was 2 to 18 years old.

Procedure and measurements

The PedsQL 3.0 Cancer Module instrument includes 27 items with 8 subscales: pain and hurt (2 items), nausea (5 items), procedural anxiety (3 items), treatment anxiety (3 items), worry (3 items), cognitive problems (5 items), perceived physical appearance (3 items), and communication (3 items). The child instrument differs by age group: 5 to 7, 8 to 12, and 13 to 18 years. The parent's version also differs by child's age group: 2 to 4, 5 to 7, 8 to 12, and 13 to 18 years. The participants evaluated how often a particular problem occurred in the past month, using a 3-point Likert scale (0 = never, 2 = sometimes, 4 = often) for children 5 to 7 years and a 5-point Likert scale (0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = almost always) for children 8 to 18 years and for the parents of all ages. For children aged 5 to 7 years, a Face Scale with 3 pictures varying from a smiling face to a sad face was used.

The PedsQL 4.0 Generic Core Scales includes 23 items with 4 subscales: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). The instrument for children differs by age group: 5 to 7, 8 to 12, and 13 to 18 years. The parent's version also differs by child's age group: 2 to 4, 5 to 7, 8 to 12, and 13 to 18 years.

Similar to the PedsQL Cancer Module, a 3-point Likert scale is used for children 5 to 7 years old and a 5-point Likert scale is used for children 8 to 18 years old and for parents of children of all ages.

The questionnaire was self-administered for parents and children aged 8 to 18 years, and interviewer-administered for children aged 5 to 7 years. According to the original English version, the interviewer was the child's parent. After the parent completed the parent proxy report separately from their child, they read out the questions for the child's self-report and marked the answers. Parents and children aged 8 to 18 years completed the questionnaire independently after reading the instructions on their own. Parents were also questioned about their age, job, academic background, and economic status.

The child's physician answered questions about the patient's sex, date of birth, age, tumor pathology, date of diagnosis, date of completion of therapy (chemotherapy, radiation therapy, and surgery), existing comorbid disease or major developmental disorders, and whether the cancer was newly diagnosed or recurrent disease.

Participants were 282 families of children with cancer aged 2 to 18 years. Children aged 5 to 18 years answered the PedsQL child self-reports (n = 212) and the parents of children aged 2 to 18 years answered the PedsQL parent proxy-reports (n = 253). Eight children and their parents were excluded from the study because 1 patient was 20 years old, 6 patients were diagnosed with brain tumor, and 1 patient had Down syndrome. Finally, the questionnaires from 204 children and 245 parents were collected and analyzed.

Test-retest reliability was assessed at Tokyo Metropolitan Kiyose Children's Hospital (the predecessor of Tokyo Metropolitan Children's Medical Center). Forty families with children in stable condition according to their attending physician agreed to take a retest after 1 week. Finally, 28 children and 39 parents completed the questionnaires.

Statistical analyses

Statistical analyses of the study were conducted by SPSS 16.0J for Windows (SPSS, Inc., Chicago, USA) and the significance level was set at 0.05. We used pair-wise case deletion for missing values, and if more than 50% of the items were missing, the score was not computed. Items were reverse-scored and linearly transformed to a 0 to 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Higher scores indicated better quality of life.

For characterization of the sample, Fisher's exact test was used to examine the differences by treatment status. Multiple regression analysis was done for the significant factors by Fisher's exact test. For descriptive analyses, we calculated the mean, standard deviation, median, minimum, and maximum scores and skewness.

Reliability was determined by internal consistency using Cronbach's coefficient alpha and test-retest reliability using Spearman's intra-class correlation coefficient (ICC). Internal consistency was considered good when Cronbach's coefficient alpha exceeded 0.70. ICC between the initial test and retest was measured according to the following values: 0.40 representing moderate, 0.60 good, and 0.80 excellent correlation.

Validity was assessed through factor validity, convergent and discriminant validity, concurrent validity, and clinical validity. Factor validity was examined by exploratory factor analysis. The extraction method was principle factor analysis. Rotation method was Promax with Kaiser normalization on the 27 items. Factor loading greater than 0.30 was regarded as significant.

Convergent and discriminant validity were examined by multitrait scaling analysis [19]. We calculated the range of correlation coefficients and the success rate of each scale. Concurrent validity was assessed by Spearman's correlation coefficient between the PedsQL 3.0 Cancer Module and the PedsQL 4.0 Generic Core Scales, and the comparison of the scores of child self-reports with those of other self-rating depression scales for children. We analyzed the correlations by Spearman rather than Pearson correlations because of non-normal distributions.

Initially, we predicted that the 'pain and hurt' and 'nausea' subscales of the Cancer Module were correlated with the physical health scale of the Generic Core Scales. Similarly, we predicted that the 'procedural anxiety,' 'treatment anxiety,' and 'worry' subscales of the Cancer Module were correlated with 'psychosocial health' and 'emotional functioning' subscales of the Generic Core Scales. 'Cognitive problems,' 'perceived physical appearance,' and 'communication' subscales of the Cancer Module were compared with the 'social functioning' and 'school functioning' subscales of the Generic Core Scales.

Moreover, we assessed the correlation of the 'procedural anxiety,' 'treatment anxiety,' and 'worry' subscales of the Cancer Module with the Depression Self-Rating Scale for Children (DSRSC) [20] and the Center for Epidemiologic Studies Depression scale (CES-D) [21]. These scales have already been translated into Japanese and the Japanese versions have been validated. DSRSC and CES-D scores of less than 15 were considered to be within the normal range and scores 16 or greater were suspicious for depression.

To assess clinical validity, we compared the total and subscale scores between on-treatment and off-treatment status by Kruskal-Wallis and Mann-Whitney U tests. Feasibility was determined by the amount of time required to complete the questionnaires and the percentage of missing values.

We calculated the sample size needed to produce medium correlation (0.30) in the examination of convergent and discriminant validity. We set the type I error at 1% and the statistical power at 90%; thus the calculated sample size was 154. We estimated that approximately 50 to 70% of participants would agree to participate, so we decided to administer this test to 220 to 308 parents and their children.

For the retest, sample size was calculated on the basis of an expected ICC from 0.60 to 0.80. Setting the type I error at 5% and the statistical power at 80%, calculated sample size was 13. We estimated that approximately 30 to 50% of retest questionnaires would be returned; thus we decided to administer the retest to 40 parents and their children.

Ethical considerations

This study was approved by the Institutional Review Board (IRB) at each hospital. In our country, people are sensitive to direct expression about cancer, so we used alternate terms in introductory writings and questionnaires, such as the Japanese version of the Pediatric Quality of Life Inventory Brain Tumor Module [22]. For participation in this study, informed consent was required from all parents. For children aged 5 or over, informed assent was also required.

Results

Characterization of the sample

Participants' characteristics are shown in Table 1. The average age of the children was 10.5 years (Standard Deviation [SD] = 3.9 years) and 55.1% of the patients were male. One hundred sixty-six patients (76.8%) had hematological diseases, and the remaining patients (22.0%) had solid tumors. The guardians who answered the questionnaires were predominantly mothers (93.9%) and about half of them were 40 to 60 years old. On-treatment status means the patient was receiving medical treatment such as chemotherapy, radiation therapy, or surgery (n = 88; 35.9%). Off-treatment status means the patient completed all therapy by the time of the assessment (n = 155; 63.3%). In this study, half of the patients had been off treatment for over 12 months (n = 124; 50.6%). Even though medical fees were almost completely covered by public insurance in Japan, half of the guardians rated their economic level as 'low' because most mothers had to quit their job to take care of their children.

There was no statistically significant difference in the ratio of patient's sex, guardians who answered the questionnaires, their academic background, or their evaluation of economic level by treatment status.

For significant factors such as children's age, diagnosis, and age of guardian, multiple regression analysis was done (Table 2). None of the comparisons were statistically significant for the total score of the PedsQL Cancer Module, so that we considered the 3 treatment groups to have the same patient characteristics.

Descriptive analysis

The child self-reports and the parent proxy-reports showed comparatively good concordance in all scales (Tables 3 and 4). Scale scores were consistently higher for child reports than for parent reports. For both child and parent reports, 'pain and hurt,' 'nausea,' and 'treatment anxiety' had higher scores than other subscale scores for all ages. On the other hand, the subscale 'communication' had a tendency to be low for all ages. However, the scores for 'cognitive problems' and 'perceived physical appearance' were lowest in adolescents (13-18 y).

Reliability

Cronbach's coefficient alpha for the total scale and each subscale exceeded 0.70 in both the child self-reports and parent proxy-reports (Tables 3 and 4). However, for children aged 5 to 7 years, Cronbach's coefficient alpha ranged from 0.53 to 0.67 in the 'pain and hurt,' 'cognitive problems,' 'perceived physical appearance,' and 'communication' subscales in self-reports.

Table 5 shows test-retest reliability analysis of the PedsQL Cancer Module scales in each age group. ICC values among the children ranged from good to excellent except for the 'treatment anxiety' subscale for 5- to 7-year-olds and 13- to 18-year-olds and the 'worry' subscale for 8- to 12-year-olds. ICC values among the parents ranged from good to excellent.

Validity

Validity was assessed through factor validity, convergent and discriminant validity, concurrent validity, and clinical validity. Although the original English version has an 8-factor structure [11], exploratory factor analysis identified 7 factors for both child self-report and parent proxy-report in our Japanese version (Tables 6 and 7). The first item of 'worry' (worrying about side effects from medical treatments) loaded on the 'nausea' factor, and the second and third items of 'worry' (worrying about whether the medical treatments were working and worrying about reoccurrence or relapse) loaded on the 'communication' factor in the child self-report. Moreover, the first item of 'cognitive problems' (difficulty figuring out what to do when something bothers him/her) loaded on the 'perceived physical appearance' factor. In the parent-proxy report, the first and the second items of 'worry' loaded on the 'nausea' factor, and the third item loaded on the 'treatment anxiety' and 'perceived physical appearance' factors. Factor-item correlations

Table 1 Characterization of the sample

Subject	Child On-Tx (n = 88)		Child Off-Tx = <12 (n = 33)		Child Off Tx >12 (n = 124)		Total sample (n = 245)		
	n	%	n	%	n	%	n	%	*P* value
Age									0.002
2-4 (parents only)	23	26.1	6	18.2	12	9.7	41	16.7	
5-7	28	31.8	9	27.3	25	20.2	62	25.3	
8-12	16	18.2	12	36.4	47	37.9	75	30.6	
13-18	21	23.9	6	18.2	40	32.3	67	27.3	
Sex									0.357
Male	51	58.0	21	63.6	63	50.8	135	55.1	
Female	37	42.0	12	36.4	61	49.2	110	44.9	
Diagnosis									0.002
Newly diagnosed	67	76.1	27	81.8	115	92.7	209	85.3	
Recurrent disease	21	23.9	6	18.2	9	7.3	36	14.7	
Tumor pathology									0.050
Leukemia	70	79.5	21	63.6	75	60.5	166	67.8	
Malignant lymphoma	7	8.0	4	12.1	11	8.9	22	9.0	
Neuroblastoma	4	4.5	2	6.1	11	8.9	17	6.9	
Wilms tumor	3	3.4	0	0	8	6.5	11	4.5	
Rhabdomyosarcoma	0	0	1	3.0	3	9.7	4	1.6	
Hepatoblastoma	1	1.1	0	0	2	2.4	3	1.2	
Other solid tumors	2	2.3	3	9.1	14	11.3	19	7.8	
Unknown	1	1.1	2	6.1	0	0	3	1.2	
Relationship to patient									0.257
Mother	80	90.9	32	97.0	118	95.2	230	93.9	
Father	3	3.4	1	3.0	5	4.0	9	3.7	
Other guardian	0	0	0	0	0	0	0	0	
Unknown	5	5.7	0	0	1	0.8	6	2.4	
Age of guardian									0.030
21-28	1	1.1	0	0	4	3.2	5	2.0	
29-34	17	19.3	7	21.2	16	12.9	40	16.3	
35-39	32	36.4	12	36.4	28	22.6	72	29.4	
40-60	33	37.5	13	39.4	74	59.7	120	49.0	
Unknown	5	5.7	1	3.0	2	1.6	8	3.3	
Guardian's academic background									0.065
Junior high school	3	3.4	0	0	1	0.8	4	1.6	
High school	32	36.4	14	42.4	41	33.1	87	35.5	
Vocational school	13	14.8	2	6.1	29	23.4	44	18.0	
Junior college	20	22.7	6	18.2	22	17.7	48	19.6	
University	14	15.9	10	30.3	28	22.6	52	21.2	
Graduate school	0	0	1	3.0	0	0	1	0.4	
Other	1	1.1	0	0	1	0.8	2	0.8	
Unknown	5	5.7	0	0	2	1.6	7	2.9	
Guardian's evaluation of economic level									0.485
Very high	1	1.1	0	0	4	3.2	5	2.0	
High	23	26.1	13	39.4	35	28.2	71	29.0	
Low	44	50.0	16	48.5	65	52.4	125	51.0	
Very low	14	15.9	4	12.1	18	14.5	36	14.7	
Unknown	6	6.8	0	0	2	1.6	8	3.3	

On-Tx: on treatment sample; Off-Tx = < 12: off treatment = < 12 months sample; Off-Tx > 12: off treatment > 12 months sample. *P* value is calculated by Fisher's exact test.

Table 2 Multivariable analysis of the total score of the PedsQL Cancer Module

Factor	SE	β	t	*P* value
Age	.362	.051	.556	.579
2-4 (parents only)				
5-7				
8-12				
13-18				
Diagnosis	2.866	-.108	-1.529	.128
Newly diagnosed				
Recurrent disease				
Age of guardian	.242	.155	1.673	.096
21-28				
29-34				
35-39				
40-60				
Unknown				
Treatment status	1.198	.298	4.207	<.0001
Child On Tx (n = 88)				
Child Off Tx = < 12 (n = 33)				
Child Off Tx > 12 (n = 124)				

Calculations were done by multiple regression analysis.
SE: standard error of the mean.
On Tx: on treatment sample; Off Tx = < 12: off treatment = < 12 months sample; Off Tx > 12: off treatment >12 months sample.

were between 0.30 and 1.00 in the child self-reports, and 0.44 and 1.00 in the parent proxy-reports.

Convergent and discriminant validity were examined by multitrait scaling analysis (Table 8). After excluding item duplication, we calculated correlation coefficients between each item and the subscale that it belonged to. The success rate was determined by the percentage of items where the convergent correlation exceeded the discriminant correlation. All scales demonstrated extremely high success rates ranging from 95 to 100% in all ages.

We calculated intraclass correlation coefficients between the child self-reports and parent proxy-reports (Table 9). For the entire sample, strong correlations ranging from 0.50 to 0.79 were demonstrated between the same subscales. Physical health scales ('pain and hurt' and 'nausea') demonstrated the strongest correlations.

Concurrent validity was assessed 2 ways. First, we compared Spearman's correlation coefficients between the PedsQL 3.0 Cancer Module and the PedsQL 4.0 Generic Core Scales (Table 10). The correlation coefficients between the total score of the Cancer Module and the Generic Core Scales were over 0.70 for both the child self-reports and the parent proxy-reports. However, correlation coefficients between the 'procedural and treatment anxiety' and 'social functioning' subscales in the child self-reports were weak. For both child reports and parent reports, 'pain and hurt' and 'nausea' subscales showed the strongest correlation with the 'physical health' subscale. For children, the 'procedural anxiety' and 'worry' subscales were strongly correlated with 'physical health' and 'emotional functioning'; the 'cognitive problems' subscale was strongly correlated with 'school functioning'; and 'perceived physical appearance' and communication' subscales were strongly correlated with the 'social functioning' subscale. For parents, all subscales except 'pain and hurt' and 'nausea' subscales showed a strong correlation with the 'emotional functioning' subscale.

Second, the correlations between the PedsQL scale scores and child self-rating depression screening scores (DSRS-C or CES-D) were examined (Table 11). For the children who were considered depressed, both the DSRS-C and CES-D scores were strongly correlated with the 'emotional functioning' score and total score of the Generic Core Scales. For children aged 8 to 15 years, DSRS-C scores were strongly correlated with 'procedural anxiety,' 'worry,' 'perceived physical appearance,' and 'communication' scores, and the total score of the Cancer Module. For children aged 16 to 18 years, CES-D scores were moderately correlated with 'treatment anxiety' and 'communication' scores of the Cancer Module. Both DSRS-C and CES-D scores of children were strongly correlated with the total score of their parent's CES-D scores (correlation coefficient: 0.986 for DSRS-C, and 0.771 for CES-D; data not shown).

For clinical validity, we compared the total and subscale scores between on-treatment and off-treatment status by Kruskal-Wallis and Mann-Whitney U tests (Table 12) because only treatment status was a significant factor among patients' characteristics for the total score of the PedsQL Cancer Module (Table 2). Off-treatment status was divided into 2 groups (= < 12 mo and > 12 mo) and analyzed separately.

Children who had been off treatment over 12 months and their parents demonstrated significantly higher scores than those on treatment except for 'cognitive problems' and 'perceived physical appearance' subscales. On the other hand, physical and emotional quality of life scores associated with anti-cancer treatment were significantly improved among them.

Social and school functioning subscales, such as 'cognitive problems' and 'perceived physical appearance' had not improved long after the completion of treatment, and 'communication' scores of children had not improved within 12 months of completion of treatment.

Feasibility

The percentage of missing values was 0.68% for child self-reports and 0.98% for parent proxy reports. According to the pilot testing, the time required to complete the questionnaires was estimated to be 5 to 10 minutes

Table 3 Score distributions of the Japanese version of the PedsQL Cancer Module (Child self-report)

Subscale	n	mean	(SD, range)	α	floor	ceiling	skewness
Total	193	77.89	(15.35, 29.79-100)	0.78	62.54	93.24	-.620
Pain and hurt	202	84.72	(19.66, 0-100)	0.72	65.06	104.38	-1.177
Nausea	199	82.96	(23.96, 0-100)	0.88	59.00	106.92	-1.548
Procedural anxiety	203	72.90	(30.96, 0-100)	0.87	41.94	103.86	-1.032
Treatment anxiety	203	93.14	(17.01, 0-100)	0.84	76.13	110.15	-3.400
Worry	202	76.61	(25.91, 0-100)	0.80	50.70	102.52	-1.101
Cognitive problems	201	72.39	(22.09, 6.25-100)	0.72	50.30	94.48	-.546
Perceived physical appearance	204	70.34	(28.58, 0-100)	0.75	41.76	98.92	-.797
Communication	204	67.03	(27.01, 0-100)	0.74	40.02	94.04	-.596
2-4 years							
Total							
Pain and hurt							
Nausea							
Procedural anxiety							
Treatment anxiety				NA			
Worry							
Cognitive problems							
Perceived physical appearance							
Communication							
5-7 years							
Total	58	73.27	(14.57, 43.33-100)	0.67	58.70	87.84	.039
Pain and hurt	61	84.02	(19.38, 50-100)	0.53	64.64	103.40	-.735
Nausea	61	76.72	(23.86, 0-100)	0.82	52.86	100.58	-1.295
Procedural anxiety	62	55.11	(36.91, 0-100)	0.88	18.20	92.02	-.159
Treatment anxiety	61	88.25	(22.62, 0-100)	0.79	65.63	110.87	-2.275
Worry	60	73.61	(28.01, 0-100)	0.73	45.60	101.62	-.915
Cognitive problems	60	73.13	(23.11, 12.5-100)	0.67	50.02	96.24	-.572
Perceived physical appearance	62	70.43	(28.22, 0-100)	0.67	42.21	98.65	-.786
Communication	62	59.95	(26.90, 0-100)	0.60	33.05	86.85	-.422
8-12 years							
Total	72	79.36	(15.94, 32.71-100)	0.82	63.42	95.30	-.923
Pain and hurt	75	86.17	(20.51, 0-100)	0.84	65.66	106.68	-1.825
Nausea	73	83.84	(25.65, 5-100)	0.91	58.19	109.49	-1.715
Procedural anxiety	75	78.22	(27.57, 0-100)	0.89	50.65	105.79	-1.393
Treatment anxiety	75	94.56	(14.14, 25-100)	0.83	80.42	108.70	-3.636
Worry	75	78.78	(25.79, 0-100)	0.83	52.99	104.57	-1.130
Cognitive problems	74	71.35	(20.70, 5-100)	0.72	50.65	92.05	-.600
Perceived physical appearance	75	72.00	(29.69, 0-100)	0.80	42.31	101.69	-.906
Communication	75	66.67	(28.08, 0-100)	0.76	38.59	94.75	-.590
13-18 years							
Total	62	80.25	(14.79, 29.79-100)	0.82	65.46	95.04	-.925
Pain and hurt	66	83.71	(19.11, 37.5-100)	0.75	64.60	102.82	-.799
Nausea	65	87.85	(20.97, 10-100)	0.90	66.88	108.82	-1.775
Procedural anxiety	66	83.59	(19.61, 25-100)	0.69	63.98	103.20	-1.162
Treatment anxiety	67	96.02	(13.71, 0-100)	0.94	82.31	109.73	-5.666
Worry	67	76.87	(24.18, 0-100)	0.85	52.69	101.05	-1.330
Cognitive problems	66	70.30	(23.20, 20-100)	0.82	47.10	93.50	-.305
Perceived physical appearance	67	68.41	(27.96, 0-100)	0.81	40.45	96.37	-.735
Communication	67	74.01	(24.38, 0-100)	0.83	49.63	98.39	-.810

n: number of individuals, SD: standard deviation, α: Cronbach's coefficient.

Table 4 Score distributions of the Japanese version of the PedsQL Cancer Module (Parent proxy-report)

Subscale	n	mean	(SD, range)	α	floor	ceiling	skewness
Total	188	74.91	(15.25, 24.95-100)	0.79	59.66	90.16	-.573
Pain and hurt	242	82.85	(22.00, 0-100)	0.89	60.85	104.85	-1.221
Nausea	233	80.49	(25.70, 0-100)	0.93	54.79	106.19	-1.324
Procedural anxiety	242	63.19	(31.76, 0-100)	0.92	31.43	94.95	-.503
Treatment anxiety	241	84.89	(19.00, 0-100)	0.90	65.89	103.89	-1.352
Worry	242	81.37	(21.91, 0-100)	0.87	59.46	103.28	-1.321
Cognitive problems	203	68.78	(21.61, 8.33-100)	0.84	47.17	90.39	-.470
Perceived physical appearance	243	73.77	(24.92, 0-100)	0.86	48.85	98.69	-.903
Communication	241	62.21	(25.42, 0-100)	0.81	36.79	87.63	-.416
2-4 years							
Total	38	76.31	(16.37, 40.83-100)	0.81	59.94	92.68	-.478
Pain and hurt	41	86.89	(18.32, 25-100)	0.83	68.57	105.21	-1.365
Nausea	39	72.18	(24.78, 30-100)	0.91	47.40	96.96	-.140
Procedural anxiety	40	58.13	(35.03, 0-100)	0.89	23.10	93.16	-.213
Treatment anxiety	41	75.61	(26.51, 0-100)	0.94	49.10	102.12	-.849
Worry	41	87.60	(22.52, 0-100)	0.93	65.08	110.12	-2.110
Cognitive problems	40	78.13	(20.03, 25-100)	0.88	58.10	98.16	-.607
Perceived physical appearance	40	83.54	(23.76, 16.67-100)	0.91	59.78	107.30	-1.571
Communication	40	65.83	(28.48, 0-100)	0.78	37.35	94.31	-.701
5-7 years							
Total	56	73.70	(13.04, 39.32-100)	0.68	60.66	86.74	-.114
Pain and hurt	61	84.63	(19.15, 37.50-100)	0.79	65.48	103.78	-.893
Nausea	59	78.98	(27.34, 0-100)	0.94	51.64	106.32	-1.530
Procedural anxiety	62	47.58	(33.11, 0-100)	0.93	14.47	80.69	.102
Treatment anxiety	61	83.47	(17.58, 25-100)	0.85	65.89	101.05	-1.091
Worry	61	84.97	(17.80, 33.33-100)	0.80	67.17	102.77	-1.061
Cognitive problems	62	70.87	(19.89, 6.25-100)	0.87	50.98	90.76	-.402
Perceived physical appearance	62	76.61	(21.12, 0-100)	0.84	55.49	97.73	-1.018
Communication	61	58.20	(25.84, 0-100)	0.85	32.36	84.04	-.320
8-12 years							
Total	71	74.26	(16.48, 25.42-98.75)	0.82	57.78	90.74	-.855
Pain and hurt	75	81.00	(25.78, 0-100)	0.94	55.22	106.78	-1.376
Nausea	72	82.99	(26.48, 0-100)	0.95	56.51	109.47	-1.637
Procedural anxiety	75	68.56	(28.59, 0-100)	0.94	39.97	97.15	-.868
Treatment anxiety	74	87.16	(17.07, 33.33-100)	0.84	70.09	104.23	-1.443
Worry	75	79.00	(24.21, 0-100)	0.87	54.79	103.21	-1.309
Cognitive problems	75	64.80	(22.09, 5-100)	0.83	42.71	86.89	-.190
Perceived physical appearance	75	69.11	(25.99, 0-100)	0.82	43.12	95.10	-.745
Communication	74	60.92	(24.71, 0-100)	0.80	36.21	85.63	-.458
13-18 years							
Total	61	76.41	(15.57, 39.06-100)	0.84	60.84	91.98	-.416
Pain and hurt	65	80.77	(21.88, 25-100)	0.90	58.89	102.65	-.835
Nausea	63	84.21	(22.95, 5-100)	0.93	61.26	107.16	-1.631
Procedural anxiety	65	75.00	(25.17, 0-100)	0.88	49.83	100.17	-.709
Treatment anxiety	65	89.49	(14.45, 50-100)	0.92	75.04	103.94	-1.046
Worry	65	76.79	(21.22, 0-100)	0.86	55.57	98.01	-1.016
Cognitive problems	66	67.95	(23.60, 15-100)	0.89	44.35	91.55	-.445
Perceived physical appearance	66	70.45	(26.16, 0-100)	0.86	44.29	96.61	-.741
Communication	66	65.15	(23.75, 0-100)	0.85	41.40	88.90	-.271

n: number of individuals, SD: standard deviation, α: Cronbach's coefficient.

Table 5 Test-retest reliability of the Japanese version of the PedsQL Cancer Module

	2-4 years α ICC	5-7 years α ICC	8-12 years α ICC	13-18 years α ICC
Child self-report (n = 19)				
Pain and hurt		.42 .54	.38 .94**	.94 .94**
Nausea		.49 .80**	.86 .50	.92 .99**
Procedural anxiety		.72 .97**	.86 .46	.64 .67
Treatment anxiety	NA	-.06 -.12	.94 .76*	.91 .20
Worry		.90 .85**	.94 .20	.74 .92**
Cognitive problems		.66 .79**	.75 .74	.84 .93**
Perceived physical appearance		.79 .87**	.75 .45	.90 .97**
Communication		.83 .76**	.81 .85*	.92 .78*
Total		.79 .83**	.68 .79*	.85 1.00**
Parent proxy report (n = 38)				
Pain and hurt	.92 .86**	.85 .72**	.95 .99**	.99 .99**
Nausea	.95 .92**	.95 .83**	.89 1.00**	.98 .92*
Procedural anxiety	.98 .97**	.98 .95**	.96 .87*	.84 .75
Treatment anxiety	.81 .68*	.42 .34	.85 .74	.95 .89**
Worry	.95 .94**	.72 .51	.97 .87*	.95 .87**
Cognitive problems	.94 .90**	.92 .73**	.83 .71	.89 .92**
Perceived physical appearance	.94 .92**	.88 .86**	.82 .65	.94 .79*
Communication	.89 .81**	.88 .80**	.25 .25	.73 .71*
Total	.98 .97**	.92 .71*	.89 .86*	.93 1.00**

α: Cronbach's coefficient alpha, ICC: intraclass correlation coefficient, NA: not applicable, *P = < 0.05, **P = < 0.01 (2-tailed)

Table 6 Exploratory factor analysis of the PedsQL Cancer Module in child self-reports

Subscale	Item	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7
Pain and hurt	P1	-.08	.13	-.10	.07	-.06	-.06	**.94**
	P2	.07	-.07	.03	-.02	.06	.01	**.77**
Nausea	N1	**.85**	.02	-.03	.13	-.06	-.06	.03
	N2	**.89**	.04	.03	-.07	.05	-.07	-.03
	N3	**.59**	.20	-.06	-.06	.15	.02	-.11
	N4	**.85**	.00	.07	.16	-.17	.04	.05
	N5	**.98**	.01	-.09	.01	-.08	.01	-.08
Procedural anxiety	PA1	.17	.11	-.03	**.62**	.17	-.17	.04
	PA2	-.03	-.13	.09	**.87**	-.10	.11	.05
	PA3	.03	-.05	.00	**.83**	-.01	.12	-.02
Treatment anxiety	TA1	-.07	.04	**.87**	.10	.12	-.09	-.08
	TA2	-.02	-.02	**1.00**	-.08	-.10	.07	.01
	TA3	.06	.05	**.67**	.08	.10	-.05	-.03
Worry	W1	**.51**	-.10	.08	-.05	.29	.10	.12
	W2	.20	-.14	.14	-.11	**.64**	.03	.07
	W3	.21	-.20	.01	-.17	**.59**	.09	.05
Cognitive problems	CP1	-.07	.16	-.05	.01	.22	**.30**	.22
	CP2	-.04	**.54**	-.09	.01	.22	.05	-.08
	CP3	.12	**.73**	-.07	-.01	.04	-.17	.03
	CP4	-.02	**.54**	.11	-.03	-.01	.04	.14
	CP5	.05	**.70**	.18	-.12	-.14	.20	.01
Perceived physical appearance	A1	.19	.22	.00	-.10	.02	**.41**	.02
	A2	-.01	-.12	.02	.02	.05	**.82**	-.05
	A3	-.06	.12	-.05	.12	-.05	**.81**	-.02
Communication	C1	-.14	.23	-.02	-.02	**.75**	-.02	-.06
	C2	-.11	.20	.08	.19	**.67**	-.14	.00
	C3	-.02	.04	-.10	.18	**.48**	.30	-.12

Extraction method is principle factor analysis by Promax rotation with Kaiser normalization.
Factor loading greater than 0.30 shown in boldface.

Table 7 Exploratory factor analysis of the PedsQL Cancer Module in parent proxy-reports

Subscale	Item	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7
Pain and hurt	P1	-.01	.04	.00	-.04	.17	-.04	**.85**
	P2	.11	-.03	.01	.08	-.06	.03	**.93**
Nausea	N1	**.87**	-.08	.03	.03	-.05	-.02	.11
	N2	**.94**	.03	.01	-.11	-.08	.03	.08
	N3	**.60**	-.02	.08	.17	.16	.03	-.13
	N4	**1.00**	-.01	.03	-.02	-.18	.06	.04
	N5	**1.00**	-.01	-.07	-.10	-.05	.01	-.04
Procedural anxiety	PA1	.10	.07	**.85**	-.08	-.04	-.03	.00
	PA2	-.13	-.02	**.90**	.15	.02	-.09	.01
	PA3	.06	.00	**.95**	-.08	.00	.07	.00
Treatment anxiety	TA1	-.05	-.06	.12	**.83**	.00	.04	.02
	TA2	.08	.13	-.11	**.85**	-.18	.09	-.02
	TA3	-.06	.02	.00	**.90**	-.14	.08	.06
Worry	W1	**.66**	.00	.07	.08	.16	.00	-.06
	W2	**.45**	.00	-.05	.27	.27	-.13	-.01
	W3	.13	-.15	-.01	**.44**	**.49**	-.24	-.06
Cognitive problems	CP1	.04	**.55**	.07	.09	.09	.11	.02
	CP2	-.03	**.75**	.05	-.12	.03	.03	-.04
	CP3	-.11	**.89**	-.02	.01	-.12	-.12	.11
	CP4	-.01	**.77**	-.06	.17	.00	-.06	.02
	CP5	.08	**.86**	.05	-.02	.01	.01	-.10
Perceived physical appearance	A1	.27	.24	-.10	-.08	**.50**	-.01	.07
	A2	-.13	-.10	.07	-.09	**.83**	.06	.12
	A3	.00	.04	-.06	-.18	**.95**	.08	-.04
Communication	C1	.11	.01	-.01	.03	.02	**.86**	-.04
	C2	-.04	-.09	-.04	.10	.09	**.93**	.03
	C3	-.17	.12	.07	.12	.38	.29	.02

Extraction method is principle factor analysis by Promax rotation with Kaiser normalization.
Factor loading greater than 0.30 shown in boldface.

(median, 8 min) for the child self-report and 2 to 5 minutes (median, 3 min) for the parent proxy report. This would be enough to demonstrate the feasibility of the Japanese version of the PedsQL 3.0 Cancer Module.

Discussion

The present study demonstrated the reliability, validity, and feasibility of the Japanese version of the PedsQL Cancer Module. The guardians who answered the questionnaires were much older than the Brazilian subjects [16], it may reflect the rising age at first birth among Japanese women.

For internal consistency, Cronbach's coefficient alpha for the overall scale exceeded 0.70 except for the 'pain and hurt,' 'cognitive problems,' 'perceived physical appearance,' and 'communication' subscales in child self-reports for children aged 5 to 7 years. The Cronbach's coefficient alpha ranged from 0.53 to 0.67 in these subscales. The same tendency was shown in the original English version (0.38 to 0.63) [11]. The reason may be that children under the age of 7 years can only describe the general amount of pain they feel. Therefore, it is sometimes difficult to accurately measure the level of pain even using very simple scales [23]. As Dr. James W. Varni mentioned [11], child self-report scales that cannot achieve 0.70 should be used only for descriptive or exploratory analyses and further testing is needed for practical use.

For test-retest reliability, patients were selected who were considered to be stable and were not expected to change before completing the questionnaires for the second time. Patients did not receive treatment between the first and second completions of the questionnaires. The ideal length of the interval between the first and the second tests was not determined. A period of 2 to 14 days in considered adequate [24-27], so we used a 7-day interval in this study. ICC values among children were good to excellent, except for 3 subscales. First, for the 'treatment anxiety' subscale in 5- to 7-year-olds, the children gave the same answer for the second item, 'getting anxious about going to the doctor.' However, 2 other items, 'getting anxious when waiting to see the

Table 8 Multitrait scaling analysis of the PedsQL Cancer Module

Subscale	Children			Parents		
	Convergent validity	Discriminant validity	Success rate	Convergent validity	Discriminant validity	Success rate
Total	0.46-0.83	0.02-0.61	99.5%	0.51-0.92	0.03-0.62	100%
Pain and hurt	0.56	0.06-0.44	100%	0.80	0.06-0.47	100%
Nausea	0.56-0.80	0.14-0.48	100%	0.66-0.92	0.18-0.62	100%
Procedural anxiety	0.72-0.83	0.02-0.35	100%	0.80-0.89	0.03-0.51	100%
Treatment anxiety	0.69-0.75	0.08-0.39	100%	0.79-0.81	0.11-0.52	100%
Worry	0.62-0.67	0.12-0.61	100%	0.70-0.83	0.15-0.60	100%
Cognitive problems	0.46-0.67	0.04-0.47	98.0%	0.62-0.77	0.03-0.45	100%
Perceived physical appearance	0.48-0.68	0.09-0.42	100%	0.66-0.80	0.16-0.45	100%
Communication	0.46-0.68	0.14-0.44	100%	0.51-0.79	0.19-0.42	100%
2-4 years						
Total				0.28-0.94	0.01-0.81	99.0%
Pain and hurt				0.77	-0.01-0.60	100%
Nausea				0.57-0.94	0.14-0.62	98.0%
Procedural anxiety				0.64-0.90	-0.01-0.81	96.0%
Treatment anxiety		NA		0.84-0.86	0.01-0.80	100%
Worry				0.78-0.94	0.02-0.54	100%
Cognitive problems				0.70-0.91	0.13-0.55	100%
Perceived physical appearance				0.54-0.62	0.19-0.56	100%
Communication				0.28-0.72	0.01-0.61	96.0%
5-7 years						
Total	0.31-0.88	0.00-0.49	99.0%	0.57-0.91	0.00-0.56	100%
Pain and hurt	0.39	0.00-0.35	100%	0.59	0.00-0.38	100%
Nausea	0.50-0.71	0.00-0.38	100%	0.68-0.91	0.02-0.56	100%
Procedural anxiety	0.67-0.88	0.03-0.41	100%	0.78-0.88	-0.01-0.41	100%
Treatment anxiety	0.66-0.70	0.01-0.46	100%	0.71-0.77	0.08-0.45	100%
Worry	0.46-0.65	-0.02-0.43	100%	0.60-0.71	0.00-0.52	100%
Cognitive problems	0.39-0.54	0.01-0.49	97.0%	0.63-0.83	0.00-0.42	100%
Perceived physical appearance	0.31-0.56	0.03-0.44	96.0%	0.63-0.81	0.08-0.43	100%
Communication	0.31-0.54	0.02-0.40	96.0%	0.57-0.79	0.00-0.43	100%
8-12 years						
Total	0.47-0.97	0.00-0.90	100%	0.43-0.87	0.01-0.78	98.0%
Pain and hurt	0.66	0.12-0.54	100%	0.88	0.07-0.57	100%
Nausea	0.79-0.99	0.11-0.65	100%	0.77-0.93	0.05-0.78	98.0%
Procedural anxiety	0.97-0.98	0.11-0.90	100%	0.87-0.96	-0.02-0.35	100%
Treatment anxiety	0.97-0.98	0.12-0.41	100%	0.69-0.73	0.13-0.52	100%
Worry	0.95-0.97	0.26-0.55	100%	0.64-0.88	-0.02-0.77	96.0%
Cognitive problems	0.94-0.98	0.00-0.44	100%	0.51-0.77	0.01-0.77	98.0%
Perceived physical appearance	0.93-0.96	0.11-0.45	100%	0.52-0.80	0.08-0.43	100%
Communication	0.47-0.65	0.15-0.46	100%	0.43-0.79	0.11-0.45	96.0%
13-18 years						
Total	0.51-0.91	0.08-0.64	98.0%	0.48-0.92	0.13-0.56	100%
Pain and hurt	0.71	0.15-0.46	100%	0.81	0.26-0.50	100%
Nausea	0.62-0.86	0.08-0.58	100%	0.48-0.92	0.16-0.55	98.0%
Procedural anxiety	0.51-0.75	0.10-0.42	100%	0.78-0.87	0.17-0.50	100%
Treatment anxiety	0.86-0.91	0.13-0.51	100%	0.81-0.91	0.24-0.56	100%
Worry	0.67-0.83	0.19-0.54	100%	0.71-0.87	0.22-0.53	100%
Cognitive problems	0.54-0.69	0.06-0.57	95.0%	0.65-0.81	0.14-0.53	100%
Perceived physical appearance	0.52-0.72	0.24-0.64	96.0%	0.73-0.76	0.25-0.48	100%
Communication	0.56-0.79	0.19-0.58	96.0%	0.59-0.81	0.13-0.51	100%

Convergent and discriminant validity is calculated by Pearson correlation coefficient, NA: not applicable